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Management of gunshot wound to the lumbosacral spine in a 17-year-old girl without neurological impairment.

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We report the case of a young girl (17-year-old) wounded by an accidental gunshot. The bullet entered through the skin midline over the navel area, passed through the stomach perforating the vena cava and, by breaking the right pedicle of L4, moved inside the vertebral canal (bridging the cauda equina) stopping just in front of the body of S2. Because of the sudden onset of acute abdomen due to a massive retroperitoneal hematoma, the patient underwent emergency explorative laparotomy with the evacuation of the hematoma and the suture of the perforated cava vein, the peritoneum, and the stomach. No neurological deficits were observed after the gunshot. Two weeks later, the patient underwent spinal surgery to remove the bullet from the spinal canal, which was performed successfully without any instrumentation and with no onset of new neurological signs and symptoms or surgery-related complications. Patient was discharged on day 9 after surgery in good general conditions.

Spinal cord gunshot injuries (GSI) are penetrating spinal traumas, which lead to significant morbidity and mortality. Gunshot wounds (GSWs) represent an increasing cause of spinal cord injury in the urban setting having an incidence accounting for 16% of all spinal cord injury, ranging from 13 to 44% depending on the country (1-3). The 78 to 94% of these patients are young (30 years old) and most of them suffer from secondary neurological impairment due to spinal cord trauma (2, 4).

GSW injuries of the spine are classified in three main types accordingly to the position of the bullet relative to the spine and the involvement of internal organs.

In GSWs type I, or transfixing, small fragments are found inside the canal. This is the most frequent type of injury (>70%); In GSWs type II or intracanal, the whole bullet is inside the canal, comprising

20.4% of cases; GSWs types III are intervertebral lesions because the bullet is inside the intervertebral disc space. In these subtypes perforation of abdominal organ or hemopneumothorax can occur more frequently (GSWs type III type A-B) (2). The incidence of concomitant lesions of vital organs is 20% (5). Vital organs are mainly involved in case of lumbosacral regions GSW whereas massive bleeding may endanger the life of patient and therefore should be promptly identified and treated (2).

The management of GSWs of the spine is a controversial issue and both conservative and surgical treatment has been widely discussed (2). The severity of neurological impairment, according to the American Spinal Injuries Association (ASIA A-C), the level of spinal cord injuries (Thoracic > Cervical > Lumbosacral/Cauda-equina) and the type of cervical or thoracolumbar injury, according to

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Thoracolumbar Injury Classification and Severity Scale (TLICS) as well as Cervical Spine Injury Classification System (SLIC) have been investigated as possible outcome predictors (6).

In absence of neurological or vital organs impairment, septic and long-term complications such as chronic pain or bullet migration should be considered and eventually treated.

We present a 17-year-old girl patient with GSW type II lumbosacral injury with vital organs involvement. The bullet caused a stomach and cava vein laceration, a wedge and monolateral pedicle fracture of L4, ending in the spinal canal in proximity of S2 within the nerve fibers of the cauda equina.

Case description

A 17-year-old girl patient accessed the emergency department (ED) of a suburban hospital with a GSW. At admission, vital signs were stable without neurological impairment, (GCS 15, ASIA E). Clinical inspection showed a bullet entry point in the supra-umbilical midline region. Exit point was not visible. Computer tomography scan (CT scan) demonstrated an acute retroperitoneal hematoma, evidence of retained bullet fragment in the vertebral canal in proximity of S2 associated with fracture of right pedicle and wedge of L4. Tetanus prophylactic and broad-spectrum antibiotic therapy were started immediately (Tazobactam 18 g/day, Metronidazole

1,5 g/day, Ceftriaxone 6 g/day). The patient underwent explorative laparotomy surgery with acute blood loss, treated with blood transfusions. During abdominal surgery, anterior and posterior perforation of the stomach antrum in the pre-pyloric area were observed as well as peritoneum laceration.

The presence of great amount of retroperitoneal blood was intraoperatively showed due to perforation of the anterior wall of the cava vein in proximity of L4. No perforation of bowel or arteries was found. The surgeons could successfully suture all the perforated structures without any complication. After surgery, the patient was moved to the intensive care unit (ICU). Neurological status was intact. Antibiotic therapy was stopped 7 days after injury. No fever or infection-related signs or symptoms were observed. Approximately two weeks after surgery the patient suffered from nausea and vomiting which could not lead to a regular alimentation, so she underwent parenteral nutrition. For what concerns other symptoms, she just suffered from slight low back pain; cautiously she did not stand up. Sphincterial functions were intact (anal manometry was normal, urinary catheter was removed on day 11 after laparotomy, replaced immediately for urinary retention and then definitely removed on day 13). One month after injury, the patient was moved to the 2° Spine unit of “IRCCS Galeazzi” (Milan, Italy) for removal of the bullet inside the spinal canal. Surgery was performed with patient in prone position after general anaesthesia.

Intraoperative landmark was acquired thanks to plain X-ray, which led to precise localization of the bullet. A small skin incision was made, targeted on the acquired landmark. Superficial muscular fascia was dissected and prepared for additional subsequent dura repair. Muscular fibers were dislocated laterally to visualize sacral bone on its paramedian right side; using chisels, a small bony square (“open door”) area was removed to reveal the dura mater. Under the bony layer; blood clots mixed to soft tissue and cerebrospinal fluid (CSF) were found. After accurate dissection and suction of the bloody component, dura mater breakage with CSF leak was recognizable. The laceration of the dura, not clearly visible on preoperative CT scan, was found postero-medially;



FIG 1. Frontal (A) and lateral (B) X-Rays showed a foreign body in the spinal canal in proximity of S2.



FIG 2. Axial (A) and sagittal (B) CT scan showed fracture of right pedicle and wedge of L4. C: axial view showed intracanal bullet fragment in S2.

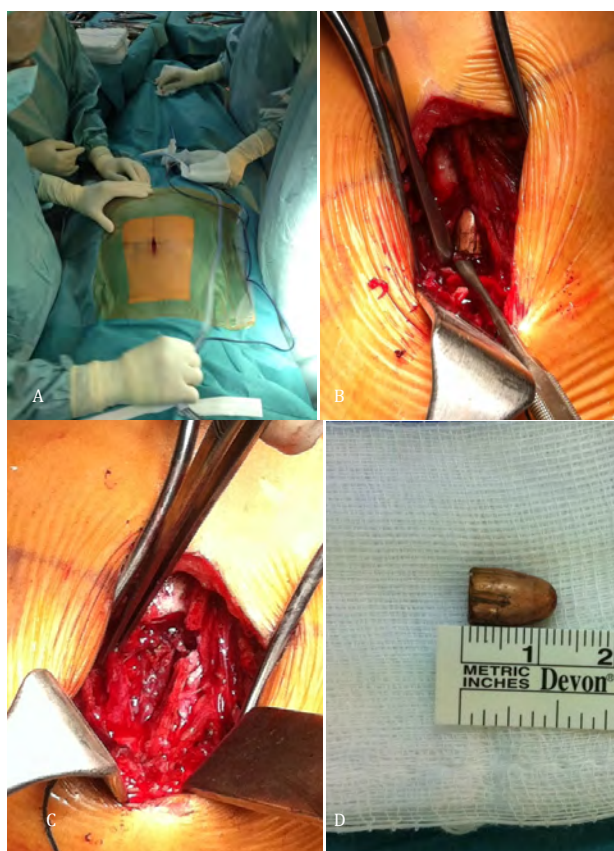


FIG 3. (A-D) Surgical field before and after removal of bullet fragment.

underneath, the bullet was recognizable, surrounded by blood clots, within nerve fibers of the sacral roots. Careful dissection of the bullet from the surrounding nerve fibers was performed using intraoperative EMG. At the end, the bullet was entirely removed. No injuries to the sacral roots were found. Accurate suture of the dura layer with apposition of autologous

fatty pad, muscular fascia prepared at the beginning and fibrin glue was performed to repair CSF leakage.

No complications were observed after surgery; patient was able to stand up on day 2 and walk without any assistance. She developed no headache or other CSF leakage associated conditions; wound healing was normal considering age and clinical status and she did not suffer from any sphincter disturbance. It was not planned to treat the fracture of L4 considering it stable and unilateral, without spinal canal involvement. The patient was discharged after 4 weeks from the original trauma (10 days after spinal surgery) clinically and neurologically intact.

Follow up at 6 years after removal of the bullet is normal: patient is healthy, with no neurological deficits. A CT scan and a MRI of the spine showed normal findings after surgery.

DISCUSSION

Although surgical removal of retained bullet into the spinal canal/dural sac is still controversial, the demand of surgical care is increasing in the last years (7).

Despite vascular complications or vital organs injuries are considered for an emergency management, spinal involvement is not usually life-threatening and often an early decompression does not mean a definite neurological recovery (6, 8-9).

The only absolute early surgical indications are represented by presence of CSF fistula, documented neurological impairment progression associated with radiological evidence of neurological compressions and spinal instability (4).

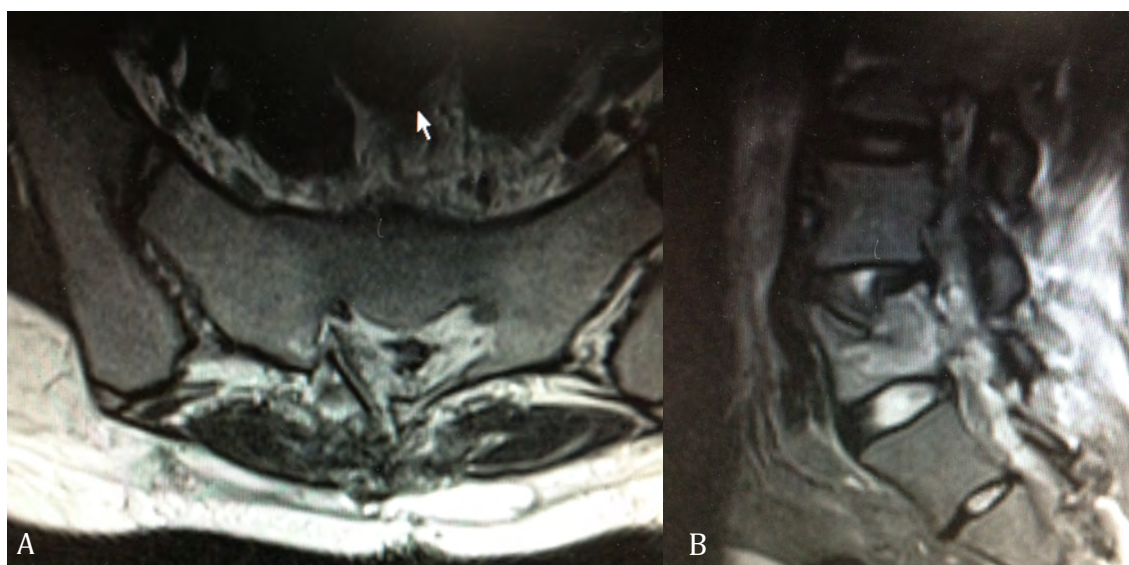


FIG 4. axial (A) and sagittal (B) postoperative MRI showed L4 fracture without loss of body height or lumbar alignment and complete sacral canal decompression.

Where some authors suggest not to proceed to bullet removal because of surgery-related risks (infections, roots damages), other authors are favourable to the surgery considering the risk of neurological deterioration and formation of sterile abscess or granuloma in the bullet area (10-12). In absence of neurological involvement, surgical management is even more controversial, but the impact of possible delayed complications on the morbidity and mortality of these patients should be carefully considered.

Infections (superficial or deep, meningitis, abscess) or the bullet ferromagnetic properties or its migration in the dural sac may represent potential causes of morbidity and mortality, likewise the direct spinal cord injury (7).

Migration of the bullets inside the spinal canal many years after being shot is not so uncommon and may cause late onset of pain, discomfort or neurological deficits (10-12). According to literature, some cases of delayed cauda equina syndrome due to migratory bullet were recorded and, in these cases, surgical management was recommended by the authors (13-15). A late surgery might be associated to higher intraoperative risks and more invasive surgical decompression to remove the bullet. Moreover, in the presence of intradural bullet fragment, a dural

tear should be suspected, even if is not recognised on preoperative CT scan examination (16).

In our case, an early open posterior approach to the lumbosacral region was performed in order to decompress spinal canal and to remove the bullet fragment. During surgery, we repaired a dural breakage with CSF leakage that was undiagnosed on preoperative radiological imaging, preventing a delayed CSF leak. Our purpose was to avoid delayed complications as persistent pain, delayed neurological symptoms onset, infection or fragment dislocation. Therefore, for these reasons and for the age of our patient (very young), although she was neurologically intact, an early surgery has been preferred.

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Video-assisted anterior retroperitoneal approach to the lumbar spine. A minimally invasive technique improved by the use of an endoscopic camera to treat lumbar spinal diseases. Consideration over 269 patients

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We describe the technique we routinely use to perform the retroperitoneal anterior approach using a rigid endoscope coupled to a HDD screen to assist mini-open retroperitoneal anterior approach. Our experience was compared to those reported in the literature for the standard mini-open retroperitoneal approach. We retrospectively analyzed a total of 269 consecutive patients, 109 males and 160 females, underwent anterior lumbar approach in our department, using video-assisted anterior retroperitoneal approach to the lumbar spine. 202 patients had a single L5-S1 or L4-5 ALIF (75.09%), 14 patients received a double level ALIF (5.3%), while 53 patients underwent a double anterior and posterior approach (19.8%). The average preoperative VAS and Oswestry Disability Index (ODI) scores were 9.1 ± 6.3 and 79.3 ± 11.9 . At least 16 months follow-up (from 16 months to 5 years), the average VAS and ODI values had improved to 1.6 ± 1.5 and 13.1 ± 13.2 , respectively ($p < 0.05$). The mean length of stay was 4.3 ± 3.5 days. There were 6 major complications (2.2%) related to the approach: major vascular injuries (iliac vein injury) occurred in a total of 3 patients (1.1% of cases), whereas retrograde ejaculation occurred in 3 patients (2.75% of male cases in the series). No wound or deep infections occurred. In our opinion, this technique, compared with other mini-open approach, potentially reduces perioperative morbidity, length of surgery, surgical approach-related complications, and hospitalization.

Anterior lumbar spine access is common treatment of degenerative disc disease (DDD) and chronic spinal instability as well as in failed posterior surgery (1-4). Anterior retroperitoneal approach allows for a direct disc space exposure to obtain a complete disc removal to perform an anterior interbody fusion (ALIF) or total disc replacement (TDR) (5). Since the first anterior interbody placement of bone graft by Carpenter (6), the two most widely used approaches are the retroperitoneal and the transperitoneal. The retroperitoneal approach is the most commonly

used as it preserves the anatomical structures of the abdomen more than the transperitoneal route (7-10). Drawbacks of open transperitoneal or traditional retroperitoneal approaches are: size of surgical incision and possible associated tissue trauma that means more postoperative morbidity, major risk of retrograde ejaculation in male for L5-S1 dissection, hospitalization time and longer recovery period. Therefore, to decrease the risks related to the traditional approaches, several minimal invasive techniques have been developed (11-13).

Key words: ALIF, Minimal Invasive, Endoscopic, Lumbar Spinal Diseases, Degenerative disc disease

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In this paper we describe the technique we routinely use to perform the retroperitoneal anterior approach using a rigid endoscope (30 degrees -10 mm cold light endoscope coupled to a HDD screen) to assist mini-open retroperitoneal anterior approach. We also compare our experience to those reported in the literature for the standard mini-open retroperitoneal approach.

MATERIALS AND METHODS

In this surgical technique report, we retrospectively analyzed a total of 269 consecutive patients, 109 males and 160 females, who underwent anterior lumbar approach in our department between January 2010 and December 2014. The mean age was 44.8 ± 10.3 years for men and 47.2 ± 10.7 years for women. The mean duration of follow-up was 3 years.

We selected patients with symptomatic DDD or symptomatic degenerative spondylolisthesis characterized by persistent or recurrent severe low back pain, with or without radiculopathy in which ALIF was performed associated or not with posterior stabilization. Patients with

isthmic spondylolisthesis, or patients with an incomplete documentation or that were unable or unwilling to answer to the follow-up questionnaires were excluded.

Preoperative diagnosis, pre and postoperative functional status with the Oswestry Disability Index (ODI) and VAS, number of treated levels, type of surgical procedures performed, mean duration of surgery, blood loss, surgical related complications, general peri- and postoperative complications, length of stay have been collected. All patients received cycles of conservative treatment (medication, physical therapy, pain therapy) for a period of at least 6 months before surgery.

We treated 269 patients: 202 patients had a single L5-S1 or L4-5 ALIF (75.09%), 14 patients received a double level ALIF (5.3%), while 53 patients underwent a double anterior and posterior approach (19.8%).

Statistical analysis

Statistical analysis was performed in order to consider significant differences in the groups. Results were compared using the Student's T test, while analysis of variance (ANOVA) test was used to compare the results of the single groups



Fig. 1. Intraoperative disposition of the surgeon and his assistants. Notice how the monitor shows the deep structures (in this case the intervertebral space) that are recorded by the endoscopic camera, shown in the box on the right.

Surgical technique description

Each patient is positioned supine with both legs and lumbar spine in neutral position. A slight Trendelenburg position is obtained tilting the operating table, allowing the upward shift of abdominal structures. The first surgeon stands on the right side of the patient (Fig. 1).

The first part of the surgery is carried out without the use of the endoscope and the main steps are no different from the standard mini-open approach. A transverse modified Pfannenstiel incision of 4 cm is made, for L5-S1 or pararectal on the left side for L4-L5. The anterior sheath of the left rectus abdominis muscle is dissected



Fig. 2. *Intraoperative endoscopic view of ureter (indicated with an anatomic claw) and common iliac artery (on the right).*

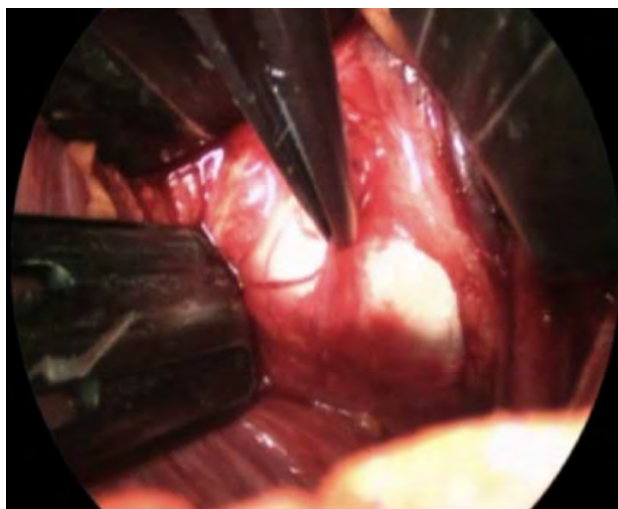


Fig. 3. *Intraoperative endoscopic view of the disc exposition and of the middle sacral vessels (pinched with an anatomic claw).*

longitudinally from the left side, about 2 mm lateral to the linea alba and the left rectus muscle retracted upward and laterally with careful blunt finger dissection of the extraperitoneal space. Once the peritoneal sac has been exposed and bluntly pushed aside, a short incision in the far lateral tract of the arcuate line (Douglas Line) allows visualization of the retroperitoneal space, the psoas muscle and genitofemoralis nerve. It is mandatory to identify the ureter and the left common iliac artery and vein (Fig. 2) to expose L5-S1 (medially) or L4-L5 (laterally) discs. Under direct visual and endoscopic control (30 degrees -10 mm cold light endoscope coupled to a HDD screen) the preparation of the anterior surface of intervertebral disc is performed taking care of the inferior hypogastric plexus.

L5-S1 disc is exposed between the two common iliac veins and arteries (Fig. 3) after coagulation of the middle sacral vessels. In cases of L4-L5 discectomy, the left common iliac vein is retracted medially after ligation of the left ileo-lumbar vein in most of the cases. Therefore, a retractor with blades is placed and fixed to the vertebral bone with 3 pins. The 30° endoscope allows a magnified and bright visualization of the surgical corridor, that sometimes is very deep and angled (i.e. in high sacral slope). Two flaps from the anterior ligament and anulus are prepared as lateral limit of the surgical corridor to protect the vascular structures during discectomy and implantation. The vertebral bodies are then mobilized with a spreader, restoring the height of the intervertebral space.

At this stage, the endoscope is introduced vertically in the surgical corridor allowing direct view of the superior and inferior endplates, depending on the cranio-caudal orientation of the instrument (Fig. 4). A deep light source and a magnification on the screen allow the complete visualization of the procedure for all surgical team and make the endplates removal easier and more effective. In the case of a posterior annular defect or extruded disc herniation, the endoscope is useful to explore the posterior edge of the disc. After completing discectomy, templates of increasing sizes are introduced to restore the optimal segmental lordosis and the definitive cage is implanted.

Anterior fusion is then performed by the implantation of a hydroxyapatite-filled porous tantalum cage secured by a plate fixed with 3 or 4 screws (Fig. 5). A drain is finally inserted at the end of the procedure.

RESULTS

All the 269 patients completed the final follow-up. All patients presented a complete data set in our database, since all clinical data were prospectively collected. Intraoperative details as blood loss, length of surgery and hardware were obtained from clinical reports (Table I-IV).

A single L5-S1 level was treated in 186 patients (69.2%), 82 men and 104 women with mean age of 44.6 ± 9.3 years.

The mean duration of surgery was 81.9 ± 29.5 min and intraoperative blood loss was 91.4 ± 197.5 millilitres. The mean length of stay was 4.7 ± 2.4 days. The mean preoperative VAS and ODI values were 9.1 ± 5.9 and $78.6 \pm 12.9\%$, respectively, whereas the final follow-up VAS and ODI values were 1.5 ± 1.5 and $12.3 \pm 12.3\%$, respectively. There were 3 major complications related to the operation: 1 iliac vein injury, 2 retrograde ejaculations. 12 patients had postoperative anaemia.

A single L4-L5 level was treated in 16 patients (5.9%), 5 men and 11 women with a mean age of 51.9 ± 12.5 years. The mean duration of surgery was 100.5 ± 35 min. Intraoperative blood loss was 153.7 ± 721 millilitres. The mean length of stay was 4.5 ± 3.8 days.

The mean preoperative VAS and ODI values were 8.2 ± 1.2 and $83.6 \pm 11.3\%$, respectively,

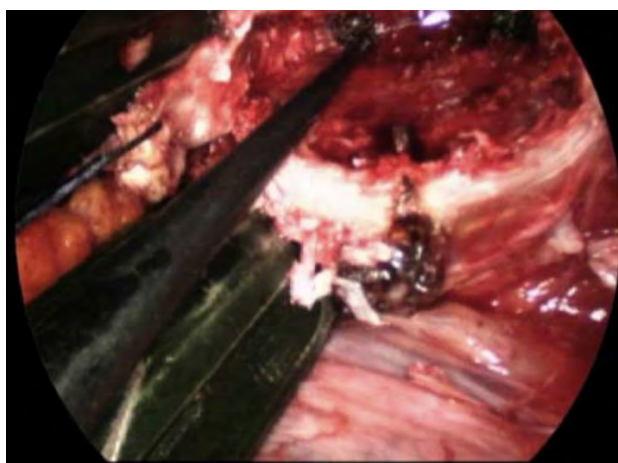


Fig. 4. Intraoperative endoscopic view of the intervertebral space preparation. A sharp instrument is used to remove the cartilaginous layer of the endplate.

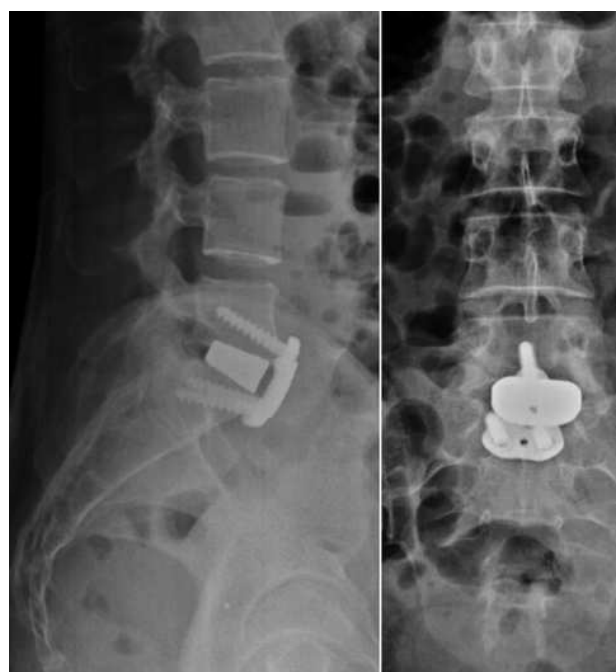


Fig. 5. Postoperative X-ray (lateral and AP views) of an L5-S1 ALIF. The patient has been treated with a tantalum cage and a three-screw anterior plate. This construct has the same stability as an anterior cage with four pedicle screws.

whereas the post-operative VAS and ODI values were 1.7 ± 1.3 and $6.6 \pm 8.8\%$, respectively. Complications related to L4-L5 access were observed in 2 patients: 1 lesion of the left iliac vein and 1 case of retrograde ejaculation. 3 patients developed postoperative anaemia.

Two-level L3-L5, L4-S1 anterior approach was performed in 14 patients (5.2%), 1 male and 13 women with a mean age of 46.5 ± 14.7 years. 10 patients (71.4%) underwent L4-S1 anterior interbody fusion, 2 patients (14.3%) had a L3-5 ALIF, while 2 (14.3%) had a L5-S1 ALIF plus an L4-5 TDR.

The mean duration of surgery was 129.6 ± 62.4 min. Intraoperative blood loss was 462.1 ± 532.4 millilitres. The mean length of stay was 6.5 ± 2.4 days. The mean preoperative VAS and ODI values were 9.2 ± 0.9 and $85 \pm 11.9\%$, respectively, whereas the post-operative VAS and ODI values were 1.4 ± 1.3 and $10.4 \pm 9.1\%$, respectively. In this group, complications related to the approach were observed in 1 patient (7.15%) who had lesions of the left iliac vein and postoperative anaemia.

A circumferential (360°) approach was performed in

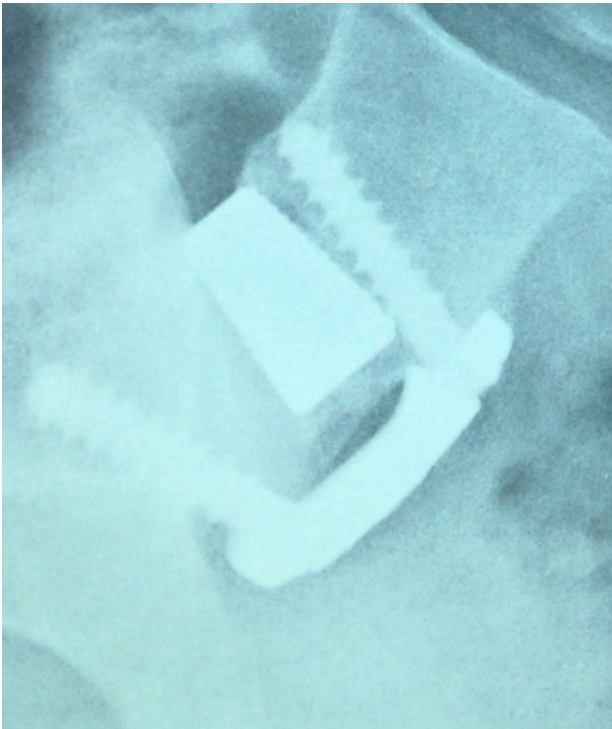


Fig. 6. 1-year follow-up lateral X-Ray of a L5-S1 ALIF showing intersomatic fusion.

a total of 53 patients (19.7%), 21 men and 32 women with a mean age of 50.2 ± 11.6 years. The mean duration of surgery (including change of position) was 232.4 ± 106.8 min. Intraoperative blood loss was 400 ± 263.3 millilitres. The mean length of stay was 6.6 ± 5.1 days. The mean preoperative

VAS and ODI values were 8.6 ± 1.3 and $83.2 \pm 8.5\%$, respectively, whereas the post-operative VAS and ODI values obtained were 1.6 ± 1.5 and $10.8 \pm 17\%$, respectively. In this group, no complication related to the surgical technique was observed in any patient. Two patients developed postoperative anaemia.

Aside from the 53 patients who had circumferential fusion, pure ALIF was performed in a total of 216 patients (80.3%). In two cases a L5-S1 ALIF was performed together with a L4-5 TDR.

The average preoperative VAS and ODI scores were 9.1 ± 6.3 and 79.3 ± 11.9 , respectively. At last follow-up, the average VAS and ODI values had improved to 1.6 ± 1.5 and 13.1 ± 13.2 , respectively. These differences were statistically significant ($p < 0.05$). The mean length of stay was 4.3 ± 3.5 days.

There were 6 major complications (2.2%) related to the approach: major vascular injuries (iliac vein injury) occurred in a total of 3 patients (1.1% of cases), whereas retrograde ejaculation occurred in 3 patients (2.75% of male cases in the series). No infections related to the surgical wound or the implant were observed during the follow-up.

Comparing these groups with ANOVA test, we noticed a statistically significant difference ($p < 0.001$) in surgical time, intraoperative blood loss, postoperative blood transfusions, and length of hospitalization.

Table I. Group 1 description, L5-S1 anterior approach.

Patients	186 M = 82 F = 104 Age (avg. In years) 44.6 ± 9.3
Duration of surgery (min)	81.9 ± 29.5
Blood loss (ml)	91.4 ± 197.5
Length of stay (days)	4.7 ± 2.4
VAS (preop and postop value)	9.1 ± 5.9 , 1.5 ± 1.5
ODI (preop and postop value)	$78.6 \pm 12.9\%$, $12.3 \pm 12.3\%$
Complications, technique related Left iliac vein lesion	1
Retrograde ejaculation	2
Complications, postop Postoperative anemia	12

Table II. *Group 2 description, L4-5 anterior approach.*

Patients	16 M = 5 F = 11 Age (avg. In years) 51.9 ± 12.5
Duration of surgery (min)	100.5 ± 35
Blood loss (ml)	153.7 ± 721
Length of stay (days)	4.5 ± 3.8
VAS (preop and postop value)	8.2 ± 1.2 , 1.7 ± 1.3
ODI (preop and postop value)	$83.6 \pm 11.3\%$, $6.6 \pm 8.8\%$
Complications, technique related Left iliac vein lesion	1
Retrograde ejaculation	1
Complications, postop Postoperative anemia	3

Table III. *Group 3 description, two levels anterior approach.*

Patients	14 M = 1 F = 13 Age (avg. In years) 46.5 ± 14.7
Duration of surgery (min)	129.6 ± 62.4
Blood loss (ml)	462.1 ± 532.4
Length of stay (days)	6.5 ± 2.4
VAS (preop and postop value)	9.2 ± 0.9 , 1.4 ± 1.3
ODI (preop and postop value)	$85 \pm 11.9\%$, $10.4 \pm 9.1\%$
Complications, technique related Left iliac vein lesion	1
Retrograde ejaculation	0
Complications, postop Postoperative anemia	1

Table IV. *Group 4 description, combined anterior-posterior approach.*

Patients	53 M = 21 F = 32 Age (avg. In years) 50.2 ± 11.6
Duration of surgery (min)	232.4 ± 106.8
Blood loss (ml)	400 ± 263.3
Length of stay (days)	6.6 ± 5.1
VAS (preop and postop value)	8.6 ± 1.3 , 1.6 ± 1.5
ODI (preop and postop value)	$83.2 \pm 8.5\%$, $10.8 \pm 17\%$
Complications, technique related Left iliac vein lesion	0
Retrograde ejaculation	0
Complications, postop Postoperative anemia	2

DISCUSSION

The value of mini-open techniques compared to traditional approaches in terms of reduction of perioperative complications and reduction of operative time has been widely reported in the literature (12-14). The differences between standard mini open ALIF and video assisted technique mainly consists in the use of a 30° endoscope during the dissection, discectomy and implantation phases.

Compared with other mini-open techniques, the video assistance allows a greater magnification and brightness of the surgical field. The 30° angulated camera allows a better view during dissection in multilevel approach and in the discectomy phase in a single level approach, with a complete visualization of endplates, annulus and posterior edge, in order to obtain accurate preparation of the disc space. In our practice, endplates preparation under direct visual control is one of the most important steps of this approach, in order to improve fusion rate, find the best cage fit, restore the ideal lumbar lordosis giving an adequate anterior support. Disc decompression is performed under continuous visualization reducing surgical time and risk of complications especially in multilevel operations. Moreover, each operator (assistants, scrub nurses) can see the screen following every single step of the procedure that means better coordination and collaboration among surgeons and medical staff.

With this video assisted technique, access-related complications rate is not significantly different to those reported in the literature. We had 1.1% of vascular complication such as iliac vein laceration and 2.75% of retrograde ejaculation, whereas in the literature vascular complication rate ranges from 1.9% to 18%, retrograde ejaculation from 0.44 to 25% in standard mini-open approaches (15-19). None of our mini-open surgeries have been commutated to an open procedure.

According to Kaiser et al., an L5-S1 ALIF is associated with the shorter procedures time when using the mini-open approach (171.9 versus 185.0 min of the traditional approach) (13). Our mean time for L5-S1 surgery is slightly inferior (81.9 ± 29.5 min), showing how the use of the endoscope does

not increase the operative time. Escobar et al. reported that the duration of surgery for a single-level fusion was 170 min in patient operated with a retroperitoneal endoscopic technique for a single level fusion. In case of two or more levels of fusion, the operative time was 272 min (20). Our mean time for two levels approach is slightly inferior (129.6 ± 62.4 min). Moreover, our L5-S1 ALIF group showed further less intraoperative blood loss than the other groups (91.4 ± 197.5 , $p < 0.001$) and this data are similar to other mini-open approach and result better than those of the traditional approach (range from 55 to 153 mL) (14). In our series, the average hospital stay for single level surgery was 5 days (range from 4.7 to 5.5) whereas in other series is 7.5 days for the same surgery (range, 6-10 days) (15-21).

Considering the surgical-related complications, the results observed in our population show a low overall ratio (1.1% of major bleeding and 2.75% of retrograde ejaculation).

To avoid or reduce significantly retrograde ejaculation, we perform the hypogastric plexus dissection using small cotton pads when necessary displacing laterally the plexus (11-13). We use bipolar forceps (never monopolar) for coagulation of the small vessels.

Our study, even if it encloses a huge number of patients and is just a surgical technique report, shows some limits: the retrospective analysis decreases the power of the study, and the length of follow-up is too short to evaluate fusion rates.

The mini-open video assisted approach is useful during dissection of retroperitoneal space, discectomy and implantation of the cages, allowing a magnified and bright visualization of the deep structures. In our experience, this technique potentially reduces perioperative morbidity, length of surgery and hospitalization as well as surgical approach-related complications.

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Modifications of spinopelvic parameters and acetabular orientation after spinal surgery for adult deformity in patient who underwent bilateral total hip arthroplasty

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The spine and the hip are two anatomical districts that have close biomechanical relationship. The management of their degenerative disorders involves an in-depth biomechanical analysis of the patient, in order to define the proper hip-spine relation, using different biomechanical classifications that have been proposed in recent years. The changes in the spino-pelvic and acetabular parameters induced by prosthetic hip surgery and spinal surgery must be carefully evaluated, calculated and foreseen in the pre-operative phase, as they play a crucial role in defining the clinical success or failure of the operations. In this paper we present a case of a patient who underwent spinal surgery after a bilateral THA analyzing both spino-pelvic parameters and acetabular orientation and highlighting the strict relations between spine and hip.

The regular increasing number of diagnosed spine-hip syndrome (SHS) cases and the failure of hip replacement prosthesis is producing a growing interest and awareness in the scientific community on the importance of an overall biomechanical assessment of the lumbopelvic complex (LPC) according to the concept of kinematically aligned total hip arthroplasty (THA) proposed by Rivi re et al. (1).

SHS can be defined as a clinical condition characterized by the simultaneous concomitance of clinically manifest hip and spine osteoarthritis (OA). It is a disorder that affects mainly the elderly being the result of a degenerative process strictly connected to aging (2). A literature review showed a prevalence of 21.2% to 60.4% of lumbar back pain (LBP) in patients affected by hip osteoarthritis, who are candidates for primary total hip arthroplasty (THA) (3).

The diagnostic and kinematic evaluation of this clinical condition is based on the measurement of

spinopelvic parameters, which allow to categorize the patient's LPC biomechanics according to different kinematic classifications that have been proposed in recent years. In patients who underwent THA before planning surgery at the spine an accurate evaluation of LPC biomechanics analysing spino-pelvic and acetabular parameters must be assessed as their modifications are correlated (4).

In this paper we present a case of a patient who underwent spinal fusion after a bilateral THA analyzing both spino-pelvic parameters and acetabular orientation and highlighting the strict relations between spine and hip.

Case presentation

A 73-year-old male patient suffering from chronic low back pain came to our attention. He underwent previous decompression surgeries in L4-L5-S1 and an interspinous fixation in L3-L4. Furthermore, 10 years before the patient underwent a bilateral

Key words: spine-hip syndrome; spine-hip relation; total hip arthroplasty; lumbar fusion; ALIF; spino-pelvic parameters; acetabular anteversion

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THA. He had performed a standing full-spine X-ray (EOS^R), CT scan and MRI of the lumbosacral spine which documented residual stenosis L3-L5 and lumbar kyphosis (Fig. 1-3).

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the editor in chief of this journal.

Considering the absence of pain relief after all possible conservative treatments, revision surgery was scheduled. A complex operation was planned: an anterior retroperitoneal interbody fusion (ALIF) in L5-S1, posterior spinal decompression and L3-S1 instrumented fusion with interbody cage in L3-L4 and L4-L5 (transforaminal approach - TLIF) (Fig. 4-6).



Fig. 1. Pre-operative pictures.



Fig. 2. Pre-operative standing full-spine X-ray.

Both in preoperative and in postoperative standing full-spine X-rays (EOS^R) spino-pelvic and acetabular parameters have been evaluated (Table I, II). Ideal values were calculated according to mathematical formulas defined by le Huec et al. (6).

After spinal procedure values of pelvic tilt (PT), lumbar lordosis (LL) and sagittal vertical axis (SVA) near to ideal ones have been achieved: PT decreased from 25° to 8° (ideal), LL increased from 20° to 54° and SVA decreased from 49 mm to -25 mm, showing a good restoration of the sagittal contour and balance of the spine (Fig. 7, 8, Table I). Also acetabular parameters changed: at the right side lateral inclination changed from 56° to 52° and antiversion changed from 38° to 23°, while at the left side lateral inclination varied from 51° to 47° and antiversion from 30° to 14° (Fig. 9, table II).

At the last clinical and radiological follow-up check carried out 12 months later, the patient reported subjective well-being and maintenance of a good sagittal profile.

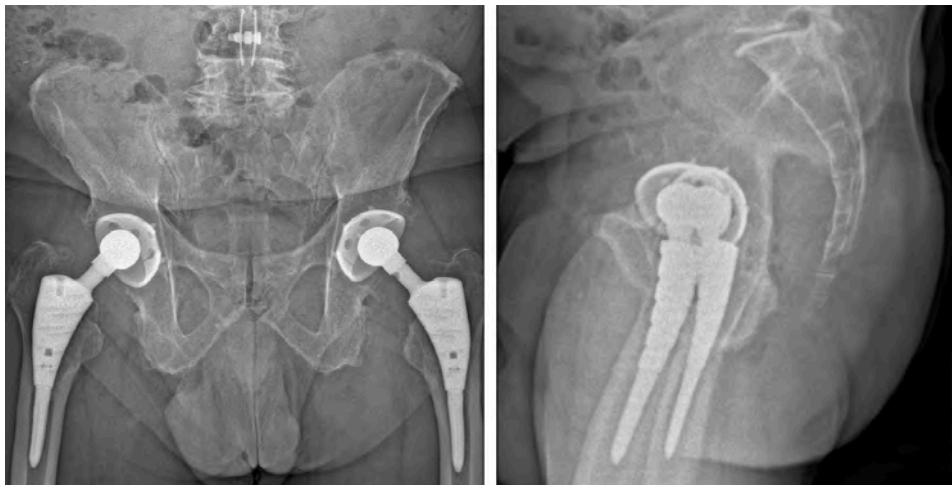


Fig. 3. X-rays of pelvis performed before spinal surgery.

Table I. Spinopelvic parameters.

SPP	Pre-op Values	Ideal Values	Post-op Values
PI	40°		40°
PT	25°	7°	8°
SS	16°	34°	33°
LL	20°	51°	54°
L4-S1	28°	35°	48°
TK	41°	38°	59°
SVA	49°	< 70°	-25°

Table II. Acetabular parameters.

ACETABULAR PARAMETERS	Side	Pre-op	Post-op
Lateral inclination	Right	56°	52°
	Left	51°	47°
Antiversion	Right	38°	23°
	Left	30°	14°

DISCUSSION

In literature, the spine-hip relation and the spine-hip syndrome are well-defined issues, with an increasing interest in the last decade (1-5). In fact, it is mandatory to evaluate the morphology of the whole spine when treating hip osteoarthritis and vice versa, as these two anatomical districts are biomechanically strictly correlated (1-8).

Most of pathological conditions in the lumbar spine lead to a sagittal malalignment caused by a progressive loss of lumbar lordosis increasing pelvic retroversion because of compensation, therefore reducing the curvature and flexibility of LPC (1, 6).

The compensatory mechanisms in patients with degenerative conditions of the spine affect the whole spine itself and the lower limbs. At the spinal level, there is a thoracic hyperextension, at the lower limbs



Fig. 4. Post-operative pictures.

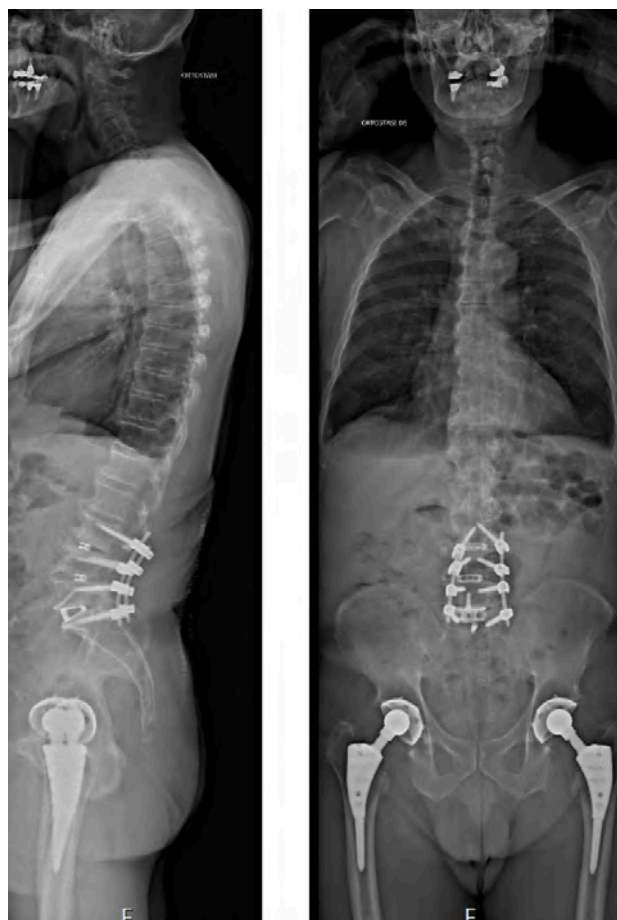


Fig. 5. Post-operative standing full-spine X-ray.



Fig. 6. X-rays of pelvis performed after spinal surgery.

there is an increase in pelvic retroversion (the pelvic tilt increases) and a consequent increase in acetabular anteversion. The hips undergo to hyperextension and the knees are flexed (3,7). Therefore, to treat properly a patient who has already undergone bilateral THA with spinal pathologies a whole biomechanical

evaluation of both spine and hip must be performed.

At first, analyzing spine biomechanics, we have to consider Roussouly classification (6) that stratifies population's spine shape in four types according to sacral slope (SS), and to pelvic incidence (PI): type 1 and 2 if $SS < 35^\circ$ (and $PI < 45^\circ$), type 3 if $35^\circ < SS < 45^\circ$ (and $45^\circ < PI < 60^\circ$) and type 4 if $SS > 45^\circ$ (and $PI > 60^\circ$). Our patient could be included into a type 2 according to the Roussouly's classification (6).

Type 2 is characterized by a small sacral slope (less than 35°) and has a flattened lower arch of the lumbar profile with very little curvature: the back is "flat". Moreover, patients who have a low PI (types 1 and 2 of Roussouly classification), have a low LPC range of motion (ROM) and so they have a greater need for the use of each hip's cone of mobility, being called "hip users". On the contrary, subjects with a high PI (types 3 and 4 of Roussouly classification) have a high LPC ROM and therefore their need to use each hip's cone of mobility is low. They are



Fig. 7. Comparison pre-operative and post-operative pictures.

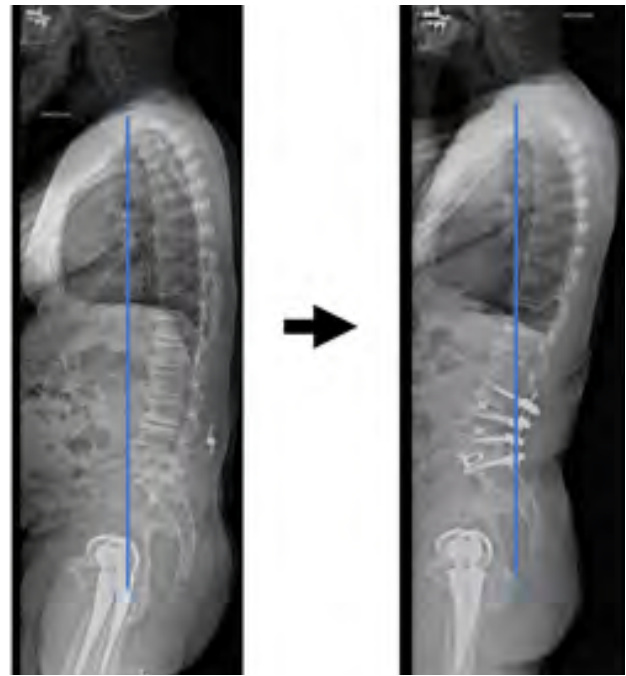


Fig. 8. Comparison between lateral projections of pre-operative and post-operative X-rays of the spine.

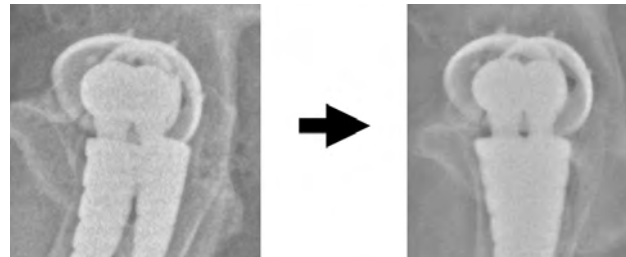


Fig. 9. Comparison between lateral projections of pre-operative and post-operative X-rays of the hips.

called "spine users" (1).

Our patient, having a PI of 40° belongs to the category of "hip users".

Rivière et al. (1) realized the Bordeaux classification aiming to assess the relationship between the risk of dislocation and edge loading in THA and type of spine-hip relationships (SHRs), by considering spino-pelvic parameters and pelvic mobility. Eight different types of SHR and three risk-categories have been described. The values of the spinopelvic parameters of our patient determine his insertion in the 1D type according to this classification. Category 1D is reserved for patients with sagittal imbalance with a stiff LPC.

The sagittal imbalance of SHR "D" substantially

affects patients' quality of life and THR outcomes and therefore usually requires correction with spine surgery in order to improve the standing functional acetabular or cup orientation. SHRs "D" belongs to the risk-category 3, which defines a high risk of dislocation, impingement due to the high stiffness and degeneration of LPC. Patients in this risk category would therefore be likely to benefit from dual mobility implants. Patients with SHR 1D have a low PI and are therefore not affected by a severe pelvic retroversion in standing position, which makes anatomical implantation of a high tolerance implant (36/40 mm head diameter) a good solution.

The essential concept which can be deduced from biomechanical studies on spine-hip relation, is that in low grade PI, corresponding to type 1 and type 2 of Roussouly's classification, the adoption of compensatory mechanisms of degenerative spine deformity is not allowed: full hip extension and SS decrease occur. Small PI induces a limited increase in degenerative hypolordosis and a small capacity of pelvic retroversion. In this case the suggestion is to treat the hip first, choosing a double mobility acetabulum in THA.

The values of the acetabular parameters of our patient (Table II) show his acetabular positioning to be slightly outside the "safe zone" of the acetabular cup. The safe zone is a concept that still remains controversial, defined for the first time in 1978 by Lewinnek et al. (4) as anteversion in acetabular prosthesis of $15^{\circ} \pm 10^{\circ}$ and the lateral inclination of $40^{\circ} \pm 10^{\circ}$. If the orientation of acetabular cup is inside the "safe zone" the postoperative dislocation rate is 1.5% and increases to 61% if the position is outside the "safe zone".

Total Hip replacement has restored a complete ROM of the joint, allowing the hips to perform a maximum compensation of lumbar hypolordosis induced by the degenerative condition of the spine, improving the possibility of joint extension. However, this compensatory mechanism (pelvic retroversion) put the acetabular positioning outside of the safe zone increasing the risk of dislocation, impingement and asymmetrical edge loading. So, a proper spinal surgery with a reconstruction of lumbar lordosis must be performed; this way PT decreases and, as a consequence, also acetabular anteversion (AA) does.

The literature reports that the relationship between pelvic tilt and AA is narrow and has a certain regularity. Buckland et al. (4) pointed out that the change in anteversion and pelvic tilt is close to 1:1. Anda et al. (4) demonstrated that every single degree of change in the pelvic tilt would lead to a 0.5° change in acetabular anteversion. Patients who have undergone THR and have a balanced spine show a similar adjustment in spine pelvis alignment in different positions (3).

According to these studies, the variation of the PT of 17° necessary to get its ideal value, could have determined a variation of the AA such as to return to the acetabular cup in a positioning inside the safe zone. To gain this goal a precise surgical strategy is mandatory, as the lumbar lordosis must be restored in an effective way; an iatrogenic flatback could lead to an increase of pelvic retroversion and to a worsening of acetabular orientation. Considering that the 2/3 of the LL (6) is located in the L4-S1 segment (except in Roussouly 4) the most effective strategy to achieve this result is to choose an anterior approach (ALIF), especially in L5-S1.

The ALIF technique is a minimally invasive surgical procedure that provides a retroperitoneal pathway to the spine. Unlike other surgical techniques of access to the spine, ALIF allows access for reconstruction of the anterior spinal column with large implants (bone or cages) with greater power of disc distraction and, thanks to the resection of the anterior longitudinal ligament it is possible to implant cages with up to 30° of lordosis (9, 10), not achievable with other posterior approaches. The positioning of lordotic cages and the posterior stabilization have determined a restoration of the LL and of the sagittal balance of the spine. This resulted in a reduction in the need for compensation, as evidenced by a decrease in the compensatory pelvic retroversion, quantified by the PT (from 25° to 8°). The modification in pelvic retroversion led a change in the acetabular anteversion. In this case, for a 17° decrease in PT, the acetabular anteversion decreased by 15° to the right and 16° to the left, passing from 38° to 23° to the right and from 30° to 14° to left. This extent of the AA variation can be superimposed on the data concerning the PT-AA relationship found in the literature (5) (Table II, Fig. 9). These values of AA

following spinal surgery are within the safe zone.

In a patient who underwent bilateral THA, the planning of spine surgery, with the restoration of specific ideal values of the spinopelvic parameters, is essential to define the maintenance of the correct positioning of the acetabular cup inside the safe zone even after spinal surgery.

Failure to plan could produce a modification of the three-dimensional orientation of the acetabular cup outside the safe zone with a consequent substantial increase in the risk of impingement, edge loading and dislocation of THA.

Pre-operative planning is therefore a crucial phase in defining the surgical strategy to pursue the concept of kinematically aligned THA. To restore properly LL, especially the L4-S1 segment, ALIF technique is the most effective and direct surgical procedure, allowing, in an exclusive way using minimally invasive techniques (12-13) compared to the other surgical ways, the positioning of large dimension lordotic cages, with a considerable tissue (muscles) sparing and a better fusion rate (11).

The calculation of the spinopelvic parameters, the biomechanical classification of the patient's spine-hip relation, the modification of AA after the vertebral surgery on the basis of the ideal PT values that must be achieved are fundamental steps in scheduling spine surgery in a patient with a bilateral THA to avoid the failure of prosthetic surgery with the need for revision and repositioning of the acetabular cup.

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Use of lordotic cages in L5-S1 Anterior Lumbar Interbody Fusion (ALIF) procedures

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Anterior Lumbar Interbody Fusion (ALIF) has gained popularity in the last few years, thanks to its numerous advantages. Recently the use of lordotic cages has been described, allowing theoretically a better lordosis restoration of the lumbar disc space. We described the results obtained with the use of lordotic cages in 27 patients who underwent ALIF procedure for L5-S1 disc degenerative disease, in terms of segmental lordosis and global lumbar lordosis changes.

Anterior Lumbar Interbody Fusion (ALIF) is a surgical technique for spinal fusion that encountered an increasing interest by spinal surgeons (1-3). The evolution of this surgical technique, from the first description to the minimally invasive 'perinavel' approach (4) has recently been published (3). The use of the anterior access allows the surgeon to have access to the disc space, avoiding traumas to paraspinal muscles and epidural scarring and fibrosis (17, 18, 25). Many studies have demonstrated the superiority of ALIF if compared to Transforaminal Lumbar Interbody Fusion (TLIF) in terms of disc height restoration and lumbar lordosis restoration (LL) (1, 12, 14, 19).

The cages used in anterior approach have traditionally a certain degree of lordosis, between 8 and 12 degrees (22). Recently, the use of lordotic cages (more than 15°) have been described, ranging up to 30 degrees of angle (7, 11, 23, 24). The importance of reaching an optimal restoration of LL especially in L5-S1 has been widely investigated (7, 11, 23, 24, 25). The ideal value of distal lordosis accounted for

62% of the total lordosis. The proportion of lumbar lordosis given by every level increased gradually, from 4% for L1-L2 to 35% for L5-S1 (26). The aim of this study is to evaluate the variation in segmental lordosis at the L5-S1 (SL) segment with the use of lordotic cages in patients with L5-S1 degenerative disc disease (DDD).

MATERIALS AND METHODS

We have analyzed 27 patients who underwent ALIF procedure for DDD at the L5-S1 level from January to December 2018. This study is focused on the evaluation of SL and LL before and after the lordotic-ALIF procedure. Lordotic interbody cages (15°-20°-25°) have been implanted in each degenerated L5-S1 disc space with the aim to achieve for SL and LL the ideal value restoration.

Inclusion criteria were: L5-S1 DDD as the cause of low back pain (with or without radicular pain) once all other possible causes were excluded or where conservative treatment over a period of at least 6 months

Key words: Anterior Lumbar Interbody Fusion (ALIF), Lordotic cages, anterior lumbar surgery, degenerative disc disease, minimally invasive anterior spinal fusion

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failed. Exclusion criteria were presence of lumbar scoliosis (Cobb $> 20^\circ$), presence of infections, tumor disease, previous fusion at the same or other lumbar levels or isthmic lysis or spondylolisthesis.

All patients have been investigated with a lumbosacral Magnetic Resonance Imaging (MRI) and a full spine standing X-Rays (with EOS imaging[®]) in the preoperative, immediate postoperative and during the follow-up at 6 months. Each approach was performed with video-assisted surgical technique, as previously described by the senior author R. B (2). A mini-retroperitoneal-ALIF L5-S1 was performed and a lordotic cage with anterior plating was positioned. Segmental lordosis in L5-S1 (SL) has been analyzed preoperatively, in the immediate post-operative and during the follow-up at 6 months. Intraoperative and postoperative complications have been recorded (Fig. 1).

RESULTS

The study included 27 patients, 9 males (33.3%) and 18 females (66.7%) undergoing lordotic ALIF procedures at the L5-S1 level for DDD. The mean age was 46.9 ± 10.5 , range 29-72. The mean length of the hospital stay was 4.8 ± 1.2 days. No infections were

registered. In two cases during the approach, a small peritoneal lesion occurred, and it was immediately repaired with a suture without further complications in the postoperative period. No vascular injuries were registered. In males no cases of retrograde ejaculation have been reordered. There were no cases of thrombotic events during the follow-up.

The mean L5-S1 SL was 8.5 ± 3.8 degrees (range 2.4-15.1) in the preoperative period. Twenty-seven lordotic cages were implanted in collapsed L5-S1 disc space:

four 25° cages, thirteen 20° and ten 15° . Mean value of implanted cages was 18.7° (median value $20^\circ \pm 3.4$).

After the ALIF procedure, the mean L5-S1 SL was 21.5 ± 3.8 (range 13.5-30.0) in the immediate post-operative period and 21.4 ± 3.8 (range 13.3-30.0) at the 6-month follow-up. The difference between the preoperative SL and the immediate postoperative SL was statistically significant ($p < 0.001$). The mean increase in SL was 13 degrees (range 4.0-23.9).

Concerning SL, the difference between the preoperative value and the follow-up value was also statistically significant ($p < 0.001$). This difference remained stable over the follow up period, despite

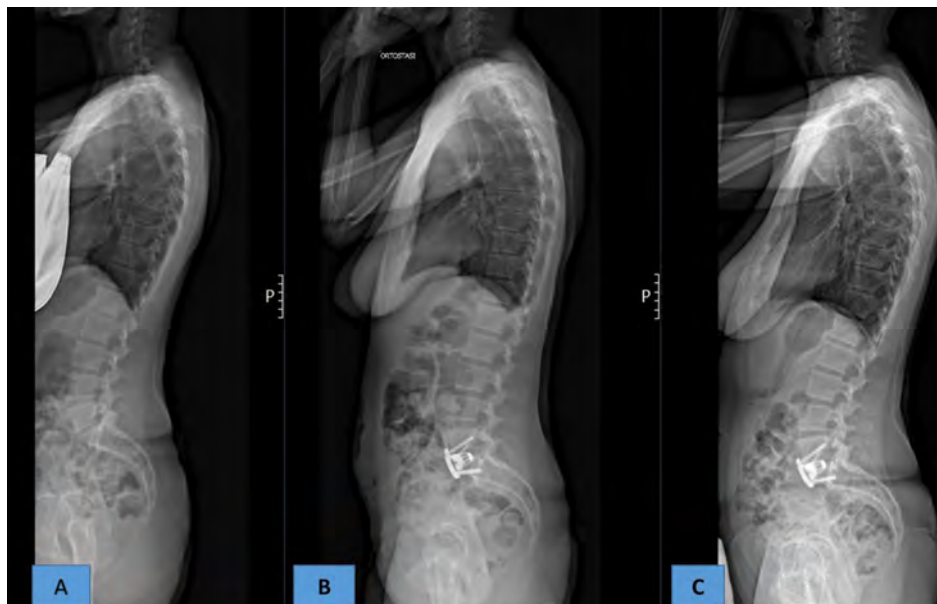


Fig. 1. Standing lateral full-length spinal X-rays showing A) preoperative, B) early postoperative and C) 6 months follow-up L5-S1 ALIF with 25° hyperlordotic cage.

Table I. mean values of Segmental Lordosis (SL) and Lumbar Lordosis (LL) in preoperative, immediate postoperative (PO) and at 6 months follow-up.

	Preoperative	Immediate PO	Follow-up
Mean SL	8.5 ± 3.8	21.5 ± 3.8	21.4 ± 3.8
Mean LL	54.1 ± 9.0	53.0 ± 8.8	60.0 ± 9.3

the difference between immediate postoperative SL and follow-up SL value was not statistically significant ($p=0.58$).

A linear regression test showed a negative relationship both between preoperative SL and the absolute variation in L5-S1 SL ($r^2=0.484$) and between the preoperative SL and the percentage variation in SL if compared to the preoperative SL ($r^2=0.804$).

The mean preoperative LL was 54.1 ± 9.0 degrees (range 36.9 – 67.9). In the immediate postoperative the mean LL was 53.0 ± 8.8 degrees (range 32.6 – 70.4) and during follow-up the mean LL was 60.0 ± 9.3 degrees (range 39.6 – 79.6) (Table I).

The difference between LL in preoperative and immediate postoperative was not statistically significant ($p=0.45$). A statistically significant

difference was noticed between preoperative and follow-up LL and immediate postoperative and follow-up LL ($p<0.001$).

DISCUSSION

In our study we focused on the segmental change in lordosis in L5-S1 disc in patients with DDD and low back pain who underwent fusion with lordotic anterior cages. ALIF seems a viable option to restore segmental lordosis at L5-S1 disc space, with optimal results.

The capability of ALIF to restore segmental lordosis has been widely described in the literature during the years. Lateral Lumbar Interbody Fusion (LLIF) is usually not able to reach the L5-S1 disc space, therefore it would not be considered in the discussion.

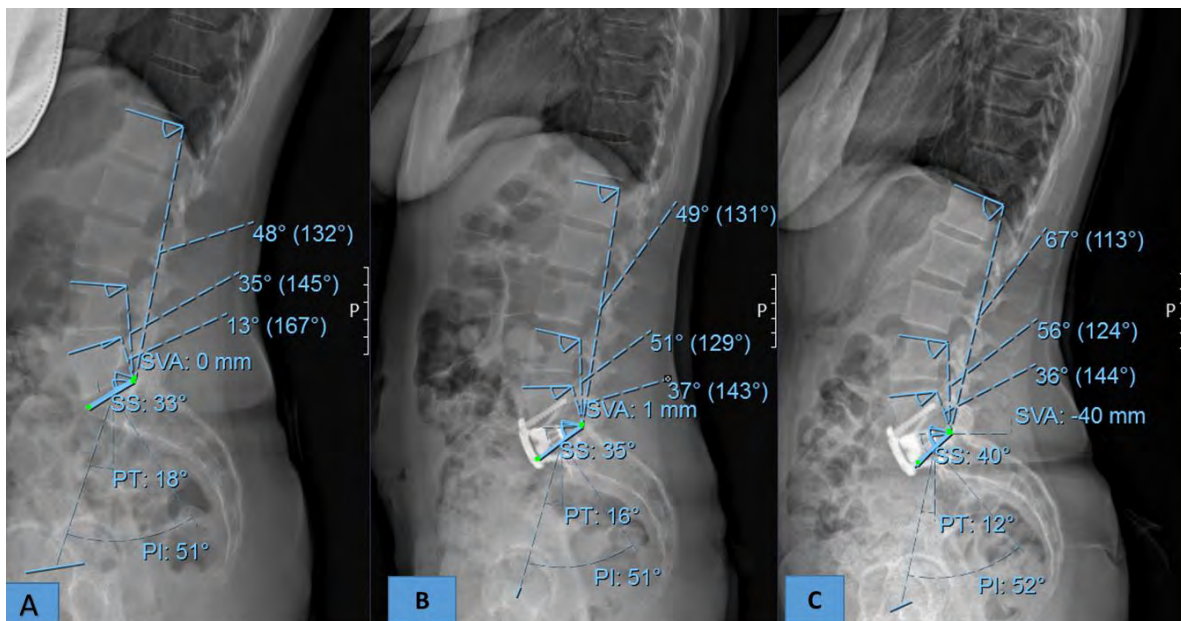


Fig. 2. Standing lateral full-length spinal X-rays with angles measurements showing A, B) the improvement of SL in the immediate post-operative period and at C) the 6 months follow-up and A, C) the improvement of LL at the the 6 months follow-up.

Before the introduction of lordotic cages, ALIF was considered superior to TLIF in both disc height and segmental lordosis restoration. Previous studies reported a mean variation in SL of 8.3° (12) and 8.6° (16). In our study the mean variation in SL was 12.9°. This demonstrates a higher power of SL restoration if compared to the older Interbody implants.

The few studies published about the use of lordotic and hyperlordotic (>20° and 30°) cages in ALIF procedures are focused on the correction of sagittal imbalance with multilevel cages supplemented with posterior instrumentation (7, 11, 24). Therefore, they do not analyze the difference in SL variation related to the use of lordotic cages. A higher increase in L5-S1 SL might help to better manage the lack of lordosis at that level.

Previous studies (12) reported an increase in LL of 6.2° after anterior lumbar fusion. The results of our study showed an increase of 6° of LL from preoperative values to the 6-month follow-up. Surprisingly, the mean LL in the immediate postoperative period was 1° inferior to the preoperative values. This might be interpreted as a

remodeling of LL during the follow-up, related to the loss of postoperative muscular contraction, due to pain.

A non-statistically significant difference between L5-S1 SL between immediate postoperative and the 6-month follow-up demonstrates any tendencies towards cage subsidence. ALIF has become increasingly popular thanks to its numerous advantages over the posterior approach. Theoretical pros of the anterior approach over the posterior one has been advocated. ALIF is a muscle sparing technique, avoiding posterior muscle detachment and denervation. The direct approach to the disc space allows for a complete and accurate discectomy to be performed. The anterior longitudinal ligament resection permits a wider interbody distraction with optimal disc height restoration and foraminal indirect decompression. Finally, the implant of lordotic cages might help in better managing sagittal profile restoration (5, 9–11, 15, 17, 18, 21). In our series, we had a very low complication rate (two small peritoneal lesion) compared to the literature (6, 8, 17, 20).

	PREOPERATIVE	EARLY POSTOPERATIVE	6 MONTHS FOLLOW-UP
Età	42		
PI	51		51
PT	18	16	12
SS	33	35	39
LL (L1-S1)	48	48	67
SL (L5-S1)	13	37	37
L4-S1	35	51	56

Fig. 3. Preoperative, early postoperative and 6 months follow up angles measurement.

Anterior approach with lordotic cages allows for better results to be achieved in terms of SL if compared to TLIF technique. The higher power of SL restoration might be helpful in both short segment fixation and sagittal balance restoration in those cases of major sagittal deformity.

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Novel directions in the study of osteoporosis: focus on gut microbiota as a potential therapeutic target

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Osteoporosis is a significant social health problem, not only in terms of pain and disability but also in terms of mortality rate. In recent years, there is an increasing interest in studying the relationship between gut dysmicrobiosis, immune system and bone health, therefore the term "osteomicrobiology" has been recently coined. This review aims to summarize the current knowledge about the link between gut dysbiosis and osteoporosis, in order to define a potential preventive and therapeutic strategy. Gut microbiota (GM) plays a major role in maintaining body homeostasis, since it is involved in several physiological processes; in recent years, the gut microbiota has shown to modulate not only local processes but also systemic responses including bone metabolism. Several potential mechanisms may explain how gut microorganisms could affect bone metabolism, i.e. influencing the host metabolism, immune system and hormone secretion. The relationship between gut dysbiosis, immunological dysfunction and bone loss could be explained by mainly focusing on T cells. Moreover, it should be noted that the relationship between GM and the endocrine system could also explicate how the microbiome influences bone status. In this context, Insulin-Like Growth Factor-1 (IGF-1), vitamin D, serotonin and leptin might play a central role. GM could have a significant impact on bone metabolism, therefore future clinical studies are necessary to develop a new multidisciplinary approach for osteoporosis treatment and prevention.

Osteoporosis is a systemic bone disease depicted by a progressive reduction of bone mass density (BMD) and concomitant destruction of the micro-architectural structure of bone, thus leading to increased bone fragility and subsequent high fracture risk (30).

Fragility fractures (FFs), mainly involve specific body regions, i.e. distal radius, thoraco-lumbar spine, femoral neck (4, 21, 27, 28, 43). In Europe, every year 3.5 million new fragility fractures occur, comprising 610,000 hip fractures, 520,000 vertebral fractures, 560,000 forearm fractures and 1,800,000 in other sites (15, 43, 44).

According to the International Osteoporosis

Foundation (IOF), osteoporosis currently has a global prevalence of 125 million people, but it will dramatically increase in the future, because of population ageing (15). Consequently, osteoporosis is a significant social health problem, not only in terms of pain and disability but also in terms of mortality rate, since in Europe in 2010 there were 43,000 deaths directly attributable to fractures.

Nowadays, the management of osteoporosis should prevent FFs and their long-terms sequelae in order to improve the patients' health-related quality of life (HRQL). Thus, a better comprehension of the physio-pathological mechanisms involved in the

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pathogenesis of osteoporosis is mandatory.

Osteoporosis is a multifactorial disorder, involving both endogenous and environmental factors, i.e. oestrogens, calcium and vitamin D deficiency, sarcopenia, prolonged bed rest and immobilization, smoking status and genetic modification in selected genes (2).

In recent years, therefore, more than sixty genes have been related to osteoporosis, including vitamin D receptor (VDR), TGF-beta, LDL receptor-related protein 5 (LRP5), Palstin-3 (PLS3) and WNT1(31).

Moreover, there is an increasing interest in studying the relationship between the immune system and bone health (36). In patients with chronic inflammatory diseases and immune system dysfunctions, an increased prevalence of osteoporosis has been reported, since the excessive production of pro-inflammatory cytokines may enhance osteoclastic activity (8).

In this context, the study of gut microbiota dysfunction may play a central role. The development and maturation of innate and adaptive immunity is significantly influenced by gut microbiota and, conversely, gut dysbiosis may alter the immunological homeostasis (8, 49)

This review aims to summarize the current knowledge about the link between gut dysbiosis and osteoporosis, in order to define a potential preventive and therapeutic strategy.

Gut microbiota and bone health

The gastrointestinal tract has a huge commensal population of microorganisms since it is colonized by more than 100 trillion microbes, who have symbiotically evolved to habituate the human gut (16). Although the microbiota composition varies in each person, there are four main classes that constitute the physiologic microbiota, i.e. *Firmicutes*, *Bacteroides*, *Proteobacteria*, and *Actinobacteria* (16).

The Gut Microbiota (GM) plays a major role in maintaining body homeostasis, since it is involved in several physiological processes, including digestion and absorption, metabolites secretion and mucosal barrier function protection (18).

However, the physiologic gut microbiota could be affected by prolonged antibiotic assumption,

gastrointestinal diseases and wrong dietary habits, thus promoting a condition of gut dysbiosis (14,16). It is reported that dysbiosis could affect life expectancy and long-term quality of life, especially in elderly people (16). In recent years, the gut microbiota has shown to modulate not only local processes but also systemic responses including bone metabolism (17). Therefore, in 2014 Ohlsson et al coined the term “Osteomicrobiology” to stress the increasing interest in studying the relationship between gut microbiota and bone health (25).

The first preclinical study focusing on the relationship between GM and bone mass was conducted by Sjogren et al in 2012, who reported an increase in trabecular bone mass and a reduced number of osteoclasts per bone surface in mice raised in germ-free conditions, compared with control mice raised in conventional conditions (35). Conversely, colonization of germ-free mice with a normal GM was able to normalize bone mass (35). These preliminary results have been subsequently confirmed in further studies demonstrating that GM enhances osteoclastogenesis and osteoclasts activity and lifespan, while it suppresses osteoblastogenesis (24). Moreover, it is reported that prolonged gut dysbiosis is associated with bone mass and microstructure changes, as well as bone mechanical properties impairment (13).

Several potential mechanisms may explain how gut microorganisms could affect bone metabolism, i.e. influencing the host metabolism, immune system and hormone secretion (8).

Gut microbiota, immune system and bone

The relationship between gut dysbiosis, immunological dysfunction and bone loss could be explained by focusing on T cells. It is clear that proinflammatory cytokines, including TNF and IL-1, increase bone resorption in postmenopausal osteoporosis (5,32) and T cells are a significant source of TNF in both ovariectomized mice and postmenopausal women (1, 7).

In vitro studies have demonstrated that T cells from ovariectomized mice produce increased amounts of TNF, which augments receptor activator of NF-kappa B ligand (RANKL)-induced osteoclastogenesis (32).

Roggia et al, in an *in vivo* study on ovariectomized mice, observed that ovariectomy increases the number of bone marrow T cell-producing TNF, finally leading to an increased bone loss (32). On the other hand, bone loss was absent in T cell-deficient nude mice, but it was restored by adoptive transfer of wild type T cells (32). These findings show that there is not a significant bone loss in mice lacking the capacity to produce TNF or lacking the expression of TNF receptors.

Moreover, focusing on T cells specific lineages, Th17 cells and Regulatory T cells (Tregs cells) are specifically involved in bone metabolism. Th17 cells produce IL-17, a cytokine that exerts pro-osteoclastogenic effects. In women, an association between increased levels of serum IL-17 and osteoporosis has been reported and silencing of IL-17R or use of anti-IL17 antibodies result in protection against bone loss (9, 23, 41, 50).

Tregs cell is a suppressive population of CD4⁺ T cells, whose numbers and/or activity alteration have been implicated in several chronic inflammatory diseases. It is known that oestrogens increase the relative number of Tregs, while Tregs prevent ovariectomy-induced bone loss (34, 39).

In germ-free mice, a lower number of CD4⁺ T cells in the bone marrow and lower levels of bone marrow TNF was observed. These findings correlate with reduced osteoclastogenesis and an increased bone mass, compared with wild-type mice (35).

Therefore, the interactions between GM and T cells partially explicates how microbiota could influence bone health.

Gut microbiota, endocrine environment and bone

The relationship between GM and the endocrine system could also explicate how the microbiome influences bone status (17). In this context, Insulin-Like Growth Factor-1 (IGF-1), vitamin D, serotonin and leptin might play a central role.

IGF-1 is an important regulator of bone remodelling: exogenous IGF-1 promotes the growth of longitudinal femoral (47), whereas IGF-1 receptor deletion has a negative effect on the growth plate and in the process of the formation of secondary ossification centre (45).

Recent acquisitions have shown that GM is able to dynamically modulate circulating IGF-1 in the host (48) with different microbiota-derived metabolites, including short-chain fatty acids (48). In mice with physiological GM, compared with germ-free mice, circulating IGF-1 increased in both short-term and long-term (48).

The importance of Vitamin D in bone metabolism is well-established since it stimulates intestinal calcium absorption and regulates calcium homeostasis, including calcium channel: TRPV6 and calbindin-D9K (37). It is important to remark that GM has a key role in Vitamin D transport and uptake: intestinal resistance to vitamin and the subsequently impaired calcium absorption are strongly correlated to gut dysbiosis. These phenomena tend to increase in elderly patients, thus D contributing to osteoporosis (38).

5-Hydroxytryptamine (5-HT, or serotonin) has a double action on bone metabolism: if produced in the circulation, 5-HT inhibits bone formation, whereas produced in the brain like a neurotransmitter, has a positive effect on bone mass (10). More than 90% of 5-HT is synthesized in the human gut (12), therefore recent studies had focused on the role of intestinal microbiota in regulating circulating levels of 5-HT. *In vitro* studies have shown that some bacteria -namely Corynebacteria, Streptococci, and Escherichia coli – may produce 5-HT in culture (33). Furthermore, *in vivo* studies have confirmed that the serum concentration of 5-HT in germ-free mice is significantly lower than that in normal mice (35). Finally, both preclinical and clinical studies have confirmed that some bacteria in healthy mice and humans can modulate the circulating level of 5-HT (40).

Leptin is a vertebrate-specific hormone, mainly produced by adipocytes and small intestine enterocytes. It is implicated in several physiological processes, including energy expenditure regulation, appetite and bone mass. Leptin can act on bone with both direct and indirect mechanisms (42). With reference to direct mechanisms, it is important to remark that bone marrow adipocytes secrete leptin; leptin receptors could be found in osteoblasts and chondrocytes; leptin impacts on osteocalcin

metabolism and it can regulate bone growth by regulating Fibroblast Growth Factor-23 (FGF-23) levels (42). Indirect mechanisms imply brainstem and serotonergic signalling, by modulating the circulating levels of IGF-1, cortisol, oestrogens and parathyroid hormone (42).

In last years some evidence linking GM to leptin are emerging; these findings may have a significant impact on bone metabolism. (42). It is reported that the use of vancomycin may cause a rapid reduction of circulating leptin levels in rats (19).

Moreover, some bacteria species, i.e. *Bifidobacterium*, *Lactobacillus*, *Lactococcus* and *Mucispirillum*, - are positively correlated with serum leptin concentration, whereas other species, i.e. *Bacteroides*, *Clostridium* and *Prevotella*- shows an inverse correlation (29). Finally, Naruszewicz et al. have observed, in a group of smokers, that the use of probiotics may reduce their leptin levels (22).

How to address gut microbiota

Based on the reported findings, effort should make in clinical practice to maintain a physiologic GM. Consequently, correct eating habits, regular physical activity, avoidance of smoking and excessive energy intake, prevention of obesity, refusal of inappropriate antibiotic therapies, should be highly encouraged (11).

Furthermore, the correct use of probiotics could be also useful, since they act by modifying GM composition, intestinal and immune system, thus giving systemic benefits to the host (46). Consequently, according to the preclinical studies, probiotic supplementation, together with a correct lifestyle, may be useful in preventing bone loss in healthy individuals and slowing its progression in osteoporotic patients (6).

In preclinical studies, supplementation with *Bacillus subtilis* revealed effective in reducing the number of osteoclasts and increasing osteoblasts, whereas supplementation with *Lactobacillus reuteri* was capable to block both type-1 diabetes-induced osteoporosis and ovariectomy-induced osteoporosis in mice, by reducing osteoclastogenesis (3, 26, 51).

However, McCabe et al. in another preclinical study showed that *Lactobacillus reuteri* ingestion increases osteoblast serum markers and dynamic

measures of bone formation in male mice, while it has no effect on bone parameters in female mice (20).

This interesting finding emphasizes that there could be a gender-specific response to probiotic supplementation. Further clinical trials are needed to better study this relationship in the human organism.

Future developments

GM could influence the bone health by acting on the host metabolism, immune and endocrine system. Consequently, GM could be a potential therapeutic target in the treatment and prevention of osteoporosis, in addition to the standard treatment currently available.

However, most of the current knowledge on this topic derives from *in vivo* studies, thus some of the data presented in this review need to be further validated in clinical studies. Future multicentre clinical studies are necessary to better understand the relationship between GM and osteoporosis in the human organism, in order to develop a new multidisciplinary approach aiming to treat and prevent osteoporosis.

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Blood transfusion, hospital stay and learning curve in robotic assisted total hip arthroplasty

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Total Hip Arthroplasty (THA) has been defined the surgical procedure of the century considering its outcome and cost-benefit ratio (1). Both standard and robotic assisted procedures are increasing, thus, comparison between standard and robotic surgery become useful to understand the cost-benefit of the latter. The prerequisites of the robotic assisted arthroplasty are precision, accuracy, limitation of errors and safety but, on the other hand, its cost is the main drawback. The primary endpoint of our research was to evaluate differences in terms of blood transfusion rates between standard manual and robotic arm assisted THA. All the robotic procedures have been managed using semi active Robotic Arm interactive orthopaedic System (RIO® MAKO Stryker surgical corporation) in a group of patients who underwent primary uncemented total hip arthroplasty (THA) for osteoarthritis or avascular necrosis. Secondary endpoints were the evaluation of length of hospital stay (LOS), age category, gender and the impact of the learning curve on surgical time in the robotic surgery sample. Our retrospective cohort study was conducted between July 2014 and December 2018. Data have been collected from the Tuscany regional hospital discharge register, extracting the relative Hospital Discharge Forms (SDO). During the period of the study, 1537 patients underwent uncemented total hip arthroplasty for osteoarthritis or avascular necrosis. The sample was divided in two subgroups: 1142 patients (74.3%) operated on with standard manual technique and 395 patients (25.7%) operated on with Mako-Stryker Robotic System. In the descriptive analysis, the average values of age and days of hospitalization with 95% CI were calculated. Mean significance was assessed by the T student test. The association between surgical modality and gender was assessed with the chi-square test. The multivariate logistic regression model was used to evaluate the risk of transfusion (outcome variable), between conventional and robotic surgical techniques. The significance threshold was set up at $p < 0.05$. During the period of the study we observed a decrease in standard surgery and an increase in robotic surgery; an increasing number of women per year underwent total uncemented total hip arthroplasty. We found a statistical significance in favor of robotic procedures in terms of transfusion percentage (OR 6.10, 95% CI 2.96-12.59, $p < 0.001$), highlighting the greatest risk in women (OR 1.90, 95% CI 1.30-2.78, $p = 0.001$), length of hospital stay ($Mr = 4.24$, $SD = 2.04$, 95% CI 4.04-4.44) ($Ms = 8.04$, $SD = 2.84$, 95% CI 7.88-8.21), ($p < 0.01$). Operative time in the robotic sample decreased substantially with the rise of surgical experience (106.75 ± 13.4 mins in 2014; 82.79 ± 15.95 mins in 2018) ($p < 0.01$). Since the Robotic procedure is a technologically demanding process, an adequate surgical learning curve is mandatory. Our paper, comparing conventional vs robotic assisted THA, showed in favor of the robotic one, a statistically significant reduction of number of transfusions ($p < 0.001$) and length of hospital stay ($p < 0.01$).

Key words: blood transfusion, total hip arthroplasty, learning curve, Mako robotic system

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Total hip replacement is the best solution to treat end stage coxarthrosis or advanced osteonecrosis of the hip no longer susceptible to conservative therapy (1, 2). Given the increased life expectancy and the increasing functional demands of patients, the number of total hip replacement procedures is steadily increasing and will increase by 174% in 2030 (3). In the last twenty years, all total hip replacement technology, with the exception of the negative experience of metal-on-metal bearing couples in standard prostheses, has achieved surprising results in terms of press-fit, osseointegration and low wear in metal-on-polyethylene, ceramic-on-polyethylene and ceramic-on-ceramic bearings (4, 5). Nevertheless, the number of precocious revisions related to component malpositioning remains high at 20%-40% (6, 7). Malpositioning of components can lead to negative phenomena such as instability, impingement and edge loading. These phenomena can negatively affect the survival of the prosthesis, leading to increased wear and dislocation, but also reduce the performance of the prosthesis, even if not revised, in terms of complete recovery of daily activities, index of patient satisfaction and limiting the achievement of the so-called forgotten joint (8).

Until a few years ago the concepts of planning, execution and postoperative images evaluation were based mainly on two planes: coronal and sagittal. Hence the basic concepts of hip prosthesis in terms of center of rotation, offset, length and cup coverage angles (9-11). To correctly position the prosthetic components, the surgeon usually reproduces the planned two-dimensional parameters using bone and soft tissue landmarks during traditional surgery. However, this requires a lot of experience and a long learning curve typical of a so-called high-volume surgeon (12).

With the introduction of the robotic assisted total hip prosthesis, many publications in literature have demonstrated the goodness of this technique (13-14). Most of these papers tended to demonstrate the greater safety and error reduction but above all, the superiority of the robotic technique over the standard one in terms of accuracy and precision of the tridimensional positioning of the prosthetic components (15-16).

The MAKO (17) robotic technique is so-called image based. Patient's bone data is derived from preoperative digital imaging. In this specific case it is a CT-scan with sections dedicated to the pelvis, hip and knee. The CT-scan is loaded on a digital platform so that a 3D digital model can be reconstructed coinciding with the specific anatomy of the patient. At this point it is already possible to perform extremely precise planning, considering the real anatomical parameters of the patient. This allows the surgeon to make precise preoperative planning in terms of sizing, positioning and orientation of the components in order to reconstruct not only the classical parameters such as cup coverage, length and offset but also the relative cup and femur version on the axial plane (18-19).

The CT based planning performed with MAKO is to be understood as dynamic, i.e. even if completed pre-operatively, it can be modified during surgery with a precision of one millimeter and one degree, being able to verify both with 3D processed CT and verification with the multiplanar reconstructions (MPR) sections, the expected real time results according to possible changes made intraoperatively. Hence the possibility to correct both before and during surgery the individual anatomical orientation defects with the prosthetic components, restoring with greater precision the anatomical and biomechanical parameters on different planes.

The intraoperative part of the procedure involves ample bone morphing of both the femur and the cup through a flow chart of bone measurements that are automatically integrated with the preoperative CT scan of the patient, considerably increasing the accuracy of the result. Following the standard procedure it is possible not only to reproduce with millimetric precision the osteotomy of the femoral neck as planned but also to orient the femoral stem in the real anteversion with respect to the posterior bicondylar or epicondylar axis of the femur in order to obtain the best combined version (femur anteversion plus cup anteversion according to the initial deformity and the sex of the patient) (20). Prior to this, few works have evaluated the advantages of robot-assisted total hip prosthesis compared to the traditional one in terms of transfusion rate,

hospitalization time and surgical time as a function of the learning curve in robotic technique.

Our work aims to analytically quantify these latter parameters in a large and homogeneous sample of patients undergoing uncemented total hip prosthesis for osteoarthritis or avascular necrosis.

MATERIALS AND METHODS

The study was approved by Ethics Committee for Clinical Trials of Tuscany Region with Prot. n°13111-2018 (June 18, 2018) and Det.n°1594 (June 20, 2018). The retrospective study includes the collection of the regional hospital discharge forms (SDO) of 1537 patients undergoing uncemented THA. Data have been compared and verified with the Mako Robot System archive of all patients operated in the hospitals of the former USL8 (Local Health Center) in Arezzo, Italy.

The inclusion criteria for which the extraction of the data was requested concerned all the patients operated on with total uncemented hip prosthesis in elective surgery for coxarthrosis or avascular necrosis of the femoral head from July 1, 2014 to December 31, 2018. The reason of choosing to start from July 2014 was dependent on the fact that the first MAKO-assisted robotic hip prosthesis was performed at our USL8 in Arezzo in July 2014. During the study period 1537 standard and robotic THA interventions were performed in election, of which 395 in robotics (25.7%) and 1142 using conventional techniques (74.3%).

The surgical team was the same for both types of surgery but always under the supervision of two experienced senior surgeons, namely the two orthopaedic head physicians of the former USL8. All patients were operated through a posterolateral approach with a minimally invasive technique when possible and saving the piriform tendon when possible. In all cases the transosseous reinsertion of the extrarotators was performed. In most of the cases drainage was not used but from the extraction of the SDO data it was not possible to quantify the percentage relative to the sample in study.

Beyond the same surgical approach for both manual standard or robotic assisted technique, the two subgroups were homogeneous for all other parameters such as age, sex, comorbidity, ASA, health center antibiotic protocol (21-22), pain protocol (23), blood management (24), rehabilitation protocol (25). All demographic data and

outcomes of the studied sample were collected by an independent operator not involved in the study.

The basic measurements included the percentage of the operated subjects, the age at the time of surgery with calculation of the average, the age groups, the gender, the average operating time in robotics to assess whether there was a decrease in terms of minutes and therefore an improvement in the robotic learning. Then the data of the days of hospitalization, the total number of transfused and non-transfused patients. The results of all data collected were compared with descriptive analysis to establish any basic differences between the two groups: conventional vs. robotic assisted.

Statistical analysis

The statistical analysis was carried out using the statistical software STATA13.0 (*StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP*). In the descriptive analysis the average values of age and days of hospitalization with 95% CI were calculated. The significance of the averages was evaluated by T student's test. The association between surgical mode and sex was evaluated with the chi-square test. The multivariate logic regression model was used to assess the risk of transfusion (outcome variable) between conventional and robotic surgical procedure; in addition to the surgical technique, age as confounding and sex as covariate were included in the model.

RESULTS

The study shows that from July 2014 to December 2018, 1537 uncemented THA interventions were performed for coxarthrosis or avascular necrosis of which 395 in robotics (25.7%) and 1142 using standard methods (74.3%) (Table I).

The average follow-up was 33 months (min 6, max 60). The average age of patients is reported in Table II:

- the average age of total patients (1537) is 68.73 ± 11.26 (min 19 / max 93)
- the average age of 1142 pcs operated using standard procedure is 69.9 ± 11.31 (min 20/max 93)
- the average age of the 395 pcs operated in robotics is 65.32 ± 10.39 (min 19/max 88)

The 70-79 age group is the one with the highest

Table I. Study sample from 2014 July to 2018 December.

	STANDARD THA	ROBOTIC THA	TOTAL THA
2014	260 95.94% 22.77%	11 4.06% 2.78%	271 100.00% 17.63%
2015	252 79.25% 22.07%	66 20.75% 16.71%	318 100.00% 20.69%
2016	229 74.3% 20.05%	79 25.65% 20.00%	308 100.00% 20.04%
2017	171 62.18% 14.97%	104 37.82% 26.33%	275 100.00% 17.89%
2018	230 63.01% 20.14%	135 36.99% 34.18%	365 100.00% 23.75%
TOTAL	1142 74.30%	395 25.70%	1537 100.00%

percentage (35.32%) of the total number of patients operated on. Followed by a percentage of 29.21% of the total number of operated patients in the 60-69 age group. The age groups below 60 and above 80 are equivalent to around 16-17%.

As far as the gender is concerned, the total number of females in the THA is 851 (55.37%) against 686 (44.63%) males (Table III), with statistical significance (Pearson $\chi^2=4.82$ $p=0.028$) (Table IV).

The females operated on with robotic technique were 23.50%, while males 28.43%. Specifically, in hip arthroplasty females are 29% more likely than males (OR 1.29, 95% CI 1.02-1.62, $p<0.05$) to perform traditional surgery; but if we also consider age, the value decreases and loses its significance (OR 1.15, 95% CI 0.91-1.46, $p=0.22$). Therefore, it seems to be a factor more related to age and not to sex.

The trend to operate older people regardless of gender is confirmed. This is an important factor because the novelty of the robot-assisted technique concerns precisely the ability to operate trying to restore the anatomical and biomechanical characteristics sex related and different between men and women, such as for example in the range of combined anteverision in the hip (cup and femur anteverision) which in women has a range between 30°-50° and in men between 25°-45° with different

biomechanical results between males and females as described by Dorr (26). The robot allows to reach the proper combined anteverision range with an average difference of 10° between men and women.

Blood transfusions

The total number of transfused and not-transfused patients in the intra and postoperative time of both samples robotics and standard was evaluated to highlight any statistical differences between the two groups. In THA: (Table V, VI);

- with the standard technique 128 Pts were transfused (11.21%) while the remaining 1014 (88.79%) had no transfusions.

- with the robotic technique 8 Pts were transfused (2.03 %) while the remaining 387 (97.97%) had no transfusions.

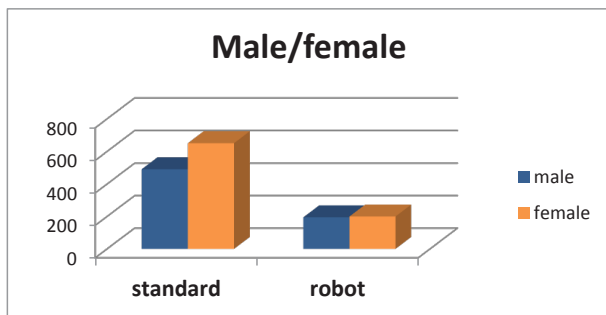
Considering all the 1537 cases, 136 Pts (8.85%) were transfused, while the not transfused were 1401 (91.15%). We found a statistical significance on

Table II. Age category in THA.

AGE CATEGORY	STANDARD THA	ROBOTIC THA	TOTAL THA
16-39	16 80,00%	4 20,00%	20(1,3%) 100.00%
40-59	171 63,81%	97 36,19%	268(17,43%) 100.00%
60-69	299 66,59%	150 33,41%	449(29,21%) 100.00%
70-79	427 78,64%	116 21,36%	543 (35,32%) 100.00%
80+	229 89,11%	28 10,89%	257(16,72%) 100,00%
TOTAL	1142 74,3%	395 25,7%	1537(100,00%) 100.00%
MEAN AGE	69,90 ±11,31	65,32 ±10,39	68,73 ±11,26

Table III. Gender in THA standard vs robotic.

GENDER	STANDARD THA	ROBOTIC THA	TOTAL THA
M	491 71.57%	195 28.43%	686 100.00%
F	651 76.50%	200 23.50%	851 100.00%
TOTAL	1142 74.30%	395 25.70%	1537 100.00%

Table IV. Bar chart of gender in standard vs robot assisted ($Ft > Mt$, $p < 0.05$).

the difference in transfusions between robotics and standards in favor of the robotics group. (Pearson $\chi^2=30.68$; $p < 0.001$).

Statistical analysis of transfusion data shows that the standard method compared to robotics exposes patients to a transfusion risk 6 times higher (OR 6.10 95% CI 2.96-12.59, $p < 0.001$), but if we put both age and sex as confounding variables (i.e. adjusting for age and sex) the risk is reduced to 4.69 while remaining significant (OR 4.69, 95% CI 2.25-9.76, $p < 0.001$). In detail, in hip arthroplasty, considering transfusions as outcome variables, it is noted that

women are about 90% more likely to be transfused than men (OR 1.90, 95% CI 1.30-2.78, $p = 0.001$). If we consider age, the risk decreases to 64% but remains significant (OR 1.64, 95% CI 1.11-2.41, $p = 0.011$).

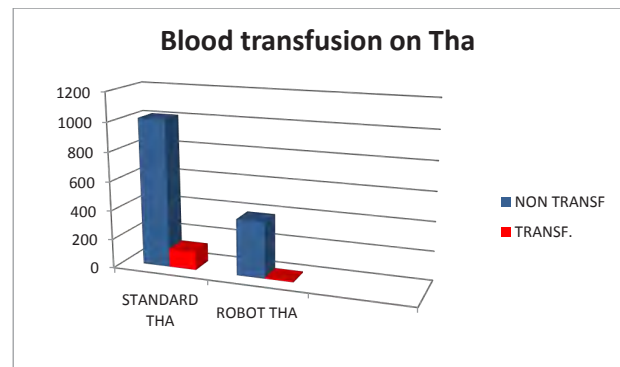
Length of hospital stay (LOS)

There is a statistical significance with regards to the days of hospitalization between the standard group compared to the robotics one. The average number of days spent in of the whole sample is 7.07 (SD = 3.13).

In Robotic Pts the average stay was 4.24 days with a standard deviation of 2.04 (M=4.24, SD=2.04, 95% CI 4.04-4.44) while in the group of standard Pts the average stay was 8.04 days with a standard deviation of 2.84 (M=8.04, SD= 2.84, 95% CI 7.88-8.21) ($p < 0.01$). (Table VIIA, Table VIIB).

Robotic THA learning curve

Being able to analyze all the data recorded in the Robot's computer, we were also able to evaluate both

Table VI. Blood transfusion in robotic vs standard THA ($p < 0.001$).**Table V.** Blood transfusion and not in THA.

THA	NOT TRASFUS	TRANSFUS	TOTAL
STANDARD	1014 88.79%	128 11.21%	1142 100.00%
ROBOT	387 97.97%	8 2.03%	395 100.00%
TOTAL	1401 91.15%	136 8.85%	1537 100.00%

robotic (robotic time) and global operating times (skin to skin) of all 395 operations performed with MAKO. The robotic time does not coincide with the global time of the intervention defined as skin to skin, i.e. from incision to complete suture. Robotic time means the time between the positioning of the trackers and their removal after the intraoperative verification of the result of the implanted prosthesis before the beginning of the suture. It has gone from an average robotic time of 63 (± 10.72) mins in 2014, to 54 (± 13.1) mins in 2015, to 58 (± 13.75) mins in 2016, to 52 (± 10.67) mins in 2017, reaching 45 (± 12.12) mins in 2018 ($P < 0.01$).

The starting point of the curve presumably indicates the basic level of surgical skill and the organizational level of the operating room staff with the Robot after the theoretical and practical courses for certification to Mako robotic surgery, while the final point shows a presumed level of competence with a slope of the curve that indicates the staff's learning speed, even if influenced by multiple factors related to both the surgeon ability and independent factors (Table VIII).

The skin-to-skin operating time of all MAKO interventions was also evaluated. The average was 106.75 (± 13.4) mins in 2014, 97.32 (± 16.36) mins in 2015, 98.1 (± 15.15) mins in 2016, 89.66 (± 13.96)

Table VIII. Learning curve: robotic time ($p < 0.01$).

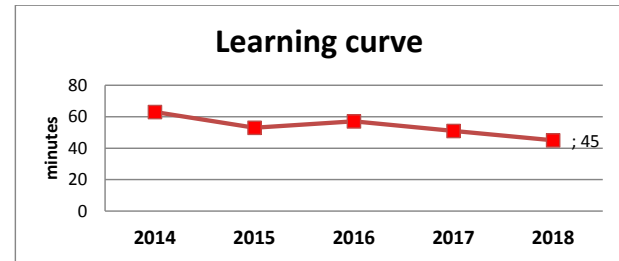
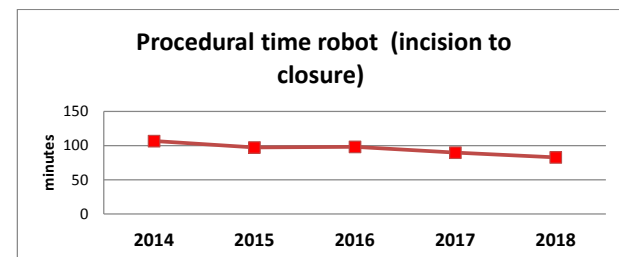


Table IX. Learning curve- global time incision to closure (from 2014 to 2018, $p < 0.01$).



mins in 2017, and 82.79 (± 15.95) mins in 2018. There is statistical significance ($p < 0.01$) between the Pts operated in 2014 and those operated in 2018, with slope of the curve indicating learning speed, considering the global operating time (Table IX).

Both on the basis of our experience and of what reported in the literature on robotic THA learning curves (27, 28), we wanted to compare the skin to skin and robotic times of the first 30 cases with the last 30 cases in order to evaluate their statistical significance (Table X, XI).

Considering the robotic operating times of the first 30 cases operated in 2014/2015 compared to the last 30 in 2018, the difference between the observed averages is significant ($p < 0.01$). In 2014 $Mr = 63.96$, $SD = 15.28$, in 2018 $Mr = 43.35$, $SD = 10.17$ (Table X).

Considering the skin-to-skin operating time of the first 30 cases operated in 2014/2015 compared to the last 30 in 2018, the difference between the observed averages is significant for $p < 0.01$ (in 2014 $Mr = 107$, $SD = 19.53$, in 2018 $Mr = 74.83$, $SD = 14.69$) (Table XI).

If we assess Table XII, we can observe the trend of the two learning curves: the global skin-to-skin time and the robotic time between the first 30 and the

Table VII. A) Length of hospital stay in THA. B) Pie chart of length of hospital stay in standard vs robotic THA ($p < 0.01$).

A	PATIENTS -Tha	DAYS	MIN/MAX
	TOTALE (1537)	7.07 $\pm$ 3.13	0- 38
	STANDARD (1142)	8.04 $\pm$ 2.84	1- 38
	ROBOT (395)	4.24 $\pm$ 2.04	1- 12

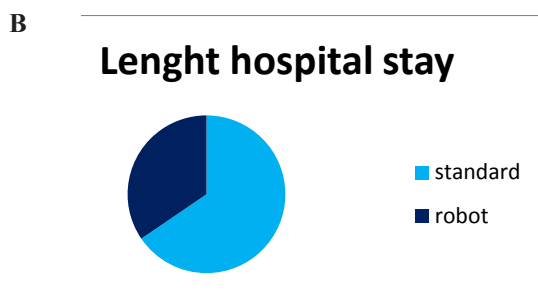


Table X. Learning curve: robotic time of first 30 vs last 30 cases ($p < 0.01$).

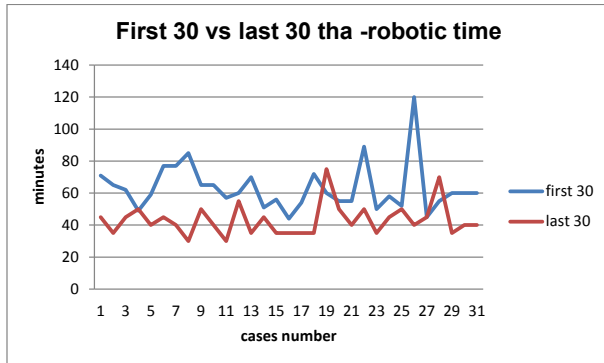


Table XI. Learning curve- incision to closure time of first 30 vs last 30 cases ($p < 0.01$).

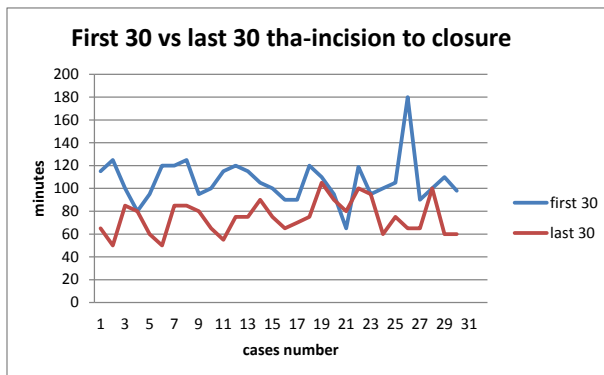
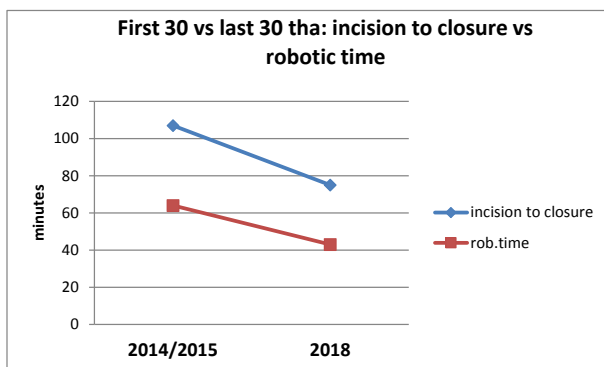


Table XII. Learning curve: incision to closure time vs robotic time of first 30 vs last 30 cases ($p < 0.01$).



last 30 cases performed with MAKO. If we compare the linear slope in time between the two parameters, we can observe that the slope of the skin-to-skin time function is greater than that of robotic time. This means that within the methodology of the robotic intervention, the reduction of the robotic time induces a speeding up of the non-robotic times both before

the positioning of the trackers and after their removal after the performed implant. These are the surgical approach, the femur exposure and the suture.

DISCUSSION

Robot-assisted surgery is constantly increasing in all surgical specialties (29, 30). In literature, many papers, not only retrospective like ours, but prospective randomized, have shown the superiority of the results of total hip replacement with the robotic technique over the standard manual. The best results have been reported in terms of precision and accuracy in the positioning of the components and therefore as the best anatomical, biomechanical and kinematic results (19), safety of the procedure i.e. no complications related to the robot, error limitation. Further works have highlighted the superiority of MAKO in hip replacements also considering early clinical results such as pain reduction, faster functional recovery and generally better PROMs in patients operated with the Robot (31, 32).

In our previous work, comparing the days of hospitalization and functional results - Proms between 120 standard procedures vs. 100 robotic procedures, we observed a statistical significance in favor of the robot with regard to length of hospital stay while functional results were better in the Mako sample but the difference disappeared at one year of follow-up (33). On the contrary, there are other works and meta-analyses that do not report statistically significant results in favor of robotics, especially in terms of functional results and implant survivorship (34).

Since the advent of Mako in THA is less than 10 years old, it is too early to have certain comparative data on implant survival from literature and especially from national registries. This important data will have to be followed carefully but since the best prerequisite for robotics is the stereotactic accuracy of the prosthetic implant, the increased survival of robotic prostheses should also be demonstrated over time. Since all the negative aspects of robotic orthopaedic surgery are considered to be due to the high direct costs (cost of Mako per procedure) and indirect costs (especially the surgical time), we wanted to examine in an objective way the impact

of the learning curve on the duration of surgery and especially the possibility of recovery of indirect costs but very important for organizational costs and safety of treatment, i.e. the number of days of hospitalization and the number of patients transfused.

At our former local health center (USL8) in Arezzo (currently part of ASL Toscana Sudest) Mako was acquired in July 2014, the month in which our robotic orthopaedic surgery experience began. Although the study period ends on December 31 2018, since we do not currently have the hospital discharge forms (SDO) of 2019 but are able to consult the real time data of the Mako computer, until September 2019, a total of 844 robotic prostheses were performed at our institution: 474 total hip arthroplasty (THA), 306 partial knee arthroplasty (PKA) and 65 total knee arthroplasty (TKA).

Considering the Mako data until December 2018 for a total of 395 THA, we had no intraoperative complications. Among the first 15 cases, in two patients we had the loss of bone morphing data acquired due to femoral tracker mobilization, so that the surgery was successfully completed manually. We did not have any cases of deep venous thrombosis (DVT). Of the 395 robotic cases until December 2018, two patients ($2/395 = 0.05\%$) were operated on again, 1 for deep infection with two stages procedure ($1/395 = 0.02\%$) and 1 for relapsing dislocation ($1/395 = 0.02\%$).

Over time we realized empirically, observing the clinical differences between the two procedures, that the robotic sample tended to have a faster

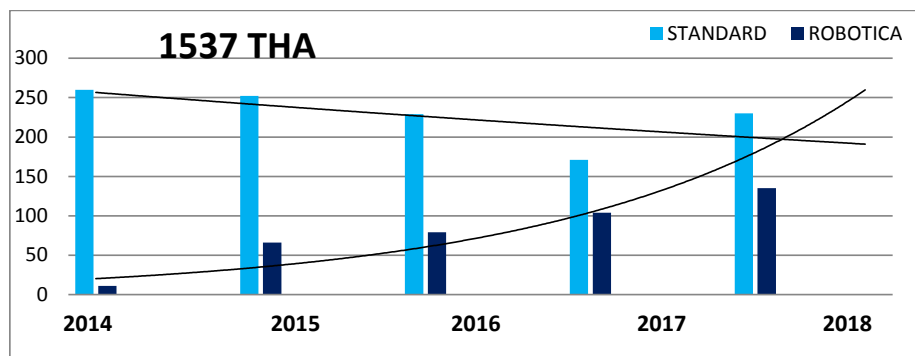
recovery for the purpose of discharge, fewer minor complications, less pain, better proprioceptive perception and greater patient satisfaction. The latter parameter could also depend on the psychological conditioning of the patient for having been operated on with advanced technology, but still represents a positive aspect for the patient and a coefficient of attraction for the hospital and the surgical team.

From July 2014 to December 2018, at our Local Health Center, the use of robotic THA has had a significant increase from 4.06% in 2014 with a gradual increase over the years, arriving between 2017 and 2018 to an average of 36% per year compared to the standard surgery that has decreased in percentage (from 96% to 63%) (Table XIII).

As far as the gender is concerned, it should be noted that in traditional surgery women are operated on more than men, and even if it is adjusted for age, the risk remains significant. While until about 10 years ago, clinical studies reported that although women suffered more from arthrosis at the main joints (35), but due to cultural conditions the largest percentage of operations were on males (36). Today the percentage of women operated on with arthroplasty is significantly increasing, exceeding, in some cases, by far the males (37, 38).

Many clinical studies state that an advanced age and a high comorbidity rate may be responsible for more transfusions, although the most important risk factor remains the level of preoperative haemoglobin (39). However, our two subgroup samples were uniform with regard to all

Table XIII: 1537 standard and robotic THA from 2014 to 2018.



preoperative clinical conditions such as: age, sex, comorbidities, ASA score, preoperative diagnosis (coxarthrosis or osteonecrosis) same surgical approach, same perioperative medical management (40) and application from 2014 of the patient blood management (PBM) protocol (24).

In fact, with the improvement of the learning curve and the improved stereotactic control of the positioning of the prosthetic components, increasingly difficult cases with greater anatomical alterations have been operated on with Mako. During the preoperative anesthesiological examination carried out at the hospital facilities of the former USL8, in all the patients on surgical note for elective surgery, all the indications of the Patient blood management (PBM)(24) were followed according to the directives of 21/05/2010 with WHO Resolution WHA63.12 for the introduction of the PBM strategy (41) , and in 2012 with the PBM promotion in Italy by the CNS in line with the WHO Resolution.

Since the value of pre-operative Hb is the main independent risk factor for receiving transfusion support with erythrocyte concentrates, all deficiencies of iron, vitamin B12 and folate, when detected in the pre-operative phase, have been treated (42).

The core objective of the PBM program is therefore to avoid or minimize the risk of transfusions (43, 44). The study of To J, Sinha R et al. (45) reports that an elderly woman with 11 g/dl preoperative hemoglobin who has to undergo THA surgery has a 76% chance of having a transfusion, while 48% if she had to undergo TKA surgery. If it is possible to optimize the value around 13g/dl, the transfusion probability is reduced to 45% for THA and 19 % for TKA. It has been shown how females and an advanced age > 65 years, if considered together, increase the transfusion risk.

In many other studies, transfusion risk factors were also evaluated as the BMI (46), the time of the intervention, the ASA scores. In the study by M.Carling et al. (47) reinforces the concept that the only significant predictive factor is the preoperative value of the haemoglobin and that there is a greater possibility of transfusions in the THA rather than in the TKA, perhaps tied to the use of the tourniquet in the TKA, but this has not yet been demonstrated (48).

Our work shows that in THA, the robotic technique represents a variable reducing the risk of homologous blood transfusion. In fact, in our experience, patients operated on with the standard technique were transfused in 128/1142 (11.21%) while with the robotic technique they were transfused in 8/395 (2.03%). There is therefore a statistical significance on the difference in transfusions between robotics and standards to the advantage of robotics. (Pearson $\chi^2=30.68$; $p<0.001$). Moreover, the standard method, compared to robotics, exposes to a transfusion risk 6 times greater (OR 6.10 ,95% CI 2.96-12.59 $p<0.001$), but if we put both age and sex as confounding variables (therefore adjusting for age and sex) the risk is reduced to 4.69 remaining significant (OR 4.69, 95% CI 2.25-9.76, $p<0.001$). In detail, considering transfusions as outcome variables, we note that women are more likely to be transfused than men, about 90% more (OR 1.90, 95% CI 1.30-2.78, $p=0.001$). If we consider age, the risk decreases to 64% but remains significant (OR 1.64, 95% CI 1.11-2.41, $p=0.011$).

Yi Ying in 2018 (49) reports no statistical difference in the number of transfusions in a retrospective comparative work between 45 cases with standard method and 45 conventional THA. The author attributes this to, a low number of cases for statistical significance.

In our work, on the other hand, while analyzing only the data of patients transfused for the two methods with the robotic technique, the need for homologous blood transfusions is reduced. The reason why the robotic technique induces less blood loss is not clear. The hypotheses are related to a reduced need for exposure of anatomical bone and soft landmarks, having one direct anatomical reference with images on the computer monitor and the other related to the unnecessary sequential reaming of the cup with less time of bleeding exposure of the cup during milling. Data on the number of hospitalization days (LOS) also showed statistical significance between the standard group and the robot group in favor of robotics (Table VIIA and Table VIIB).

In Robotic Pts the average stay was 4.24 days with a standard deviation of 2.04 ($M=4.24$,

SD=2.04, 95% CI 4.04-4.44), in the standard Pts group the average stay was 8.04 days with a standard deviation of 2.84 (M=8.04, SD=2.84, 95% CI 7.88-8.21, $p<0.01$). If we take into account the fact that within a Regional Health System, the optimization of beds occupation is of primary importance, so that an increase in the turnover of the operated patients is inversely proportional to the reduction of the days of hospitalization and this can constitute a stable and programmable process in elective surgery, a stable reduction of the days of hospitalization can be translated into a reduction of indirect costs per operation with the possible increase in their number.

Considering that the average cost of a day's hospitalization in the orthopaedic area at our institution alone is €808.56 and that the average stay in robotic surgery was about 4 days compared to about 8 days in standard surgery, we have an indirect cost saving for each robotic surgery of $€808,56 \times 4 = €3.234,24$. This cost reduction is combined with the availability of a bed for 4 days with increased surgical productivity in that area.

The last point of discussion is the impact that the learning curve of a technologically advanced method such as robotic orthopaedic surgery can have on operating times and therefore as indirect costs of the procedure. From 2014 to 2018, both the robotic and the skin-to-skin time have been significantly reduced from an average of 63 min and 106 min in 2014 to an average of 45 min and 82 min in 2018 ($p<0,01$). The comparison of the two curves between the first and the last 30 cases also shows a statistical significance ($p<0.01$), which means that the learning curve is important and significant and its negative impact on operating room times is progressively reduced over time. In fact, after the end of this study, in 2019, due to further skill of the surgical team, the whole skin-to-skin operating time was further reduced up to 74 minutes of average (82 mins in 2018 vs 74 mins in 2019).

In our current practice the global time of a robotic hip exceeds that of the conventional technique by no more than 10 minutes. This means that with a good learning curve the indirect costs of the increased operating time of the robotic technique can be reduced. Table XII, comparatively highlighting the slope of linear reduction in time between skin-to-

skin time and robotic time shows how the slope of the global time function is greater than that of robotic time. The skill acquired over time by the operating team reduces not only the pure robotic technical time but even more so the non-robotic times of the robotic technique with the consequent reduction of the impact on operating room turnover.

The diffusion of robotic technology in orthopaedic surgery is going slowly for several reasons, even if there are two main ones : a) the cultural problem, that is the difficulty in changing one's working methods in favor of more complex techniques that require application, theoretical risks and the putting oneself back into play in a procedure that is well known and which obtains good results, b) the difficulty for health technology assessment (HTA) representatives to be able and know how to quantify the cost benefit ratios of a complex methodology such as orthopaedic robotics.

This technology should be considered as a medium and long term investment balancing the immediate direct costs, the immediate indirect costs with the reduction of early and late indirect costs and above all the theoretical health and long term cost savings such as the reduction of implant revisions, the reduction of theoretical risks from transfusion and the theoretical reduction of litigation for the complete demonstrability of a precise prosthesis implantation with non-technical errors. Our study has some limitations: through the analysis of regional hospital discharge forms it was not possible to trace the amount of blood lost, the number of transfused blood units for each individual patient and the pre-transfusion haemoglobin threshold value.

Robotic Orthopaedic Surgery is an emerging new technology that requires further studies for a proper evaluation of the short- and long-term cost-benefit ratio. As part of the assessment of indirect cost reduction, we can say that a good learning curve of robotic technique in THA tends to reduce to the point of cancelling out the differences with conventional technique with regard to the initial higher costs of operating room time. The reduction of transfusions in favor of robotics leads to cost savings and a reduction of all risks from homologous blood transfusion. The reduction in hospitalisation

days, again in favor of robotic surgery, represents a further reduction in indirect costs with the possibility of increasing surgical turnover in the context of an elective prosthetic surgery.

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Arthroscopic transosseous versus suture anchor repair: clinical outcomes in patients with bilateral rotator cuff tears

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The aim of our study was to define if Arthroscopic Transosseous Rotator Cuff Techniques should have comparable results to those of the suture-anchors technique in a single row configuration. We reported the preliminary results of a consecutive population of 22 patients who underwent a rotator cuff treatment on the left and right sides for average medium-sized thickness tears with minimal fatty infiltration with the two different techniques: transosseous rotator cuff repair technique on one side and single row with suture-anchors on the other side, in different times. Subjective evaluation with DASH questionnaires, Constant Scores and Numerical Rating Scale (NRS) for pain evaluation, have been submitted pre and postoperatively after both operations. A statistical analysis was performed to assess the superiority of one technique and to compare pre and postoperative ROM data and clinical outcomes. A transosseous rotator cuff repair was performed in 7 patients on the dominant arm, while the other 15 patients had dominant arm cuff tear lesions repaired by using suture-anchors technique. At last follow-up a significant improvement, in shoulder pain and function, was referred at both sides. Also, DASH, Constant Scores and NRS for pain evaluation improved with both techniques, but no statistical difference was found between them. Arthroscopic transosseous rotator cuff repair technique shows comparable results to those of the suture-anchors technique in a single row configuration.

Rotator cuff tears are the most common shoulder disorders and can be degenerative or traumatic (1). Anatomic studies of rotator cuff tears in cadavers have noted a prevalence ranging from 17% to 72% (2, 3). Rotator cuff repair is one of the most common surgical procedures performed on the shoulder, the benefits of which are well known (4). Surgical management has shown predictable pain relief and functional improvement, with good overall patient satisfaction (5).

For many years open rotator cuff repair, first described by Codman in 1911, was considered the

gold standard of surgical management for full-thickness tears (6). Open repair with transosseous fixation has shown good to excellent long-term clinical outcomes (7, 8) and is well supported in a variety of biomechanical studies (9). Nowadays, excellent fixation strength and outcomes have been obtained by arthroscopic rotator cuff repair (10), a technique which has increasingly been adopted in surgery. Some of the advantages are preservation of the deltoid origin and decreased postoperative pain and stiffness, the opportunity to study the entire glenohumeral joint for associated pathologies and

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the ability to fully characterize tear patterns (11-13).

The use of suture anchors for fixation of the rotator cuff tendons to the bone has become the gold standard of arthroscopic rotator cuff repair. In the literature, a variety of fixation techniques and configurations have been described, ranging from single-row (SR), to double-row (DR) and to double-row transosseous equivalent (TOE) (14). To date, the ideal method of rotator cuff repair remains unknown, since using many anchors for a valid repair increases surgical time and implant costs.

The search for improved methods recently led to the development of an all-arthroscopic transosseous (TO) rotator cuff repair technique (2), the aim of which is to replicate the open transosseous repair fixation method while conferring all the advantages of the arthroscopic technique (9). There are few data regarding outcomes after arthroscopic TO rotator cuff repair, but early published reports have been promising with similar conclusions to those on anchor-based techniques (15, 16). To date there are no comparative clinical studies evaluating outcomes after either arthroscopic anchor-based or transosseous rotator cuff repair.

We report the preliminary results of a consecutive population of patients who underwent rotator cuff treatment using two different techniques: transosseous rotator cuff repair technique on one side and the single row with suture-anchors technique on the other. Both were performed at different times.

MATERIALS AND METHODS

Between June 2011 and October 2015, we identified 22 patients who had been operated on both shoulders with the two different techniques, an overall total of 44 rotator cuff tears. All patients presented a primary rotator cuff tear on the right shoulder that presented on the left shoulder after an average delay of 3 years. There was a minimum period of 9 months between the two procedures (average 3 years). All patients presented a history of shoulder pain on both sides, associated with limited movement that did not respond to conservative treatments such as physiotherapy, NSAIDs, or corticosteroid injection.

The patients and the operative techniques were chosen in a consecutive series and were prospectively enrolled

and evaluated. Dominant arm cuff tear lesions were repaired by the transosseous rotator cuff repair technique in 7 patients and by anchors in a single row configuration in 15 patients (Table I). All procedures were performed by our senior author. Subjective evaluation was obtained for both procedures using DASH questionnaires and Constant Scores, submitted pre- and, post-operatively and at follow-up (average ± 3 years 6months) (range 2-5). Numerical Rating Scale (NRS) was obtained before surgery and at three months intervals post-operatively.

MRI was performed pre-operatively to determine the type of tear and the amount of fatty infiltration in the torn rotator cuff tendon. The patients were classified as retraction and infiltration average grade 2 according to Fuchs (17). Patients with gleno-humeral arthrosis, previous humeral fractures, revision rotator cuff repair, adhesive capsulitis or neurological arm deficit were excluded from the study. A tenotomy of the LHB was performed in all cases.

All post-operative outcomes were classified depending on Constant scores: excellent (90-100), very good (80-89), good (70-79) and fair (60-69). Fifteen subjects underwent MRI at two years follow-up.

Surgical technique

All the arthroscopic rotator cuff repairs were performed in the lateral decubitus. Three classical portals were used in the procedures; routine diagnostic arthroscopy was followed by subacromial decompression/bursectomy. Tenotomy of the biceps at supraglenoid tubercle was performed in case of fraying, tenosynovitis, or instability of the tendon. After subacromial decompression, footprint preparation and appropriate release of the rotator cuff, intersecting transosseous bone tunnels were created using the Taylor System.

The number of tunnels was determined at the time of surgery based on the tear size and the number of tendons torn. One transosseous tunnel per centimeter of tearing in the sagittal plane was performed. The size of the tear in the coronal plane (i.e. amount of retraction) does not typically influence the number of tunnels used for the repair. Our preference is to shuttle three high-tensile strength sutures through each tunnel: two #2 Orthocord® (Ethicon, Somerville, NJ) semi-permanent sutures and one #3-4 Force Fiber™ (Tornier, Edina, MN) permanent suture. The sutures were passed through the rotator cuff using a combination of anterograde/retrograde delivery

technique, retrieved and tied in either a simple, XBOX or mattress configuration. No bone augmentation device or patch augmentation was used in any patient in this study (Fig. 1).

In the rotator cuffs repaired using the suture-anchors technique, a standard procedure with a single row configuration was performed, with an average of 2 anchors in an Alex-stich configuration (18) (Fig. 2).

Post-operative treatment

Postoperatively, all the shoulders were placed in an arm sling with abduction pillows for five weeks, regardless

of tear size. Immediate passive and active-assisted elbow/wrist/hand motion and scapular kinetic exercises were started the day after surgery. Supervised physical therapy was initiated within the first 7-10 days after surgery. Immediate supine passive anterior elevation and external rotation was performed for the first six weeks. Active ROM was started at two months after the removal of the sling and gentle strengthening typically began by week twelve. Full release to all activities is patient specific but is generally allowed at six months after surgery. Internal Review Bord (IRB) approval was obtained before the start of data collection. Written informed consent was obtained from all patients included in the study.

Statistical analysis

A statistical analysis was performed to assess the superiority of one technique and to compare ROM data and clinical outcomes pre- and post-operatively and at 42 months follow-up. All patient information was reported in our database in a standardized form. Completed forms were computerized in a database created by File Maker Pro. Data were analysed by STATA MP11 software. Sample size calculation was carried out based on preliminary data on the trend of Constant Score mean values at the times of follow-up and by considering a 5% margin of error and a 95% confidence level. A minimum sample of 15 cases were confirmed.

Qualitative variables were expressed as proportions using the Chi-Square test for comparison and expressed as a mean with a standard deviation. The Student's t test for paired samples was used to compare the means at different times. The level of significance was set at $p < 0.05$.

RESULTS

In this prospective study of 44 shoulders all 22 patients were evaluated. Twenty (91%) patients were males and 2 (9%) were females, the average age at the time of surgery was 57 years for the anchor group (SA) and 61 years for the transosseous group (TO).

Of the 22 shoulders treated with the TO technique 7 (32%) were on the dominant arm whereas of the 22 shoulders treated with the SA technique 15 (68%) were on the dominant arm.

An average follow-up was 42 months (9-75 months). For the anchor group (SA), the average follow-up

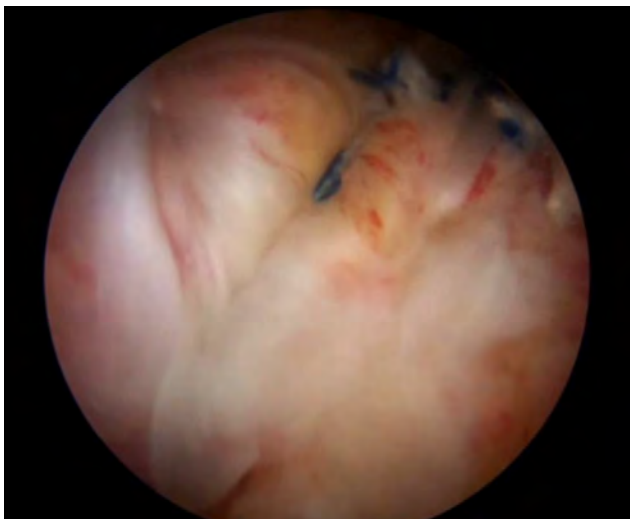


Fig. 1. Arthroscopic transosseous suture at the end of the procedure of rotator cuff repair.



Fig. 2. Arthroscopic repair with Alex-stitch suture of rotator cuff tear.

was 45 months (9-75), while for the TO group it was 40 months (9-70).

The lesions were medium sized (supraspinatus and infraspinatus) in 30 shoulders (15 in the SA group and 15 in the TO group) and small sized (only supraspinatus) in 14 shoulders (7 in the SA group and 7 in the TO group). The retraction and the infiltration grade according to Fuchs and Goutallier was average grade 2 (range 1-3) in both groups (17, 19).

At the last follow-up a significant improvement, in shoulder pain and function were referred for both sides. Compared to the pre-operative situation, passive glenohumeral joint range of motion improved in both the anchors and the transosseous group in all directions, according to individual parameters that made up the Constant scores.

The mean values for preoperative DASH scores and Constant Scores for the transosseous operated sides are 45.8 and 41.7 (n.s.) respectively. The mean value for pain in the preoperative NRS is 8.2 in the TO group and 8.5 in the suture-anchors group (n.s.).

Postoperatively both improved as follows: DASH 12.9 and Constant Score 73.8 ($p<0.01$). At 3 months NRS for pain evaluation was 3.1 for the transosseous group and 3.3 for the suture-anchor group (n.s.). Conversely, for the suture-anchor techniques, the mean value of DASH scores was 46.2 preoperatively and 9

postoperatively ($p<0.01$) while the Constant Score was 42.8 and 83.5 respectively ($p<0.01$) (Table II).

There was no statistical significance between the two techniques used. A statistically significant improvement was demonstrated on both techniques for ROM, DASH and Constant Scores before surgery and at the final follow-up ($p<0.01$). MRI at follow-up was performed in 15 patients demonstrating good healing of the tendons regardless to the technique used.

DISCUSSION

Transosseous rotator cuff tear repair, described by McLaughlin in 1944 (20), has represented the gold standard for years. The advent of arthroscopy has brought a new framework in rotator cuff surgery, supported by the introduction of many devices for fixation over the past few years: screwed or impacted anchors, made of different materials, can be arranged using many different types of repair configurations (21). SR, DR and TOE anchor-based repair methods are well-described in the literature and have consistently demonstrated good clinical outcomes and healing rates (22). However, shortcomings remain with this technique, such as difficulty with revision surgery, due to the presence of anchors in the greater tuberosity, anchor dislodgement, knot

Table I. Dominant and non-dominant arms of patients enrolled in the two groups Transosseous group (TO) and Suture-anchors group (SA).

	Dominant arm	Non dominant arm
TO	7	15
SA	15	7
Total	22	22

Table II. No statistically significant difference in clinical scores between the two groups: $p>0.05$.

	Dash score preop	Constant preop	NRS preop	Dash postop	Constant F.U.
SA	46.2	42.8	8.5	9	83.5
TO	45.8	41.7	8.2	12.9	73.8

impingement (16) and, eventually, greater tuberosity bone osteolysis (23).

Arthroscopic transosseous technique has been developed to overcome these limitations, combining the minimal invasiveness of the arthroscopic procedures with the biomechanical advantages of the open procedures (2). A further advantage of the arthroscopic transosseous technique should be the possibility of releasing stem cells and growth factors from the bone tunnels to improve tendon healing (24). Few studies regarding clinical outcomes have been published recently (15, 16, 22) but none compare the clinical results of arthroscopic anchor vs transosseous technique. We identified a unique group of 22 patients who underwent rotator cuff tears surgery between 2011 and 2015 with both techniques performed by the same senior surgeon. All patients firstly underwent an anchors rotator cuff repair in a single row configuration on one side and subsequently a transosseous repair on the other.

As Flanagan et al (22) reported in their recent paper, for the objective data, we also found an improvement in ROM in all planes in both shoulders. In both cases subjective outcomes improved but no statistically significant difference was detected between the two techniques.

DASH score for physical function and symptoms in the upper limb revealed an improvement from 45.8 to 12.9 ($p < 0.01$) in the transosseous shoulders and from 46.2 to 9 ($p < 0.01$) in the anchor one.

Constant scores improved in all elements from pain to daily activity and strength.

According to the Constant scores for the shoulder treated using the transosseous technique, results were excellent in 11 patients, very good in 7, good in 3 and fair in 1. For the shoulders treated with the suture-anchor technique the results were excellent in 10, very good in 9, good in 2 and fair in 1 patient. Patients were not able to appreciate any subjective difference comparing the results in both shoulders.

In a recent perspective randomized controlled trial by Randelli (25) postoperative pain decreased more quickly after the transosseous procedure, but this data was not confirmed by our study. Our paper avoids a possible bias of a subjective evaluation of pain, because the same subjects were operated on

both shoulders.

In our population no significant complication was observed. Tunnels breakages were not reported, because this device placement is located about 15-20 mm distally to the greater tuberosity, in a region with a good bone stock (15). Furthermore, no intraoperative fractures of the greater tuberosity were encountered in this series.

One strength of the study is that it is the first to compare the two techniques in the same subjects. The limitations of the study are the small sample of subjects and the short follow-up. The low number of patients is correlated to the singularity of the population study. However, this also permits a subjective patient evaluation as regards both techniques. The short MRI follow-up does not confirm the presence of a postoperative re-tear.

Arthroscopic transosseous rotator cuff repair technique leads to significant short-term improvement and satisfactory subjective outcome scores with low complication/failure rates (26-28). More comparative outcome studies following either transosseous or anchor-based arthroscopic rotator cuff repairs with longer follow-up and larger samples are needed to confirm any qualitative difference in the two techniques.

Compliance with ethical standards

All procedures performed for this study were in accordance with the Ethical Standards of the Institutional and National Research Committee and with the Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the Institutional Review Board of our Institute. Written informed consent was obtained from all people included in the study.

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A survey on surgeon practice shows lack of consensus on the management of primary shoulder stiffness

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Shoulder stiffness is a condition of painful restriction in active and passive glenohumeral range of motion, which can arise spontaneously or as consequence of a known cause. Numerous therapeutic approaches are available; however, no consensus has been reached on the best algorithm for successful treatment. The aim of this study was to investigate local practice patterns regarding management of primary shoulder stiffness. Randomized controlled trials reporting results of shoulder stiffness treatment were collected and analyzed prior to study begin. Controversial elements in the treatment of primary shoulder stiffness were identified and a survey was created and administrated to clinicians participating at an annual national congress dedicated to shoulder pathologies and their treatment. 55 completed questionnaires were collected. Physical therapy was recommended by 98% of the interviewed. The use of oral corticosteroids was considered by 58% and injections of corticosteroids by 60%. Injective therapy with local anaesthetics was considered by 56% of the clinicians and acupuncture by 36%. 38% of the interviewed did never treat shoulder stiffness surgically. Various strategies to manage shoulder stiffness have been proposed and high-level evidence has been published. Numerous controversial points and a substantial lack of consensus emerged both from literature reviews and from this survey. The treatment of shoulder stiffness should be tailored to the patient's clinical situation and the stage of its pathology, aiming primarily at identifying risk factors for recurrence, reducing pain, restoring range of motion and function and shortening the duration of symptoms.

Shoulder stiffness is defined as a painful restriction of active and passive glenohumeral range of motion (ROM) (1). It is a common condition, affecting between 2% and 5% of the general population, mainly of female gender, with peak incidence between 40 and 60 years of age. Although frequently self-limiting, shoulder stiffness can lead to long-term pain, disability and reduction in quality of

life. Therefore, a vast portfolio of treatment options has been developed, ranging from conservative therapies to surgical approaches. Recommended treatment goals are to address known risk factors to avoid relapses, to reduce pain, to restore ROM, to improve function and to shorten the symptoms. Since different forms and stages have been described for this disease, the choice between treatments needs

Key words: Shoulder stiffness, adhesive capsulitis, frozen shoulder, treatment, steroid, results, review, survey

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to be tailored to the patient's clinical situation. Although several studies have tried to outline the most appropriate treatment options, no consensus has been obtained on which treatment algorithm represents the best choice for the patient.

Between 2006 and 2014, the Cochrane Company summarized the evidence derived from the randomized controlled trials (RCTs) available at that time on different approaches to shoulder stiffness treatment (2-7). More recently, a review of the literature was performed to identify RCTs reporting results of shoulder stiffness treatment from December 2005 onwards, thus updating the evidence-based indications provided by the Cochrane Company (8). Analysing the available evidences, several still controversial points emerged. Thus, a survey was created and administrated during a national congress focussed on shoulder pathology and treatment, with the aim to assess the treatment algorithm of the clinicians toward this frequent condition.

This paper reports and discusses the results of the survey, comparing the gathered data with the results of the available studies with a high level of evidence, which should be considered a guide for clinical practice.

MATERIALS AND METHODS

Prior to the study beginning, a systematic literature review was performed, to identify controversial elements in the management of primary SS. This research updated an existing set of Cochrane systematic reviews (2-7) adding and the new RCTs published in the following years (8). This preliminary analysis highlighted lack of consensus especially on the following points:

- Recommended modalities of physical therapy;
- Oral corticosteroids: indications for administration;
- Injective corticosteroids: indication, frequency and timing for administration;
- Injective corticosteroids: technique and site of injection;
- Alternative conservative treatments;
- Surgical treatments: indication, timing and techniques.

A multidisciplinary research group including clinical researchers and orthopaedic surgeons prepared a survey. The survey was then distributed at a national

congress focussed on shoulder pathology and treatment and dedicated both to hospital clinicians and practitioner active in the outpatient setting. The survey was composed of two sections: the first focussed on general and personal information, including demographic data, region of origin, place(s) of work, education and professional role. The second investigated the attitudes toward the treatment of shoulder stiffness, with references to both conservative and surgical approaches.

Completion of the questionnaire was voluntary, and no incentives were offered. Ethical approval for the study was not required. Responders gave an implicit informed consent to the treatment of their data in an anonymous way. Sample size calculation was based on a participant to item ratio of 5:1 to perform factor analysis (9).

Data obtained from the completed questionnaires were entered into a spreadsheet for analysis (Microsoft Excel Package Office 2007 for Windows). Statistical analysis and plotting of the data was then performed using GraphPad Prism v 6.0 software (GraphPad Software Inc.). The Kolmogorov-Smirnov normality test was used to evaluate the normal distribution of the sample. Continuous variables were expressed as the mean $\pm$ standard deviation (SD) or medians and first and third quartiles (Q1 - Q3) as appropriate. Response rates were summarized in terms of proportions of respondents. The results of the survey were reported following specific guidelines.

RESULTS

A total of 55 completed questionnaires were collected. The mean age of the responders was 48.1 ± 11.9 years, with 22.4 ± 11.4 years of experience as orthopedic surgeons. The ratio between clinician working predominantly in hospital and those working mainly in an outpatient care setting was 3:2. Most interviewed clinicians reported seeing 2-3 patients affected by shoulder stiffness per month (Fig. 1).

Physical therapy was recommended by 98% with a similar distribution between physician suggesting a single type of physiotherapy and a combination of different types of physical therapy (Fig. 2A). Active and against-resistance exercise were preferred by the majority of the interviewed (83%, Fig. 2B).

The 58% of interviewed considered the use of oral corticosteroids, most of them as a salvage option

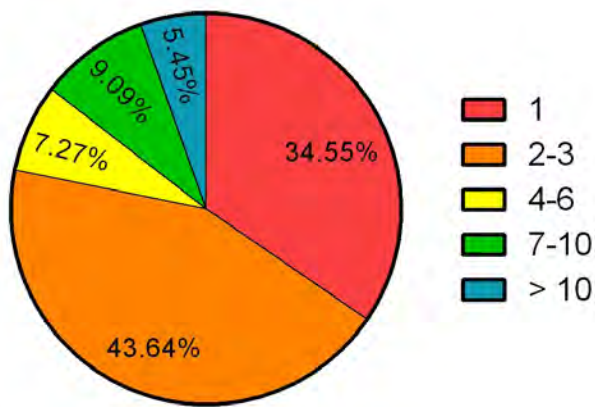


Fig. 1. Number of patients seen per month

after treatment failure with repeated corticosteroid injections (Fig. 3).

The 60% of clinicians considered injections of corticosteroids (Fig. 4A); approximately the half of

them report to prescribe them both in stages I and II (Fig. 4B), as soon as the diagnosis of shoulder stiffness has been made (Fig. 4C).

More than 60% of the responders agreed on an upper limit of three injections (Fig. 5A), but no consensus was obtained on distance between repeated injections (Fig. 5B).

Over two thirds of those using injective steroids indicated ultrasound as unnecessary to guide injections (Fig. 6). A single subacromial injection was preferred to a single intra-articular injection and a double injection (Fig. 7).

Among alternative treatments for shoulder stiffness, injective therapy with local anaesthetics and acupuncture were most frequently considered. Platelet-Rich-Plasma injections, hyaluronic acid injections and nerve blocks were indicated from approximately 20% of the interviewed physicians (Fig. 8).

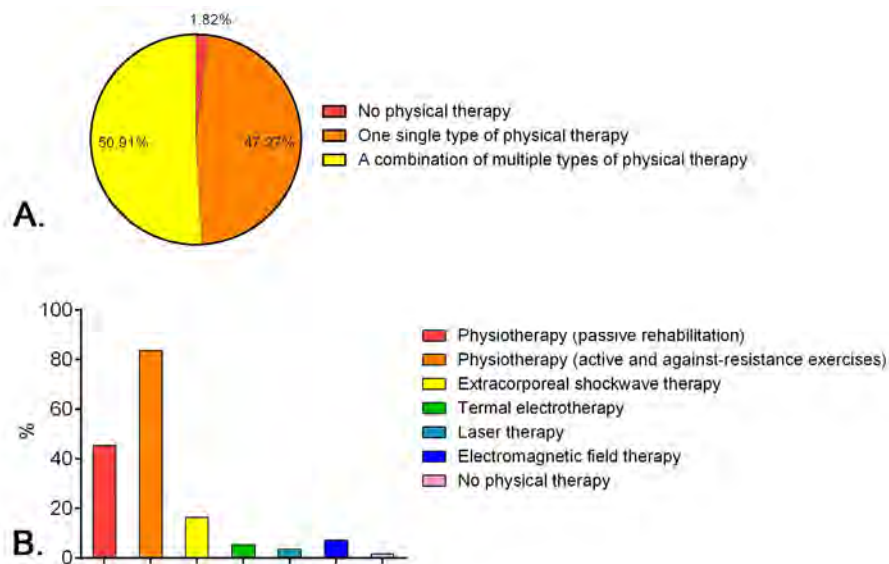


Fig. 2. Attitude towards physical therapy strategies; A. Single therapy or multimodal therapy; B. Types of physical therapies.

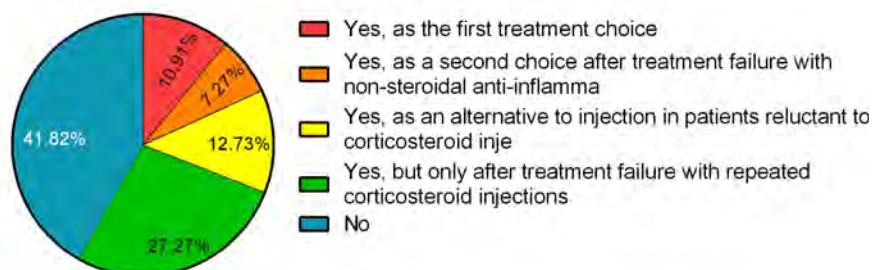


Fig. 3. Use of oral corticosteroids

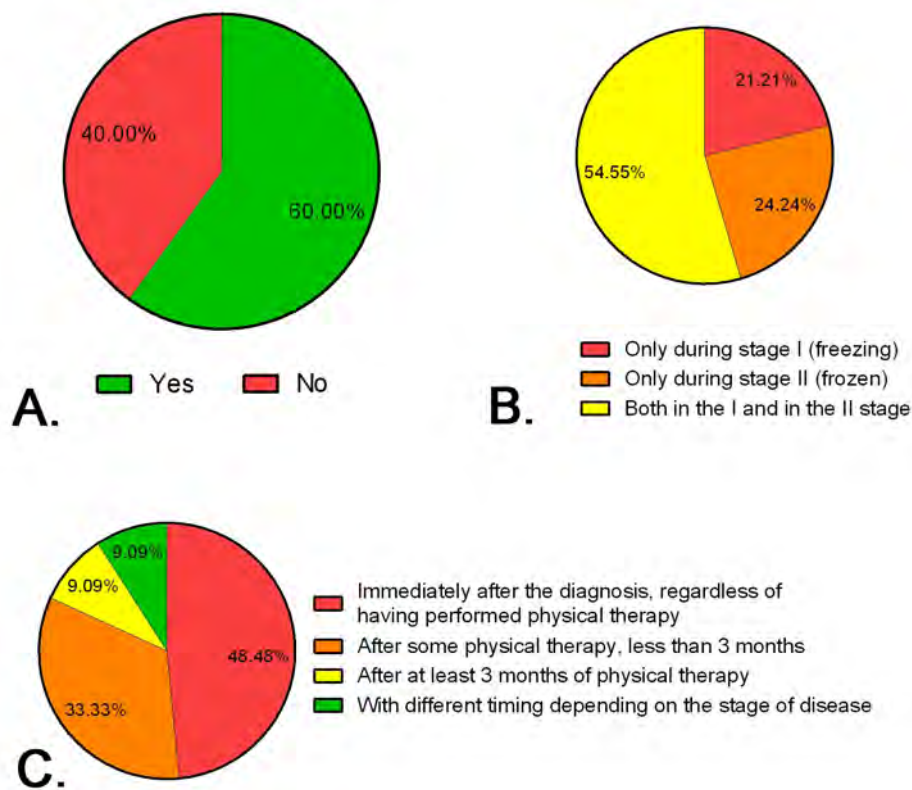


Fig. 4. Use of injective corticosteroids; A. General attitude towards use of injective corticosteroids; B. Attitude in relation to disease stage; C. Attitude in relation to disease onset and previous physical therapy.

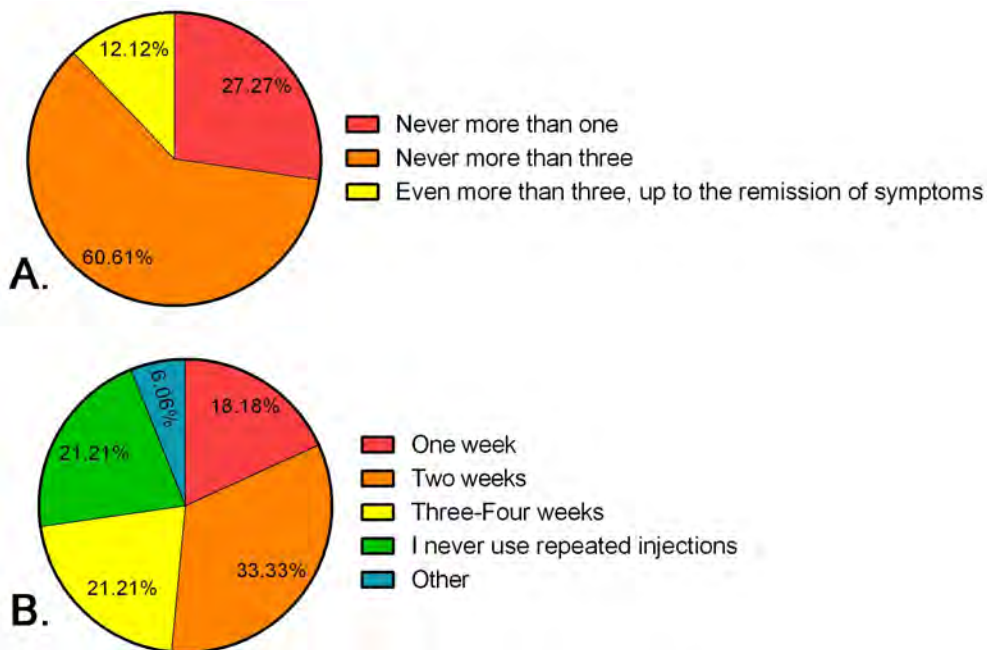


Fig. 5. Repeated corticosteroid injections: A. Number of corticosteroid injections recommended; B. Distance between repeated injections.

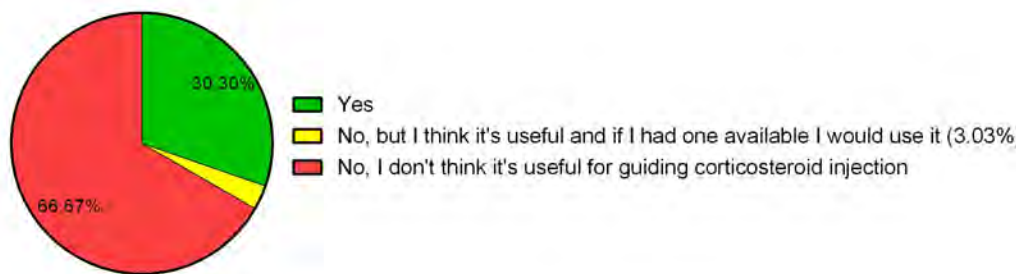


Fig. 6. Use of ultrasound to guide corticosteroid injections.

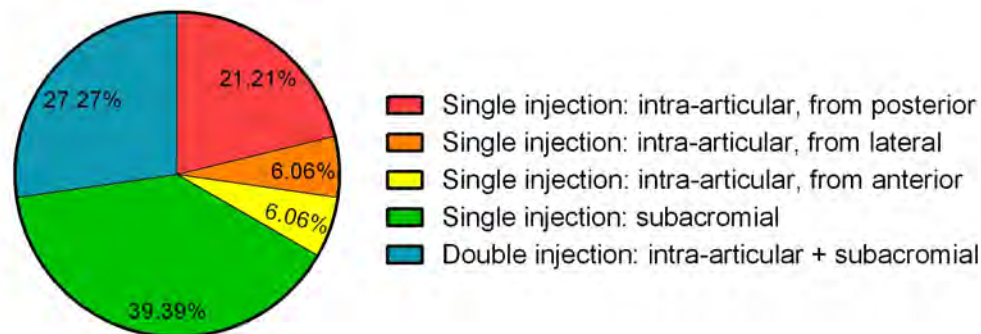


Fig. 7. Technique of corticosteroid injections.

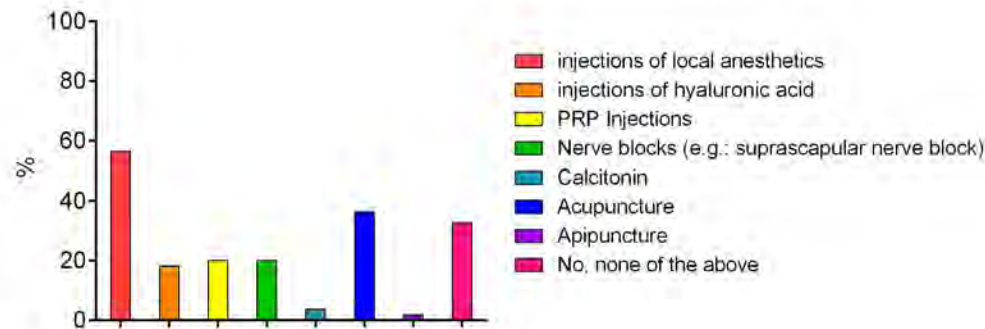


Fig. 8. Other types of conservative treatment (excluding physical therapy, anti-inflammatory drugs and oral or injective corticosteroids).

A minority of responders considered hydrodilatation, whereas manipulation under anaesthesia was considered by one third of them, mainly in the thawing stage, after the failure of other treatments (Fig. 9A and 9B). The 38% of interviewed subjects declared not to treat shoulder stiffness surgically and 38% of the remaining allocated to surgery not more than 5% of their patients (Fig. 10).

One third of those considering surgery indicate it after at least three months of failed conservative

treatment, another third after at least 6 months and 20% at least 12 months. (Fig.11). Arthroscopic capsular release associated to rotator interval release and arthroscopic pancapsular release were equally distributed among the survey's participants, overwhelming open approaches (Fig. 12).

DISCUSSION

The results of this survey indicate a lack of

consensus regarding the management of shoulder stiffness. Shoulder stiffness is a frequent condition, affecting up to 5% of the general population. Although numerous risk factors for shoulder stiffness have been described, research is still required to define the exact aetiology and pathology of primary shoulder

stiffness: an unspecific underlying pro-inflammatory condition has recently been postulated to be a possible predisposing risk factor for its development, which could explain also the known associations with fibromyalgia, hormonal and metabolic diseases, such as diabetes, hyper-, and hypothyroidism (10, 12).

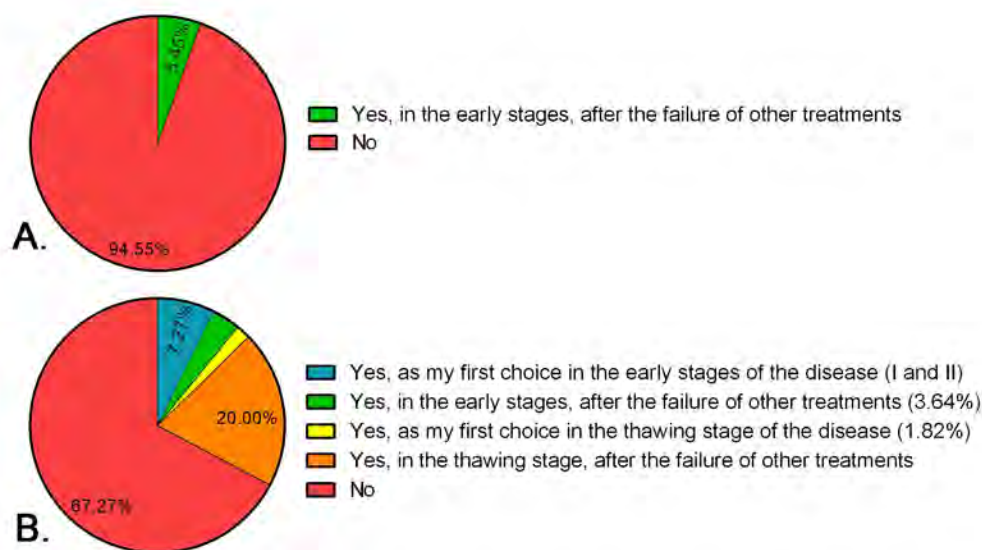


Fig. 9. Attitude towards hydrodilatation and manipulation under anesthesia; A. Indications for hydrodilatation; B. Indications for manipulation under anesthesia.

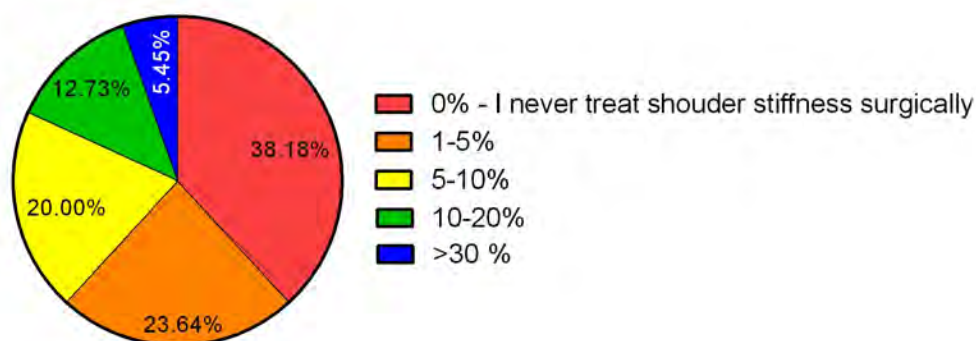


Fig. 10. Frequency of surgical treatment indication.



Fig. 11. Delay between begin of conservative treatment and indication to surgical treatment.

Recommended treatment goals are to address the known risk factors to avoid relapses, to reduce pain, to restore ROM, to improve function and to shorten the symptoms duration. Conservative therapy is the mainstay of treatment for shoulder stiffness and a multimodal and activity-oriented program is nowadays recommended as first-choice treatment.

The indication to prescribe physical therapy was the only item of the survey, where a substantial agreement was obtained. This is in accordance to the currently available literature, which suggests a conservative treatment including physical therapy as first approach to shoulder stiffness. Among the numerous physical therapy approaches available, the responders to this survey appeared to prefer active and against-resistance exercises, highlighting an interesting difference with the results of a previous survey on a different population, mainly composed of hospital surgeons, indicating passive rehabilitation as the first-choice approach.

In agreement to recent literature recommendations, more than the half of the interviewed surgeons preferred multimodal therapy. The goals of physical therapy should include pain reduction, ROM restoration and functional regain, preventing or reducing capsular contracture in the early phases and improving ROM in the latter stages of the disease. Together with passive and active exercises, laser therapy, thermal electrotherapy and pulsed electromagnetic field therapy can support the therapist achieving these goals (3).

Although laser therapy appeared to be neglected by the respondents to this survey, it is the only form of electrotherapy for which a prospective placebo-controlled clinical trial was performed, showing

promising results at early follow-up (13). Similarly, just 16% of the responders considered extracorporeal shockwave therapy although it was described as safe, efficacy, tolerable and with only transient side effects ¹⁴. These findings could suggest a lack of information or a lack of availability on the territory of these useful therapeutic approaches.

The administration of oral steroids can be recommended for short periods in patients without comorbidities, since it can reduce pain and disability, and improve ROM (2). This treatment was adopted by almost 60% of the responders, only 11% of them indicating this as a possible first-choice option. In contrast to this attitude towards oral steroids, injective corticosteroids were frequently considered as a first-choice treatment as soon as the diagnosis of shoulder stiffness was made. The Cochrane Company selected 12 clinical trials investigating the role of injective corticosteroids in the treatment of primary shoulder stiffness, in two of which a possible beneficial role was suggested (5). These findings were confirmed by recent publications, including two meta-analyses (8). Currently, no evidence-based suggestions regarding the ideal number of injections has been published; however, it appears that most surgeons agree on an upper limit of three injections (11).

30% of the interviewed surgeons reported to use US imaging to guide injections, three times more than what appeared in a previous survey conducted in a different setting (11). Ultrasound-guided injections were recently associated to higher accuracy and superior results as compared to blind injection, on the other hand requiring more time and yielding to additional costs (15).



Fig. 12. *Surgical technique.*

Interestingly, in this small survey 40% of the respondents performed a single subacromial injection, avoiding delivering steroids into the joint cavity. The site of injection is, indeed, a topic of open discussion: most high-level publications indicate that the efficacy of subacromial injections is inferior to intra-articular injections, although recent evidence suggests that the subacromial space could play a role in the aetiology of the diseases, justifying a combination of both subacromial and intra-articular injections (16).

A vast portfolio of alternative or adjunctive treatment options is available to the orthopaedic surgeon: more than the half of the respondents considered the intra-articular injections of anaesthetics, which was indeed demonstrated to reduce pain and improve patients' compliance to physiotherapy, possibly improving its results (17). However, the negative effects of local anaesthetics on cartilage should be kept in mind when performing this procedure, especially on a repetitive basis. More than one third of the respondents considered acupuncture as a valid treatment option: this, together with bee venom acupuncture, is well established in traditional oriental medicine; although these approaches are not widespread in Europe and USA, in recent RCTs showed that they are safe and efficient (18).

Injections of hyaluronic acid and platelet-rich-plasma, proposed as an adjunctive treatment by approximately 20% of the interviewed physicians, are not supported by current literature since they didn't provide benefits as compared to a physiotherapy program or IA corticosteroid injections or their efficacy was not tested adequately against a currently accepted gold-standard. The application of a suprascapular nerve block is a well-tolerated and safe method, which can effectively reduce physiotherapy-related pain, and was considered as an adjunct to physical therapy by 20% of the respondents; further studies are necessary to clarify if the benefits provided are enough to justify the increased technical efforts, risks and added costs.

Hydrodilatation refers to the arthrographic distension of the glenohumeral joint capsule: this approach was neglected in the survey population, in accordance to the results of a recent meta-analysis

unable to identify clinically significant benefits in terms of pain reduction and ROM improvement (19). As opposed to hydrodilatation, manipulation under anaesthesia was considered by one third of the responders: however, considering the concerns about the possible serious complications derived from forceful rotation manoeuvres (1) and the lack of superiority when compared to IA steroid injections with distension and hydrodilatation, the use of manipulation under anaesthesia in the treatment of shoulder stiffness is not supported by current literature.

Evidence-based indications for surgical treatment are limited since most cases of shoulder stiffness can be effectively managed conservatively. Moreover, surgical indication remains highly subjective and derives from an individualized decision of the surgeon based on each patient's history, symptoms and stage of the disease. The 38% of interviewed subjects declared not to treat shoulder stiffness surgically and 38% of the remaining allocated to surgery not more than 5% of their patients. Timing for surgical treatment is also controversial, both in the available literature and among the participants to this survey, one third of which indicate as minimum time of failed conservative treatment three months, another third 6 months and 20% 12 months. Arthroscopic arthrolysis and capsular release is preferred over open procedures as it is a less invasive intervention. The addition of a posterior capsular release permits to obtain a more rapid improve in ROM within the first 3 months postoperatively, however without improve patient function or ROM at 6 months (20).

This survey investigated the attitudes of physicians both working in a hospital and in the outpatient setting towards the treatment of primary shoulder stiffness. The results, in agreement with previous reports, indicate a lack of consensus regarding the management of this frequent pathology and suggest the need of developing a common treatment guideline based on the high-quality evidences reported in literature. Furthermore, initiatives to raise awareness among general practitioners and orthopedic surgeons are required, especially regarding the available adjuncts to rehabilitation treatment and the novel results of clinical trials on injective corticosteroid treatment.

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Effect of intravenous ferric carboxymaltose supplementation in non-anaemic iron deficient patients undergoing hip and knee arthroplasty

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Preoperative anaemia and non-anaemic iron deficiency are independent risk factors for perioperative blood transfusion, morbidity, and mortality. Although the efficacy to treat anaemia with iron infusion before elective surgery has been widely studied, the literature offers few data about the efficacy of treating iron deficient, non-anaemic patients before elective surgery. This retrospective study assessed the effect of preoperative ferric carboxymaltose (FC) administration on the concentration of Haemoglobin (Hb) in iron deficient, non-anaemic individuals following total knee or hip arthroplasty. A treatment group of 83 non-anaemic iron deficient individuals scheduled for arthroplasty were administered a 1000mg FC infusion over 15 minutes 4 weeks prior to surgery. In the control group (n=62) FC was not administered preoperatively. No individual from either group was given any iron supplement following the pre-operative visit. Blood tests were performed and analysed 4-weeks before surgery, on admission, and then 2-days, 4-days and 4-weeks postoperatively. Number of blood transfusions performed and adverse events were recorded. Hb concentration did not change substantially after iron supplementation prior to surgery. No difference in the number of blood transfusions was observed. In the treatment, group postoperative Hb concentration recovered significantly more quickly compared to control (p=0.0047). No adverse event was reported. The administration of FC in non-anaemic iron deficient individuals quickens the restoration of Hb concentration following THA or TKA procedures.

Orthopedic hip and knee replacements are associated with considerable blood loss and they may expose the patients to the effects of postoperative anaemia and allogenic blood transfusion, that could negatively impact functional outcomes (1). Preoperative anaemia is an independent risk factor for increased postoperative complications and several

expert groups recommend its treatment before elective surgery as a good clinical practice (2, 3).

In recent years, the Patient Blood Management (PBM) guidelines (4) also highlighted the importance of treating non-anaemic iron deficient patients. Iron deficiency, in fact, is clinically relevant and could favour post-operative anaemia (5, 6). Although the

Keywords: blood management; ferric carboxymaltose; arthroplasty; iron deficiency; transfusions.

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efficacy of treating anaemia with iron infusion before elective surgery has been widely studied, the literature offers few data about the usefulness of treating iron deficient non-anaemic patients before elective surgery (7). Previous studies have shown that patients with iron deficiency without anaemia undergoing cardiac surgery received more RBC transfusion than patients with iron store within range (8).

In a study by Spahn et al. it was demonstrated that patients with iron deficiency treated with ferric carboxymaltose infusion the day before surgery did not benefit from blood transfusions' reduction, but had quicker restoration of Hb level after surgery (9). Multiple randomized controlled trials (RCTs) have been performed on the effectiveness of FC on replenishing iron stores in iron deficient individuals. Its effectiveness in iron deficient individuals (with or without anaemia) affected by chronic heart failure, chronic kidney disease, inflammatory bowel disease, cancer/chemotherapy, or gynaecological/obstetric diseases has been showed (10, 11).

Based on these premises, pre-operative intravenous (IV) iron administration could influence the recovery of Hb concentration following THA or TKA procedures in non-anaemic, iron deficient individuals. The iron formulation selected for the present study was ferric carboxymaltose (FC): it is an effective and well-tolerated treatment for rapidly replenishing iron stores in different types of patients, including those affected by chronic gastrointestinal inflammatory conditions, thus showing an advantage compared to orally administered iron supplements, due to the fact that inflammation inhibits iron uptake from the gut via a hepcidin induced mechanism (12).

Furthermore, FC can be administered to patients in higher dosages in a single infusion (1000 mg over 15 minutes) (13). FC has a structure characterized by an iron core tightly bound to a matrix. Following administration, the product is rapidly taken up by the cells of the reticulo-endothelial system (RES), particularly by the liver and spleen, where the iron component is split from its matrix. Here the iron is immediately bound and stored, mainly under the form of ferritin. This process enables its slow release via iron-binding proteins, and avoids the potential toxicity associated to labile iron (13, 14).

The stable chemical structure of FC results in a low immunogenic potential and toxicity, allowing it to be administered in high doses (13, 14). These beneficial features of FC collectively have a positive economic impact on iron-deficiency anaemia treatment, as shown by a German model which estimated a reduction of treatment cost by €786 per case when using FC compared to standard care (15).

The aim of this retrospective study was 1) to evaluate the safety and effectiveness of intravenous FC supplementation, administered 4 weeks prior to surgery, on improving the postoperative Hb concentration of non-anaemic, iron deficient patients who underwent hip or knee arthroplasty, and 2) to compare the outcomes of the aforementioned treatment group to a control group of similar patients who did not received iron supplementation.

MATERIALS AND METHODS

Ethical Considerations

This present retrospective study was submitted and accepted by our institution's Ethical Review Board and complies with all aspects of good clinical practice and the principles of the Helsinki declaration. All patients included in this study approved and signed a consent form allowing the use of their data for research purposes. The data were collected in a database, which was anonymized, and analysed by an independent statistician.

PATIENT SELECTION

This retrospective cohort study analysed two groups of iron deficient, non-anaemic individuals: a treatment group, where patients received a single dose of intravenous FC supplementation 4 weeks prior to surgery, and a control group where patients did not receive any iron supplementation before surgery. The FC group and the control group were composed of 83 and 62 individuals respectively, all of whom adhered to the following inclusion and exclusion criteria:

Inclusion criteria:

Individuals aged 35-80 years old, non-anaemic males with a Hb concentration ≥ 13 g/dL and ≤ 14 g/dL or non-anaemic females with a Hb concentration ≥ 12 g/dL and $\leq$

14 g/dL, with an American Society of Anaesthesiologists (ASA) classification of I, II, or III, displaying iron deficiency defined as a serum ferritin concentration <100 µg/L, in accordance with the international consensus statement on the perioperative management of anaemia and iron deficiency (16), and displaying normal CRP values.

Exclusion criteria:

Anaemic patients; individuals affected by end-stage renal disease or hepatic insufficiency; affected by or carriers of genetic hematologic diseases; undergoing orthopaedic surgery due to septic issues; previously treated with anticoagulant therapy (aside from acetylsalicylic acid), who were administered other types of iron supplementation different from intravenous FC prior to surgery or throughout the perioperative period.

The patients recruited in the control group were those who, despite our institution's preoperative protocol, did not or could not be administered i.v. FC due to following reasons: 1) known allergy or intolerance to FC or other previously administered iron supplements (n=20); 2) refusal of undergoing i.v. FC therapy (n=15); 3) other causes (n=27). All subjects underwent surgery (total hip or total knee arthroplasty) in our Institution between February 2016 and July 2017.

Table I: *Demographic data, thromboprophylactic status and type of medications administered for both the treatment (FC) and control groups.*

Inclusion/exclusion criteria	Age between 35-80 y/o Males (Hb ≥ 13 g/dL and ≤14 g/dL); Females (Hb ≥ 12 g/dL and ≤14 g/dL) Ferritin <100µg/L PCR <0,5 mg/L	Age between 35-80 y/o Males (Hb ≥ 13 g/dL and ≤14 g/dL); Females (Hb ≥ 12 g/dL and ≤14 g/dL) Ferritin <100µg/L PCR <0,5 mg/L
Patient groups/parameters	1000mg IV iron supplementation	No iron supplementation
Patients n	83	62
Age, year (mean ± SD)	67.6 ± 9.5	66.0 ± 10.9
Sex (n, M/F)	8/75	8/53
Surgical Procedure (THA, TKA)	THA: 50 TKA: 33	THA: 38 TKA: 24
ASA classification	16 pts. I 56 pts. II 11 pts. III	11 pts. I 42 pts. II 9 pts. III
	Medications	
Aspirin therapy	11	20
VTE prevention medication	LMWH: 19 FONDAPARINUX: 4 RIVAROXABAN: 59 WARFARIN: 1	LMWH: 8 FONDAPARINUX: 2 RIVAROXABAN: 52 WARFARIN: 0

Perioperative treatment and related procedures

Four weeks prior to surgery, all patients were managed according to a standard pre-operative care, which includes a first patient visit and blood tests. Following determination of serum ferritin levels and Hb, the FC group received (the same day) a single 1000mg FC infusion. No other kind of iron supplementation was administered during the perioperative period. On the day of surgery, the individuals underwent primary hip or knee arthroplasty. The surgical procedures were performed following a tissue sparing surgical technique (17). All patients were maintained under spinal anaesthesia throughout the surgical operation. During each procedure, the blood saving techniques described by our PBM institution's protocols were strictly adhered.

In compliance with PBM guidelines (4) and our institution's protocols, blood transfusions were only performed when necessary, which was defined as Hb levels dropping below 7.5-8 g/dL for healthy individuals, or below 9-10 g/dL in patients affected by cardiovascular comorbidities or renal issues, whose condition may have worsened substantially due to anaemia. Patients who regularly took acetylsalicylic acid for their comorbidities, continued this thromboprophylactic treatment up until the day of surgery, and then restarted the treatment course the day after the operation.

Following the standard prophylaxis guidelines for venous thromboembolism in total hip and total knee arthroplasty (18), after surgery anti-coagulation medication was administered (either low-molecular-weight-heparin, fondaparinux or oral anticoagulant therapy) according to the individual clinical situation (i.e. allergy, contra-indication, surgeon's choice, etc; Table I).

Blood tests (Hb concentration, RBC count, WBC count, PLT count) were performed again on the day of admission (before the procedure), 2 days after surgery, at the discharge (usually 4 days after surgery) and 4 weeks postoperatively. All measurements analysed in the present study were performed in the same hospital laboratory. The data specifically considered for the purpose of the present study were: pre and post-operative Hb levels, WBC levels, RBC levels, PLT levels, units of RBCs transfused, length of hospital stay (LOS).

Statistical analysis

Data were described as mean and standard deviation. Differences between groups were explored

with Pearson's Chi square test or Fisher's exact test for categorical variables, or with t-student or Mann Whitney test for continuous variables, as appropriate. Intragroup variations throughout time for each group were evaluated with repeated measure ANOVA. Intergroup differences at the various time-points were evaluated using the paired t-student or Wilcoxon test, as appropriate. A p-value under 0.05 was considered significant. All analyses were made with Stata (15).

RESULTS

Patient Demographics

The FC group was composed of 8 males and 75 females, with an average age of 67.6 ± 9.5 years old. The control group was composed of 9 males and 53 females, with an average age of 66.0 ± 10.9 years old. The demographic data for both study groups were summarised in Table I.

Safety

At the end of the study, no individual from either group suffered any severe adverse event related

to the surgical procedure. Furthermore, of the 82 individuals in the FC group, no one exhibited adverse reactions (including anaphylactoid reactions, urticaria, headaches, or nausea) related to the use of FC. Patients were discharged on the fourth day following surgery. No other complication, including cases of deep vein thrombosis or embolism, occurred throughout the duration of the study.

Blood loss & Haemoglobin concentration

Four weeks before surgery, the average Hb concentration of the control group was slightly higher than that of the FC group, with respective average values of 13.5 ± 0.7 g/dL and 13.0 ± 0.7 g/dL. On the day of surgery, at admission, the average Hb concentration of both groups remained largely the same (13.3 ± 0.8 g/dl in the FC group and 13.2 ± 0.8 g/dl in the control group). Two days following surgery the Hb concentration of both groups was observed to drop to average values of 9.9 ± 1.2 g/dL for the individuals who were administered FC and of 10.6 ± 2.1 g/dL for individuals who did not take any iron supplement ($p=n.s.$).



Fig. 1: Trend of Hb over time in both treatment groups (T0=screening visit; T1=admission; T2=day 2 post-op; T3=day 4 post op; T4=4 weeks)

In the FC group, these values were followed by a small increase 4 days following surgery (10.1 ± 1.0 g/dL; $p=n.s.$), and a more substantial, significant increase was seen at 4 weeks postoperatively (11.9 ± 1.3 g/dL; $p<0.0001$). In the control group, average Hb concentration did not change significantly at day 4 following surgery (10.8 ± 1.0 g/dL; $p=n.s.$) but, similarly to the FC group, increased significantly at 4 weeks from the operation (11.9 ± 1.4 g/dL; $p<0.0001$; Fig. 1). The increase in Hb concentration between the 4-days and 4-weeks postoperative time-points was significantly different between the two groups, with a statistically higher increase in the FC group compared to the control group ($p\text{-value}=0.0047$; Fig. 2). Only 1 individual in both the FC and the control group required a postoperative blood transfusion.

White blood cell count

Four weeks before surgery, the average WBC count was of $7.05 \pm 2.74 \times 10^9$ cells/L for the FC group and of $6.37 \pm 1.74 \times 10^9$ cells/L for the control group. At admission, the average WBC count of both groups

remained unchanged ($6.6 \pm 1.8 \times 10^9$ cells/L for the FC group and $6.5 \pm 1.7 \times 10^9$ cells/L for the control group). Two days following surgery, average WBC count values rose significantly ($p<0.0001$) in both the FC group and the control group, with average values of $7.22 \pm 1.74 \times 10^9$ cells/L and $9.35 \pm 3.67 \times 10^9$ cells/L respectively. This increase was observed to be significantly greater in the control group compared to the FC group, with a $p\text{-value}=0.0013$. This trend decreased significantly for both groups (close to preoperative average value), both at the 4-day and 4-week evaluations, with values of 6.60 ± 1.69 and $6.10 \pm 2.04 \times 10^9$ cells/L for the FC group, and 7.64 ± 3.50 and $6.97 \pm 2.69 \times 10^9$ cells/L for the control group (Table II).

Red blood cell count

The variation in RBC count over time was similar to that of Hb concentration. 4 weeks prior to surgery the two groups had very similar average values of $4.71 \pm 0.70 \times 10^{12}$ cells/L for the FC group and $4.69 \pm 0.52 \times 10^{12}$ cells/L for the control group.

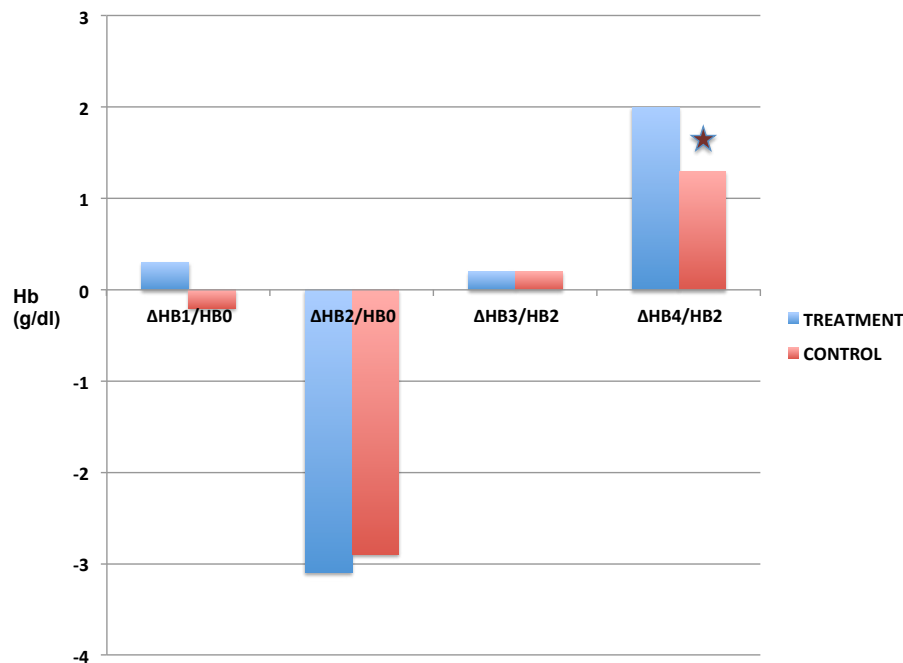


Fig. 2: Variation of HB in both treatment groups over time. A significant difference was detected in favour of FC group at 4 weeks after surgery ($p=0.0047$, see asterisk). HB0= haemoglobin at screening visit ; HB1=haemoglobin at the admission day; HB2=haemoglobin at day 2 after surgery; HB3= haemoglobin at day 4 after surgery; HB4= haemoglobin at 4 weeks after surgery.

Table II: Clinical parameters related to iron status for both groups at the various time-points.

	FC GROUP	CONTROL
Patients n (%)	83	62
Ferritin, mcg/dL (mean ± SD)	51.28 ± 27.52	45.67 ± 25.80
Serum Iron, mcg/dL (mean ± SD)	72.60 ± 28.57	83.43 ± 26.37
Hb 4 weeks prior surgery, g / dL (mean ± SD)	13.0 ± 0.69	13.5 ± 0.69
Hb 1 day prior surgery, g / dL (mean ± SD)	13.3 ± 0.83	13.2 ± 0.75
Hb 2 days post-surgery, g/dL (mean ± SD)	9.9 ± 1.17	10.6 ± 2.09
Hb 4 days post-surgery, g/dL (mean ± SD)	10.09 ± 1.04	10.80 ± 1.03
Hb 4 weeks post-surgery, g/dL (mean ± SD)	11.85 ± 1.25	11.97 ± 1.4
RBC 4 weeks prior to surgery, x 10¹² cells/L (mean ± SD)	4.71 ± 0.70	4.69 ± 0.52
RBC 2 days post-surgery, x 10¹² cells/L (mean ± SD)	3.50 ± 0.71	3.67 ± 0.70
RBC 4 days post-surgery, x 10¹² cells/L (mean ± SD)	3.55 ± 0.57	3.74 ± 0.63
RBC 4 weeks post-surgery, x 10¹² cells / L (mean ± SD)	4.95 ± 0.24	4.01 ± 0.61
WBC 4 weeks prior surgery, x10⁹ per liter (mean ± SD)	7.05 ± 2.74	6.37 ± 1.74
WBC 2 days post-surgery, x10⁹ per liter (mean ± SD)	7.22 ± 1.74	9.35 ± 3.67
WBC 4 days post-surgery, x10⁹ per liter (mean ± SD)	6.60 ± 1.69	7.64 ± 3.50
WBC 4 weeks post surgery, x10⁹ per liter (mean ± SD)	6.10 ± 2.04	6.97 ± 2.69
RBC transplants (n)	1	1

Similarly to Hb concentration and WBC count, average RBC count values did not differ substantially on admission in either group ($4.52 \pm 0.56 \times 10^{12}$ cells/L for the FC group and $4.54 \pm 0.73 \times 10^{12}$ cells /L for the control group). On the second day following surgery, average values dropped significantly to ($3.5 \pm 0.7 \times 10^{12}$ cells/L and $67 \pm 0.7 \times 10^{12}$ cells/L) for the FC and control group respectively (p -value < 0.0001 vs 4-weeks prior to surgery). On day 4 following surgery, average values saw marginal differences in both the FC group ($3.55 \pm 0.57 \times 10^{12}$ cells/L; p -value = n.s.) and control group ($3.74 \pm 0.63 \times 10^{12}$ cells/L; p = n.s.) Four weeks postoperatively, both groups displayed significant increases ($p < 0.0001$), with the FC and primadi control groups having average values of $4.95 \pm 0.24 \times 10^{12}$ cells/L and $4.01 \pm 0.61 \times 10^{12}$ cells/L respectively (Table II).

Platelet count

Four weeks prior to surgery the average PLT count was of $239.72 \pm 71.81 \times 10^3/\mu\text{L}$ and $259.90 \pm 53.49 \times 10^3/\mu\text{L}$ for the FC group and the control group respectively (p = n.s.). On admission the average values of either group did not differ compared to 4 weeks prior ($233.35 \pm 124.42 \times 10^3/\mu\text{L}$ for the FC group and $235.48 \times 10^3/\mu\text{L}$ for the control group; p = n.s.). On the second day following surgery, the average PLT count dropped significantly to $179.6 \pm 83.0 \times 10^3/\mu\text{L}$ and $206.4 \pm 44.8 \times 10^3/\mu\text{L}$ for the FC group and the control group, respectively. On the fourth post-operative day and four weeks following surgery, an increase in average PLT count was observed in both groups, with values returning to those seen preoperatively ($284.68 \pm 111.63 \times 10^3/\mu\text{L}$ for the FC group and $258.46 \pm 99.50 \times 10^3/\mu\text{L}$ for the control group, without significant inter-group difference.

DISCUSSION

The main finding of the present study is that in the group of non-anaemic, iron deficient patients, the pre-op administration of intra-venous FC resulted in a significantly higher recovery of Hb from the discharge of the patients to the 4 weeks evaluation compared to the control group.

In this retrospective study, the effect of FC on the perioperative outcomes of non-anaemic but iron deficient individuals were evaluated on 83 patients, and compared to a control group of 62 patients. FC proved to be an extremely safe product, with no patients exhibiting any hypersensitivity or anaphylactoid reactions or other side effects directly related to the supplement. Regarding postoperative anaemia prevention, the FC treatment did not improve the Hb before surgery.

Nevertheless, the significant difference in Hb concentration variation between the two groups over time, suggests that FC does indeed influence postoperative recovery. Whilst the control group was seen to have similar Hb levels up to 4 days following surgery and the general trend in Hb was basically the same in the two groups, a significant difference in favour of FC group was observed from discharge to the 4 weeks evaluation, when a faster Hb recovery was documented, thus suggesting a potential “delayed” effect of FC supplementation that warrants further evaluation at longer follow-up.

In fact, despite an increase in Hb values was observed from discharge to 4 weeks after surgery both in control and FC group, only in the latter this increase was statistically significant. It suggests that a further beneficial effect could be achieved in terms of HB recovery, especially considering that, one month after surgery the Hb values were still considerably lower than those before surgery.

It is also important to note that no difference in the number of blood transfusions between the groups occurred: this finding was largely expected since non-anaemic patients have lower risks of post-op transfusion. Aside from Hb concentration, a significantly lower increase in average WBC count was observed in the FC group 2 days post-procedure compared to the control group. Whilst this may

allude to FC having a substantial impact on WBC count, the values for both groups were still in the expected range for postoperative leucocytosis (19), thus weakening any such hypothesis.

Nevertheless, further studies on whether FC has an effect on the postoperative immune response may be of interest. Indeed, recent researches have shown that in mice, iron has an immune-modulatory effect by altering macrophage functional phenotype (20). Specifically, in iron-rich environments these cells, which ordinarily play an important role in iron homeostasis by degrading and recycling senile erythrocytes, were seen to increase the expression of proteins *Arg 1* and *Yml*, markers of the anti-inflammatory M2 macrophage phenotype. Conversely, a low IL-12/IL-10 cytokine ratio, in combination with decreased CD86 and MHC-II expressing cells, and reduced *iNOS* expression, were linked to a down-regulation of M1 pro-inflammatory macrophages.

Furthermore, iron-rich diets and/or supplementation maintained these anti-inflammatory effects even under lipopolysaccharide (LPS) induced inflammatory conditions, both *in vitro* and *in vivo*. Following this rationale, the administration of FC might have established a protective anti-inflammatory environment by stimulating macrophages to polarise to an M2 phenotype, therefore altering the body's natural inflammatory response to surgical stress. These immune-modulatory actions may therefore suggest that pre-emptive administration of FC might have a positive impact on improving PBM procedures in other ways than quickening recovery of Hb concentration.

However, the present data are highly preliminary, and more focused research on the matter is required. Despite the positive results reported above, it is important to address the limitations associated to this study: first, its retrospective design associated with the short follow-up evaluation (4 weeks after surgery), which is actually the main limiting factor considering the results obtained in the present evaluation, that need to be confirmed at longer evaluation. Unfortunately, patients' dispersion after the first month was pretty high due to the fact that many of them continued their clinical follow-up

in an outpatient setting and received blood tests in other laboratories and at variable time-points, thus preventing us from further, sounding evaluations.

Both in the FC and control group, a clear “sex” bias may appear to be present, with males only composing 10% and 13% of their respective sample population. This disparity however does reflect the epidemiology of iron-deficiency seen in the general population (21). Although all viable patients were included in this study, the effect of FC on non-anaemic iron deficient males should be further explored in the future. To resolve these issues in future research, a prospective study with a rigorous methodology, data-gathering process, and a target number of male and female patients, of varying ages, would be able to circumvent such limitations and provide a more sounding evaluation.

Currently, pre-op. IV iron administration might be an effective treatment for iron deficient patients, especially for those affected by comorbidities such as chronic heart failure, chronic kidney disease, and inflammatory bowel disease (22, 23). In the present study, pre-op intra-venous FC administration in iron deficient non-anaemic patients allowed quicker recovery in Hb concentration at 4 weeks following surgery. Further studies are needed to verify if the positive Hb trend associated to FC administration is also maintained at longer follow-up evaluation. The use of FC might therefore be considered for introduction within PBM guidelines, especially in the setting of fast-track orthopaedic surgery.

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Two-stage total hip arthroplasty for septic arthritis through the minimally invasive direct anterior approach

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The use of minimally invasive direct anterior approach to perform total hip arthroplasty is gaining increasing popularity for its short-term advantages, compared to other approaches. Nevertheless, its use in hip revision surgery has been criticized. We report here the first case of hip septic arthritis treated with two-stage THA through this tissue-sparing approach, with good implant positioning and functional results.

Total hip arthroplasty (THA), the “surgery of the century”, is one of the most successful procedures in orthopaedics (1, 2). Over the past decade, the orthopaedic literature focused on reducing the invasiveness of THA. As a consequence, the minimally invasive Direct Anterior Approach (DAA) has gained popularity (3, 4). This approach is associated with less soft tissue trauma than others, because the arthroplasty is performed through intermuscular and internervous planes; for this reason, dynamic hip stability is improved and the risk of hip dislocation after surgery is decreased (5). Furthermore, the DAA preserves the hip external rotator muscles, limiting postoperative limping and providing faster functional recovery and reduced dislocation rates (6, 7). Nevertheless, the DAA has been judged less suitable for hip revision surgery, compared to other hip approaches (8). To our knowledge, no articles described a two-stage total hip arthroplasty for septic arthritis through DAA. We report here the first case.

Case presentation

A 64-year old female was admitted for strong right hip pain. A few days later she had a worsening of her neurological status and started an empiric therapy with linezolid and meropenem for possible meningitis. Lumbar puncture showed Gram positive cocci after staining, but no specific pathogen was identified at the cultural exam. As soon as her conditions improved, she was discharged after a month with moxifloxacin as antibiotic therapy for 3 weeks. A month later, she complained low back pain with gait impairment. After a neurosurgical consult and a lumbar MRI, a spondylodiscitis at D12-L1 level was diagnosed. The vertebral biopsy, performed after antibiotic withdrawal, showed negative results for microscopic, histologic and cultural tests. A new antibiotic therapy with ciprofloxacin alone and then in combination with vancomycin was introduced, but the patient still complained low back pain and right hip pain. After a new worsening of inflammatory indices in the following months, she moved to

Key words: hip septic arthritis; two-stage THA; two-stage THR; implant coatings; direct anterior approach.

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another hospital, where she was treated for 1 month with meropenem and vancomycin for osteomyelitis D12-L1. PET and MRI of lumbar spine and pelvis showed the healing of the spondylodiscitis, but also an involvement of the right hip joint. After the orthopaedic consult, a diagnosis of right hip septic arthritis of unknown origin was made (Fig. 1). Therefore, staged total hip arthroplasty through DAA was planned.

The patient underwent the first surgery, with local debridement and implant of an antibiotic-loaded hip spacer (Spacer G, 46 mm, short stem, Tecres, Tecres SpA, Sommacampagna, VR, Italy) (Fig. 2).

Immediate postoperative physio-kinesiotherapy was started, together with antibiotic therapy with ceftriaxone for 5 weeks, and after 5 days the patient was discharged. After two months, the patient underwent the second surgical stage, during which the spacer was removed and THA was implanted (Mpace cup 48 mm, polyethylene liner, Amistem-H standard Stem size 2, ceramic head 32 mm size S, Medacta, Medacta International, Castel San Pietro, Switzerland). The implant was covered with antibacterial hydrogel DAC (Defensive Antibacterial Coating, Novagenit Srl, Mezzolombardo, Trento, Italy) added with Meropenem 1g and Vancomycin 1g (Fig. 3). The THA was performed using the Medacta Leg positioner, an operatory table with a leg holder, specifically introduced for DAA.

Both surgical stages were performed through minimally invasive DAA. Tissue cultures collected



Fig. 1. Preoperative x-ray showing the septic arthritis of the right hip.



Fig. 2. First stage postoperative x-rays: antibiotic-loaded cement spacer.

during surgeries resulted negative. The day after the last surgery the patient was able to walk with two crutches and weight-bearing as tolerated, with a good pain control. In the following days she became more confident in walking and going up and downstairs. After 5 days she was discharged without antibiotic therapy and with normalization of CRP and inflammatory indices at blood exams. At last follow-up after 3 months, the patient fully recovered, with normal hip range of motion, and she can walk without crutches, limping or pain.

DISCUSSION

The demand of THA, especially through minimally invasive approaches, is incessantly increasing because they ensure to patients quick pain relief and restored joint functionality, allowing a rapid return to activity and therefore a better quality of life (9, 10). Compared to other approaches to the hip, DAA is associated with less blood loss and faster recovery (7, 9). Nevertheless, the DAA is not yet a well-established approach for hip revision surgery because of the suboptimal joint exposure. Moreover, surgeons prefer approaches that are easier to be extended proximally and distally when intraoperative complications occur. In spite of the amount of literature regarding DAA for THA as a routine



Fig. 3. *Second stage postoperative x-rays: total hip arthroplasty performed through minimally invasive direct anterior approach to the hip, with good implant positioning.*

approach to the hip, only few articles have described hip revision surgery through DAA, and there are no papers describing a two-stage treatment for hip septic arthritis through this minimally invasive approach.

Bouveau et al, described the use of DAA in one-stage revision metal-on-metal hip resurfacing arthroplasties, to limit soft tissue trauma and obtain a fast function recovery thanks to the optimal post-operative hip stability (11). In their experience, 15 patients underwent revision through DAA, reporting outcomes as very good in 5 cases, good in 8 cases, and poor in 2 cases. No hip required a re-revision in the 7-year follow up, so they concluded that DAA for this kind of revisions could be a successful approach.

Horsthemke et al., presented the results of one-stage aseptic cup revision using DAA, performed in 48 patients, reporting DAA as a good option for hip revision, allowing for good cup positioning and a lower risk of complications (most of all, dislocations) (12).

In our experience, the exposure of the acetabulum and femur was crucial for a correct component positioning. This was reached thanks to a specific instrumentation, a correct positioning of the patient and a well-trained team.

The choice of a two-stage treatment, as well as the decision of using the DAC as antibacterial implant coating, were precautional measures, due to the

unsuccessful isolation of the causative pathogen. Our report is far from presenting DAA as a gold standard in case of two-stage hip revisions. Nevertheless, staged hip revision through DAA was, in our case, a safe and successful procedure, with fast patient recovery, reduced length of stay and complete infection eradication at last follow up. If this result is confirmed by future bigger studies, in the following years the DAA may become a replicable and reliable procedure for hip revisions too, with better clinical results.

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Effects of NGF and BDNF on chondrocytes: a microarray analysis

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Osteoarthritis (OA) represents an inflammation-driven injury of articular tissues, progressively leading to structural and functional joint impairment. The main symptom of OA is pain. Although it has been well established that OA represents a whole joint disease, the source of pain remains to be clarified. Nowadays, it has been well established that neurotrophines expression is evident in joints affected by OA. In addition, elevated NGF levels are found in the synovial fluid of patients with inflammatory or degenerative rheumatic diseases, including OA, rheumatoid arthritis and spondylarthritis. Growing evidences indicate that blocking NGF signaling using an anti NGF agent (i.e. tanezumab) provides effective pain relief. This study analyzed the effects of NGF and BDNF on cultured human chondrocytes by evaluating and their effects on chondrogenesis, chondrocyte differentiation and cartilage degeneration through a microarray analysis. The whole transcriptome analysis performed in this study highlighted how NGF and BDNF could be able to induce a proinflammatory response in human chondrocytes. Moreover, NGF and BDNF treatments seems to be able to induce the activation of several genes involved in the OA pathogenesis as IL17AR, HLA-DRB1, GDF-15, NR1D1, MCF2L and TGF-Beta.

Osteoarthritis (OA) represents a paradigm example of inflammation-driven injury of osteoarticular tissues, progressively leading to structural and functional joint impairment. OA is the most common chronic degenerative joint disease both in humans. It affects up to 15% of the adult population at some point in their life through pain and decreased functionality (1). The main symptom of OA is pain. Although it has been well established that OA represents a whole joint disease, the source of pain remains to be clarified. Pain is usually linked to synovial inflammation (2). Inflammatory mediators are produced by the synovial fibroblasts and chondrocytes of osteoarthritic patients.

Currently, there is no effective therapy able to reverse the progressive nature of OA. However, clinical practice points out that several patients suffer, without any clinical evidences of synovitis, indicating an alternative source of pain (3). Targeting acute inflammation in joint tissues affected by OA represents a relevant challenge that may prevent tissue loss, by regulating the acute/chronic inflammation shift, impeding unfavorable fibrogenic processes, hence ultimately stimulating self-healing and functional regeneration.

Nowadays, it has been well established that Nerve Growth Factor (NGF) expression is evident in joints affected by OA (4). In addition, elevated

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NGF levels are found in the synovial fluid of patients with inflammatory or degenerative rheumatic diseases, including OA, rheumatoid arthritis and spondylarthritis (5). Furthermore, the increase of β -NGF has been recognized in pain modulation, and several experimental and clinical studies evidenced a role for β -NGF as one of the regulators of pain processing and sensitivity (6). Indeed, growing evidences indicate that blocking NGF signaling using an anti NGF agent (i.e. tanezumab) provides effective pain relief (7).

Similarly, the neurotrophin brain-derived neurotrophic factor (BDNF) is reported to be involved in the joint inflammatory process, and its production is increased in response to pro-inflammatory cytokines. It has been demonstrated that plasma BDNF was significantly increased in patients with knee OA compared with healthy controls (8). Recent clinical evidence also supports a peripheral role of BDNF in OA, with synovial expression of high-affinity receptor tropomyosin receptor kinase B (TrkB) associated with higher OA pain (9).

In this study, we postulated that increased levels of BDNF and NGF in OA synovial fluid might be associated with modification of intracellular pathways of articular chondrocytes and pain perception in knee OA patients. Therefore, the objective of this study was to analyze the role of NGF and BDNF in the inflammatory process of OA and their effects on chondrogenesis, chondrocyte differentiation, cartilage degeneration and pain.

MATERIALS AND METHODS

Chondrocyte cultures

Healthy cartilage was harvested from the medial surface of the lateral condyle of the knee in 3 subjects (1 male, 2 females) of similar age (35 ± 3 years), undergoing arthroscopic procedures for acute injury. None had OA, rheumatic, autoimmune, or metabolic disease. All participants provided a written informed consent. Cartilage samples were minced into small pieces under aseptic conditions and washed in Dulbecco's Modified Eagle's Medium/Ham's Nutrient Mixture F12 (DMEM/F12) containing 1% antibiotics. After enzymatic digestion

through Collagenases type I A (Sigma Aldrich, St. Louis, MO, USA) at 0.25% in DMEM/F12, cells were passed through a 70 μ m nylon filter (BD Falcon, Bedford, MA, USA), centrifuged at 1200 rpm for 4 minutes, suspended in DMEM/F12, seeded in 75 cm² flasks and allowed to expand for three weeks as described (4). Cells were used at a third passage at a concentration of 5000 cells/ml.

Cultures were subdivided into three groups: two treatments groups, receiving respectively 200 ng/ml of NGF-Beta (Immunotools, Friesoythe Germany) (group A) or 200 ng/ml of BDNF (Immunotools, Friesoythe Germany) (group B) and an untreated, control group (group C). The medium containing BDNF and NGF-Beta, alternatively, were replaced twice weekly. The effects of both BDNF and NGF exposure were evaluated in chondrocytes monolayers after 14 days.

Cell phenotype

Cells were seeded in chamber slides at a concentration of 5000 cells/ml. At 14 days for histochemical analysis, cells were stained for 30 min with Alcian blue pH 1.0 to evaluate cartilage glycosaminoglycans production. Cells for immunohistochemistry were incubated with anti S-100 polyclonal antibody. The reaction was detected using the Dako LSAB + System-HRP kit according to the manufacturer's instructions. The percentage of stained cells was assessed by computerized morphometric analysis using Leica Application Suite 4.1 by examining five random field/culture.

RNA isolation

Total RNA was extracted from control and treated cells using Trizol reagent (Life Technologies, Paisley, Scotland, UK) and further on-column purified using RNeasy Mini Kit (Qiagen Inc., Valencia, CA, USA), which allows genomic DNA-free RNA isolation, according to the manufacturer's instructions. Three independent experiments were performed for each group. Total RNA was quantified using a UV spectrophotometer, whereas quality and integrity were assessed by Agilent 2100 Bioanalyzer (Agilent Technologies, Palo Alto, CA, USA) according to the manufacturer's instructions, to rule out DNA contamination and RNA breakdown in the samples.

Microarray analysis

Total RNA was used to create biotin labelled library to

be hybridized on GeneChip® Human Transcriptome Array 2.0 (Affymetrix, CA, USA), which contained probe sets for over 285,000 full-length transcripts (both coding and non-coding transcripts). The samples preparation for microarray hybridization was carried out as described (10).

Briefly, double-stranded cDNA (ds-cDNA) was synthesized from less than 1 micrograms of total RNA and primed with a poly-(dT)-T7 oligonucleotide. The cDNA was used for in vitro transcription reaction in the presence of T7 RNA polymerase during 16 h at 40°C; resulting antisense RNA (cRNA) was purified and then used for single-strand cDNA (ss-cDNA) synthesis.

Purified ss-cDNA was fragmented (35–200 nucleotides), labelled with Biotin-linked DNA Labelling Reagent and then hybridized, together with hybridization controls, to the microarrays for 16 h at 45°C. Using the GeneChip Fluidics Station 450 (Affymetrix, CA, USA), the biotin-labelled ss-DNA was revealed by successive reactions with streptavidin R-phycoerythrin conjugate, biotinylated anti-streptavidin antibody and streptavidin R-phycoerythrin conjugate. The arrays were finally scanned in an Affymetrix GeneChip® Scanner 3000 7G (Affymetrix, CA, USA).

Gene Expression Data Analysis

The CEL files, which store raw data collected from Affymetrix scanner and result from the hybridization, were analysed using Expression Console software (Affymetrix, CA, USA). Raw data were normalized using gc RMA methods, followed by an additional ‘per gene normalization’ procedure, in which the data for a given gene are normalized to the median expression level of that gene across all samples (11). A data table (rma), together with the relative CEL and relevant information about the experiment, is available at [http:// www.ncbi.nlm.nih.gov/ geo/](http://www.ncbi.nlm.nih.gov/geo/) under accession GSE#####

Gene expression values were then analyzed using the Transcriptome Analysis Console (Affymetrix® Technologies). Differentially expressed genes were identified using unpaired one-way ANOVA and only the genes that match our criteria (p -value < 0.005 and fold change > 1.2) were selected in this study. The following gene list was annotated to the Gene Ontology (GO) database (www.geneontology.org), in order to assigning a category to each gene in the list, according to three defined “ontologies” (terms representing gene properties

and function): cellular component, biological process and molecular function.

RT-PCR analysis

In order to confirm Microarray analysis results, the expression of seven marker genes associated to chondrocyte differentiation, degeneration and articular pain *IL17AR*, *HLA-DRB1*, *GDF-15*, *NR1D1*, *MCF2L*, *TGF-Beta* was determined by real-time PCR (RT-PCR) at 14 days after culture in the three groups of cells. cDNA was amplified by RT-PCR using Power SYBR® Green PCR master mix (Applied Biosystems). Gene expression levels were normalized to the expression of the housekeeping gene RPL13 and are presented as fold changes relative to expression in control cells. Results are the mean of 5 observations selected randomly. Quantification was done with the delta/delta calculation method using 7500 Software v2.0.5 (Applied Biosystems).

Statistical Analysis

A non-parametric approach was used, as variable were not normally distributed. Statistical significance was set at a level of probability of 0.05. Changes in gene expression are given as fold change; > 1.2-fold change expression for upregulation and <1.3-fold change for downregulation were considered significant (p <0.05).

RESULTS

IL17AR, *HLA-DRB1*, *GDF-15*, *NR1D1*, *MCF2L*, *TGF-Beta* expression data through microarray analysis are reported in Table I.

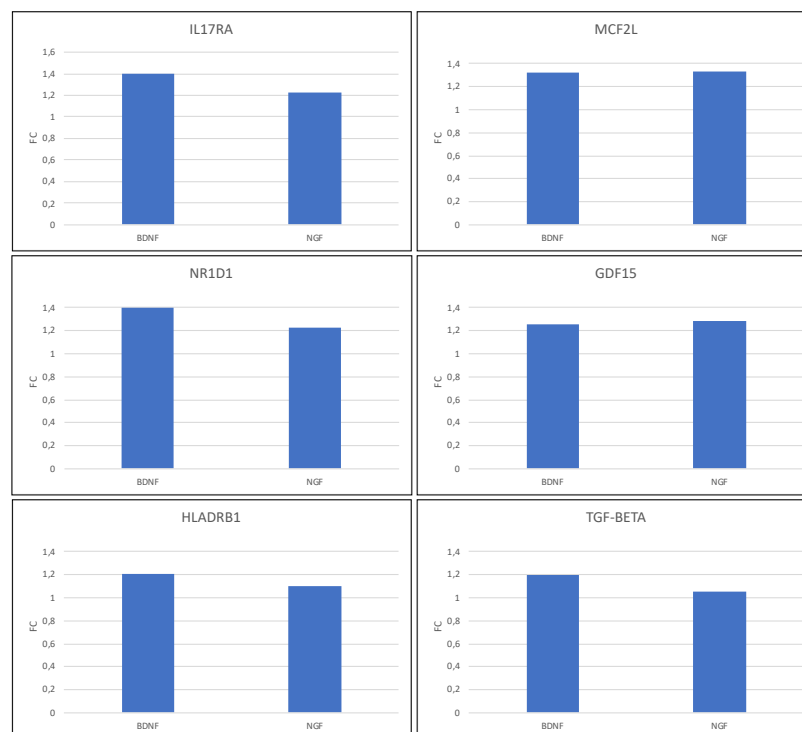
These data were confirmed through RT-PCR data as reported by Fig. 1.

DISCUSSION

Although Osteoarthritis (OA) has generally been proposed as a degenerative disease, recent work suggested that low-grade inflammatory processes could promote disease symptoms and accelerate disease progression. Some of the cartilage matrix catabolic products probably activate innate immune cells to release inflammatory cytokines, which in turn promote cartilage damage progression by altering chondrocyte function (12). The interplay

Table I. Genes upregulated in cells treated with NGF and BDNF showing a statistical FC increase.

GENE	NGF TREATMENT		BDNF TREATMENT	
	FC	P-value	FC	P-value
IL17RA	1.33	0.008	1.31	0.009
HLA-DRB1	1.37	0.003	1.28	0.04
<i>GDF-15</i>	1.3	0.04	1.3	0.05
<i>NR1D1</i>	1.25	0.05	1.31	0.003
<i>MCF2L</i>	1.21	0.03	1.21	0.04
<i>TGFB1</i>	1.24	0.02	1.34	0.03

**Fig. 1.** Gene expression pattern. Mean gene expression values in NGF and BDNF-treated samples from 3 healthy adult individuals. Changes in gene expression are given as fold change normalized to the expression of the housekeeping gene *RPL13*; >1.5 fold change expression for up regulation were considered significant ($p < 0.05$).

between the immune system and cartilage is not well understood but evidence suggested a contribution of inflammation to joint damage (13). In this context, our study focused on the possible role of NGF and BDNF in the promotion of the inflammatory process occurring in OA patients.

A recent *in vivo* study demonstrated how NGF could contribute to the exacerbation of cartilage

erosion and loss of function in OA mice appearing as an interesting mediator in the pathogenesis of OA (6). On the other hand, overexpression of neurotrophins is known to play a critical role in pathogenesis of chronic pain underlying several disorders, including osteoarthritis (14). The whole transcriptome analysis performed in this study highlighted how NGF and BDNF could be able to induce a proinflammatory

response in human chondrocytes. Moreover, NGF and BDNF treatments seems to be able to induce the activation of several genes involved in the OA pathogenesis. In particular, *IL17RA* (interleukin 17 receptor A, MIM * 605461), *HLA-DRB1* (major histocompatibility complex, class II, DR beta-1, MIM * 142857), *GDF-15* (growth/differentiation factor 15, MIM * 605312), *NR1D1* (nuclear receptors subfamily 1, group D, member 1, MIM * 602408), *MCF2L* (MCF2-like protein, MIM * 609499), *TGFB1*, (transforming growth factor, beta-1, MIM * 190180) result overexpressed from both treatments with neurotrophines. Interestingly, these genes have been reported to be involved in human OA through an analysis of Gene Ontology Resources and Go Annotation (15).

IL-17A is considered as an important proinflammatory cytokine involved in the pathogenesis of arthritic disorders. Indeed, it has been reported that IL-17 is able to induce “*in vitro*” the synthesis of nitric oxide and metalloproteases by chondrocytes and the production of IL-6 and IL-8 by fibroblasts (16). From our results, it has been demonstrated that NGF and BDNF are able to over express *IL-17RA* on chondrocytes making these cells more susceptible to IL-17A present in synovia. We have observed that the activation of human OA chondrocytes with NGF and BDNF can also enhance the expression of *HLA-DRB1*. The protein encoded by this gene belongs to the HLA class II beta.

It has been reported that this allele might be characterized by a five amino acid sequence termed “Shared Epitope” (SE) that is over expressed in rheumatoid arthritis (17). Based on the known role of MHC class II molecules in antigen presentation, the prevailing paradigms postulate that SE might be involved in presentation of arthritogenic self-peptides. On the other hand, SE may act as a ligand that can trigger innate immune signaling considering that it is located near the apex of the helical tri-dimensional structure (18). For these reasons, we speculate that neurotrophins might be able to over express *HLA-DRB1* on articular chondrocytes. In this way, arthritogenic self-peptides (i.e. fragments of collagen) or SE might act as a potential trigger able to initiate and/or continue the inflammatory cascade in osteoarthritis.

GDF-15 was originally identified as a factor secreted by activated macrophages. It is a member of TGF- β superfamily cytokine. It has been established that *GDF-15* is involved in chronic inflammatory pathways in rheumatoid arthritis. *GDF-15* expression is generally low in resting tissues but may increase following an adaptive stress response to diverse cellular stress indicators such as hypoxia, inflammation, and tissue injuries (19). In accordance with these evidences, we speculated that NGF and BDNF might be able to increase the expression of *GDF-15* to make chondrocytes more resilient to OA inflammation. *NR1D1*, also known as Rev-ErbA α , encodes a member of the nuclear receptor family, and is expressed in liver, adipose tissue, and skeletal muscle.

Rev-ErbA α belongs to a subfamily of orphan receptors that are repressors of target gene transcription. It has been reported that *NR1D1* is largely expressed in OA cartilage (20) and its expression is upregulated by IL-1 and proteolytic enzymes and by neurotrophines as reported by our results. Despite, it is still unclear the effect of *NR1D1* upregulation on chondrocytes within the joint, it seems to be able to regulate the expression of MMPs and aggrecanases indirectly. Indeed, it could enhance the expression of them by interfering negatively with the expression or activity of a transcription factor that represses MMP and aggrecanase expression (21).

Based on our study, it seems clear that NGF and BDNF induce an up regulation of *MCF2L* gene. To date, it has been reported that polymorphisms within the genes *GDF5* and *MCF2L*, emerged from genome-wide association scans, are linked to a greater susceptibility of OA. *MCF2L*, is located on chromosome 13 and regulates NGF. Indeed, when people affected by knee osteoarthritis are treated with a humanized monoclonal antibody against NGF, they experience less pain and show improvement in their movement. This suggests that *MCF2L* is involved in the development of osteoarthritis and provides a new focus for future research (22).

Many researchers have demonstrated a role for TGFB-1 in cartilage homeostasis. A strong correlation between lack of TGFB-1 and predisposition to cartilage damage has been shown. At the same time, TGFB-1 seems to be a potent inducer of cartilage

extracellular matrix synthesis (23). From our results, it has been reported that NGF and BDNF might be able to induce an over expression of TGFB-1. We speculate that it might represent an attempt of cartilage to restore the extracellular matrix to limit the progression of OA within the joint.

Despite neurotrophines are most likely associated with the mechanism of joint pain in OA and in the acute stage of joint inflammatory process; our results, clearly established that NGF and BDNF are able to induce an overexpression of genes involved not only in pain, but also in OA physiopathology. Taken together, our results suggest that NGF and BDNF could play a leading role in the onset of the inflammatory process underlying cartilage degeneration within the joint. Surely, further studies are necessary to address the functional role of BDNF and NGF in OA to establish new therapeutic implications.

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Posterior dynamic neutralization and hybrid stabilization in degenerative spine diseases: long-term clinical and radiological outcomes

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Dynamic spinal stabilization aims to reduce some of the problems inherent with traditional fusion. The aim of our study is to analyse clinical and radiological outcomes and to identify the causes of clinical failure in patients who underwent posterior dynamic neutralization or posterior hybrid stabilization because of degenerative lumbar spine diseases. We retrospectively analysed 80 patients at 7.1 years mean follow-up (Range: 5.1 - 8.3 years): 50 were treated with Dynamic Stabilization System (Dynesys) (mean age 47 years old) and 30 with Dynamic Transition Option (mean age 48 years old). We performed clinical pre- and post-operative evaluation using Visual Analogue Scale (VAS), Oswestry Low Back Pain Scale (ODI) and X-rays study. Results: we reported an important reduction of VAS from 7 to 2 (p<.001) and minimal disability in 65% of the patients, moderate disability in 18.2%, severe disability in 12.5% and crippling back pain in 4.3%. X-ray analysis showed a significative decrease of 3.5° with respect to the preoperative values, exactly 2° in neutral position postop, 1.2° in flexion postop and 2.5° in extension postop. Data showed greater reduction of extension than flexion in postoperative period. Dynamic neutralization limits more the extension than flexion. The correct preoperative planning, the careful selection of patients and the meticulous surgical technique are mandatory to avoid clinical failures. It is very important to identify the correct screw positioning and to avoid excessive pre-tensioning of the implant. Posterior dynamic neutralization and hybrid stabilization are valid alternative to spinal fusion in degenerative spine disease.

Dynamic spinal stabilization is a developing technique applied to spinal surgery that aims to reduce some of the unsolved problems inherent with traditional fusion. The spine must combine two contrasting biomechanical parameters: stiffness and elasticity. The instantaneous rotational axis is located in the posterior area of intervertebral disc (9) its dispersion, with the consequent spinal instability, may be caused by discal degeneration.

In 1988 Senegas et al. described the first interspinous device to prevent post-laminectomy instability (15). Traditionally, posterior spinal

column reconstruction has been performed using combinations of rods with different hook/wire/pedicle screw systems for multiple level diseases. With the spread on the market of spinal dynamic stabilization devices, several vertebral surgeons started to propose this surgical technique for symptomatic low-grade degenerative disc disease (DDD). Several biomechanical studies analysed the beneficial effect of this surgical procedure and the conclusion was that elastic stabilization reduce the bordering disc stresses applied during flexion up to 30° (3) (Fig. 1). As consequence of to these good

Key words: Posterior dynamic neutralization; Posterior hybrid stabilization; Degenerative lumbar disease

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results, the use of dynamic neutralization or hybrid stabilization systems (Dynesys/DTO Zimmer Spine, Minneapolis, MN) have spread in different lumbar spine diseases.

The current surgical indications are recurrent disc herniation, Pfirmann 3-4 DDD (Modic 1-2), low-grade lumbar stenosis and degenerative spondylolisthesis Meyerding 1. The Dynesys (Dynamic Stabilization System) consists of titanium (Ti) alloy (Protasul 100) pedicle screws, a polycarbonate urethane spacer (Sulene-PCU) and a polyethylene-terephthalate cord (Sulene-PET). The cord connects the pedicle screws and runs through the hollow core of the PCU spacers between the pedicle screws heads. The PET cord limits flexion, while the PCU spacer keeps the vertebrae in an upright position and limits the extension of the spinal segment.

Combined cord-rod construct (DTO - Dynamic Transition Option) allows the possibility to get both rigid and dynamic stabilization. This device could be used with bone graft in the rigid area to facilitate selective spinal fusion.

Dynamic stabilization aims to modulate the bearing load by controlling abnormal movement. This limits the adjacent segment stress and prevents progressive discal degeneration. The efficiency and safety of posterior dynamic stabilization have not been reported in the scientific literature. The aim of the study is to analyse the clinical and radiological outcomes and to identify the possible causes of clinical failures in DDD patients undergoing posterior dynamic neutralization or posterior hybrid stabilization.

MATERIAL AND METHODS

This is a retrospective cohort study. From 2001 to 2014, 131 consecutive dynamic neutralizations/hybrid stabilizations were performed: 83 DYNESYS (43 one-level, 40 two-levels) and 48 DTO (in 42 cases only one dynamic level, in 5 cases two dynamic levels, in 1 case three dynamic levels). Eighty patients underwent dynamic spinal surgery for the treatment of discogenic low back pain. We retrospectively analysed these patients with a 7.1 years mean follow-up (Range: 5.1 - 8.3 years): 50 Dynesys (mean age 47 years old, range: 29 - 77 years old) and 30 DTO (mean age 48 years old, range: 20 - 71 years old).

The radiological evaluation was done by the same independent observer on standard, dynamic antero-posterior (AP) and latero-lateral (L-L) lumbosacral X-rays in standing position. Radiological measurements were collected before and after surgery, at the last follow-up available.

For each patient, lumbar and segmental lordosis were measured in neutral position (N), in maximal extension (E) and flexion (F). The segmental range of motion was calculated by using the differential between the extension and flexion measurements. A small patient group performed postoperative MRI.

All patients had a clinical pre- and post-operative evaluation by means of Visual Analogue Scale (VAS); Oswestry Low Back Pain Scale (ODI) was drawn in postoperative period. We retrospectively reported the perioperative complications. Statistical analysis was performed for each pre- and post-operative parameter. Student's t test was applied to assess any difference between pre- and post-operative clinical and radiological findings.

RESULTS

It was found a statistically significant VAS reduction from 7 to 2 ($p < .001$) and minimal disability in 65% of the patients, moderate disability in 18.2%, severe disability in 12.5% and crippling back pain in 4.3% (Table I).

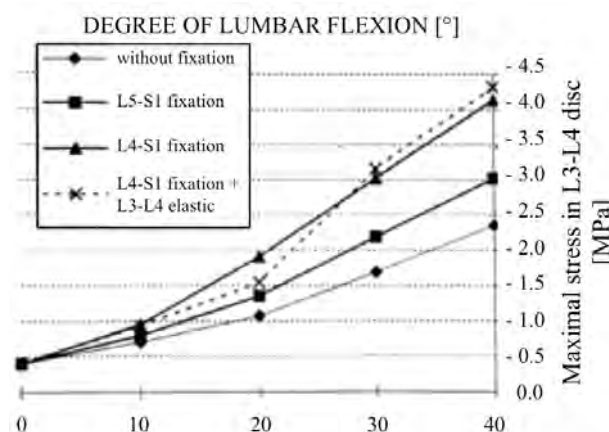


Fig. 1. The y-axis shows that the maximum strain is at the L3-L4 intervertebral disc; the x-axis shows the angle of lumbar flexion.

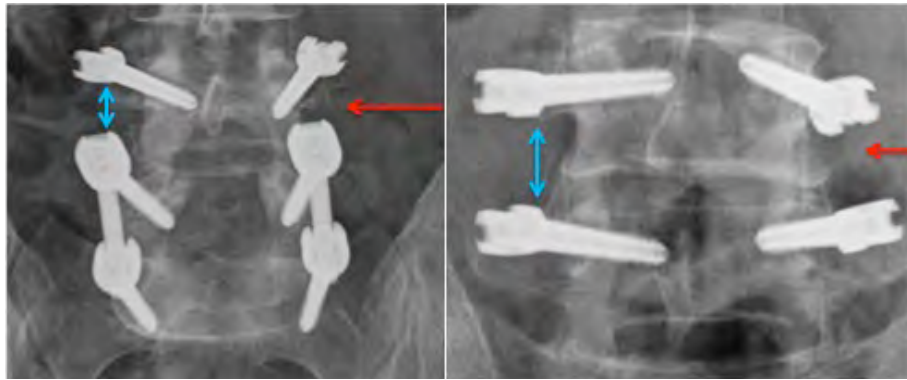


Fig. 2. Lucency in asymmetry of pedicular screws: moderate disability.

Table I. Clinical results: the incidence of postoperative Oswestry Low Back Pain Scale.

Postoperative Oswestry Low Back Pain Scale	
Scoring	Incidence (%)
0-20%: Minimal disability	65 %
21-40%: Moderate disability	18,2 %
41-60%: Severe disability	12,5 %
61-80%: Heavy Incidence	4,3 %
81-100%: Total disability	0 %

Table II. X-ray analysis: comparison of mean range of motion of the operated levels before and after surgery in Dynesys group (N: Neutral Spine Position; F: Spine Flexion; E: Spine Extension).

		Pre-Operative			Post-Operative			Variations mean			
		N	F	E	N	F	E	N	F	E	
D Y N E S Y S	L3-L4		18	15,4	18,4	16,3	14,8	16,8	-1,7	-0,6	-1,6
	L4-L5		19,5	8	22,5	16	7,5	16,5	-3,5	-1,5	-6
	L5-S1		14,8	13,6	15	14	13,2	14,5	-0,8	-0,4	-0,5
	L1-L2-L3	L1-L2	8,5	6,8	9,1	7,3	6	8	-1,2	-0,8	-1,1
		L2-L3	9	7,3	10,2	7,7	5,7	7,8	-2,3	-1,6	-2,4
	L2-L3-L4	L2-L3	11,5	9,6	14,2	10	8,8	12,7	-1,5	-0,8	-1,5
		L3-L4	24,1	22,8	26,3	21,9	20,8	23,4	-2,2	-2	-2,9
	L3-L4-L5	L3-L4	13,4	6,6	14,3	12,3	6,2	11,6	-1,1	-0,4	-2,7
		L4-L5	17,5	11,7	17,9	15,2	12,7	14,1	-2,3	-1	-3,8
	L4-L5-S1	L4-L5	18,6	16,1	20,3	17	15	19	-1,4	-1,1	-1,3
L5-S1		22,5	20,6	24,7	21,8	20,1	23,9	-0,7	-0,5	-0,8	

Table III. X-ray analysis: comparison of mean range of motion of the operated levels before and after surgery in DTO group (N: Neutral Spine Position; F: Spine Flexion; E: Spine Extension).

			Pre-Operative			Post-Operative			Variations mean		
			N	F	E	N	F	E	N	F	E
D T O	L1-L5 (2+2)	L1-L2	-1,5	-3,5	-1	-0,6	-2,7	-0,5	0,9	0,8	0,5
		L2-L3	9	7,3	10,2	7,7	5,7	7,8	-2,3	-1,6	-2,4
	L3-L5 (1+1)		10,2	8,2	11,3	7,8	5,5	9,2	-2,4	-2,7	-2,1
	L2-S1 (3+1)	L2-L3	7,4	2,5	8	4,9	-1,9	4	-2,5	4,4	-4
		L3-L4	13,5	14	14,3	6,2	2,7	4,7	-7,3	-11,3	-9,6
		L4-L5	23	10,5	24,4	13,8	12,6	15,6	-9,2	2,1	-8,8
	L3-S1 (2+1)	L3-L4	11	8	11,8	8,8	6,8	9,5	-2,2	-1,2	-2,3
		L4-L5	16,5	11	13,5	15	9,5	11,8	-1,5	-1,5	-1,7
	L3-S1 (1+2)		8,2	6,5	9,3	6	4,7	7	-2,2	-1,8	-2,3
	L4-S1 (1+1)		23,9	12,5	29,6	21,8	11,1	23,6	-2,1	-1,4	-3

The reported complications were: 2 early infections treated with antibiotic therapy; 2 transitory radicular disease; 5 asymptomatic and 2 symptomatic pedicle screw radiolucencies (Fig. 2); 5 pedicle screws malpositioning (1.06%); 1 low grade sagittal imbalance; 1 screw mobilization with sinking of superior vertebral plate and 2 DYNESIS implant failure treated with spinal fusions.

We had 8% of overall revision rate.

The range of motion analysis showed a mean significative decrease of 3.5° compared to the preoperative values (postoperatively: 2° in N; 1.2° in F; 2.5° in E). The postoperative decrease of motion was more noticeable in E than in F (mean value F: preop 12.6° – postop 11.3°; mean value E: preop 17.5° – postop 15.3°) (Table II, III).

We also compared objective and subjective clinical results and we noted that when disability in Oswestry Scale was severe (12.5%) or heavy (4.3%) with a VAS score between 6 and 8, there was a statistically significative decrease of lordosis in N and E up to 3.5° (Fig. 3).

DISCUSSION

The main finding of the study is that the dynamic spinal stabilization significantly reduces the range of motion; this limitation was more evident in extension than in flexion. Currently the raise average age and the higher functional requests of the population lead to the high incidence of low-back pain. In about 29% of patients with moderate lumbar degenerative disease conservative treatment fails whereas dynamic neutralization could be a good surgical option.

Fusion surgery was the previous gold standard treatment for degenerative spinal diseases. Gillet reported 41% of junctional segment alterations after lumbar arthrodesis, and 20% of these patients underwent a revision surgery (4). Since several disadvantages of spinal fusion were described (non-union, instrumentation failure, reduction of the spinal range of motion, adjacent segment disease, infection and donor site morbidity), new surgical instrumentations have been developed to more efficiently treat these pathologies.



Fig. 3. High disability in patient with reduced lumbar lordosis in N and E after surgery.

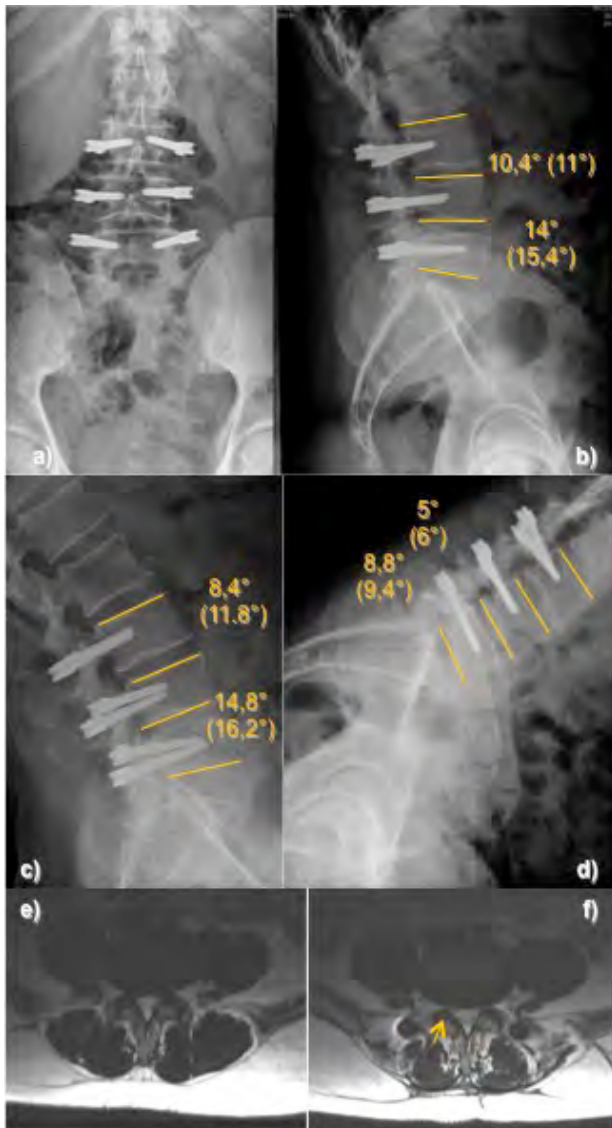


Fig. 4. Male, 36 years old treated with Dynesys L3-L5. Postoperative radiographs antero-posterior (a), lateral (b), maximal extension (c) and flexion (d) views, lordosis of single interested motion units. 5 years follow-up. N ed E < 3°, F reduced 0,6°/1°. Preoperative (e) and postoperative (f) MRI axial image showing reduction of intraforaminal stenosis after surgery.

Dynamic stabilization does not aim to correct vertebral deformities as it happens with other surgical procedures, but to modulate the abnormal motion of spinal segments (7). Dynamic neutralization reported very good results in preventing the discal height loss of Modic 1 DDD patients (11-12) compared to the spinal fusion (6). A significant reduction of low back pain and radicular pain was also noticed in grade 1 spondylolisthesis patients (13, 14, 17). A benefit is also described in lumbar stenosis (1, 2, 16). Unfavourable results are also reported (5, 8, 18). Many Authors reported asymptomatic pedicle screws lucency (14, 16) probably because of lateral positioning of the screws. It is already demonstrated the restoration of the correct segmental biomechanics after dynamic neutralization whereas there is no scientific evidence of postoperative preserved range of motion, as expected.

A recent review (10) analysed 2026 patients who underwent posterior hybrid stabilization, with a 33 month follow-up, reported clinical outcomes comparable to fusion, excellent results on decompressive effect, no clear evidence about the protective effect on junctional syndrome, and 9.4% revision rate. Improper selection of implants may be an important cause of implant failure, as the chosen construct may not withstand the physiologic loads imparted on it.

Our study showed good clinical and functional results of dynamic neutralization in a long-term follow-up and confirmed a residual existing ROM after surgery (Fig. 4). This procedure allows orthopaedic surgeons to have an appropriate surgical option for active patients with moderate discal disease and low back pain. Moreover, unfavourable clinical outcomes were noticed especially in multiple-level spinal diseases. It is fundamental

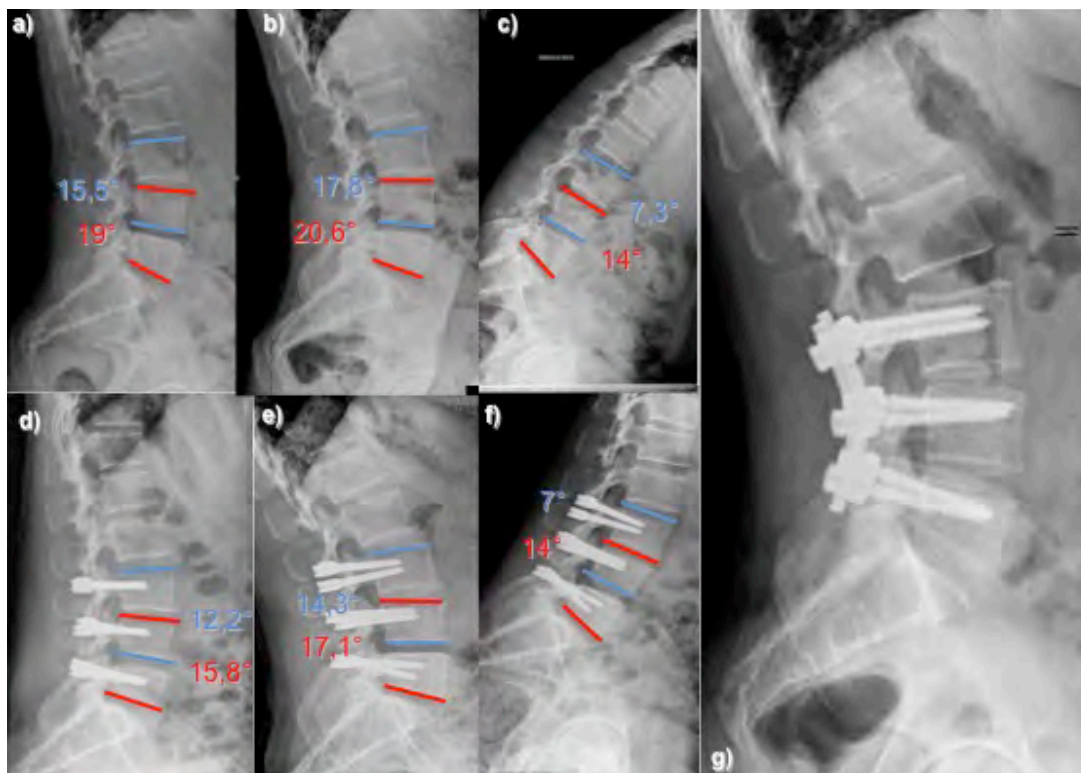


Fig. 5. Male, 43 years old treated with Dynesys L3-L5. Preoperative (a, b, c) and postoperative (d, e, f) radiographs lateral, maximal extension and flexion views. 14 months follow-up: severe disability, decrease Postop N - E > 3,5° and F unchanged. Minimal disability after rigid stabilization: asymptomatic signs of adjacent segment intervertebral disc narrowing (g).

to obtain an adequate and symmetrical pedicle screws positioning to avoid possible complications. Asymmetric pedicle screws seem to be less tolerated in dynamic stabilization than in spinal fusion surgery because of the wrong motion axis imposed by the implant.

A possible complication of posterior dynamic system is the loss of physiological spinal curves. Some data showed a greater decrease in E than in F in postoperative period. In accordance with scientific literature, we also noticed a ROM limitation associated with a decrease of segmental lordosis up to 3.5°. This undesired effect was probably due to an excessive intraoperative cord pre-tensioning (Fig. 5). Especially in large constructs, this could also influence the sagittal balance and spinopelvic parameters. These may be another possible cause of clinical failures in patients who underwent posterior dynamic instrumentations.

The effects of the dynamic neutralization or

hybrid stabilization systems (Dynesys / DTO) on spinal biomechanics and clinical outcomes are still controversial. Dynamic neutralization preserves residual movements, limits more the extension than flexion and reduces posterior spinal stress.

This study encouraged spinal surgeons to continue using these systems. It is also fundamental to avoid asymmetrical pedicle screws positioning and excessive cord pre-tensioning choosing the adequate spacers. A correct preoperative planning, a careful selection of the patients, and a meticulous execution of the surgical technique are mandatory to avoid clinical failures. This system could be considered a valid alternative to spinal fusion and anterior spine prosthesis, especially in young patients.

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Histological assessment of new bone formation with biomimetic scaffold in posterolateral lumbar spine fusion

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Spinal fusion procedures often require the use of bone grafts (autograft or allograft) to help bone healing and to increase stability. However, the application of autografts is frequently limited by donor site morbidity. In recent years, different synthetic bone substitutes have been introduced in the clinical practice to overcome these limitations. The purpose of this paper is to report a case where a biomimetic, synthetic and osteoconductive bone graft substitute was successfully implanted in a patient during lumbar spine arthrodesis. The case of a 58-year-old female subjected to lumbar spine arthrodesis with bone augmentation is described. The bone graft substitute RegenOss® (Finceramica, Faenza, Italy) was implanted during spinal arthrodesis. The successful bone integration was evaluated by X-rays. After 11 months, the patient underwent a second surgery due to spine imbalance; the debris of the bone graft was therefore collected and analyzed by macroscopic evaluation and by histology. The bone substitute was successfully implanted during a spinal arthrodesis procedure. Histologic evaluation of the removed bone graft debris showed the complete resorption of the implant and the formation of new bone, which was well integrated with the host bone. This bone substitute may represent a safe and effective alternative to autologous bone grafts, avoiding adverse events related to donor-site morbidity.

Lumbar spinal arthrodesis may require the use of bone graft to augment bone mass, achieve healing and to provide stability. Different bone graft substitutes are available: autologous cancellous bone graft from the iliac crest is nowadays considered the gold standard as it possesses osteoconductive, osteoinductive, and osteogenic properties; in addition, the risk of infections or rejection is negligible (1-3).

Thus, many authors reported the bone harvesting from the iliac crest as a safe and effective bone graft procedure (4). However, associated donor site morbidity and complications, such as pain or neurological lesions, occur in a significant number of cases, as widely reported (5-7).

Therefore, over the last 10 years, the use of growth factors such as rhBMP-2 was introduced as

Key words: bone formation, posterolateral spinal fusion, biomimetic scaffold, bone graft substitute, histology, arthrodesis

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an effective alternative to the use of iliac crest grafts (8-11); however, papers and reviews have reported severe adverse effects related to the use of this osteoinductive bone graft in spinal fusion procedures (12, 13). Synthetic osteoconductive carriers are also valid substitutes to bone autografts and they do not necessarily require the use of growth factors. In this paper, we describe the successful implantation of a novel synthetic bone graft in a spinal fusion procedure. This implant perfectly integrated with the native bone and it was also completely replaced by new bone after 1 year.

MATERIALS AND METHODS

The synthetic bone substitute RegenOss® (Finceramica, Faenza, Italy) was implanted during a spinal fusion procedure. Bone integration was evaluated by X-rays and by histology. Histologic evaluation was performed on bone fragments removed from the site of arthrodesis one year later due to the need of a second surgery to correct spine imbalance. The specimens were fixed in formalin solution, processed and paraffin embedded. The samples were then cut along the transverse plane and stained with hematoxylin-eosin.

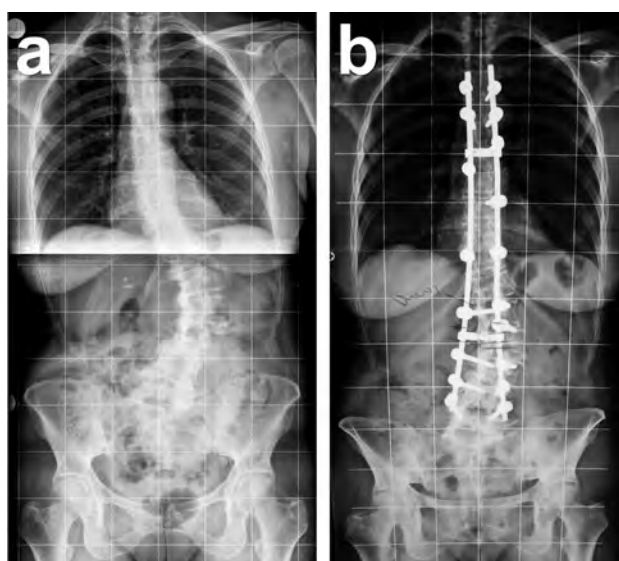


Fig. 1. X-ray imaging before surgical instrumented D5-L5 arthrodesis (a) and after the surgical procedure at 1-year follow-up (b) in anteroposterior view.

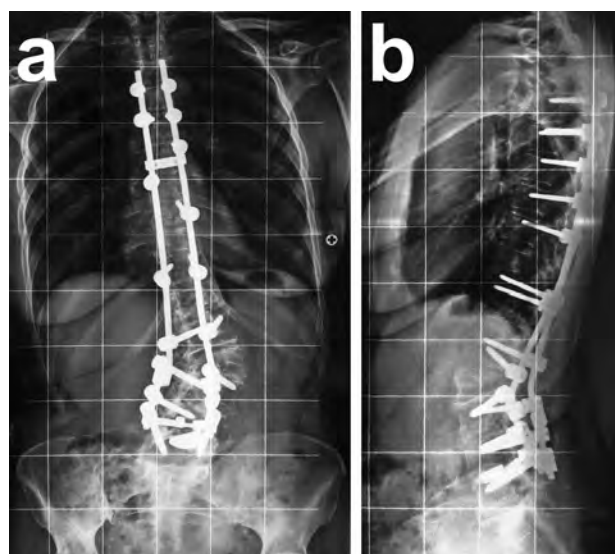


Fig. 2. X-ray imaging in anteroposterior (a) and lateral view (b) after surgical revision at 1-year follow-up.

RESULTS

A 58-year-old female was first admitted for symptomatic rigid thoracolumbar kyphoscoliosis. X-rays executed before surgery showed thoracolumbar scoliosis with kyphosis on the sagittal plane (Fig. 1. a). Hence, arthrodesis from the fifth thoracic vertebra (T5) to the fifth lumbar vertebra (L5) with pedicle screw fixation was performed.

Moreover, a Smith Petersen Osteotomy was completed from the second lumbar vertebra (L2) to the fourth lumbar vertebra (L4), and the area was covered with the synthetic bone graft to promote bone fusion. Post-operative course was regular, with no complications. However, a progressive spine imbalance with pelvic retroversion was recorded 11 months after the previous surgery (Fig. 1. b). Therefore, the patient was readmitted for surgical revision one year after the first surgical procedure.

A Pedicle Subtraction Osteotomy (PSO) of L2 and a transforaminal lumbar interbody fusion between L4 and L5 (TLIF) were performed to correct the fixed sagittal plane deformity. The outcome of the surgical revision was satisfactory and the restoration of lumbar lordosis was obtained (Fig. 2).

During the surgical revision, the area where

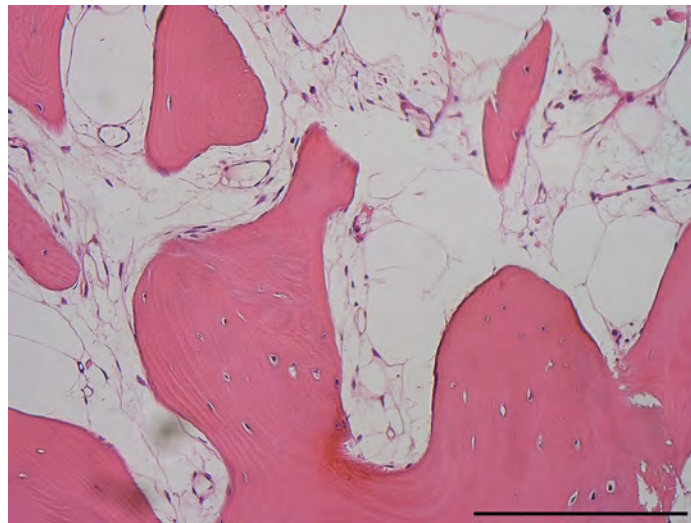


Fig. 3. Hematoxylin-eosin staining of harvested bone at 1-year follow-up. Normal histological features of trabecular bone. Lamellae and osteocytes are clearly visible within the trabeculae. Normal structure of the bone marrow is also visible with abundant fat deposits. No remnants of the biomaterial were found at this stage in all histological specimens. Scale bar = 200 μ m.

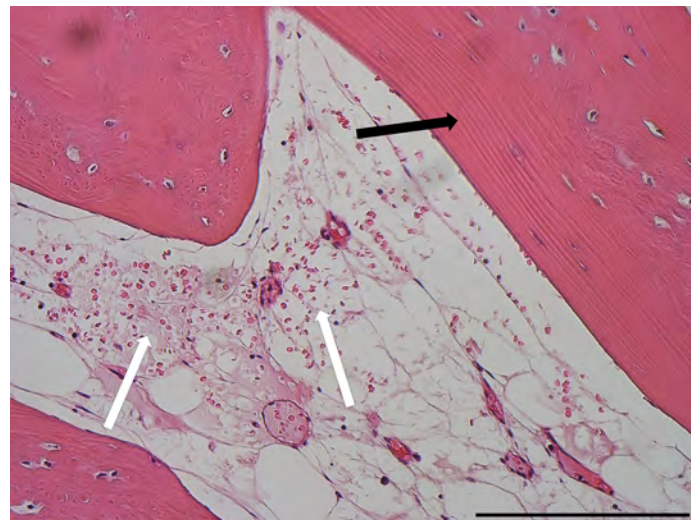


Fig. 4. Hematoxylin-eosin staining of harvested bone at 1-year follow-up, which shows normal parallel lamellae in the trabecular bone on the right (black arrow). High concentration of red blood cells is visible within the bone marrow (white arrows), probably due to the technique of tissue harvesting, which implies the use a Stille-Luer bone rongeur and concentrates the blood cells at the moment of grabbing the tissue. Scale bar = 200 μ m.

the bone graft had been previously applied, was removed to properly complete the PSO. Thus, an extensive macroscopic and histological analysis was assessed on the bone fragments derived from the bone graft. At macroscopic evaluation, no remnants of the implanted biomaterial were visible, and the quality of the newly formed bone was apparently normal with a dense bony mass formation.

The histological findings did not show any presence of fibrous tissue at the interface with host bone. At the site of the bone graft, histology also displayed the presence of newly formed bone, which had a well-organized trabecular structure resembling healthy bone (Fig. 3 and 4). Thus, the bone substitute was successfully implanted and completely osteointegrated with the native bone.

DISCUSSION

Nowadays, autograft or allograft bone substitutes are available for spinal arthrodesis together with over 60 synthetic biomaterials. However, the clinical outcome of those scaffolds is still uncertain and their benefit-cost ratio remains controversial. Autologous bone graft is limited due to site morbidity; thus, synthetic osteoconductive grafts, which can be associated with osteoinductive growth factors, may represent a valid alternative (14).

In the present report, we described the successful implantation of a bone graft during a spinal arthrodesis. In particular, the bony substitute was a biomimetic synthetic scaffold obtained by coprecipitation of magnesium-enriched hydroxyapatite nanocrystals into type I collagen fibers through a self-assembling process, mimicking natural biomineralization processes. The chemical composition of this bioceramic graft is very similar to human bone and the scaffold indeed shows good biocompatibility. Moreover, it presents biodegradable characteristics even with regard to the mineral component (the magnesium-enriched hydroxyapatite); it is resorbed either by a cellular or enzymatic pathway allowing the formation of new bone tissue.

In this report, the bone graft was easily implanted during surgery, and it was well tolerated by the patient. At 1-year follow-up, X-rays showed bony fusion between the implant and the native bone. In addition, during the revision surgery a complete integration of the bone graft was observed and a bone consolidation forming a dense mass melted with the host bone was noted. Further histological evaluation confirmed the bony nature of the newly formed tissue. All analyses were completed after 1 year from the implantation; as shown in literature, this timing is considered a sufficient follow-up to evaluate the maturity of new ossification (2).

The features of the graft may have contributed to its complete resorption. In fact, this bone substitute is known to be usually resorbed by enzymes and cellular action over a period of 6-12 months.

This report demonstrates the potential application of a novel synthetic bone graft substitute with biomimetic properties in spinal fusion procedures.

Based on the observation of this case report, the graft may represent a safe and effective alternative to the use of autologous bone grafts, avoiding adverse events related to donor-site morbidity.

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Inter-rater reliability of classification systems of scapular dyskinesis

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Prevalence of scapular dyskinesis varies across records, with overhead athletes being more frequently affected than non-overhead athletes. A number of methods have been described to evaluate scapular kinematics and scapular dyskinesis. The “yes/no” and the “4-type” classification systems are widely accepted and diffusely used among orthopaedics and physical therapists. The inter-rater reliability for both the “yes/no” and the “4-type” classification systems may be different. Moreover, differences between physical therapists and orthopaedic surgeons may exist. Seven examiners (2 orthopaedic surgeons and 5 physical therapists) were asked to evaluate a mixed sequence of video recordings of healthy subjects and patients affected by shoulder, scapular or clavicular disorders and to assess scapular dyskinesis using the “yes/no” and the “4-type” classification systems. Cohen’s kappa coefficient (κ) and weighted kappa were used to measure inter-rater reliability. Twenty-four subjects were enrolled. In general, the “4-type” system has higher κ values than “yes/no” classification system and orthopaedic surgeons achieve higher reliability than physical therapists for both systems. The clinical evaluation of active shoulder movements permits reproducible assessment and classification of scapular dyskinesis, in particular for the “4-type” classification system. The “4-type” classification system can be used to assess and classify scapular dyskinesis, especially among orthopaedic surgeons.

Scapular dyskinesis is defined as observable variations in the normal scapular position at resting state, as well as the altered patterns of scapular motion in relation to the thoracic cage (1-3). Scapular dyskinesis is considered a nonspecific response to a painful condition in or around the shoulder, which

may arise from shoulder-related, neck-related and posture-related causes (3, 4). Prevalence of scapular dyskinesis varies across records, with overhead athletes being more frequently affected than non-overhead athletes (5, 6).

A number of methods have been described to

Key words: Dyskinesis, instability, scapula, assessment, reliability

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evaluate scapular kinematics and scapular dyskinesis, including clinical examination with observation and palpation of bony landmarks, surface 3-dimensional (3D) tracking systems, 3D tracking systems with bone-pins, 2-dimensional radiographs, 3D radiographs and CT measurements.

Nowadays, outside research settings, scapular dyskinesis is diagnosed by observing both scapulae with the patient in an upright position and the arms resting at the side. The arms can then be simultaneously elevated in the plane of the scapula while scapular motion is observed (7, 8).

Kibler's "4-type" classification system (2, 9), is frequently considered the gold standard to evaluate scapular dyskinesis. This consists of 4 grades and indicates dyskinesis with grades 1 to 3 and normal shoulder motion with grade 4. Another widely accepted classification is the "yes/no" system, which collapses all the different altered positions and movements into "yes" and designating the normal ones as "no" (2, 10, 11). Although these two systems are widely accepted and diffusely used among orthopaedics and physical therapists, their reproducibility has been seldom tested, leading to controversial results (2, 12-14).

The limitations to these classifications based on visual observation are primarily caused by the fact that the layer of soft tissue covering the scapula may hide bony prominences and movements, therefore leading to difficulty in identifying correctly the type of scapular dyskinesis (15) moreover, the experience and attitude of the examiner may influence the diagnosis, especially in borderline cases or in cases where dyskinesis is more prominent in planes different from the coronal one.

The primary goal of the study was to assess the inter-rater reliability for both the "yes/no" and the "4-type" classification systems. Secondary goal was to test if a difference exists in the level of agreement among observers when comparing these two classifications.

MATERIALS AND METHODS

Seven examiners, with extensive experience in treatment and rehabilitation of shoulder pathologies (two

orthopaedic surgeons and five physical therapists) were asked to evaluate a mixed sequence of video recordings of healthy subjects and patients affected by shoulder, scapular or clavicular disorders and to indicate if a scapular dyskinesis was present (as dichotomous variable, "yes/no" system) and to classify it according to Kibler et al. (2003) as categorical variable, "4-type" system (9). This system distinguishes normal, symmetric scapular motion (Type 4) from three grades of scapular dyskinesis: type 1 is characterized by prominence of the inferior medial scapular angle, type 2 by prominence of the entire medial border, type 3 by prominence of the superior scapular border (16). Prior to study initiation, all observers were instructed on the definitions and classifications with standardized material.

Twenty-four subjects were selected among list of healthy volunteers and among patients admitted to the Accident & Emergency Department or to the Department of Orthopaedics and Traumatology of our institution after shoulder trauma. The seven examiners remained blinded to the subject's history and clinical condition throughout the whole duration of the study. All participants agreed to participate in the study and signed an informed consent module for study participation.

After physical examination, all subjects were instructed on how to perform shoulder abduction, forward flexion, and scapular elevation. After movement familiarization, each subject was positioned for video recording and was asked to perform three consecutive cycles of complete abduction, forward flexion and scapular elevation.

The video recording was obtained for all subjects by an external examiner not involved in clinical evaluation and in subsequent dyskinesis evaluation: a digital HD camcorder (1280x720x16Mpx) was positioned at a fixed distance behind the standing subject and aimed at the previously marked T1 spinous process with a laser pointer (August International Ltd. Rawmec Business Park, Plumpton Road, Hoddesdon, UK), to achieve reproducible position and angulation. The digital camcorder was adjusted so that each subject's head, waist and elbows were visible through the full range of motion.

All video recordings were collected and submitted in a random sequence to the seven examiners for evaluation. Standardized forms were provided to each examiner to record the evaluation's results. Statistical analysis was performed using package IBM SPSS Statistics

for Windows, Version 20.0 (Armonk, NY: IBM Corp). Continuous variables were expressed as median and interquartile range or as mean $\pm$ standard deviation as appropriate, while dichotomous variables were expressed in numbers of cases and frequencies.

Cohen's kappa coefficient (κ) and weighted kappa were used to measure inter-rater reliability for dichotomous and categorical variables, respectively. Reliability was estimated for the whole sample of raters and separately for orthopaedic surgeons and physical therapists. The κ coefficient ranges from 0 (when there is no agreement beyond chance) to 1 (indicating total agreement). A κ of 0.2 is considered poor, between 0.21 and 0.4 fair, 0.41-0.6 moderate, 0.61-0.8 substantial, and more than 0.81 almost perfect. Institutional approval of the study protocol was obtained by the University of Florence (ID2405.2016).

RESULTS

Twenty-four subjects were enrolled; no difficulty in the video recording process was encountered for any subject. Demographic data of the study population is reported in Table I.

Table I. *Patients' demographics*

F/M ratio (%)	0.25/0.75
Dominant side L/R ratio (%)	0.08/0.92
Age groups (%)	
18-25	0.42
26-35	0.17
36-45	0.08
46-55	0.33

In general, the "4-type" system had higher κ values than "yes/no" classification system and orthopaedic surgeons achieved higher reliability than physical therapists for both systems. The "4-type" system showed higher reliability than "yes/no" classification system, especially for the group of subjects without trauma (Table II). 41.7% of the enrolled healthy volunteers were indicated as affected by scapular dyskinesis by at least one examiner.

DISCUSSION

The main finding of this study is that the clinical evaluation of active shoulder movements permits reproducible assessment and classification of scapular dyskinesis, in particular for the "4-type" classification system. Scapular dyskinesis can arise from several causes and produces observable alterations either in the normal scapular position at resting state or in the patterns of scapular motion (1-3, 9).

To measure and quantify the different component of shoulder motion in normal and injured patients has been a challenge for clinicians (8, 17). Researchers have tried to improve the diagnostic performance of observation and palpation techniques introducing the use of bony landmarks, surface 3D tracking systems, 3D tracking systems with bone-pins, 2-dimensional radiographs, 3D radiographs and CT measurements. All these techniques show certain limitations, related to an invasive or time-consuming nature, increased costs, radiation exposure or limited reproducibility.

For these reasons, visual observation remains the most feasible assessment method outside research settings. However, a reliable method of clinical assessment of scapular dyskinesis based on observation of shoulder range of motion has not been developed and validated yet.

Nowadays, the "yes/no" system, is widely used

Table II. *Summary of study results*

	κ values (95% CI)					
	All		Physical therapists		Orthopaedic surgeons	
"yes/no" system	0.57 (0.48; 0.66)	moderate	0.56 (0.44; 0.69)	moderate	0.91 (0.50; 1.00)	almost perfect
"4-type" system	0.61 (0.49; 0.72)	substantial	0.66 (0.55; 0.78)	substantial	0.81 (0.67; 0.94)	almost perfect

to screen patients with scapular disorders: in this system all abnormal patterns of scapular movements are grouped into the “yes” category, whereas the normal ones patterns as “no” (2, 10, 11). As opposed to this simple screening tool, Kibler’s “4-type” classification is considered a more detailed system to evaluate scapular dyskinesis and frequently is indicated as gold standard (2).

In a validation study against a 3D kinematic system, Uhl et al. recorded agreement of 61 % between 2 investigators, resulting in a κ correlation of 0.44, slightly superior to that they obtained with the “yes/no” system ($\kappa = 0.41$) (2). Our results could confirm the slight superior reproducibility of the “4-type” classification, which showed higher κ values than “yes/no” classification system.

Interestingly, orthopaedic surgeons achieved higher reliability than physical therapists for both classification systems. This could be either due to a bias caused by the higher number of physical therapists involved in the study, or to the longer experience which the two orthopaedic surgeons had as compared to the physical therapists.

Further studies comparing subgroups of examiners with different experience and professional background are needed to confirm this preliminary finding. Although the agreement was only moderate, the Authors believe that the “yes/no” method should maintain its role as a screening tool in the shoulder evaluation process (2). The “4-type” classification can be then used to confirm the diagnosis and describe the pathology in greater detail.

Overall, the agreement among all investigators was not high: this can be caused by the fact that scapular movements have a multiple-plane nature (3 rotations and 2 translations) and may present asymmetries which are not pathological. Since the examination occurs from the patient’s back, it restricts the observation to a single plane: this is an intrinsic limit especially for the “4-type” classification, which is specifically designed to identify the predominant pattern of scapular motion in a single plane (18).

Moreover, muscle and soft tissues over the scapulae may cover the bony profile and confound the examiner observing scapular movements: this could explain the increased reliability registered

when an external load is applied or when observation is combined to palpation (12, 13).

Finally, the low agreement could also be influenced by the fact that asymptomatic individuals can have postural asymmetries, also greater than 1.5 cm (19, 20), which some examiners may indicate as scapular dyskinesis. In our series, 41.7% of the healthy controls were indicated as affected by scapular dyskinesis by at least one examiner.

Possible strategies to increase the reproducibility of these classifications are the addition of manual palpation, the repetition of abduction movements against resistance and the evaluation of both elevation and lowering phases of scapular motion (12, 13). Interestingly, increasing the number of arm elevation and lowering cycles and adding an external resistance to movement was associated with an extremely high agreement percentage and an almost perfect reliability for both the “yes/no” and the “4-type” classifications (13).

This study has several limitations. First, observation of shoulder range of motion requires clinicians to allocate the assessment of asymmetry into a single plane of motion, which may be too restrictive. Moreover, a method that categorizes scapular dyskinesis into 1 of 4 categories based on observation of scapular border positions at rest and during elevation motions using asymmetry as the clinical criterion for scapular dyskinesis may overestimate the prevalence of this dysfunction, particularly in asymptomatic subjects (19).

Moreover, this study was primarily focused in determining the inter-observer agreement, and was therefore designed to have a consistently high number of observers; on the other hand, the number of enrolled subjects was limited, which could amplify bias related to borderline cases. Finally, a higher number of physical therapists as compared to orthopaedic surgeons was involved in the study, which could create a bias in the between-group comparison of the results. Further studies are needed to define the role of the examiner’s experience and professional background in the assessment of scapular dyskinesis.

The clinical evaluation of active shoulder movements permits reproducible assessment and

classification of scapular dyskinesis, in particular for the “4-type” classification system. The “yes/no” method can be maintained as a screening tool for scapular dyskinesis assessment in the shoulder evaluation process. Thanks to its superior agreement and inter-rater reliability, the “4-type” classification system can be used to confirm the diagnosis, describe the pathology in greater detail and improve communication between health care professionals.

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Bilateral THA in the same sitting for avascular necrosis of the head of the femur in sickle cell patient: our African experience

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Sickle cell anemia is protective against the malaria protozoan. The heterozygous form of the disease is not fatal, and may cause musculoskeletal disorders when sickling occurs, and small vessels are occluded. When the head of the femur is involved, this may result in hip arthritis, often bilateral, at a young age. This article describes three patients in whom bilateral total hip arthroplasty (THA) was performed in the context of a humanitarian mission in Togo, Africa.

Sickle cell disease (SCD) is a multifactorial disease caused by the presence of an inherited genetic abnormality in the oxygen-carrying protein haemoglobin in red blood cells. This leads to the synthesis of hemoglobin S, which has reduced solubility. In deoxygenated states, hemoglobin S aggregates, giving the red blood cell the typical sickle shape, producing vaso-occlusive, vasculopathic and systemic inflammatory phenomena (1). The disease manifests itself when both alleles are mutated, while in case of heterozygosis, the subjects may not have such clinical manifestations.

SCD is the most frequent hereditary hemoglobinopathy, with most patients living in sub-

Saharan Africa, where the carriers of the mutation are protected from the protozoan of malaria (2) with the majority of cases in sub-Saharan Africa. Concomitant nutritional deficiencies, infections or exposure to environmental toxins exacerbate chronic anemia in children with SCD. The resulting relative anemia is associated with increased risk of strokes, poor cognitive function and impaired growth. It may also attenuate optimal response to hydroxyurea therapy, the only effective and practical treatment option for SCD in sub-Saharan Africa. This review will focus on the epidemiology, clinical sequelae, and treatment of relative anemia in children with SCD living in low and middle-income countries in

Keywords: total hip arthroplasty (THA), direct anterior approach (DAA), girdlestone resection arthroplasty (GRA), sickle cell diseases (SCD)

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sub-Saharan Africa. Areas covered: The causes and treatment of relative anemia in children with SCD in sub-Saharan Africa. The MEDLINE database was searched using medical subject headings (MeSH). SCD causes, among other manifestations, thrombosis of the femoral head, which leads to necrosis and consequently early, often bilateral, osteoarthritis.

In advanced hip osteoarthritis, the modern surgical option for best results is total hip arthroplasty (THA). Although there is an increased risk of medical and surgical complications in patients with sickle cell disease, THA provides substantial relief of pain and improvement of function in appropriately selected patients (3). This article details the management and outcome of three patients who have undergone bilateral THA, performed in the context of a humanitarian mission in Togo, Africa.

Clinical Cases

Sickle cell anemia causes, at bone level, and especially at the level of the head of the femur, repeated micro-infarctions. This induces, necrosis of the bone components affected, and a peri-lesional osteoblastic reaction (4). Clinically, patients develop deformity of the head and the neck of the femur with a subchondral sclerosis and early secondary osteoarthritis of the hip. In a developing country, such as Togo, bilateral juvenile osteoarthritis results in marked limitation in normal daily activities and interferes with subsistence. For this reason, early treatment of juvenile arthrosis secondary to sickle cell disease is essential.

Bilateral THA at the same surgical sitting has several advantages, including reduced surgical time, a single anesthesia, and an overall reduced recovery time. In the two-week missions in the period between 11/27/19 and 4/11/19, we performed three bilateral simultaneous THA, in 30, 26- and 47-years old patients. One of the two patients had already undergone a right Girdlestone arthroplasty 7 years before the THA procedure because of the financial constraints, which did not allow this patient to have a THA at the time.

MATERIALS AND METHODS

In all the patients, an anterior approach performed

simultaneously by two surgical teams was undertaken, in consideration of several factors:

- The patients operated on this mission perform many work actions with an extreme flexion of the hips: this surgical way ensures greater stability of the prosthetic components in the short-term during this action with respect to the other surgical approaches.
- As bilateral surgery was planned, the supine positioning of the patient saves the time to position the patient.
- Having to operate bilaterally at the same time, this surgical procedure is the most efficient. In this way, the patient does not suffer two stops in his life.
- A contemporary bilateral approach reduces overall surgical time, decreasing the risk of complications such as deep vein thrombosis, pulmonary thromboembolism and respiratory complications (5).

In one case, it was necessary to perform a conversion to a direct lateral approach, due to an intraoperative fracture, which was treated with a cerclage (Fig. 1).

The prostheses used were Amistem stem, versafit cup, 28 mm metal head and polyethylene liner added with vitamin E. No drainage was placed and no blood transfusions were needed.

In one case, a hybrid approach was chosen: anteriorly on the left hip and a direct lateral with the patient supine on the right hip, as the patient had undergone Girdlestone's arthroplasty on the right hip seven years before the THA. The patients were mobilized and allowed to stand on the day of the operation: the patient with the metaphyseal fracture of the femur, on the fractured limb, mobilized toe touch weight bearing, and on the other limb weight bearing as tolerated. The other patients started immediately to walk weight bearing as tolerated on both lower limbs and walked without crutches on the fifth post-operative day. Subsequent radiographies demonstrated the progressive consolidation of the intraoperative fracture.

DISCUSSION

Patients with sickle cell disease develop profound misshaping of the head, neck and metaphysis of the femur: this makes the positioning of the femoral stem more technically demanding. These areas are denser, with a greater cortico-cancellous ratio and a high flare index. It is often difficult to locate the medullary canal, which can be obliterated by dense

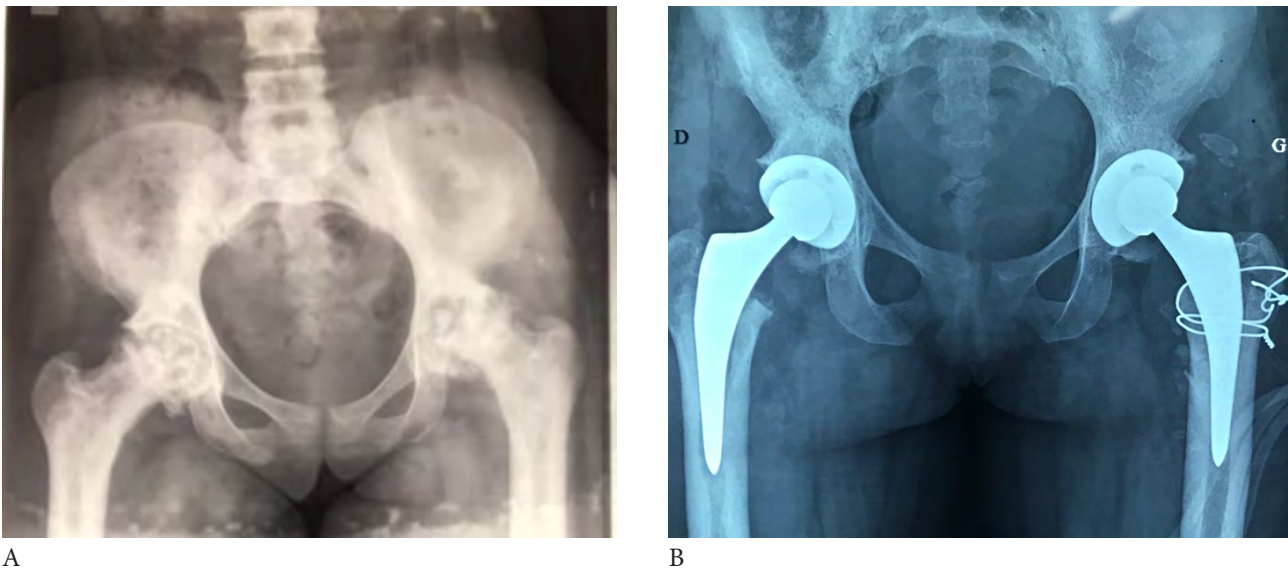


Fig. 1. Case 1, AP pre (A) and post-operative (B) plain radiographs.

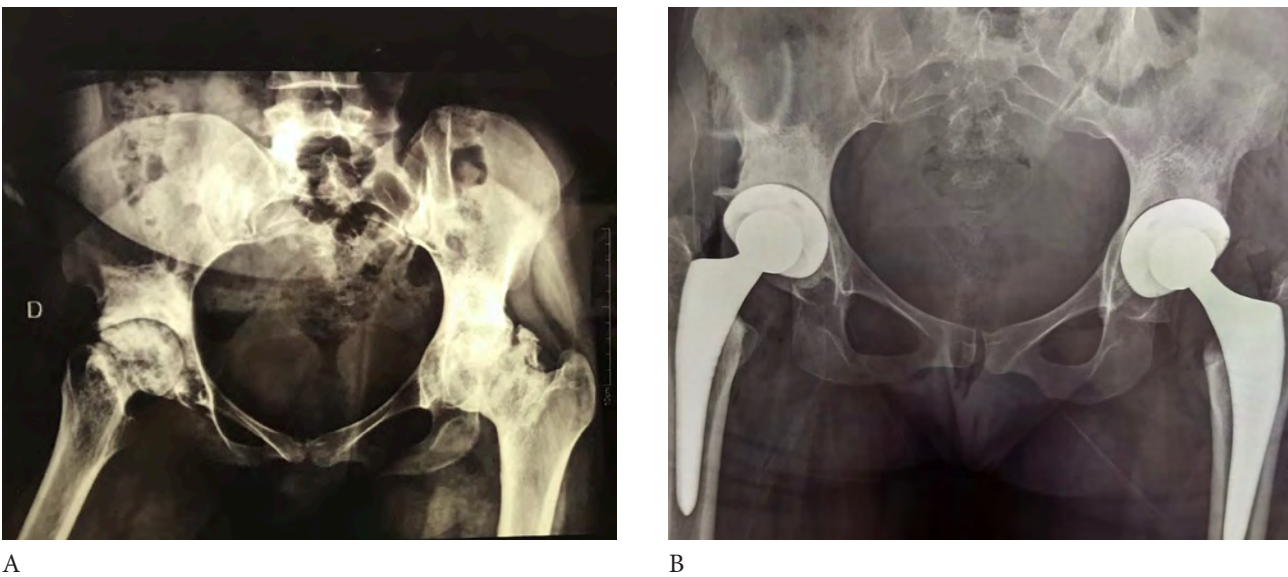


Fig. 2. Case 2, AP pre (A) and post-operative (B) plain radiographs.

cortical bone. This accounts for the high risk of intraoperative fracture. For this reason, great care should be exerted during the surgeries, especially when employing the anterior approach, when the use of off-set tools is suggested (Fig. 2).

In the patient with a hybrid surgical approach, there was no difference in the immediate post-operative period. The previously operated hip presented poor musculature both for the previous

surgery (postero-lateral approach) and for the years of inactivity. Furthermore, intraoperatively we have found the small trochanter without muscle insertion. This makes us think that, despite the important muscle deficit, with the appropriate precautions we can implant stable prostheses with excellent functionality.

As these patients were to undergo a simultaneous bilateral THA, we originally planned a simultaneous

anterior approach for both hips. However, surgeons should be conversant with other approaches, as circumstances may change intra-operatively, and exposure of the hip may have to be achieved through alternative approaches.

Given the humanitarian nature of the mission, the implants were donated one by one manufacturer (Medacta). The stems were short tapered stem with metaphyseal grip (6). For the typical flare index of the treated femurs, perhaps conical stems would have been more suitable.

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Periprosthetic joint infection from *Mycobacterium Tuberculosis* in Togo, Africa

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***Mycobacterium Tuberculosis* infections are moderately frequent in developing countries. Because of migratory flows, these diseases will always have an increasing prevalence even in those countries that do not usually present these types of cases. Extra-pulmonary tuberculosis often affects the musculoskeletal system. The sites most involved are the spine (Pott's disease) and the large joints, especially hips and knees. We describe a patient with tuberculosis of the hip, who underwent total hip arthroplasty.**

Tuberculosis can affect any joint, bone, bursae or ligament, although the most frequent locations are the spine, hip and knee, representing about 80% of all musculoskeletal localizations (1). Pathology, clinical aspects, diagnosis and treatment are discussed. Four patients are presented to illustrate the following important clinical problems concerning this disease. Diagnosis is often difficult, given the indolent nature of the disease: it is very difficult to think of tuberculosis in the absence of a diagnosis of primary pulmonary disease.

Extra-axial tuberculous arthritis can involve any joint, although the preferred locations are the large weight-bearing joints. Usually a single joint

is involved, although multiple locations may be present. The clinical presentation is characterized by slow increasing pain, swelling and functional impotence. The often present contracture of the adjacent musculature reduces daytime pain, which may reappear later with "night cries", when the contracture is released (2). With the pandemic of the human immunodeficiency virus and with the increase in the number of people who are immunocompromised, there is a resurgence of tuberculosis worldwide. The diagnosis in endemic areas generally can be made on clinical and radiologic examinations. However, whenever there is doubt because of an atypical clinical presentation or lack

Key words: *hip, total hip arthroplasty, primary musculoskeletal infection, mycobacterial infection, tuberculous abscess*

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of clinical exposure, tissue diagnosis is mandatory. If osteoarticular tuberculosis is diagnosed and treated at an early stage, approximately 90% to 95% of patients would achieve healing with near normal function. The mainstay of treatment is multidrug antituberculous chemotherapy (for 12 to 18 months).

If the spine is affected, specific symptoms and active pulmonary disease are present in only a minority of patients (3). Clinically, a synovitis leads to joint swelling, granulation tissue and the formation of a pannus. Necrotic cartilage and fibrinous tissue form the classic, and almost pathognomonic, rice bodies in synovial fluid.

Case presentation:

An African woman, from Togo, aged 55, who underwent right THA in 2007 and left THA in 2016, presented with increasing pain in her right hip. The patient reported pain for about 2 years, but, given her economic conditions, she had never had a specialistic evaluation. She came to our attention with a markedly compromised clinical picture. On physical examination, the patient presented with antalgic gait despite the use of two crutches, an extremely limited range of motion from pain, and total inability in her normal daily activities.

Plain radiographs showed migration of the acetabular cup in the abdomen (Fig. 1). A CT scan confirmed the abdominal migration of the cup and showed the presence of a voluminous periprosthetic mass that reached the abdominal vessels (iliac vessels and obturators vessels). The CT scan also showed the presence of a double contour at the level of the femur medullary canal, both at the level of the interface between cement and bone and at the level of the interface between prosthesis and cement. Moreover, the CT scan showed the leakage of cement from the femoral diaphysis, probably an expression of an intraoperative fracture in the context of the first surgery.

The patient presented a high C-reactive protein, without leukocytosis. In addition, the patient was anaemic (7.9 g/dL of preoperative hemoglobin) and required transfusion of two units of blood before surgery. The possible diagnostic hypotheses were the presence of a latent chronic infection or a metallosis, as the head of the prosthesis was in Cr-Co.

Based on the CT appearance, an abdominal access was planned to detach the vessels from the abdominal mass, to minimize the potential vascular damage caused by traction of the potential adhesions. Intra-operatively, during the intra-abdominal dissection, through a left pararectal mininvasive anterior approach, large swollen lymph nodes were excised and sent for histological examination. The mass was strongly adherent to the left common iliac vein and common iliac artery and left obturator artery vein (Fig. 2).

The mass had a very thin wall that was damaged during the dissection, with outflow of gray-yellowish material, which was collected and sent for histological and microbiological examination. At the end of the procedure, the surgical field was washed out with normosaline until caseous material was no longer evident (Fig. 3).

An incision was then made on the previous scar. When the joint capsule was incised, caseous material emerged. Again, this was collected and sent for histological and microbiological examination, and the surgical field was washed out with normosaline. The femoral stem was grossly mobile and was easily removed.

All the adhesions were then removed from the cup and, after placing a hand to protect the large vessels in the abdomen, the cup was removed. Abundant wash out was performed by communication between the abdomen and thigh. Intraoperatively, a meta-epiphyseal femoral fracture occurred, treated with a cerclage (Fig.4). A suction drain was placed in the wound and removed in the first post-operative day. The patient began to walk with two crutches 4 days after surgery, with moderate pain. No additional blood transfusion was required.

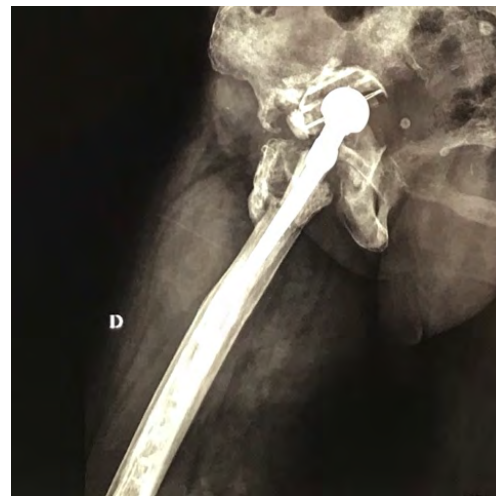
DISCUSSION

The decision to undertake a laparotomy allowed to prevent lesions of the large vessels, as the mass was strongly adherent to the iliac vessels and obturator vessels. A classical isolated approach to the hip may have resulted in a high risk of vascular lesions when attempting to remove the cup, with either a massive hemorrhage or the retention of the cup in the abdomen with the risk of a lesion of the



A

Fig. 1. AP (A) and axial (B) pre-operative X-rays.



B

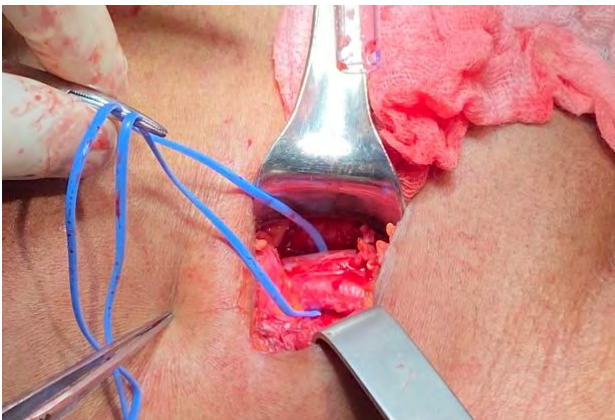


Fig. 2. Insulation and protection of iliac common artery and vein.



Fig. 4. Post-operative X rays.



Fig. 3. Mobilized femoral stem and caseous material.

pseudocapsule and tuberculous peritonitis.

In this patient, we plan standard chemotherapy for tuberculosis, lasting for at least 6 months, after which, in case of signs that the infection is not active, a new THA will be performed. We are not considering a hip arthrodesis given the great negative functional impact that would be imposed in this patient (4) even with the lowest rates, a serious concern that needs to be thoroughly studied and addressed using all possible measures. Osteoarthritis is becoming increasingly frequent also in low income countries, given the greater life expectancy and other pathologies (sickle cell disease, septic arthritis, metabolic disorders) (5,

6, 7). THA is possible solution even in these settings (8). Despite all possible precautions, periprosthetic infections remain a most fearful complications in this type of surgery (9). Infections are more frequently sustained by skin contaminating bacteria such as *S. epidermidis* or *S. aureus*, but *Mycobacterium tuberculosis* (10) is a relatively frequent cause of septic arthritis in low income countries. Pre-operatively, an infective pathology should be kept high in the list of differential diagnoses, especially in the rural areas of Africa or Asia (11).

Given the current migration flows, these cases will become more frequent even in developed countries, and they will require an increased diagnostic suspicion to be able to offer proper patient management.

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Management of intraoperative contamination of anterior cruciate ligament graft

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The options after the intraoperative graft contamination include sterilizing and implanting the graft, rejecting the graft and isolating another one from the other knee, rejecting the graft and using an allograft. The survey was prepared in Google Forms®. Only fully and correctly completed survey questionnaires were considered and included in this study. In total, 41 questionnaires in the study reported contamination. For the surgeon, the risk of contaminating the graft during the surgery is 0.2%. The mean contamination rate is 1.2 accidents per whole career. The statistical significance was observed in correlation between years of specialization and several accidents ($p < 0.05$). The graft contamination may be experienced by almost 30% of surgeons performing ACL reconstructions. Neither knowledge, nor experience and training can prevent an operating team from that situation. The only solution is to follow a strict protocol of graft preparation. According to the data gathered in this study, there is still no ideal protocol after the incident occurs.

The Anterior cruciate ligament (ACL) surgery is nowadays one of the most performed orthopedic procedures, with an approximately 200.000 cases operated in the United States annually (1). Given the increasing number of reconstruction procedures, which are performed more than a 100.000 times per year, avoiding perioperative complications is of an uppermost importance (2). A decreased range of motion or a decreased laxity are just some of the several complications that have been reported in the literature so far (3). One of the most potentially serious, as well as unexpected complications is an intraoperative contamination of the graft.

Implantation of a contaminated graft may lead to a septic arthritis, which can result in a

total knee arthroplasty or in a septic shock (4, 5). When the intraoperative graft contamination occurs, complications after the subsequent ACL reconstruction may be avoided through appropriate management of the contaminated graft. Incidences of contamination related to a dropped ACL graft are not widely studied, and a few case reports have been published on the subject (6-9).

The options after the intraoperative graft contamination include sterilizing and implanting the graft, rejecting the graft, and isolating another one from the other knee, rejecting the graft and using an allograft.

Disinfection and implantation of the contaminated graft are nowadays the most preferred choice (5-12). Several small-scale studies have been performed

Key words: intraoperative graft contamination; Anterior Cruciate Ligament Graft

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in order to test the efficacy of various disinfection techniques (7-12) The study of Hantes et al suggested that there is no correlation between the bacteria on the graft and the infection after the surgery (7).

The first survey concerning the topic was done by Izquierdo et al (8). The study confirmed that the accidental contamination exists, and that 25% of responders should be able to cope with it. However, no consensus exists on optimal management after the intraoperative ACL contamination. Moreover, the survey, which involved the arthroscopic surgeons, did not prove whether the disinfection or rejection of the graft brought better results (8). Finally, recent studies did not say anything about the pattern and circumstances of the accidental contamination (5-12).

The objective of this survey study was to collect and analyze data from the members of the national arthroscopic society about their experience with the intraoperative graft contamination. This allows to make evidence-based recommendations for the surgeons who face such complication.

MATERIALS AND METHODS

Upon receiving the consent from the Host University Bioethical Committee to perform this study, an invitation with the survey questionnaire was sent to the members of Polish arthroscopic society. The survey was prepared in Google Forms®. Only fully and correctly completed survey questionnaires were considered and included in this study (Fig. 1). The data was collected anonymously.

The following data was gathered from each participant who completed the questionnaire:

- Number of years worked as a specialist in orthopedic surgery;
- Surgical experience (in years) of arthroscopic ACL reconstructions;
- Number of ACL reconstructions performed;
- Number of ACL reconstructions per year;
- Number of accidental contaminations during the ACL reconstruction.

Each contamination case was reported and

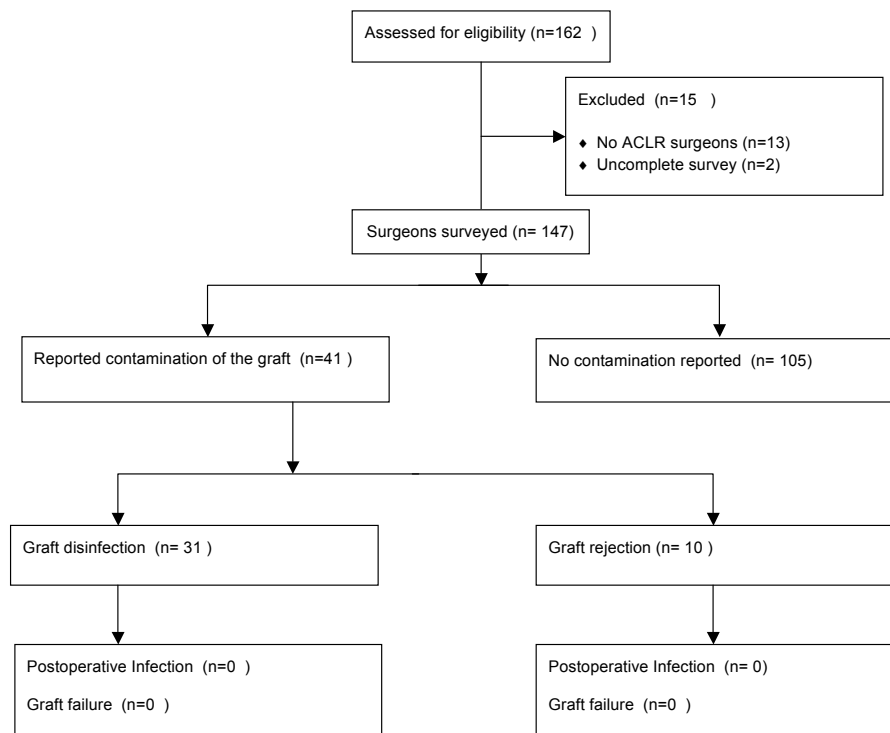


Fig. 1. Flow chart of the study.

described separately. The survey provided data on the types of contaminated grafts: semitendinosus and gracilis (STG), bone to bone (BTB), quadriceps or allograft; as well as data on the time of when the contamination incident occurred: harvesting, graft preparation, lagging, transmission, implementation. Person responsible for the contamination: main surgeon, surgeon's assistant, scrub nurse; management after contamination: graft rejection, mechanical rinsing, Chlorhexidine lavage, Bacitracin lavage, Neomycin lavage, Polimyxin B lavage, others; whether contamination impacted the mode of procedure; whether septic arthritis occurred; whether a prolonged antibiotic therapy was applied; and finally whether a reoperation was necessary. The patients

were observed after the surgery for one year (Fig. 2).

To assess normality, each group was examined by the means of the Shapiro-Wilk test. After that, all characteristics were examined by the Pearson's Chi-squared test to prove statistical significance between each group. STATISTICA® program was used to perform that evaluation.

RESULTS

In total, 41 questionnaires in the study reported contamination. For the surgeon, the risk of contaminating the graft during the surgery is 0.2%. The mean contamination rate is 1.2 accidents per whole career. The statistical significance was observed in correlation between years of specialization and several accidents ($p < 0.05$). Moreover, the statistical significance occurred in correlation between years of experience in performing ACL reconstructions and several contaminations ($p < 0.05$) (Fig. 3).

In both cases, the more experienced is the surgeon, the more contaminations were reported. A statistically significant correlation occurred between the total number of performed ACL reconstructions and several contamination cases ($p < 0.05$). Furthermore, a correlation between an annual number of ACL reconstructions and a few contamination cases was also statistically significant (Table I).

The STG constituted 90% of all contaminated grafts, whereas BTB operations were performed in 10% of surgeries. Neither quadriceps, nor allograft were performed.

In most of the cases, team members who were responsible for the contamination were an assistant surgeon (61%) and a scrub nurse (37%). Only in one case the main surgeon was responsible for the accident. (Fig. 4) presents the surgical steps, when the contamination occurred. None of the accidents happened during the harvesting or the implantation phases.

In Table II, it illustrates the phase of surgery and the person responsible for the contamination. No statistical significance was observed.

In the year after the surgery, none of the participants observed septic arthritis from the contamination. Moreover, none of the patients

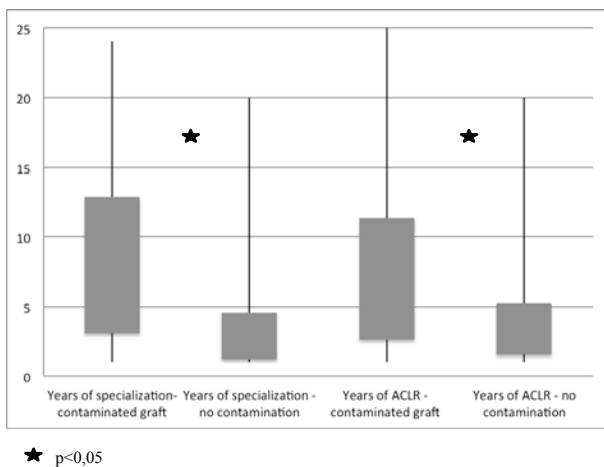


Fig. 2. Demographic analysis of participants.

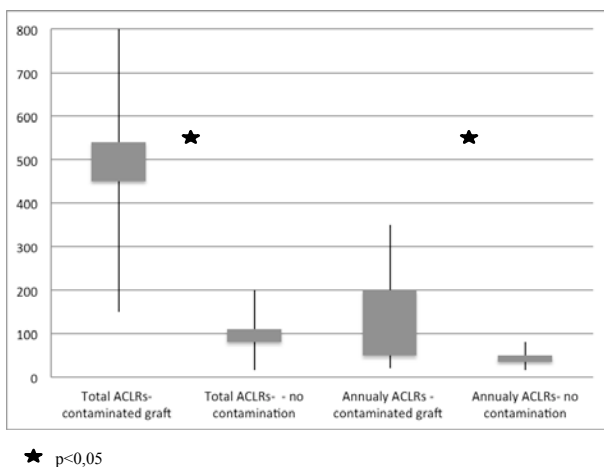


Fig. 3. ACLR's experience.

Table I. Experience in performing ACL reconstructions in comparison to contamination cases (* $p<0,05$).

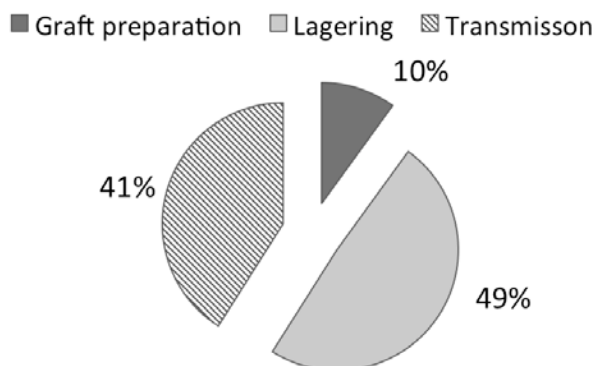
	Minimal	Maximal	Median	SD
Yet	20	4000	450	540 *
Annually	5	350	50	47 *
Accidents yet	0	5	1	0,77

Table II. Incidence phase and person responsible for the contamination.

	Collection	Graft preparation	Lagering	Transmission	Implementation
Surgeon	0	0	0	1	0
Assistant surgeon	0	4	10	11	0
Scrub nurse	0	0	9	6	0

Table III. Differences between the Present study and the survey done by Izquierdo et al.

	Izquierdo et al.	Present study
Number of participants	325	125
Number of contaminations	57	41
Mean number of annual ACL reconstructions	50	50
Graft cleansing	75%	73%
Graft rejection	25%	27%
Septic arthritis	0	0

**Fig. 4.** Phases of surgery – contamination.

required reoperation. Prolonged antibiotic therapy (avg. 7 days, range 3-10 days) was applied in all cases of graft decontamination (76%). When a new graft was used, standard prophylactic antibiotic dose was administered.

DISCUSSION

The study shows that the graft contamination

may be experienced by almost 30% of surgeons performing the ACL reconstructions. The survey primarily showed that the risk of the graft contamination grows along with the number of years performing the surgery, frequency and the total numbers of surgeries. Even more experienced surgeons would face this problem. In the previous survey, the correlation between the number of reconstructions, surgeon's experience and the amount of contaminated grafts was not observed (8). The similarities and the differences between these studies are presented in Table III. Moreover, none of the other authors recommend how to prepare surgeons to tackle the graft contamination (5-12).

The lack of correlation between the phase of operation and graft contamination, suggests that a surgeon should be prepared for the contamination to occur throughout the course of the operation. However, harvesting and implementation are the safest phases of the surgery, as no contamination was recorded at that time.

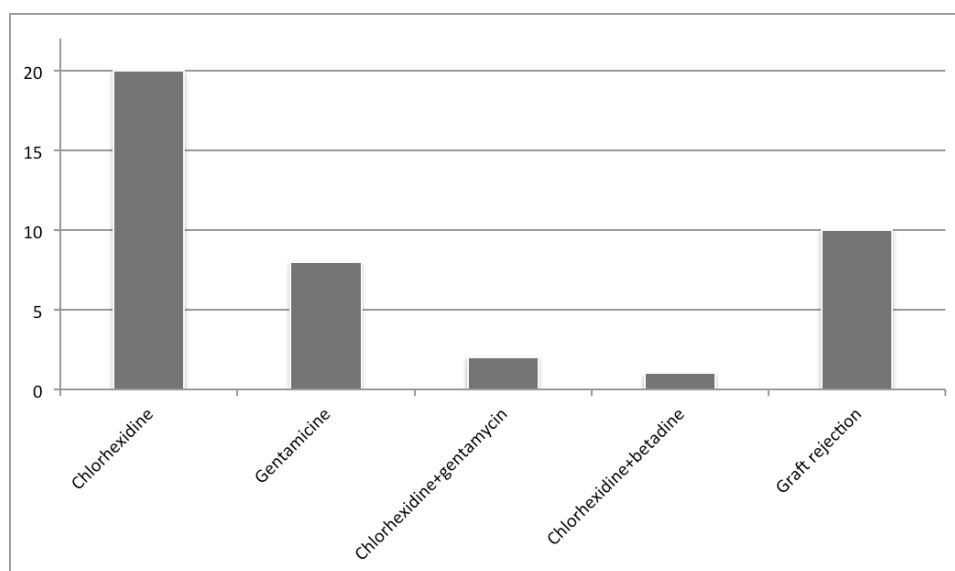


Fig. 5. *Types of post-contamination management.*

The responsibility for the accident rests on the entire operating team. However, in most cases, the assistant surgeons were the ones found accountable for the contamination. Yet, as our study proved, there is no reason to fault them, as the causes of contamination may be quite accidental. Our findings are original compared to previous survey; our findings are (8).

Participants did not choose just one, most reliable method of the post-contamination management. Several previous studies revealed that Chlorhexidine and Chlorhexidine with other antibiotic were the most frequently applied procedures (9, 11-13). The lack of statistically significant advantage of such treatment suggests that not all surgeons have scientifically based evidence to make a choice. Unlike the reviews on this topic, our study proved that there is no statistically significant difference between graft rejection and disinfection techniques in preventing the septic arthritis (13). Although, none of the cases developed the septic arthritis in the postoperative period, it is possible that disinfection techniques as well as prolonged antibiotic therapy might have an impact on the inflammation of the knee joint and future rehabilitation, which does not occur during the new, clear graft implementation. The authors suggest that our research should be a prelude to the future debate and research to find whether there is a

recognized, most preferable mode of management.

This study has some limitations: data collection depended solely on the doctors' survey reports without a direct contact with the involved patients. The assessment of the outcome was based only on the occurring infection, after the implementation of the disinfected graft. The analysis did not include information about when the incident occurred in relation to the surgical career. It was not possible to determine the knee stability and function after this type of reconstruction.

The graft contamination may be experienced by almost 30% of surgeons performing ACL reconstructions. Neither knowledge, nor experience and training can prevent an operating team from that situation. The only solution is to follow a strict protocol of graft preparation. Each of the surgical team members may be responsible for the graft contamination throughout the whole course of the surgery. Both types of procedures after the graft contamination can prevent a septic arthritis. The authors hope that this survey will begin the discussion about the most effective procedures applied after the accidental graft contamination and will inspire further research. According to the data gathered in this study, there is still no ideal protocol after the incident occurs.

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Microfracture combined with anterior cruciate ligament reconstruction compared to isolated microfractures for osteochondral lesions

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There is limited evidence whether increased growth-factor and stem-cell influx during bone tunnel drilling for ACL-reconstruction enhances clinical results of microfracture treatment of small cartilage defects. The goal of this study was to compare clinical and radiological results in patients treated with microfracture alone and patients treated with microfracture plus ACL-reconstruction. A total of 67 patients that were either treated with microfracture alone (primary stable knees, n= 40) or microfracture plus ACL-reconstruction (ACL deficient knees, n=27) were included and prospectively evaluated. Subjects were preoperatively assessed radiologically using the MR-based AMADEUS-score (Area Measurement and Depth & Underlying Structures) and clinically using the Lysholm-score before the intervention. At minimum 24-month follow-up, the regenerate tissue was assessed by the MR-based MOCART-score (Magnetic resonance observation of cartilage repair tissue) and by use of the Lysholm-Tegner-score for clinical evaluation. Preoperatively both groups had similar AMADEUS-scores. The Lysholm-score was significantly higher in the microfracture group ($p < 0.001$). In the postoperative assessment there was a significant difference ($p = 0.04$) in the MOCART-score in favor of the microfracture plus ACL-reconstruction group. The Lysholm-score significantly improved ($p < 0.001$) in the microfracture plus ACL-reconstruction group and was significantly higher than in the microfracture group ($p = 0.004$). **Conclusion:** A combination of microfracture and ACL-reconstruction leads to comparable functional results, yet superior MOCART-scores as compared to microfracture alone. ACL reconstruction enhances biological healing responses in microfracture treated cartilage and thus improves clinical outcomes by additional bone marrow influx from bone tunnels.

Cartilage defects of the knee joint have both a clinical and socioeconomic importance, potentially yielding long-term symptoms and disability as well. Indeed, there is abundant evidence that (osteo-) chondral defects represent an increased risk for the development of early osteoarthritis (OA) (1).

Several diagnostic and surgical techniques and guidelines have been developed to identify and treat patients who could benefit from a surgical approach to prevent knee OA or limit its progression (1, 2). Microfracture (MF) represents nowadays the most commonly used technique for the treatment of small-

Keywords: microfracture; ACL reconstruction; cartilage; AMADEUS; MOCART; cartilage defect

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sized cartilage defects (3), although some reports indicate inadequate tissue regeneration and early clinical outcome deterioration (4, 5).

It is known from *in vitro* and animal studies that biological stimulation as well as bone marrow activating measures may enhance outcome, quality and structure of newly formed cartilaginous tissue (6). This stimulation is triggered when performing MF and -to a greater extent- ACL reconstruction by providing an initial, yet temporarily limited large influx of mesenchymal stem cells (MSCs) and growth-factor-containing bone marrow into the joint (7). Experience derived from meniscus repair suggests that improved healing may result from the concomitant activation of bone marrow components, as verified in the context of combined ACL reconstruction and meniscus surgery (8). Therefore, bone marrow stimulation is now generally considered to yield beneficial effects on cartilage tissue maturation.

Nevertheless, knee-joint stability remains a crucial factor in the protection of the cartilage repair process since shear-forces may limit cell-differentiation and appropriate tissue formation (9).

On the other hand, the additional surgical traumatism derived by ACL reconstruction could negatively affect the clinical outcomes of the MF procedure. Thus, it was hypothesized that microfracture and concomitant ACL reconstruction in cartilage and ACL deficient knees would result in better clinical and radiological outcomes than microfracture alone in cartilage deficient knees.

MATERIALS AND METHODS

The primary goal of this prospective comparative study was to test the hypothesis that clinical and radiological results of patients surgically treated with ACL reconstruction combined with MF are not inferior to those of patients receiving MF alone for small cartilage defects of the femoral condyles.

Patients referring to our institution for evaluation and treatment of focal cartilage lesions of the knee with or without associated instability were evaluated for inclusion between 2014 and 2017. Inclusion criteria were the presence of symptomatic focal cartilage lesions at

the medial or lateral femoral condyles with a maximum size of 2.2 cm² (Outer bridge grade 3 - 4) with or without associated ACL deficiency. Furthermore, among patients with an ACL deficient knee, ACL tears with moderate to severe instability (Grade 2 and 3) had to be sports-related, diagnosed within 6 weeks of injury and confirmed with Magnetic Resonance Imaging (MRI) to be included. Further inclusion criteria were patients' age greater than 18 years, and compliance to the study protocol including availability of preoperative MRI examinations and the possibility to participate on follow-up examinations.

Exclusion criteria were previous surgery on the affected knee, multiple injuries of the ipsilateral knee with concomitant surgery (multi-ligament lesions, meniscus lesions, patellar or tibial cartilage lesions) previous conservative treatment and cartilage treatments or history of neuromuscular or systemic diseases.

Allocation to one of the two treatment groups was based on the presence of an isolated focal cartilage lesion (primary stable knees, MF) or on the presence of a focal cartilage lesion associated to an ACL tear (ACL deficient knees, MF + ACL).

Surgery was performed in general anaesthesia or spinal anaesthesia. The surgical approach for MF has been comprehensively described before (10). For ACL reconstruction, either the semitendinosus tendon alone or both the semitendinosus and gracilis tendons were harvested and reconstruction was performed in a double-bundle technique. The tibial tunnels were created at the center position of the insertion of the anteromedial bundle and posterolateral bundle. The femoral tunnels were created through the tibial tunnels, as described previously (11). After the grafts were passed through the tunnels, femoral fixation was performed with titanium buttons and tibial fixation using bioabsorbable screws. Patients allocated to MF underwent pure cartilage stimulation using the MF technique, whereas ACL-deficient patients allocated to MF + ACL received additional ACL reconstruction (MF + ACL).

Postoperatively, all patients underwent the same rehabilitation protocol including initial partial weight bearing (max. 20 kg) with subsequent stepwise increase until full weight bearing was reached about eight weeks after surgery. Furthermore, continuous passive motion was started on day one after surgery for a minimum of four hours per day. Flexion was limited to 30° for 2 weeks

and increased by 30° every second week. Patients were evaluated clinically before surgery and at a minimum follow-up of 24 months using the Tegner-Lysholm-Score (12). In addition, a pre- and postoperative MRI of the affected knee was performed (3 T or 1.5 T with MR sequences including intermediate-weighted images in at least 2 planes and a T1-weighted sequence in at least 1 plane).

Preoperatively the cartilage defect severity was radiologically classified using the AMADEUS-Score, that assesses area, depth and subchondral involvement of cartilaginous defects (13). Postoperative radiologic evaluation was done using the MOCART-Score, which uses the degree of defect filling, surface, structure, signal intensity and integration to border zones of the repair tissue and, degree of subchondral defects as parameters for the assessment of cartilage repair tissue after surgical intervention (14).

Statistical analysis was performed using SPSS (24.0, IBM, Chicago). Descriptive statistics are presented as means and standard deviation for continuous variables and as counts and percentages for categorical variables. Interval scaled data were compared using a two-sided student's test. Inter(sub)group differences were analyzed using the Kruskal-Wallis-test. p -Values < 0.05 were considered significant. A power analysis was performed to determine the sample size required for two outcomes: Lysholm-Tegner-score and MOCART-score. For the Lysholm-Tegner-score it was focused on the test of noninferiority to compare MF with MF+ACL (1-sided α = 0.05 power = 80%; expected mean difference = 0, standard deviation = 7.5). The margin was derived from a minimal important difference of 4-9 for the Lysholm-score (15). Thus, a minimum sample size of 23 was calculated. For the MOCART-score a smaller sample size was found to be sufficient as minimal important differences are described at 4-7 points.

The study was approved by the institutional review board and was in accordance with the Declaration of Helsinki (World Medical Association) in its latest version. Informed consent was obtained from all individual participants included in the study.

RESULTS

Initially, 73 patients were included into this study. Of those, 6 patients (8%) were lost to follow-up (3 in each group), so that 67 patients (age: 37.0 ± 11.1 ; males: 61%, females: 39%) were available for finale evaluation (mean follow up time: 29.3 ± 4.1 months after surgery). Demographic data of the study population is reported in Table I.

Fourty patients showed an isolated focal cartilage lesion without ACL deficiency and were allocated to treatment MF, whereas 27 patients presented a focal cartilage lesion with associated ACL deficiency and were allocated to MF + ACL.

Patients in the MF group had a preoperative Tegner-score of 3.9 ± 0.7 and a Lysholm-score of 56.8 ± 8.8 . The MF + ACL group had an insignificantly higher preoperative Tegner-score of 4.2 ± 1.1 ($p > 0.05$) and a significantly lower Lysholm-score of 48.8 ± 7.4 ($p < 0.001$). Preoperative, radiologic cartilage defect sizes did not differ significantly between MF (1.5 ± 0.4 cm²) and MF + ACL (1.4 ± 0.7 cm²; $p > 0.05$) group (Table II). Intraoperative defect sizes (MF: 1.3 ± 0.7 cm², $p = 0.73$; MF + ACL: 1.3 ± 0.8 cm², $p = 0.82$) did not differ significantly from preoperative radiologic defect sizes.

The preoperative AMADEUS-scores were 66.3 ± 14.7 in the MF and 67.2 ± 13.6 in the MF + ACL group and thus AMADEUS Grade II. Postoperatively, the MF group had a Tegner-score of 3.8 ± 0.8 and Lysholm-score of 67.5 ± 9.2 (Table III).

Table I. Summary of demographic details of each group.

	MF	MF + ACL
Male / Female	25/15	12/15
Age (in yrs.)	38.4 (18- 55)	35.2 (18 – 41)
Medial / Lateral	21/19	12/15
Left / Right	18/22	14/13

Table II. Summary of the results obtained in the subitems of the Amadeus- as well as the Mocart-score. The Grade of the Amadeus-score corresponds with the sum of the digits 1-4. The maximum of 100 corresponds with intact cartilage while 0 indicates maximal damage. Grade I signifies a score of > 75 , II > 50 , III > 25 and IV < 25 . The Mocart-score is composed of 8 subitems. Again, a score of 100 corresponds with intact cartilage while 0 indicates maximal damage. n.s. = not significant; $p < 0.05$ is considered significant.

Amadeus				Mocart			
	MF	MF + ACL	p		MF	MF + ACL	p
Defect Area (1 st Digit)	26.5 $\pm$ 6.0	29.4 $\pm$ 6.2	n.s.	Degree of defect	15.7 $\pm$ 3.2	17.6 $\pm$ 3.2	0.03
				Integration into border zone	12.9 $\pm$ 2.9	13.4 $\pm$ 2.3	n.s.
Defect Depth (2 nd Digit)	10.9 $\pm$ 4.7	7.8 $\pm$ 5.1	0.01	Surface repair tissue	7.0 $\pm$ 2.4	8.4 $\pm$ 2.3	0.02
				Structure repair tissue	2.2 $\pm$ 2.5	3.6 $\pm$ 2.2	0.03
Subchondral Defect (3 rd Digit)	20.7 $\pm$ 8.1	23.2 $\pm$ 6.8	n.s.	Signal intensity repair tissue	16.1 $\pm$ 7.5	16.4 $\pm$ 8.3	n.s.
				Subchondral lamina	2.4 $\pm$ 1.7	2.2 $\pm$ 2.5	n.s.
BME (4 th Digit)	8.3 $\pm$ 3.8	6.8 $\pm$ 4.7	n.s.	Subchondral bone	3.9 $\pm$ 2.1	4.0 $\pm$ 2.0	n.s.
				Adhesions	3.9 $\pm$ 2.1	4.6 $\pm$ 1.4	n.s.
Score	66.3 $\pm$ 14.7	67.2 $\pm$ 13.6	n.s.	Effusion	4.5 $\pm$ 1.5	4.6 $\pm$ 1.4	n.s.
Grade	II	II		Score	67.9 $\pm$ 13.2	74.8 $\pm$ 11.5	0.04

Table III. Pre- and postoperative Tegner und Lysholm-Score are presented in this table for both, MF as well as MF plus ACL group. n.s. = not significant; $p < 0.05$ is considered significant.

Amadeus				Mocart			
	MF	MF + ACL	p		MF	MF + ACL	p
Defect Area (1 st Digit)	26.5 $\pm$ 6.0	29.4 $\pm$ 6.2	n.s.	Degree of defect	15.7 $\pm$ 3.2	17.6 $\pm$ 3.2	0.03
				Integration into border zone	12.9 $\pm$ 2.9	13.4 $\pm$ 2.3	n.s.
Defect Depth (2 nd Digit)	10.9 $\pm$ 4.7	7.8 $\pm$ 5.1	0.01	Surface repair tissue	7.0 $\pm$ 2.4	8.4 $\pm$ 2.3	0.02
				Structure repair tissue	2.2 $\pm$ 2.5	3.6 $\pm$ 2.2	0.03
Subchondral Defect (3 rd Digit)	20.7 $\pm$ 8.1	23.2 $\pm$ 6.8	n.s.	Signal intensity repair tissue	16.1 $\pm$ 7.5	16.4 $\pm$ 8.3	n.s.
				Subchondral lamina	2.4 $\pm$ 1.7	2.2 $\pm$ 2.5	n.s.
BME (4 th Digit)	8.3 $\pm$ 3.8	6.8 $\pm$ 4.7	n.s.	Subchondral bone	3.9 $\pm$ 2.1	4.0 $\pm$ 2.0	n.s.
				Adhesions	3.9 $\pm$ 2.1	4.6 $\pm$ 1.4	n.s.
Score	66.3 $\pm$ 14.7	67.2 $\pm$ 13.6	n.s.	Effusion	4.5 $\pm$ 1.5	4.6 $\pm$ 1.4	n.s.
Grade	II	II		Score	67.9 $\pm$ 13.2	74.8 $\pm$ 11.5	0.04

Compared to these results, the MF + ACL group had an insignificantly higher Tegner-score of 4.1 ± 1.2 ($p > 0.05$) but a significantly higher Lysholm-score of 77.6 ± 6.3 ($p < 0.001$). In both groups, there was no significant difference between pre- and postoperative Tegner-scores. In contrast, pre- and postoperative Lysholm-scores increased significantly in both groups (MF: $p = 0.002$ and MF + ACL: $p < 0.001$). Postoperative MOCART-scores were significantly different between both groups (MF: 67.9 ± 13.2 and MF + ACL: 74.8 ± 11.5 ; $p = 0.04$).

DISCUSSION

The most important finding of this study was that patients treated with a combination of MF + ACL reconstruction did not achieve inferior results as compared to patients receiving MF alone; patients treated with a combination of MF + ACL reconstruction actually reached better clinical (Lysholm) and radiological outcome values compared to patients undergoing MF treatment only. Although both groups had similar preoperative radiological AMADEUS characteristics, MF + ACL resulted in superior radiological MOCART outcomes.

MF is a well-investigated and often-used technique for the treatment of small-sized cartilage defects. MF induces the remodeling of a fibrin clot into fibrocartilage composed primarily of type I collagen, with only minimal type II collagen by MSCs and growth factor activation (16). Meta-analysis of MF outcomes demonstrated positive short-term functional improvement.

However, there are studies suggesting limited outcomes after MF. Gudas et al. found osteochondral autologous transplants to be a superior method when assessing patients according to the international knee documentation committee (IKDC) score (17). Rotterud et al. even found deteriorating clinical and functional outcomes when assessing patients treated by MF (18). A more recent study by Volz and colleagues found inferior results of MF after five years compared to autologous Matrix-Induced Chondrogenesis (19). All these studies, however, did not separate analysis for cartilage's defect

sizes smaller or larger than 2 cm^2 although they did distinguish between these sizes descriptively. Unfortunately, there is a paucity of data exploring long-term results of this surgical technique.

Overall knee-joint stability represents one crucial factor in cartilage repair as increased shear-forces may limit cell-differentiation and appropriate tissue formation in cases of ACL ruptures (9). In contrast, there are studies suggesting that cartilage quality is diminished and osteoarthritis has an earlier onset after ACL reconstruction has been performed (20). This may be explained best by stating that those studies evaluating cartilage's quality did not address cartilage lesions in the first place or due to biomechanical reasons such as overstrain. When drilling the osseous tunnels for ACL reconstruction, there is an additional increased influx (compared to MF alone) of bone marrow derived MSCs and growth factors into the joint. It has already been shown that both, MSCs and growth factors, enhance the regenerative capacity of cartilage or stimulate other cell lines to differentiate accordingly.

The present study provides both clinical and radiological data in the context of MF plus ACL reconstruction. Notably, the Lysholm-score was preoperatively significantly lower in the MF + ACL group compared to the MF group. This was inversed at two years of follow-up when the MF + ACL group demonstrated significantly higher scores than the MF group.

So far, there is no study assessing radiological and clinical outcome parameters simultaneously for MF as compared to MF plus ACL. A recent study by Hashimoto and colleagues found significantly better KOOS and MOCART-score values for patients treated by MF and concomitant transplantation of autologous bone marrow-derived mesenchymal stem cells compared to patients treated by MF only.

The present study is the first to evaluate clinical and radiological outcome parameters of MF and concomitant ACL reconstruction. Although the present study may be criticized for its relatively small study population, power analysis was performed to assess the number of individuals to be included to sufficiently address the research question. While further studies shall include more patients, overall

study population will generally be limited by strict inclusion criteria (exclusion of patients with concomitant joint pathologies and injuries, small cartilage defect area, etc.). As the Lysholm-score does not depict clinical features of cartilage repair in complete detail, further studies may use more differentiated clinical outcome parameters. Yet, the usage of radiological, joint cartilage assessing scores strengthens the overall value of this study.

Concomitant ACL-reconstruction seems to support biological healing responses in MF treated cartilage defects, which is expressed in significantly improved clinical and radiological outcome measures and is most likely explained by an additional bone marrow influx.

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Transosseous suture loop technique for MPFL reconstruction

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Patellar dislocation represents a rare but invalidating trauma. Indeed, 94 to 100% of patients suffer from medial patellofemoral ligament (MPFL) rupture just after the first patellar dislocation, and approximately half of these patients develop recurrent dislocations. MPFL reconstruction is a commonly performed surgery for patellofemoral instability. Anatomic reconstruction of the MPFL restores patellar stability in patients with recurrent patellar instability with neutral lower limb alignment. We describe a technique, which creates an anatomic reconstruction using trans-osseous suture loop. Conclusion: Compared to similar techniques, the described procedure has the following advantages: smaller tunnels, less donor side morbidity, reduced risk of graft failure, minimal invasiveness, more appealing cosmetic results and easily reproducible. Complications and outcomes of this technique, including the risk for patellar fracture, must be further evaluated in a larger patient cohort with longer follow-up.

Medial patellofemoral complex comprises of medial patellofemoral ligament (MPFL) and the medial patellotibial ligament (MPTL). They both restrain the lateral patellar displacement. MPFL provides 60% of the restraining force to lateral patellar translation (1). Non-operative treatment still remains the gold standard for a first-time traumatic patellar dislocation in the absence of an osteochondral fracture. Clinically, up to 94 to 100% of patients suffer from MPFL rupture just after the first patellar dislocation, and approximately half of these patients develop recurrent dislocations (2). Thus, MPFL reconstruction is necessary in all cases of chronic

objective patellar instability, to re-establish the primary passive patella-femoral stabilizer.

A thorough knowledge of the anatomy and biomechanics of associated soft-tissue and osseous structures around the medial side of the knee is essential to ensure the success of the surgical procedures (3). Radiological parameters such as patellar alta, patellar tilt, an increased tibial tubercle-trochlear groove (TT-TG) distance, and significant coronal-plane malalignment should be preoperatively evaluated.

The femoral insertion of the MPFL is approximately 10 mm distal to the apex of the

Key words: medial patellofemoral ligament; reconstruction; patellar instability; surgical technique

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adductor tubercle and 16 mm proximal to the medial epicondyle (4). MPFL is in layer 2 of the medial soft-tissue structures between medial retinaculum (layer 1) and knee capsule (layer 3). The MPFL serves as the primary static soft-tissue restraint to lateral patellar translation in the first 20 degrees to 30 degrees of flexion and it is relaxed in higher degrees of flexion. In the absence of trochlear dysplasia, the trochlea produces osseous restraint beyond 30 degrees of flexion, maintaining patellofemoral stability.

Schöttle et al. (4) in his cadaveric study, described the femoral insertion at 1.3 mm anterior to the posterior cortical extension line, 2.5 mm distal to the posterior origin of the medial femoral condyle, and 3 mm proximal to a perpendicular line intersecting the posterior point of the Blumensaat line on a lateral radiograph. In our experience, Schöttle's point serves as a reliable landmark for femoral side fixation as it is easy to identify consistently the MPFL femoral insertion, which is posterior to the femoral epicondyle and anteroinferior to the adductor tubercle.

Several techniques of MPFL reconstruction have been proposed with promising results in terms of patient satisfaction and re-dislocation rate. However, each of these techniques may present peculiar problems and complications.

Graft fixation methods include suture fixation, interference screws, suture anchors, staples, and suspensory cortical fixation devices. A technique without any hardware and good clinical outcome with no hardware related complications has also been described.

In absence of standard defined practice guidelines or high-quality evidence, the performance of an MPFL reconstruction is currently guided by surgeon preference and skills and factors such as allograft availability. The aim of this study is to describe the anatomical double bundle MPFL reconstruction with a transosseous loop for the patella fixation and an open fixation at the femur.

Surgical indications

The meticulous knee evaluation is mandatory to select the right candidate for surgery. Patellar mobility is assessed in full extension and compared with the contralateral side; patellar tracking is assessed with

the help of the J sign. Limb alignment is assessed to evaluate femoral anteversion, genu valgum, and external tibial torsion. Hip and quadriceps muscular strength should be assessed.

Radiographic evaluation includes standard anteroposterior, lateral, and axial weight-bearing views. The lateral radiograph can be used to assess the patellar height and depth of the femoral trochlea. The axial radiograph can be used to assess the femoral sulcus angle, congruence angle, lateral patellofemoral tilt angle, lateral shift ratio, and absolute lateral patellar displacement. Computed tomography is used to measure the tibial tubercle and trochlear groove distance. Magnetic resonance imaging can be used to evaluate other injuries after a patellar dislocation, including a bone contusion on the lateral femoral condyle and medial patella, as well as an MPFL tear and articular cartilage injury (5).

The surgical timing in case of patellar instability is still debated. Our indications include recurrent instability despite a trial of nonoperative treatment that typically includes patella-stabilizing braces and physical therapy to include quadriceps, hip, and core muscle strengthening. In patients with osteochondral injuries and intra-articular bodies, arthroscopy is indicated for the treatment of these injuries and concomitant MPFL reconstruction. Contraindications to an isolated MPFL reconstruction include limb rotation and alignment abnormalities.

Surgical Technique

Diagnostic arthroscopy of the knee is performed to exclude intrarticular pathologies. The patellofemoral joint and cartilage status are evaluated, assessment of patellar congruence and tilt during gentle knee range of motion are also noted.

A 2-cm vertical skin incision is made to perform the gracilis harvesting. The two ends of the tendon graft are each sutured with no. 2 ethibond sutures using a whipstitch technique up to approximately 2 cm from each end.

3 cm midline vertical incision is made on the medial aspect of middle third of the patella. 2 parallel tunnels are made in patella using 2.5 mm beath pins. 1 tunnel at the junction of upper and middle third and other at junction of middle and lower third.

Small stab incision is made on the lateral side to pass the suture loops. Ultra high molecular weight polyethylene sutures are passed from the lateral side to medial side with a metal pin (Fig. 1). A pin used to pull through the suture loops from lateral to medial. 2 suture loops are held separately to avoid entanglement. Then centre of the graft is placed at the midpoint of the tunnel and fixed medially over patella with the help of pulled out threads. Five half hitches is used to secure the fixation.

Tenotomy scissors are used to dissect between the layers 2 and 3, remaining extracapsular. A blunt clamp is used to fully develop the retinacular tunnel connecting the 2 incisions between layers 2 and 3 (Fig. 2). The 2 free ends of the graft are then retrieved from the patellar side incision, shuttled to the femoral side (Fig. 3).

1.0 mm Kirschner wire is then placed in the central point between the adductor tubercle and the medial epicondyle, (Schöttle's point) and is again verified on fluoroscopy. The K-Wire is passed from medially to laterally, which is then over-drilled with 4.5 mm reamer (Fig. 4).



Fig. 1. Small stab incision is made on the lateral side to pass the ultra-high molecular weight polyethylene sutures through 2 parallel patellar tunnels (diameter: 2.5mm; 1 at the junction of upper and middle third and other at junction of middle and lower patellar third).



Fig. 2. Pin used to pull through the suture loops from lateral to medial.



Fig. 3. Free end of the loop is pulled to approximate the graft to the freshened medial surface of the patella and secured.

Graft is pulled down to the femoral side and the free ends of the thread are loaded into the pin. The pin is then pulled out from medial side to lateral side. Interference screw is then used for femoral side fixation.

The graft ends are provisionally secured to the femur to assess for the appropriate degree of lateral patellar restraint. This is performed by first placing a towel bump below the knee, maintaining 30 degrees of knee flexion (Fig. 5).

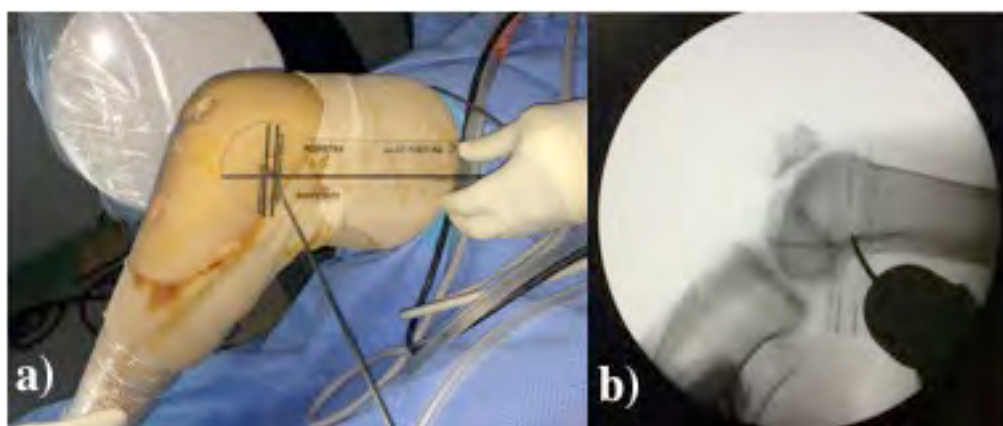


Fig. 4. *A): Clinical landmark of Schottle's point is between adductor tubercle and medial epicondyle; B): Fluoroscopic localization of the same landmark is done to confirm.*

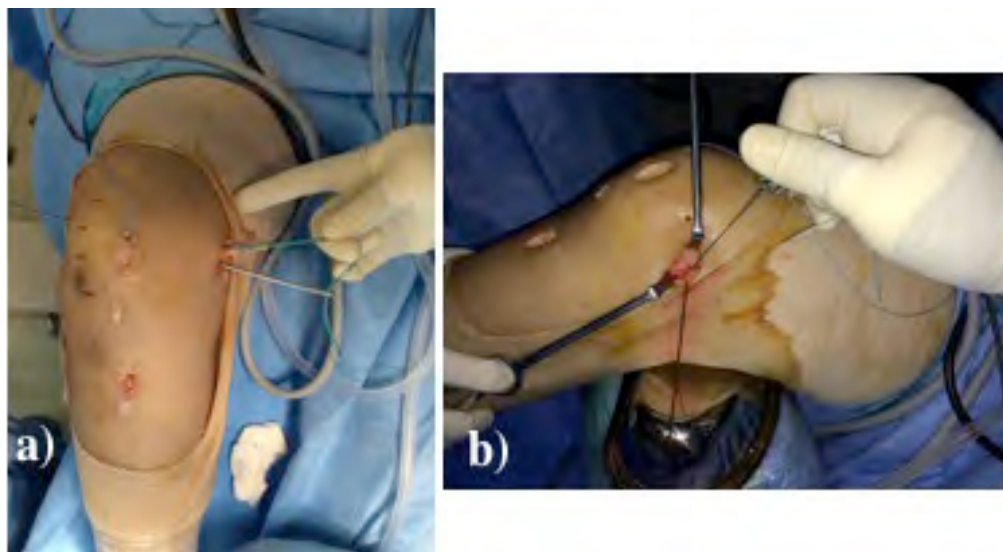


Fig. 5. *A): Threading the proximal end of the gracilis graft through the pin at the Schottle's point; B): The figure above shows guide wire in situ and cinched ethibond passed around the graft to prevent sinking of the graft during interference screw fixation.*

The patella should be observed tracking centrally in the trochlear groove, and extra-articular placement of the graft should be confirmed. Once the graft is appropriately tensioned, definitive fixation to the femur is performed. All suture ends from both incisions are cut, and the wounds are thoroughly irrigated.

During closure of the patellar incision, layers 1 and 2 are gently imbricated with non-absorbable suture only to match the resting tone of the reconstructed ligament. After closure of these layers,

lateral patellar glide is again assessed to ensure that normal mobility has been restored without over-tensioning of the retinacular layers. The remaining closure is then performed in standard fashion, and a sterile dressing is applied.

Postoperatively, supervised active knee range of motion is instituted at day 1 after surgery, emphasizing quadriceps isometrics and range of motion. Patient is advised to achieve at least 90 degrees of knee flexion at the end of 3rd week. Partial weight bearing with 2 crutches is started immediately and continued for 3

weeks. The crutch on the operated side is removed after 2 weeks. Long knee brace is applied for 2 weeks. Return to sporting activities typically occurs 3 to 6 months after surgery.

DISCUSSION

Many authors have described different techniques for MPFL Reconstruction: various transfers using quadriceps tendon (6), patellar tendon (7), semitendinosus tendon (3), or adductor magnus tendon (8). These grafts were used as a single-bundle graft, whereas few authors have used a free tendon graft in a single patellar tunnel.

However, these techniques failed to replicate the native anatomy of MPFL, which is a double bundle structure and has a broad patellar attachment, finally causing non-physiologic loads and kinematics of the patellofemoral joint. Hence, several authors have proposed a two-bundle technique using free tendon grafts (9).

The aim of this paper is to describe anatomical two-bundle MPFL reconstruction with a gracilis tendon autograft and hardware-free patellar graft fixation using transosseous tunnels. The concept of anatomical two-bundle MPFL reconstruction with hardware-free patellar graft fixation has been previously reported. However, these authors used the semitendinosus tendon, which required tunnel diameters of 5-6 mm.

Double bundle technique gives the advantage of anatomical reconstruction of MPFL. In view of its two-point fixation at patella it leads to lesser patellar rotation during flexion-extension movement and higher stability throughout a greater range of motion. Graft selection, tunnel pattern and patellar side fixation are still few topics of debate.

Larger tunnel diameters (usually 5–6 mm) are required for a semi-tendinosus graft (10). This leads to higher risk of violating the anterior cortex or cartilage. Moreover these tunnels might create stress risers with increased risk for patellar fracture (11). Furthermore, long tendon grafts combined with long tunnels increase the risk of mobilization of the graft within the tunnel, possibly leading to tunnel widening or abrasion of the graft at the tunnel.

Few authors have even studied the type of tunnel, which needs to be drilled for MPFL. V-shaped tunnel at the superomedial half of the patella through which gracilis graft was looped around was described. Two 5-mm diverging transpatellar tunnels described by Panni et al. (12) more closely replicate the course of the inferior-straight and superior-oblique bundle LeGrand et al. (13) described a technique with two oblique tunnels. Christiansen et al. (14) described a technique where the gracilis tendon was looped through two transverse 4.5-mm drill holes in the patella, comparable to our technique.

However, hardware-free patellar graft fixation has the advantage of lower risk for soft tissue irritation, implant pain, and foreign body reactions, and it also makes a cost-effective procedure. However, each of these techniques has its specific shortcomings; thus, we have developed a modified technique. We usually drill two tunnels of 2.5 mm in diameter, which is considerably smaller compared to other techniques. Smaller patellar tunnels might lower the risk of joint penetration. For looping the suture material, a small incision is required. Therefore, a longer additional lateral incision is not necessary.

Our technique for patellar graft passage requires only one incision of about 3 cm lengths at the medial patellar border, making this technique less invasive and cosmetically more appealing. Most of the patella fractures occurred during activities of daily living or minor traumas, especially transverse bone tunnels traversing the entire width of the patella, and long oblique tunnels are believed to create stress risers with a considerable risk of patellar fracture.

Hence it is important to develop a surgical technique where the risk of patella fracture is minimized. By using shorter tunnels with smaller diameters, we thought to minimize the risk of patellar fracture. To avoid patellar drill holes, suture fixation of the graft might be an alternative technique (15). However, due to less initial fixation strength, range of motion and full weight bearing are usually restricted for the first 3-6 weeks postoperatively.

Our technique provides high initial fixation strength, enabling immediate full range of motion and faster rehabilitation. Due to the lack of a control group, this article cannot answer the question

whether this technique is superior compared to other techniques. Further evaluation in a larger patient cohort with a longer follow-up is necessary to confirm the safety and effectiveness of this technique.

Compared to similar techniques, the described modification of an anatomical MPFL reconstruction with hardware-free patellar graft fixation has the advantage of smaller tunnels, less donor side morbidity, reduced risk of graft failure, minimal invasiveness, more appealing cosmetics and easily reproducible.

The preliminary results of this technique are encouraging and comparable to those of other MPFL reconstruction techniques. Complications and results of this technique, including the risk for patellar fracture, must be further evaluated in a larger patient cohort with longer follow-up.

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Kinematic versus mechanical alignment in total knee arthroplasty: a preliminary study

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Despite the great advances of the technology in the joint prosthesis and the high execution rate of total knee arthroplasty (TKA), there are still about 15% of clinical unsatisfactory rate in this surgery. TKAs are currently performed using a mechanical alignment of the knee, correcting varus/valgus deformities with the purpose to achieve a longer implant survivorship, but this surgical technique results in an alteration of the normal knee kinematics. Nowadays, the idea to restore the pre-arthritic alignment of the knee with the goal to obtain a normal kinematics and better functional results becomes more and more consistent and the kinematic alignment (KA) was developed as alternative to the mechanical one. The aim of this preliminary study is to analyse the functional outcomes in patients who underwent KA-TKA in the short-term follow-up and to compare them with those obtained in patients treated by the mechanical alignment (MA) TKA. Therefore, skeletally mature patients, with no history of previous knee surgical procedures, who underwent isolated TKA for knee osteoarthritis, were included in this study. The patients were prospectively divided into two homogeneous groups according to the different surgical techniques performed (KA-TKA and MA-TKA groups). Clinical and functional scores (VAS, KOOS-PS, MCS-12, Final KSS, and Functional KSS) were collected pre- and postoperatively at a mean follow-up of 3 three months. As a result, 26 patients were included in the study, with a mean age of 69.3 ± 7.61 years old (range: 55 - 84 years old). There were 38.5% male and 61.5% female. There were 13 patients in KA-TKA and 13 patients in MA-TKA. Three months after surgery each of the scores tested demonstrated statistically significant better outcomes in KA-TKA, compared to the MA-TKA group. MCS-12 resulted comparable in the two study groups. This preliminary study compares the short-term clinical and functional outcomes between KA and MA in total knee replacement. Further studies are required to confirm these results and to extend the sample size to obtain reliable clinical evidences.

Total knee arthroplasty (TKA) is one of the most consistently successful surgeries in orthopaedic practice. Despite several technologic developments and the high execution rate of TKA, there is still about 15% of dissatisfaction rate in this surgery. The adequate placement of the implant components is the

most important predictor of the best clinical outcome in TKA (1).

Nowadays, there are three possibilities for the alignment in TKA: anatomical alignment (AA), mechanical alignment (MA) and kinematic alignment (KA). The AA provides a varus component

Key words: total knee arthroplasty; kinematical alignment; mechanical alignment

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alignment of 2° - 3° in relation to the mechanical axis of the lower limb by cutting the tibia at 3° varus and the distal femur approximately at 8° - 9° valgus (2). The MA provides a neutral component alignment by cutting the femur and the tibia perpendicular to the relative mechanical axis and axially aligning the femoral component with the Trans-epicondylar axis (TEA), which was believed originally to be the flexion-extension axis of the native knee, creating a femorotibial joint line perpendicular to the neutral limb mechanical axis (3). The KA is a new theory for TKA, that uses new landmarks to set the 3D orientation of the femoral and tibial implants (4). This technique has three main goals: restore the native tibial-femoral articular surfaces; restore the native knee and limb alignments; restore the native laxities of the knee (5).

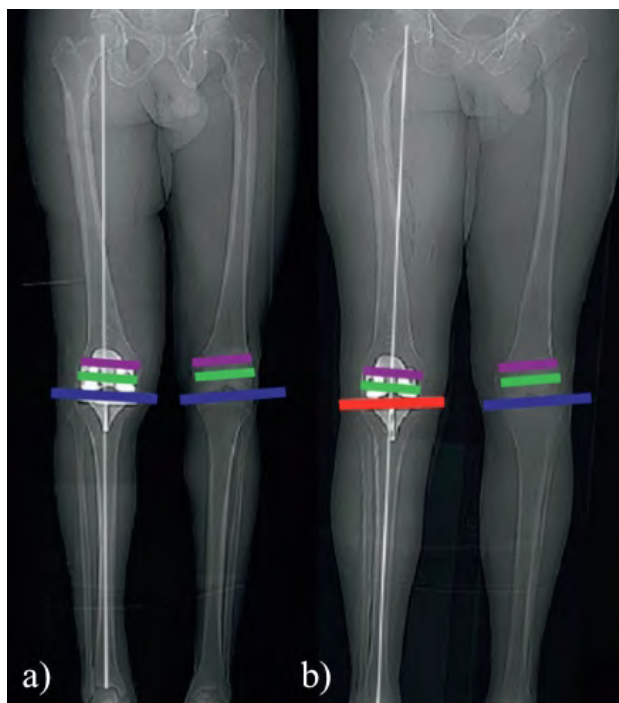


Fig. 1. *a)* Kinematic alignment TKA restores the native tibial-femoral joint surface (blue line) and the native limb alignment (white line). The axes of the femoral component are co-aligned with the flexion axes of the tibia (green line) and patella (magenta line); *b)* the mechanical alignment TKA changes the native tibial-femoral joint surface (red line), the native limb alignment, and misaligns the axes of the femoral component oblique to the flexion axes of the tibia and patella.

It is well known that there is a interindividual variability in lower limb alignment with common constitutional varus, which may require soft-tissue releases if corrected with AA or MA (6). In current years, the idea to recreate a physiological knee kinematics, to obtain better clinical and functional outcomes, started to be very popular among the orthopaedic surgeons.

The aim of this preliminary study is to analyse the short-term outcomes in patients undergoing KA-TKA, and to compare them with the outcomes obtained with MA-TKAs.

MATERIAL AND METHODS

Skeletally mature consecutive patients, with no history of previous or concomitant knee surgical procedures, who underwent isolated TKA for knee osteoarthritis, were included in this study (Fig. 1).

The patients were prospectively divided into two homogeneous groups according to the different surgical techniques performed (KA-TKA and MA-TKA groups). All patients were evaluated with clinical and functional scores at two different time points (preoperatively and three months after surgery). The scores utilized were the Visual Analogue Scale (VAS), the short form of the Knee injury and Osteoarthritis Outcome Score - Physical function (KOOS-PS), the 12-item Short Form Survey (SF-12), the Knee Society Score (KSS), and patient's perception of outcomes and their feelings about the TKA surgery (7).

Statistical analysis was performed using GraphPad Prism 6.0 software (GraphPad Software Inc., La Jolla, CA, USA). Continuous variables were expressed as the mean $\pm$ standard deviation as appropriate. The Shapiro-Wilk normality test was used to evaluate the normal distribution of the sample. Differences between pre- and post-operative measurements were analysed with t-Student test and the significance level was set at $P < 0.05$.

RESULTS

In the study, 26 patients were included, with a mean age of 69.3 ± 7.61 years old (range: 55 - 84 years old). There were 38.5% males and 61.5% females. There were 13 patients in KA-TKA and 13

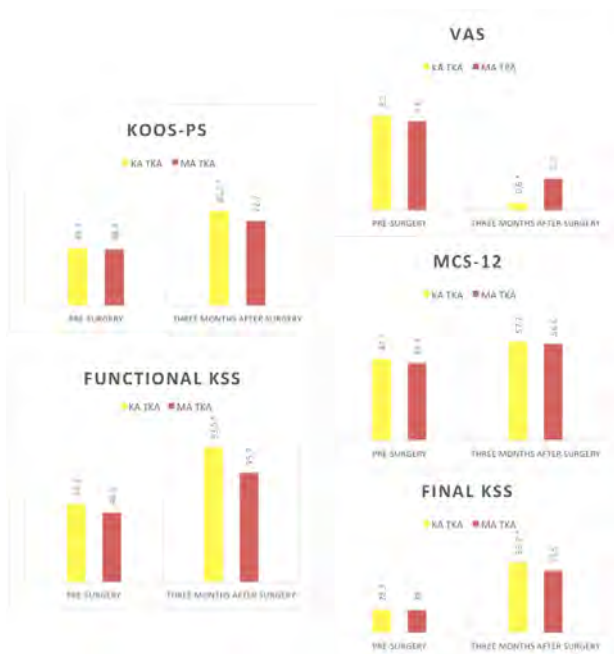


Fig. 2. Comparison between Pre- and Postoperative KA and MA TKA clinical outcomes.

patients in MA-TKA. Demographics of the study groups were reported in Table I.

No statistical significant differences in sociodemographics analysis were found, therefore, the two groups were considered homogeneous in terms of age, sex and BMI. The clinical characteristics were also considered statistically homogeneous, as no significant difference could be seen also in these variables. Clinical conditions were comparable in terms of articular disability, assessed through the KOOS-PS and the two sections of KSS, which resulted in poor clinical and functional level for both groups.

Three months after surgery each of the scores tested demonstrated statistically significant better outcomes in KA-TKA, compared to the MA-TKA group. The comparison between the two groups demonstrates significant outcome differences (p -value <0.05) in five scores tested: VAS (Preoperative KA: 8.1 ± 1.27 , MA: 7.6 ± 2.24 ; Postoperative KA: $0.6 \pm 0.54^*$, MA: $2.7 \pm 2.19^*$), KOOS-PS (Preoperative KA: 49.4 ± 14.87 , MA: 48.3 ± 15.38 ; Postoperative KA: $81.3 \pm 7.07^*$, MA: $77.7 \pm 9.71^*$), Functional KSS (Preoperative KA: 54.2 ± 18.49 , MA: 48.1 ± 14.61 ; Postoperative KA:

$93.46 \pm 10.26^*$, MA: $75.77 \pm 16.15^*$), and Final Knee Score (Preoperative KA: 28.3 ± 8.25 , MA: 28 ± 10.99 ; Postoperative KA: $85.7 \pm 3.81^*$, MA: $75.5 \pm 9.64^*$). Only MCS-12 (Preoperative KA: 47.7 ± 10.43 , MA: 45.3 ± 14.71 ; Postoperative KA: 57.73 ± 5.03 , MA: 56.58 ± 6.35) resulted comparable in the two study groups (Fig. 2).

DISCUSSION

The main finding of this study was that KA group reported significantly better clinical and functional results comparing to the MA group; both groups reported significant reduction of VAS at three months follow-up. KA patients resulted in better knee joint range of motion and daily-life abilities, assessed respectively through KOOS-PS, Final KSS, and Functional KSS. Each of these scores significantly improved after surgery for both groups and the KA group had better outcomes compared to those of the MA group. MA TKAs provide good long-term implant survivorship but its functional outcomes are disappointing (8).

The main intraoperative difference between these two techniques seems to be the patellar tracking that seems to be easier to normalized using a kinematic alignment of the knee. Patellar maltracking due to incorrect component alignment, is considered as a main reason for anterior knee pain after TKA (9). It is therefore reasonable to think that the short-term clinical differences between KA and MA may be due to a better efficiency of the extensor apparatus as well as the lower soft tissues stresses.

These better results could be bound to the more functional axis obtained after surgery, keeping the native alignment of the knee joint and soft tissue balance, and consequently reducing the alteration of the normal knee kinematics. Some Authors reported high clinical scores and superior functional outcomes in patients following kinematic TKA, when compared with MA, without risk of a catastrophic failure (10–13). A balanced TKA in flexion and extension seems to be more important than component position and alignment especially in determining short-term function after primary TKA for osteoarthritis of the knee. Therefore, our results

Table I. *Sociodemography of the study, before surgery.*

Sociodemographic characteristics	Overall (n=26)	Kinematic Alignment (n=13)	Mechanical Alignment (n=13)	p-value
Age class (y.o.)	n (%)	n (%)	n (%)	
<60	3 (11.54)	1 (7.69)	2 (15.38)	0.65
60-69	10 (38.46)	5 (38.46)	5 (38.46)	
≥70	13 (50)	7 (53.85)	6 (46.15)	
Mean age ± SD	69.3 ± 7.61	70 ± 7.08	69.1 ± 8.04	
Median age (range)	69.5 (55-84)	71 (55-81)	69 (57-84)	
Sex				
Male	10 (38,46)	6 (46.15)	4 (30.77)	
Female	16 (61,54)	7 (53.85)	9 (69.23)	
BMI				
Normal weight (<25 kg/m ²)	6 (23,08)	4 (30.77)	2 (15.38)	0.49
Overweight (25-<30 kg/m ²)	15 (57,69)	7 (53.85)	8 (61.54)	
Obese (≥30 kg/m ²)	5 (19,23)	2 (15.38)	3 (23.08)	
Mean BMI ± SD	27,95 ± 4,21	28.54 ± 4.84	27.36 ± 3.36	
Median BMI (range)	26,9 (22,07-38,97)	28.41 (23.18-38.97)	26.31 (22.07-33.79)	

are in line with recent scientific literature. While the better functional outcomes of KA technique might lead to an increased early functional outcomes, on the contrary it can cause a reduction of longer-term implant survivorship (14).

The varus tilt of tibial component has been shown to correlate with the contact stresses, even if the overall limb alignment is neutrally aligned (15). Related to a MA TKA, Nakamura et al. estimated the maximum stress on the tibial insert and on the tibial resection surface increases by 47% and 25%, respectively in the 6° varus KA TKA (12). However, 97.5% implant survivorship was reported in KA TKA with a tibial component up to 7° varus. This good results might be the consequence of a parallelism of the prosthetic femorotibial joint line to the floor when standing and walking in addition to a reliable restoration of the constitutional knee laxity (16, 17).

Some cautious Authors use computational assisted surgery to assess femoral and tibial components and restrict their indication of KA technique for patients with a small constitutional frontal limb deformity

(≤3°) and a distal femoral or proximal tibial frontal joint line with less than 5° obliquity (safe alignment zone) (18). Several limitations should be considered in this study. First, the small sample size and the short follow-up. Moreover, no radiological results were reported in this study; therefore, we were unable to correlate clinical findings with radiological outcomes. Despite these limitations, this is one of the first consecutive series to report the KA TKA outcomes. Future studies should follow to clarify and standardize the surgical decision-making process of these patients.

Total Knee Arthroplasty with Kinematic Alignment is an innovative and soft tissue sparing technique that has lesser impact on the knee joint compared to MA-TKA. This leads patients to better clinical and functional outcomes, and a more natural perception of the lower limb after surgery. These technical improvements may reduce the duration of the TKA postoperative rehabilitation protocols leading to an early return to patients' daily activities.

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Restoration of the degenerated cervical intervertebral space: how much should we distract? A magnetic resonance imaging study

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The aim of the study was to quantify normal cervical disc space measurements and to generate a normal values' database. Furthermore, during operative restoration of a degenerated intervertebral disc, it is difficult to calculate the amount of distraction required to restore the collapsed space to its normal height. A secondary purpose is personalizing the anatomical correction. Therefore, we expressed disc height based on measurements of its neighboring disc as an equation, by using simple linear regression. We reviewed MRI studies from asymptomatic healthy subjects (16 men–24 women, mean age 27.25 years). We measured midsagittal anterior, middle and posterior vertebral body and disc height, and disc diameter from C3 to T1 vertebra. We calculated mean disc height, disc height index (DHI) and disc convexity index per spinal level. C6-7 mean and anterior disc height were significantly greater than all respective measurements, except C5-6 ($p<0.01$). Middle C6-7-disc height was significantly greater compared to respective measurements in every other level ($p<0.01$). C5-6, C6-7 and C7-T1 mean disc height is significantly greater in men. Middle disc height is the greatest among disc heights in every spinal level. DHI does not differ between sexes, it increases from C3-4 to C5-6 with a slight decrease in C6-7, while its value significantly decreases in C7-T1 ($p<0.0001$). These measurements could be used for anatomical, individualized restoration of the degenerated intervertebral disc; thus, avoiding overdistraction. Our data could improve preoperative templating or implant design.

Normal intervertebral disc anatomy in the cervical spine is disrupted during the degenerative cascade, which results in pain generation and neurological damage. It has been previously reported that symptomatology is elicited due to compression of normal neural structures from disc prolapse, osteophytes and ligament hypertrophy, as well as neural ingrowth inside the degenerated disc (1-3).

Cervical spine degeneration begins early in the second decade of life, it is present in the majority of middle-aged patients and it is the commonest cause of neurological dysfunction, according to the historic study by Irvine et al. (4). This process is unavoidable with aging; relieving patients with nerve root symptoms or myelopathy can be worrisome for the treating physician. Friedenber and Miller showed that the

Key words: anatomy; imaging; intervertebral disc; neurosurgery; overdistraction

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most affected segments in the cervical spine are C5-6, C6-7 and C4-5, in descending frequency (5). When conservative modalities fail to control symptomatology, operative treatment is a suitable option.

As documented in earlier studies, the two most used surgical procedures are total disc replacement (TDR) and anterior cervical discectomy and fusion (ACDF), with good to excellent functional results and small perioperative risk (6, 7). Part of the operative technique is removal of the collapsed, painful disc and distraction of the degenerated intervertebral space, to decompress nerve roots at the intervertebral foramina and to position the implant.

However, the amount of distraction performed lies on the surgeon's discretion and experience and the force applied by distraction instruments, rather than achieving disc space restoration to previous, normal values. An oversized implant could lead to unpleasant and difficult to control postoperative complications.

Our effort was to quantify normal intervertebral

disc space; therefore, we measured anterior, middle and posterior disc height along with other imaging indices from magnetic resonance imaging (MRI) studies of the cervical spine in healthy controls, to create a database of normal values. Furthermore, we expressed each normal disc height based on values of its adjacent disc height with the aid of first-degree equations. We aspire to help calculate the exact amount of perioperative intervertebral distraction required to avoid complications from over- or under-distraction, that may compromise the surgical outcome.

MATERIALS AND METHODS

The study protocol and research ethics were approved in the 5/30-04-2014 Board meeting of the Faculty of Medicine (registration number 44118 in the National Archive of PhD Theses). We selected 40 normal cervical MRIs from the University database; all subjects were documented to be asymptomatic for cervical

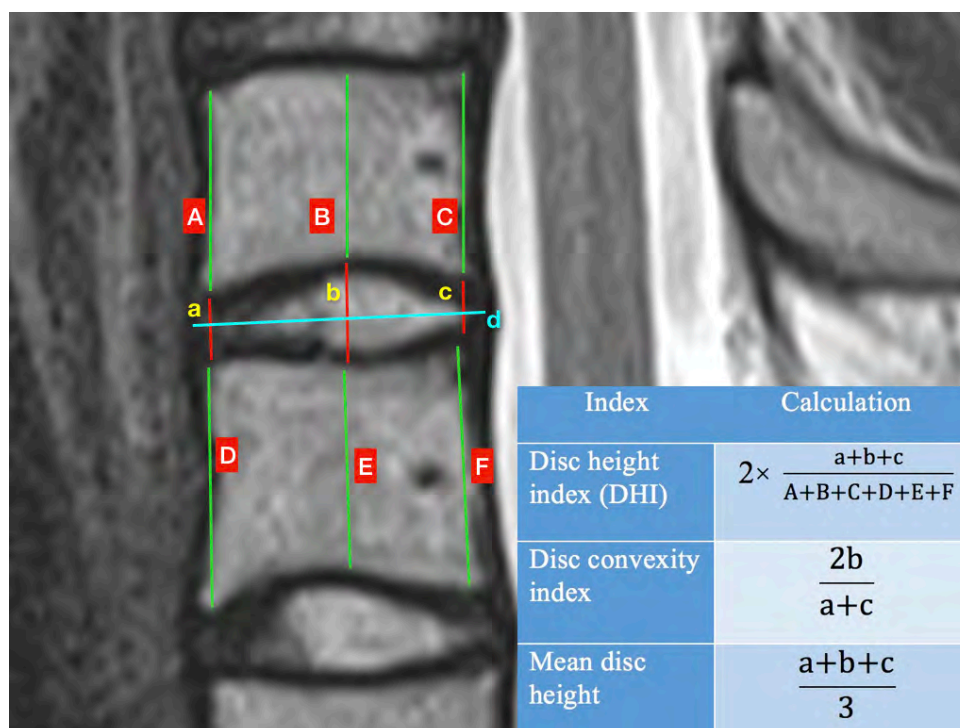


Fig. 1: Midsagittal T2w cervical spine C5-C6 level. **A**=anterior vertebral height, **B**=middle vertebral height, **C**=posterior vertebral height of cephalad vertebra. **a**=anterior disc height, **b**=middle disc height, **c**=posterior disc height, **d**=disc diameter. **D**=anterior vertebral height, **E**=middle vertebral height, **F**=posterior vertebral height of caudal vertebra. Bottom right part of image: calculation of each imaging index based on lettering in left part of image.

spine symptomatology. All intervertebral discs were characterized as Pfirrmann grade I or II, according to the Pfirrmann disc degeneration grading system, by two independent observers (8). Each observer was blinded to the other observer's measurements. Each observer was also blinded to his own prior measurements and there was a 7-day interval between the first and second measurements. Inter- and intra-observer agreement of this methodology has been previously published for lumbar spine measurements; thus, it was not measured in this study (9).

Exclusion criteria were scoliosis, discs with degeneration Pfirrmann grade III or higher, any disc protrusion, Schmorl nodes, Modic changes, congenital

spine defects, previous spinal fractures, spinal tumors, and previous spinal surgery.

All MR imaging examinations were performed at 1.5T scanner (PHILIPS, NL) and for the purposes of the present study, the sagittal T2W pulse sequence was used (TR- 3000–4000 μ s, TE-115 μ s, slice thickness: 4 mm; Gap-0.4, matrix-220 $\times$ 232 FOV-FH-275 mm). All measurements were performed in midsagittal T2W images on OsiriX suite software. All MR examinations took place during morning hours to avoid dispersion of measurements due to diurnal variation of disc height.

Anterior, middle and posterior height of vertebral bodies and intervertebral discs, as well as disc diameter, from C3 to T1 vertebra were measured. From these initial measurements, the following indices were calculated: mean disc height, disc height index (DHI) and disc convexity index and they are defined in Fig. 1.

DHI, previously introduced by Jarman et al, helps minimize the inter-subject variations in overall size of the vertebral column, enabling inter-subject analyses with different biometrics, and it correlates disc height with vertebral height (10). Mean age of 40 subjects (16 men - 24 women, range 19-42 years) was 27.25 years with standard deviation (SD) of 6.53 years. Mean age for women was 28.08 (SD 5.78) and mean age for men was 26 years (SD 8.19). Biometrics were available in 19 out of 40 subjects (11 women-8 men). Their mean body weight was 71.58kg (SD 15.03), their mean body height was 1.73m (SD 0.073) and mean body mass index (BMI) was 23.75 (SD 3.96) (Table I).

Analysis of variance (ANOVA) was performed and mean values of DHI, disc diameter, mean disc height and disc convexity index were compared for each intervertebral space. Mean disc height was compared with the adjacent one by using Student's independent samples t-test and the Bonferroni correction (p value of less than 0.01 was considered statistically significant). Mean values of DHI and mean disc height were compared between men and women. Simple linear regression was used to verify whether height variation of an index level could be predicted by disc height of its adjacent level and first-degree equations were created. Finally, the effect of age, gender and BMI on measurements in each intervertebral space was studied by using multiple regression. All statistical analyses were performed on Microsoft Excel.

Table I. *Sample demographics.*

Total sample	(years)
<u>40 subjects</u>	
mean age (+SD)	27.25 (6.53)
range	19-42
<u>16 men</u>	
mean age (+SD)	26 (8.19)
range	19-42
<u>24 women</u>	
mean age (+SD)	28.08 (5.78)
range	19-38
Available biometrics in:	
<u>19 subjects (11 women-8 men)</u>	(years)
mean age (+SD)	22.26 (2.68)
range	19-28
	(Kg)
mean weight (+SD)	71.58 (15.03)
	(m)
mean height (+SD)	1.73 (0.073)
mean BMI (+SD)	23.75 (3.96)

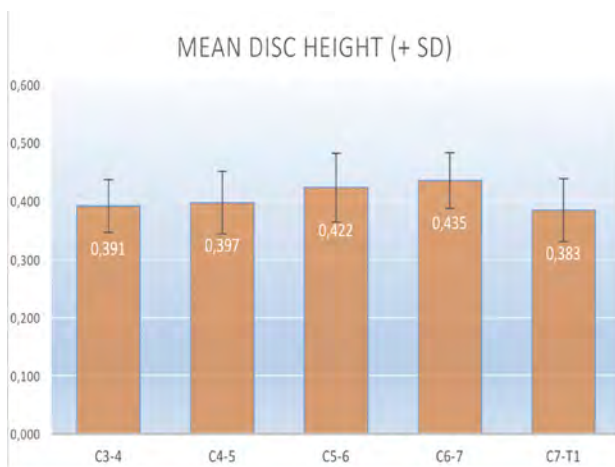


Fig. 2. Chart. Mean disc height (and standard deviation) in centimeters per spinal level.

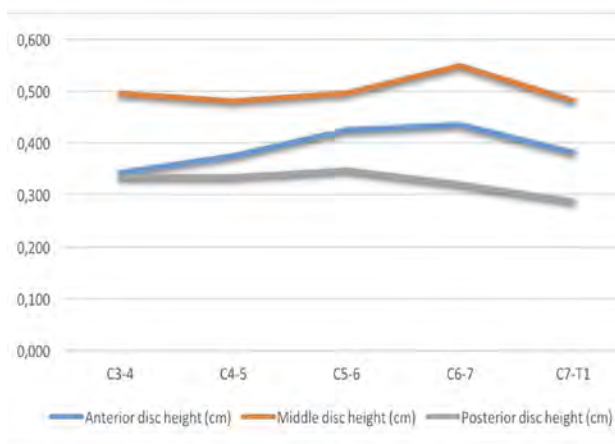


Fig. 3. Chart. Variation of anterior, middle and posterior disc height per spinal level.

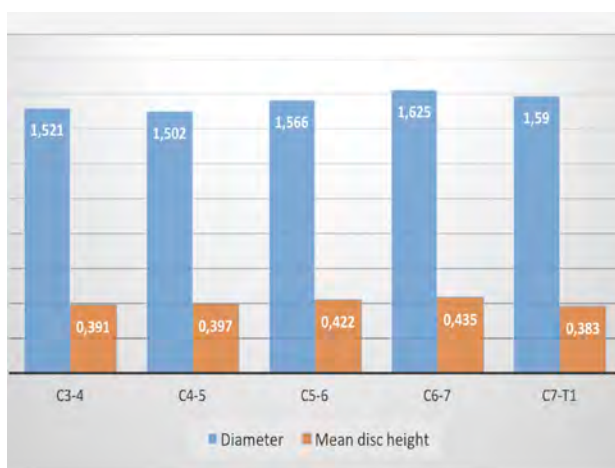


Fig. 4. Chart. Diameter and mean disc height per spinal level (in centimeters).

RESULTS

Mean and anterior disc height per spinal level

C6-7 mean disc height and anterior disc height was significantly greater than C3-4 ($p<0.01$, $p<0.0001$), C4-5 ($p<0.01$, $p<0.01$) and C7-T1 ($p<0.001$, $p<0.01$). Values did not differ with C5-6 ($p=0.3$, $p=0.6$) (Fig. 2, 3).

C5-6 mean disc height was significantly greater than C3-4 ($p=0.01$) and C7-T1 ($p<0.01$). It did not differ from C4-5 ($p=0.05$). C5-6 anterior disc height was significantly greater than C3-4 ($p<0.001$) and C7-T1 ($p<0.01$).

Middle disc height per spinal level

C6-7 was significantly greater compared to every other level ($p<0.01$) (Fig. 3).

Posterior disc height per spinal level:

Values appear to increase descending from C3-4 to C5-6, and they appear to decrease moving towards C6-7 and C7-T1. Posterior disc height at the C5-6 level was statistically greater than C7-T1 ($p<0.001$). Mean values are shown in table II, which is intended as a database for future reference.

Overall multiple regression model for sex and age effect on mean disc height was statistically significant ($p<0.01$) for C5-6 ($R^2=0.22$), C6-7 ($R^2=0.28$) and C7-T1 ($R^2=0.28$). Sex had a statistically significant effect on mean disc height. Mean disc height in men in these levels is significantly greater than in women (Table III). In 19 subjects, where height and weight were available, multiple regression for sex, age, height and weight effect, showed that the model was significant ($p<0.05$) for C6-7 mean disc height ($R^2=0.435$), and subjects' height was the only factor with a statistically significant effect ($p<0.05$).

DHI increases from C3-4 to C5-6, a slight decrease is observed in C6-7, while its value significantly decreases in C7-T1 ($p<0.0001$). There is no statistically significant difference between men and women (Tables III-IV). Disc convexity index decreases from C3-4 to C5-6 and increases significantly in C6-7 and C7-T1 compared to C5-6 ($p<0.01$). Disc convexity index does not differ between C6-7 and C7-T1 in a statistically significant way. Its value is always above 1, indicating

Table II. Mean measurements and standard deviation (SD) of various disc heights per spinal level.

Level	Anterior disc height (cm) (SD)	Middle disc height (cm) (SD)	Posterior disc height cm) (SD)	Mean disc height (cm) (SD)
C3-4	0.343 (0.065)	0.495 (0.058)	0.334 (0.071)	0.391 (0.045)
C4-5	0.375 (0.09)	0.48 (0.055)	0.334 (0.078)	0.397 (0.054)
C5-6	0.425 (0.09)	0.496 (0.068)	0.347 (0.07)	0.422 (0.059)
C6-7	0.435 (0.08)	0.549 (0.055)	0.32 (0.063)	0.435 (0.048)
C7-T1	0.381 (0.082)	0.481 (0.068)	0.287 (0.057)	0.383 (0.054)

Table III. Mean measurements for disc height index (DHI) and mean disc height per spinal level in men and women.

Level	DHI men	DHI women	Mean disc height (in cm)	Mean disc height women (in cm)
C3-4	0.327	0.352	0.405	0.381
C4-5	0.343	0.394	0.413	0.41
C5-6	0.386	0.383	0.456	0.4
C6-7	0.369	0.367	0.466	0.414
C7-T1	0.29	0.265	0.419	0.36

Table IV. Mean measurements of disc height index (DHI) and disc convexity index and standard deviations per spinal level.

Level	DHI (SD)	Disc convexity index (SD)
C3-4	0.342 (0.046)	1.482 (0.207)
C4-5	0.359 (0.054)	1.389 (0.253)
C5-6	0.384 (0.019)	1.301 (0.172)
C6-7	0.368 (0.038)	1.472 (0.191)
C7-T1	0.283 (0.04)	1.474 (0.269)

Table V. First degree equations expressing each intervertebral disc space, based on its neighboring disc space.

Level	$y=a + b*x$	R^2
C3-4	$C4-5=0.12 + 0.7*C3-4$	0.35
C4-5	$C5-6=0.12 + 0.76*C4-5$	0.48
C5-6	$C6-7=0.18 + 0.6*C5-6$	0.56
C6-7	$C7-T1=0.13 + 0.58*C6-7$	0.26

a convex disc shape (Table IV). Anteroposterior disc diameter gradually increases when descending from C3-4 to C6-7, while it slightly decreases in C7-T1, however difference between levels did not reach statistical significance (Fig. 4).

We expressed mean disc height as a first-degree equation ($y=a+b*x$), where y is mean disc height of an index level and x is mean disc height of its adjacent level, by using simple linear regression. Normal mean disc height could therefore be calculated or predicted for a specific level if normal height of an adjacent disc is known. For C4-5, C5-6, C6-7 and C7-T1, the regression model was significant ($p<0.0005$) (Table V).

DISCUSSION

From our results, there is an obvious trend of increasing anterior and middle disc height from C3-4 to C6-7. Posterior disc height follows a different trend, since there is slight increase from C3-4 to C5-6, and then it decreases. Middle disc height is the largest height dimension at any cervical spinal level, followed by anterior disc height. Disc convexity

index reflects these trends. Its values decrease from C3-4 to C5-6, since anterior and posterior disc height increase while middle disc height remains roughly the same. Caudal to C5-6, disc becomes more convex due to the increase in middle disc height and decrease in anterior and posterior disc height. DHI values gravely decrease at the C7-T1 level, due to simultaneous decrease in disc height and increase in C7 and T1 vertebral height.

Women have smaller disc height from C5-6 to C7-T1. However, DHI values do not differ between men and women, which shows that disc height to vertebral height ratio remains steady, which means that there is an equal differentiation in vertebral body height values in women.

Finally, BMI, subjects' stature and age does not affect disc height variation, although age did not have great range among groups (19-42 years in total sample, 19-28 years in biometrics sample). Equations calculated from normal values could be used to predict the correct amount of intervertebral space distraction when a degenerated disc needs to be restored to normal height. Like our methodology, inter- and interobserver agreement and reliability between two raters has been proven excellent in a previously published research (9).

Understanding normal anatomy of the intervertebral space in the sub-axial cervical spine is crucial to choose the correct treatment, and more specifically it is essential for preoperative planning. Intervertebral disc height and anteroposterior disc diameter are important measurements for preoperative templating for both ACDF and TDR. Our study analyzed a young, healthy control population, and it defined values that can be used as future reference and with modern imaging technique. Frobin et al measured disc height among other anatomical details in the cervical spine, in a population with higher mean age than ours and with a completely different methodology using lateral radiographs. In contrast with our results, disc height did not appear to differ between men and women, mean values were smaller than ours and the pattern of increasing disc height from C3-4 to C6-7 and then a decrease to C7-T1 is not evident in their data. In addition, the authors comment that "disc height amounts to roughly 1/3 of the vertebral

height", which corresponds to DHI values in our study (11). More recently, a study with a smaller, older population and measurements performed from CT scans, recognizes the pattern of increasing height from C3-4 to C6-7 (12). However, their values appear to be smaller than ours and values between sexes are not compared. Similar to our results, anterior disc height is slightly higher than posterior height, while middle disc height is the largest among the two. In another cadaveric study, Pait et al performed mean disc height and anteroposterior disc diameter measurements in six cadaveric specimens from elderly subjects, with reported values slightly higher than ours (13). Finally, Lu et al report similar results concerning anterior, middle and posterior disc height, from measurements performed in 20 cadaveric specimens from elderly subjects (14). They also add that the axis of the anterior disc space was lower than that of the posterior disc space, which means that disc orientation is slightly cephalad. All anatomic measurements mentioned above are important since they contribute to normal cervical spine alignment and lordosis.

Choosing the appropriate size of implant is of uttermost significance for a successful outcome both in ACDF and TDRH. It is not however defined with clarity from the published literature or from technical brochures of different implants, as emphasized by an earlier report (15). Specific problems arise from perioperative overdistraction of the intervertebral space and consequent fitting of an oversized implant; thus, leading to abnormal load transfer. Normal axial loads in the cervical spine resemble a tripod, with 36% of loads transferred through the anterior column and 32% of loads applied bilaterally through the zygapophyseal joints posteriorly (16).

Over distraction seems to increase anterior column loading and decrease posterior loads, especially during flexion of the cervical spine. The greater the distraction force applied to insert a large implant, the greater is the risk to increase compressive loading on the implant that favors subsidence into the implant and the development of pain. According to literature, there is a critical point of distraction, beyond which distraction is no longer beneficial and it becomes damaging.

In a report by Olsewski et al, distraction beyond

3mm of a C5-6 segment, caused significant decrease on the ratio of posterior element load to graft load, and normal cervical lordosis was also disrupted (17). More recently, Lu et al calculated that distraction up to 120% of initial intervertebral space had minimum effect on range of motion in a fused C5-6 level (18). Distraction beyond that percentage lead to decrease in range of motion, and the greatest decrease was observed in distraction equal to 160% of initial height, in lateral bending movements. It also resulted in increase in risk of adjacent level disease occurrence.

Forces applied on the zygapophyseal joints are affected by distraction as well. It was recently shown that the relationship between intervertebral space distraction and distance between the articular processes of two consecutive vertebrae is statistically significant (19). Consequently, overdistracted of a contracted joint capsule of a degenerated zygapophyseal joint can injure the joint and destabilize the spinal unit.

Furthermore, in a cadaveric study, distraction over 2mm of initial intervertebral height appears to increase pressure on the nerve root at the intervertebral foramen, despite an apparent increase in space (20). This phenomenon is probably due to connections between the joint capsule ligaments and the nerve root, that can compress the nerve root in the axial level, despite an increased space on the sagittal level. On the other hand, Yang et al stress that inappropriate fitting of a small implant and under correction of intervertebral space could result in failure to relieve from pain and an unstable spinal unit due to implant subsidence and/or nonunion (21).

Main limitations of the present study are the relatively small sample size and the lack of experimental data to support our suggestion that anatomic restoration of the collapsed intervertebral space yields better clinical results.

We have measured and documented the dimensions the cervical intervertebral disc space with the use of specific imaging indices. We present anatomical data from a healthy population that can be employed as database for future reference. We provide a reliable method for anatomical, individualized restoration of the degenerated

intervertebral disc space without overdistracted. Our results could be applied to improve preoperative templating, or even implant design.

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Prediction of reparability of meniscal tears in athletes using magnetic resonance imaging

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Meniscal tears account for approximately 15% of all knee injuries and almost 25% of them require surgical procedures. Magnetic Resonance Imaging (MRI) is widely used for noninvasive assessment of the knee joint and is considered reliable and a powerful tool for the detection of soft tissue injuries of the knee. The aim of the study was to evaluate the sensitivity, specificity, and accuracy of magnetic resonance imaging (MRI) to predict the meniscal tears repair in sports practitioners. 104 incoming consecutive patients who underwent knee joint ligament reconstruction and/or arthroscopy for the treatment of meniscal injury at knee joint were imaged using a 1.5-T MRI scanner prior to arthroscopy. MRI images were evaluated for anterior cruciate ligament (ACL), articular cartilage, and meniscal injury. Images were correlated with arthroscopic findings, used as the gold standard. The sensitivity, specificity, and accuracy of MRI in predicting meniscal repair were 61.1%, 65.94%, and 64.58%, respectively. The agreement between MRI and arthroscopy yielded a kappa index of 0.236, indicating fair agreement. When the menisci were evaluated separately, 65.85% sensitivity, 45.45% specificity, and 54.16% accuracy were found for the medial meniscus, while 46.15%, 79.51%, and 75.0% for the lateral meniscus, respectively. The accuracy was 62.09% in whose patients that arthroscopy was performed up to 3 months after MRI and 67.18% in those that this time frame was more than 3 months before surgery. The 54 meniscal injuries occurred more frequently in the posterior horn; most injuries had a longitudinal pattern and were located in the red-red (vascular) zone. We suggest that magnetic resonance imaging is only moderately accurate for the prediction of meniscus reparability.

Meniscal tears account for approximately 15% of all knee injuries and almost 25% of them require surgical procedures (1, 2). Compared to meniscectomy, meniscal repair has been shown to reduce the risk of later degenerative joint disease (3, 4). Magnetic Resonance Imaging (MRI) is widely

Keywords: knee, meniscus, repair, healing, meniscal tears, magnetic resonance imaging, arthroscopy

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used for noninvasive assessment of the knee joint and is considered reliable and a powerful tool in the detection of soft tissue injuries of the knee (2, 5, 6).

Commonly there is a lack of agreement between physical examination, imaging and arthroscopic findings regarding the diagnosis of meniscal tears (7-9). The ability to predict the meniscal reparability would be useful to optimize surgical planning and patient preparation, as repair is a time-consuming procedure that requires specific equipment, trained staff, and more extensive post-operative care. The use of MRI for predict reparability has been a challenge for radiologists and surgeons with conflicting results in the literature (6, 7, 10-17).

The aim of this study was to evaluate the accuracy sensitivity, specificity, and concordance of MRI findings in the predictability of meniscal repair, utilizing arthroscopy as the gold standard.

MATERIALS AND METHODS

This level III retrospective cohort study was conducted from April 2007 to December 2014, with patients scheduled to undergo surgical treatment of an anterior cruciate ligament (ACL) tear and/or meniscus repair. All arthroscopies were performed by the same fellowship trained knee surgeon.

Patient demographics are outlined in Table I. We included patients with isolated meniscal tears or associated ACL tear detected on MRI or at the time of arthroscopy. Revision surgery and patients over the age of 45 years were excluded. A convenience sampling approach was used.

All patients had positive meniscus clinical tests (McMurray test and Apley test) and/or MRI evaluation followed by knee arthroscopy. Due to referral patterns, a variety of radiology centers were used. Most of them were sent to centers of their own choice using standard knee protocol on a 1.5-T MR magnet. The MRI protocols included axial, sagittal and coronal sequences; each sequence included T1-weighted, T2-weighted, fat-suppressed T2-weighted. The meniscus repair predictability was performed according to the criteria of Bernthal and coworkers (18).

Arthroscopies were performed by the same major surgeon and surgery team. Surgeries were done in a hospital environment utilizing a tourniquet (350 mmHg) and a 4-mm, 30° angle, Karl Storz arthroscope equipped with a Stryker 3 CCD video camera. The patients were placed in dorsal decubitus position and, after exsanguination by retrograde compression, the limb was positioned at 90 degrees. Standard anteromedial and anterolateral arthroscopy portals were used for instrumentation and a probe was used to measure the meniscal tears and determine the vascularity. The presence of an unstable injury greater than 10 mm or injury in meniscus without degenerative aspect or injury associated with parameniscal cyst were indications for meniscal repair.

The arthroscopic findings were the gold standard. True positive and true negative results were considered when MRI finding was confirmed by arthroscopic evaluation. Numerical data (quantitative variables) were expressed as mean $\pm$ standard deviation (SD), median, interquartile range, minimum and maximum. Categorical data (qualitative variables) were expressed as frequency (n) and percentage (%).

The analysis of the numerical data was performed using Shapiro-Wilk test. For the variables with normal distribution a parametric test, Student's t-test, was used. The Mann-Whitney test was used for non-normal data. The level of statistical significance was set at $p < 0.05$. Fisher exact test was used for qualitative data. The statistical analysis was performed using GraphPad Prism

Table I. *Patients characteristics and study groups.*

Characteristics	Repaired meniscus (n=54)	Non-repaired meniscus (n=138)	p Value
Age mean $\pm$ SD (range)	27.11 $\pm$ 6.56 (14 to 43)	27.48 $\pm$ 7.05 (14 to 47)	0.932 ^a
Sex			
male	45	125	0.206 ^b
female	9	13	
Side			
right	30	66	0.422 ^b
left	24	72	
Interval between MRI and arthroscopy (days)			
median	50.0	55.0	
IQR	36.5 – 141.0	40.0 – 128.0	0.652 ^a
range	1 – 1380	1 – 1380	

version 5.00 software for Windows. Accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were evaluated considering the arthroscopic finding as the standard of reference.

Kappa index according to Landis and Koch (19) was used for concordance analysis. The study was approved by the local ethics committee (approval no.: 738.980, July 23, 2014, Ethics Committee on Research, INTO, Rio de Janeiro, Brazil).

RESULTS

A total of 122 consecutive patients undergoing arthroscopy for possible meniscal pathology, with or without ACL reconstruction were enrolled. Of these, 18 patients aged >50 years and 23 who had only an isolated ACL injury, in whom neither MRI nor arthroscopy detected meniscal tears, and 8 with MRI performed in equipment with less than 1.5 tesla were excluded. Therefore, 96 patients with a mean age of 27.3 years (SD, 6.85 years; range, 14 to 47 years) were included, 11 women and 84 men.

After the surgical procedure, the cases were allocated to one of two groups according to whether the meniscal repair was required or not: repaired meniscus group (REP, n=54) and non-repaired meniscus group (Non-REP, n=138), for a total of 192 (lateral and medial) menisci analyzed. The cases in the Non-REP group had the following outcomes: no meniscal injury (n = 102); partial meniscectomy (n = 27); or arthroscopic rasp to debride the edges and stimulate bleeding of stable tears (n = 09).

Patients in the REP and Non-REP groups did not

differ in age, sex, laterality, or in the time interval between MRI and arthroscopy (Table I). Sixty-two patients had arthroscopy performed up to 3 months after MRI and were considered “short waiters”. In 32 patients the MRI was performed more than 3 months before surgery and were considered “long waiters”. The accuracy of MRI in predicting reparability was 62.09% and 67.18%, respectively.

Based on the criteria for repair (see patients and methods section) applied to both groups (n = 192 menisci) on MRI, 54 cases were predicted to be repairable. MRI was successful in predicting repair in 33 cases but failed in 47 cases (false positive) (Table II).

Of these, 20 had no injury (Fig. 1), 21 underwent partial meniscectomy (Fig. 2), and 6 had stable tears and underwent arthroscopic rasp to debride the edges and stimulate bleeding. As for the 112 cases predicted by MRI to be non-repairable, 21 were repaired (false negative) and 91 were not (Table II).

In 1 of the 21 repaired cases, there was no MRI evidence of injury, but diagnostic arthroscopy was performed due to strong clinical evidence (Fig. 3). The other 22 cases had associated ACL injury; 3 cases also had cartilage injury. In these cases, either the injury showed complex features on MRI or the meniscus appeared normal on MRI (Fig. 4).

The sensitivity, specificity, and accuracy of MRI in predicting meniscal repair, using arthroscopy as the gold standard, were 61.1%, 65.94%, and 64.58% respectively. The overall positive predictive value (PPV) was 41.2% and the overall negative predictive value (NPV) was 81.25%. The analysis of agreement

Table II. Menisci reparability on Magnetic Resonance Imaging and Arthroscopy.

Magnetic resonance	Arthroscopy			P value
	Repaired	Not repaired	Total	
Repairable	33	47	80	0.001
Non-repairable	21	91	112	
Total	54	138	192	

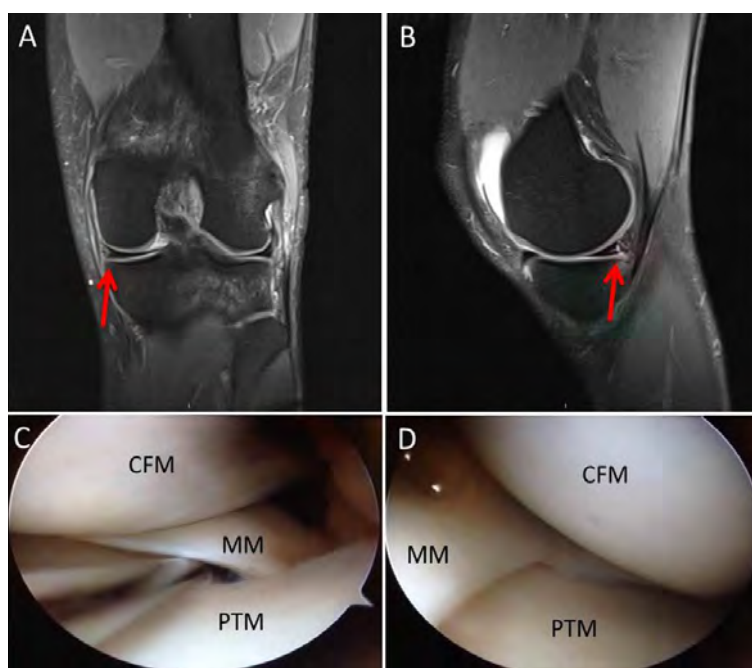


Fig. 1. A false positive case for meniscal repair: Magnetic resonance imaging (MRI) with predictability of meniscal repair and posterior arthroscopy showing meniscus without a tear. A 24 years old male, recreational athlete with trauma and twisting in his left knee in soccer practice. MRI in coronal; (A): and sagittal; (B): views evidencing meniscus-capsular injury in the red-red zone of the medial meniscus (arrow). In the arthroscopy, 60 days after MRI, the posterior horn; (C): and the meniscus body; (D): presented normal and reconstruction of the anterior cruciate ligament was performed. MM: medial meniscus; CFM: femoral medial condyle; PTM: tibial medial plateau.

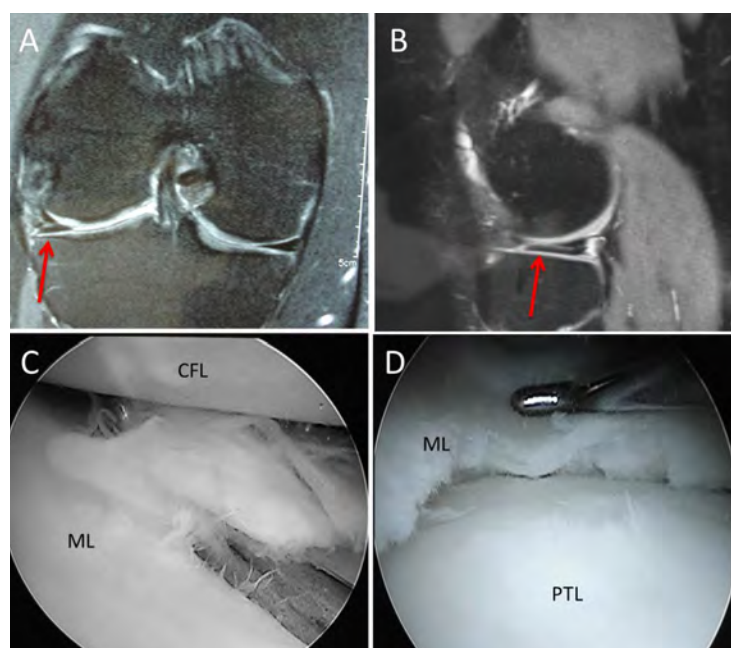


Fig. 2. A false positive case for meniscal repair: Magnetic resonance imaging (MRI) with predictability of meniscal repair and arthroscopy with irreparable and flap tear. A 20 years old male, professional athlete with trauma and twisting in his right knee in soccer practice. MRI in coronal (A): and sagittal; (B): views evidencing horizontal tear in the red-white zone of the lateral meniscus (arrow); (C): In the arthroscopy, performed 120 days after MRI, the meniscus presented a radial tear with unstable and degenerative flap tear, without repair conditions and the patient underwent partial meniscectomy; (D): ML: lateral meniscus; CFL: femoral lateral condyle; PTL: tibial lateral plateau.

between MRI and arthroscopy in predicting repair yielded a kappa index of 0.236 (95% CI 0.101-0.371, $p < 0.001$), indicating fair agreement.

When the menisci were separately evaluated, there was 65.85% sensitivity, 45.45% specificity, 47.36% PPV, 64.10% NPV, and 54.16% accuracy for the medial meniscus (Table III). For the lateral meniscus there was 46.15% sensitivity, 79.51% specificity, 26.08% PPV, 90.41% NPV, and 75.0% accuracy (Table IV). The 54 meniscal injuries in the REP group occurred more frequently in the posterior horn; most injuries had a longitudinal pattern and were located in the red-red (vascular) zone.

DISCUSSION

The present study evaluated 192 consecutive

menisci by MRI, and the presence of injury was subsequently confirmed by arthroscopy. In our sample, MRI was not a good predictor of a repairable meniscus. This type of study has important clinical implications since MRI is currently an extremely common part of preoperative planning to assist the surgeon in the optimal treatment and for guiding patients as to the treatment options and rehabilitation.

MRI is the investigation of choice for evaluation of the knee. It is noninvasive, operator-independent, radiation-free, and it does not require contrast media, allowing the complete evaluation of all internal structures of the knee.

Patients aged >45 years were excluded from the present study because degenerative changes in the meniscus, which produce a heterogeneous signal, occur in this patient group. Although a heterogeneous

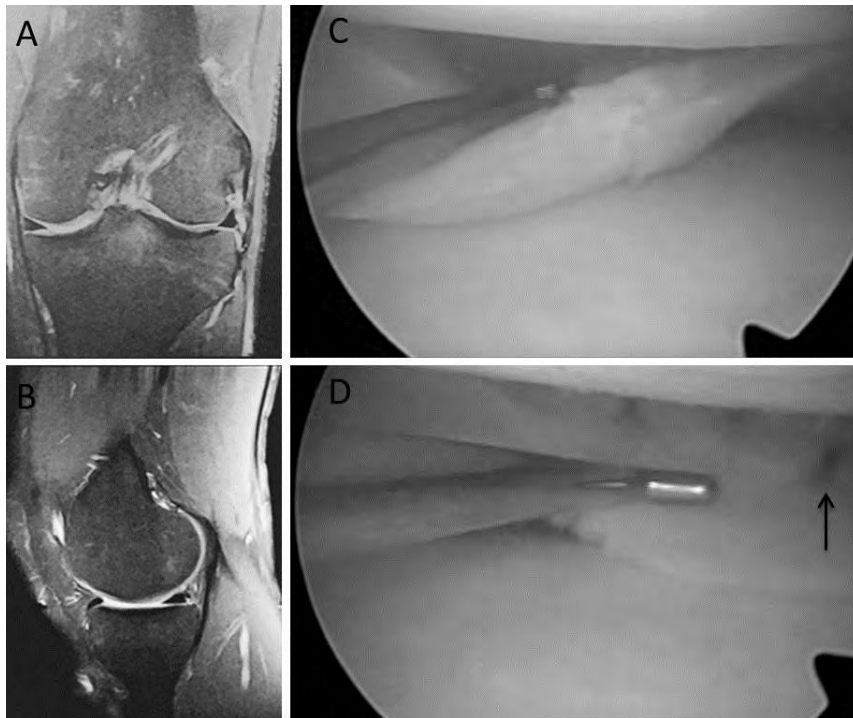


Fig. 3. A false negative case for meniscal repair: Magnetic resonance imaging (MRI) without predictability of meniscal repair and arthroscopy with suturable injury. A 33 years old male, a professional athlete with clinical evidence of injury of the medial meniscus (MM), but without confirmation at MRI and submitted to diagnostic arthroscopy and MM repair. MRI in coronal; (A): and sagittal; (B): views were normal, without injury. In arthroscopy; (C): the MM presented a meniscus capsular injury (red-red zone), longitudinal and unstable with repair conditions; (D): Realization of the meniscus repair. An arrow indicates a stitch.

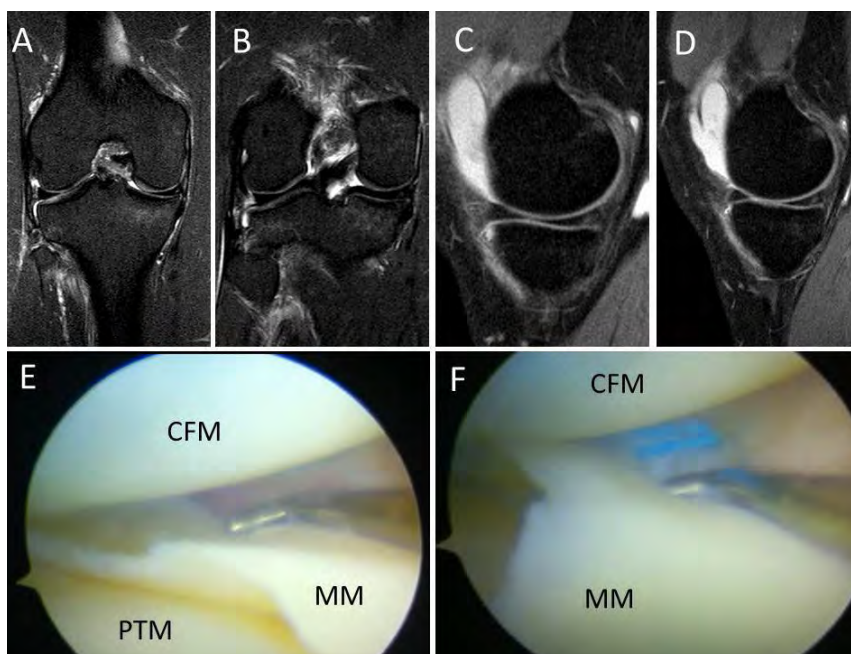


Fig. 4. A false negative case for meniscal repair: Magnetic resonance imaging (MRI) without evidence of meniscal injury (non-REP group) and arthroscopy with suturable injury. A 26 years old male, recreational athlete with trauma and twisting in the right knee in alpine skiing practice. MRI in coronal (**A** and **B**): and sagittal; (**C** and **D**): views showing meniscus without injury. In arthroscopy; (**E**): 46 days after MRI, the medial meniscus presented a longitudinal injury in the red-red zone (meniscus-capsular); (**F**): the meniscus repair associated with anterior cruciate ligament reconstruction was performed. MM: medial meniscus; CFM: femoral medial condyle; PTM: tibial medial plateau.

meniscal signal is associated with poor quality of meniscal tissue, it is not a contraindication to repair, probably because of the use of an arthroscopic rasp to debride the edges and stimulate bleeding (11).

The median time between MRI and arthroscopy was 50.0 days in the REP group and 55.0 days in the Non-REP group, with no statistically significant difference. Injuries may occur in the time interval between MRI and arthroscopy. These injuries, however, may have been lost in early MRI studies. This occurs more commonly in patients with isolated ACL injuries. A shorter interval between the ACL injury and reconstruction surgery reduces the likelihood of developing associated meniscal injury since instability due to ACL deficiency increases the forces on the medial meniscus.

Meniscal repair is an effective method for the treatment of certain types of meniscal injuries since it can restore the function of the meniscus as a shock absorber. However, not all meniscal injuries are repairable. Given the differences in operating room

resourced (time and equipment) and postoperative rehabilitation, having this information before surgery would be helpful for both the surgeon and the patient.

In our study, MRI was successful in predicting meniscal repair in 33 cases but failed in 47. The sensitivity, specificity, and accuracy of MRI in predicting meniscal repair, using arthroscopy as the gold standard, were 61.1%, 65.94%, and 64.58% respectively. The overall PPV was 41.2% and the overall NPV was 81.25%. There were 47 false-positive cases and 21 false-negative cases.

Few studies have addressed this issue (6, 10, 11, 18). One of the first studies on this topic included 106 patients and 115 injuries, which were evaluated by 3 examiners, a general radiologist, an orthopedic surgeon, and a radiologist specialized in the musculoskeletal system. There were no differences in prediction accuracy between the 3 examiners (10). Overall, MRI had a sensitivity of 29%, specificity of 89%, an accuracy of 74%, PPV of 50%, and

Table III. *Medial meniscus reparability on Magnetic Resonance Imaging and Arthroscopy.*

Magnetic resonance	Arthroscopy			P value
	Repaired	Not repaired	Total	
Repairable	27	30	57	0.298
Non-repairable	14	25	39	
Total	41	55	96	

Table IV. *Lateral meniscus reparability on Magnetic Resonance Imaging and Arthroscopy.*

Magnetic resonance	Arthroscopy			P value
	Repaired	Not repaired	Total	
Repairable	6	17	23	0.074
Non-repairable	7	66	73	
Total	13	83	96	

NPV of 80%, and the authors concluded that MRI was of little use in the prediction of meniscal repair. More recently, Bernthal et al. (18) evaluated the efficacy of MRI in predicting meniscal repair in 58 patients with sutured meniscal tears and 61 patients with tears treated with meniscectomy, based on the same criteria used in the present study. The analyses were performed only by senior musculoskeletal radiologists and included MRI scans obtained from a single site. All patients with MRI scans performed with more than 3 months before arthroscopy were excluded. However, the authors could not ensure that the arthroscopic criteria defined by the surgeons for repair were strictly adhered to in the intraoperative decision making since the surgical procedures were performed by different teams. The authors concluded that MRI was not an effective or efficient tool to predict repair, based on a sensitivity of 47%, specificity of 74%, an accuracy of 60%, PPV of 63%,

and NPV of 59.0%. However, this might reflect a failure of the author's team rather than an inability of MRI since the surgical procedures were performed by different teams. In our study, all procedures were performed by the same surgeon and 32 patients with MRI scans taken more than 3 months before arthroscopy were included.

Nourissat et al. (11) showed 94% sensitivity of MRI in predicting meniscal repair, which is in contrast with our results. However, analysis of their methods showed that the authors selected the type of injury, in addition to the presence of bias related to the type of MRI equipment used. They reviewed 200 images produced by 1-T and 1.5-T scanners and excluded 100 cases without full-thickness longitudinal tears, which may be a significant selection bias that might have resulted in different data. Excluding tears deemed unsuitable for repair is a selection bias that overestimates the predictive

ability of MRI by artificially improving the results.

The 21 cases of a false negative (i.e., those considered as non-repairable by MRI and later repaired) may include injuries more than 3 mm from the meniscus synovial junction since we adopted a maximal distance of 3 mm as our MRI criteria for reparability. Matava et al (10). were uncertain about the possibility of repairing meniscal injuries with peripheral rim length from 3 to 5 mm but did not consider these injuries to be irreversible. When using a 3 mm rim length as criteria for predicting meniscal reparability, we may have incorrectly excluded a part of the population in which arthroscopic meniscal repair was later found to be possible; however, rim length was the least subjective variable described (18).

The site and pattern of injuries may influence the prediction of meniscal repair. In our study, most repaired injuries had a longitudinal pattern (45/54). Bucket-handle (or longitudinal) injuries with rim width of less than 4 mm and tear length of 10 mm or greater length and low signal intensity in the inner meniscal fragment have a higher likelihood of actually being repairable (6). However, these criteria are not accurate for injuries located in the popliteal region of the lateral meniscus. Very specific criteria based on MRI signal intensity may be difficult to interpret both for evaluating spontaneous healing and for predicting meniscal reparability. Therefore, heterogeneous or high-intensity MRI signal on the axial portion of the meniscus does not compromise arthroscopic meniscal reparability.

A more recent retrospective study assessed preoperative MRI scans of 63 patients who underwent arthroscopic meniscal repair (20). Thirty-eight out of 63 patients (60%) had a medial meniscus tear, of which 22 were a subluxed bucket-handle tear. Of the 25 patients with a lateral meniscus tear, 12 were subluxated as a bucket-handle tear. Tear length and rim width as assessed by preoperative MRI showed good intra- and interobserver agreement, whereas the status of the meniscus did not exhibit good agreement. Tear length and rim width were the only two measures with a good interobserver agreement. However, they do not predict reparability of longitudinal meniscal tears. The above study used the following criteria for meniscal reparability: (1) peripheral rim smaller

than 4 mm; (2) a tear longer than 10 mm, regardless of total tear length; and (3) minimal damage to inner and peripheral meniscal fragments.

Guidelines for arthroscopic meniscal repair published in 2014 were based on visual criteria to identify injuries located at red-red or red-white zones and on the use of a probe to assess tear size. In our study, arthroscopy was the gold standard. Prediction of meniscal reparability using MRI was based on criteria outlined by Bernthal, (18) that a tear larger than 10 mm, within 3 mm of the meniscosynovial junction indicate injuries in the red-red zone. We found a great correlation between these criteria and arthroscopic findings since the majority (34/54) of the repaired injuries were located in this zone. The patient who did not undergo meniscal repair did not meet these criteria and, in those with persistent injury, meniscectomy or arthroscopic rasp to debride the edges and stimulate bleeding was performed.

Exceptionally, seven injuries located in the white-white zone and one case of radial injury underwent meniscal repair. Although these cases did not meet predetermined criteria, decision-making was based on patients' age, given the meniscus is essential for preserving knee joint function. In addition, Matava showed good clinical outcomes in this group at a 2-year follow-up after meniscal repair of tears located in the white-white zone (10). Therefore, we believe surgeons should be prepared to perform arthroscopic meniscal repair, in young patients,

The limitations of our study include the fact that it relied on information provided in medical records, MRI reports of meniscal injuries, surgical reports and descriptions with a varied level of detail. Another point is the fact that there was a variable interval between MRI and arthroscopy, but with a least impact in the accuracy of meniscal repair predictability. This could be addressed by looking at the accuracy in the short waiters (62.09%) vs. long waiters (67.18%). Additionally, the study did not include a control group with intact ACL. A control group would have enabled to assess differences in knees with and without ACL injuries and investigate the sensitivity of MRI to detect lateral meniscus tear in the setting of concomitant ACL injury.

Conversely, the strengths of the study included

the fact that all surgeries were performed by the same surgeon, thus avoiding inter-surgeon biases and possible conflicting intraoperative decisions, and the fact that the study included only patients with isolated meniscal injuries or associated with ACL injuries. Another point was the use same power MRI scanners (1.5 T). Moreover, our sample is large, with a similar size to that of studies on the same subject, and there is no study in the literature predicting reparability in medial meniscus and lateral meniscus separately.

The present study highlights the use of MRI to predict meniscal repair. Surgeons should be aware of the time frame from MRI to arthroscopy. In conclusion, the results of this level III retrospective cohort study demonstrate that MRI was not reliable or accurate for predicting meniscal repair and showed weak agreement with arthroscopy. Of importance is the time frame from MRI to arthroscopy once there is a better accuracy in patients undergoing arthroscopy up to 3 months after MRI.

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Sport injuries in professional volleyball players

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Recently there has been a considerable surge in interest in volleyball by both physiotherapists and orthopaedic surgeons. Only few previous studies specified the nature, frequency, and demographics of volleyball injuries. The study was conducted during two league seasons. After the approvals of local bioethics committee and clubs' authorities, contact with the club's doctors was established. A special survey was designed to standardize the process of acquiring data on a weekly basis. One-hundred-and-ninety-eight women and 301 men were under supervision of the research group. On average, 45% of all players (56% males and 26% females) suffered from injuries and musculoskeletal disorders over two seasons. Relatively high incidence of injuries during matches was between 17.3 and 33.8 injuries per each 1000 hours of playing. Almost 50% of musculoskeletal problems occurred in the first phase of the season. Over 50% of musculoskeletal problems were reported during trainings. The blockers are the most affected players in both sex groups. Acute injuries mainly involved knee and ankle joints, while chronic problems affected knee, shoulder, spine and abdominal muscles. Professional volleyball is not a safe sport, especially during a league season. Attention should be especially paid to ankle, shoulder and knee joints, which are the most commonly injured structures. The study revealed that blockers were the most susceptible to injuries and should be protected by special training regime. These findings can help to prepare sports medicine personnel and to guide further related research to prevent injuries among volleyball professionals.

Over the last few years, volleyball has become a very popular sport and consequently, professional volleyball leagues were established in many countries. Volleyball as a professional sport has also changed significantly in terms of, among others: heavy training regime, increased number of games and training hours, specified training techniques for different positions, more dynamic style of playing. All these changes have caused prolonged overuse of

musculoskeletal system and affected considerably the rate of injuries among players. Nevertheless, there is still lack of studies analysing the frequency and circumstances of traumas in professional volleyball. Some studies among professional players suggested that ankle, hand, shoulder and elbow are the most affected parts of the body (1-4). There was only one complex study in professional volleyball league (1), the others mainly concerned youth and non-

Key words: volleyball injuries, musculoskeletal disorders, knee and ankle

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professional games (2, 5-10). Other studies dealt only with specific types of the injuries, which occurred during the game or training (8, 9, 11-13). A recently published study conducted during International Volleyball Federation (FIVB) tournaments showed that the ratio of injuries was very low and authors concluded, that professional volleyball players had lower injury ratio even than amateurs (14). Several studies showed higher risk of injury than reported during the FIVB tournaments (2). The aim of the study was to prospectively analyse the frequency and factors contributing to injuries during two consecutive professional league seasons.

MATERIALS AND METHODS

When Medical University of Lodz's Bioethical Committee gave their consent to perform this research, invitations were sent to all elite club authorities. Only the clubs whose authorities gave consent were included in this study. The research was a prospective study among volleyball players from both male and female elite professional Polish leagues. The study was performed during two seasons 2013/2014 and 2014/2015. The study is based on a prepared survey reported weekly by medical doctors from clubs all over Poland. Only acute injuries or musculoskeletal disorders, which excluded a player from the 100% of training load for at least 7 following days, were taken into consideration. In the first season 2013/2014 the study involved 7 out of 10 clubs from women's leagues and 11 of 12 clubs from men's leagues. In the next season 2014/2015 there were 8 out of 12 clubs from women's and 12 out of 14 clubs from men's leagues. The men's league was extended in season 2014/2015 from 12 to 14 teams, as well as women's league from 10 to 12.

Ninety-four women and 143 men in the former season and 104 women and 158 in the latter season were under control of the study. In total, in the first season there were 137 games played in women's league and 174 games in men's league. In the next season the numbers increased significantly – 189 games by women and 246 by men. Both groups were professional volleyball players, which means that they train at least four times per week and each

training session lasts more than 90 minutes. The players train during the whole year with one or two months of holidays. Preparation period before each season starts in August, then the league season starts in October and it ends in April or May. The season is divided into three parts: the first phase (teams play against each other within a league), revenge phase (teams play for the second time with all teams) and play-offs (the best teams play in a cup and eventually one team becomes the winner).

The following data was gathered from the reports (Variables):

- age of the players,
- experience of the player (years of professional training),
- the position on the court,
- the training load before the injury (percentage of typical training),
- time of occurrence: training or game,
- type of training,
- part of a game,
- field situation, which means a type of volleyball skill (attack, block, dig, serve),
- contact or non-contact injuries,
- part of the season when the injury occurred (first matches, revenge matches, play-offs)
- protection used by the player (every kind of orthotics or physiotherapeutic support was recorded),
- the diagnosis,
- type of injury or health problems (acute or chronic),
- type and duration of the treatment,
- the duration of the rehabilitation,
- type of surface (Taraflex™, parquet and the others).

Taraflex™ is a kind of artificial surface made of PVC, that is applied in indoor volleyball courts. Firstly, each group was examined by Shapiro-Wilk normality test. Gender groups and following seasons were examined separately by Pearson's Chi-squared test to prove statistical significance between each group. Student-T tests and ANOVA variations tests were also performed in order to analyse the statistical

significance of the comparisons. STATISTICA® program was used to perform that evaluation.

RESULTS

The 275 players from women's and men's league, participated in the study over a two-year period and 222 injuries were recorded. (Table I) On average, 56% male players and 26% female players reported injuries during two seasons. Statistically significant

differences in frequency of incidences between men and women in each and both seasons were observed ($p < 0.05$). The average age for volleyball players was 26.7 (SD 3.7) in women's group and 26.3 (SD 4.7) in men's group and was comparable. The injured players were on average younger in both groups (women 25.3, man 25.7), but no statistically significant difference between the injured and the uninjured players was observed in either groups.

The average height for male players was 193

Table I: *Participants and injuries in two seasons.*

	2013/2014			2014/15			Both		
	Women	Men	All	Women	Men	All	Women	Men	All
Players	94	143	237	104	158	262	198	301	499
Injuries	21	77	98	31	93	124	52	170	222

Table II. *Incidence of accidents by type of activity and number of injuries per 1000 hours.*

	Men 2013/2014	Men 2014/2015	Women 2013/2014	Women 2014/2015	Average percentage
Injuries per 1000h	14,2	15,4	6,8	8,5	100%
Match injuries per 1000h	33,8	31,4	17,3	18,1	54%
Training injuries per 1000h	8,3	9,2	3,9	5,1	28%
Injuries during preparatory period per 1000h	24,1	26,7	10,3	13,3	18%

Table III. *Occurrence of injuries by the period of season.*

	First phase	Revenge games	Play-offs
Women	46,2%	28,9%	25%
Men	48,8%	33,5%	17,7%
All	48,2%	32,4%	19,4%

centimetres (SD 6.6), and weight of 84 kilograms (SD 7.8). The average height for female players was 182 (SD 5.3) and weight of 72 kilograms (SD 4.5). The incidence of injuries was divided into three categories. In both gender groups more than 50% of all injuries happened during trainings, and this difference was significant ($p < 0.05$) (Table II).

The calculations concerning the incidences rate per 1000h were performed (95% CI) (Table II). The data was divided into three groups, as previously presented. The differences between the number of training injuries and match injuries, as well as training injuries and preparatory period reached the statistical significance in both sexes and seasons ($p < 0.05$). The injuries occurred most frequently in the first phase of the season, and this difference was statistically significant ($p < 0.05$). (Table III)

The variations between genders and two seasons were statistically insignificant. The players were divided into three groups according to years of professional training – under 10 years of training, between 10 and 15 and over 15 years (Fig. 1). In summary no difference between the three groups was observed. In the women group, however, the differences in frequency of injuries reached statistical difference ($p < 0.05$) with less experienced players being more prone to injuries.

Before the injury, 13.5% of all players used orthotic equipment, recommended by the physiotherapists, related to the body part, which was affected by the accident. The equipment such as tapes, braces and

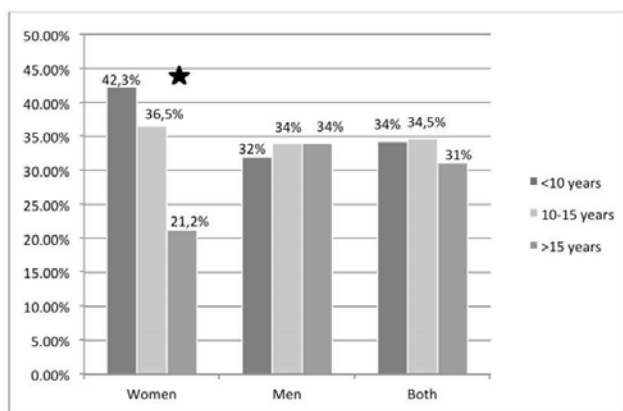


Fig. 1. Percentage of injuries related to the experience in volleyball.

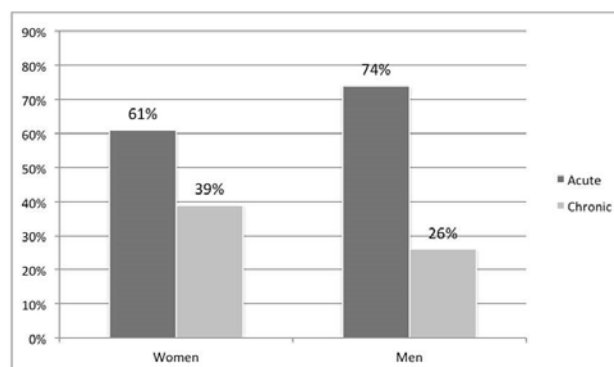


Fig. 2. Type of musculoskeletal problem by sex.

orthoses were recommended by physiotherapists to prevent injuries. Among the injured players, orthotic device was applied more frequently by women (31% to 8%) and it was statistically significant ($p < 0.05$). No differences between injured and uninjured players were noted. One third of injured female players had reduced training loads for one month prior to the accident due to various reasons, comparing to 12% of male players ($p < 0.05$). The reduced training load is described as lower than typical for this player (100%) training load prior to the accident. Only slight differences between the genders were observed in chronicity without statistical significance (Fig. 2). In both groups the alterations between the seasons were insignificant.

In general, acute injuries affected most ankles (30%), knees (22%) and hips (11%). There were differences between women and men: knee injuries were twice more common among female players, and ankle sprains more frequent in male athletes (Table IV).

The most frequent location of chronic problems among players was the knee, followed by shoulder, back and abdominal muscles. (Table V) Variations between genders were noted especially in shoulder problems, but not statistically significant. The blocker position was in both genders the most vulnerable position (Table VI).

The differences between two gender groups were not significant in terms of game situations when the accidents occurred (Fig. 3). The average duration of the treatment was 8,13 weeks (SD 7.73) for women

Table IV. *Presentation of acute injuries among men and women.*

Injured body part	Women	Men	All
Ankle	20 %	28%	30%
Knee	32%	17%	22%
Hip	17%	10%	11%
Shoulder	7%	15%	9%
Hand	4%	10%	8%
Abdominal muscles	8%	6%	7%
Back muscles	6%	4%	5%
Elbow	3%	4%	3%
Foot	1%	4%	3%
Other	2%	2%	2%

and 4.5 (SD 3.08) for men. It was significantly longer in female athletes ($p < 0.05$). Most injuries were treated non-operatively 87.4%. The 17% of injuries in men and 11% in women required surgical intervention.

Non-contact mechanism was noted in 83% of the accidents, followed 197 by collision with other player in 13%, and collision with the equipment around the field (4%). Finally, the type of surface was analysed and showed statistically significant effect between men and women. (Table VII) Teraflex™ was the most dangerous surface for all the players ($p < 0.05$).

DISCUSSION

The study shows a representative demographic

pattern of injuries in male and female volleyball at elite level. This survey provides detailed information on injuries among professional volleyball players during two league seasons, as opposed to previous studies from the '90, which were from small, amateur leagues. (5-7, 10, 15) Our main finding was that more than half of the male athletes would suffer from trauma during the seasons.

Similar frequency was previously reported in smaller leagues (5-7), however, the number of injuries during tournaments was much lower (14). Furthermore, the most important argument for the risk in volleyball is the incidence rate. In the previous studies, the incidence rate was relatively low both during matches (3.8/1000 hours) and during the whole season (2.6/1000 hours and 1.7-4.2/1000 hours). The league season has become longer, training regime has been intensified and number of games might influence injury ratio, while tournaments are mostly two-week or three-week events.

This study also revealed that the first part of the both seasons is most affected by injuries. That is a new finding compared to previous studies. In this period nearly half of the all injuries occurred. The preparations before the season are very strenuous and are performed usually more than one month before the league starts. At the beginning of the season players may be fatigued and they may benefit special attention from physiotherapists. Interestingly the training/rest ratio is more favourable in the later parts of the season. In this survey, most of the accidents occurred during trainings; conversely recent studies showed that the number of such accidents was three times lower in practise (7, 14).

Table V. *Presentation of chronic health problems among men and women.*

Chronic problems	Women	Men	All
Back pain	15%	28%	25%
Knee	30%	24%	24%
Shoulder	35%	13%	20%
Abdominal muscles	10%	18%	15%
Ankle	7%	10%	9%
Hip	2%	6%	6%
Others	1%	1%	1%

Table VI. *Percentage of injuries by position on the field.*

Position on the court	Women	Men	All
blocker	44%	36%	38%
receiver	12%	28%	27%
opposite	13%	18%	17%
setter	21%	10%	11%
libero	10%	7%	8%

Table VII. *Percentage of injuries by type of surface.*

Surface	Taraflex™	Parquet	Others
Women	56%	15%	29% ★
Men	68%	28%	4% ★
All	65%	25%	10% ★

★ = $p < 0.05$

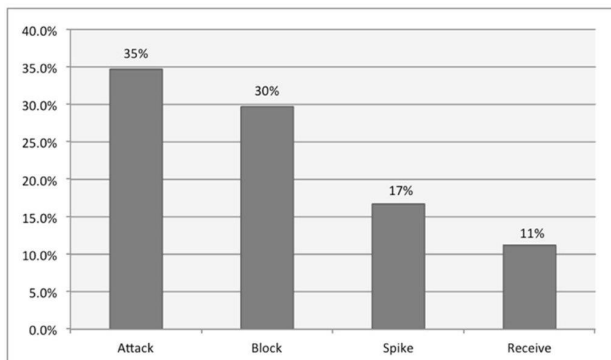
The high percentage of women players who did not completely participate in the training load and then suffered from an injury is not surprising. During the season, sometimes coaches do not have any other choice so they decide to take the player who is not yet perfectly healed but could guarantee results. As a result, women statistically suffer from long-term chronic injuries more often than men.

Teams are usually prepared for acute traumas; however, they are inevitable. They relate to all kinds of activities that are performed in volleyball: jump,

attack, block. Chronic injuries result from repetitive micro-traumas, which could be related to specific types of injuries, such as back pain or jumper's knee. In this study the differences between men and women were observed. Chronic health problems were previously described among men (6, 7), but they were not examined in the group of women. Women mostly suffered from shoulder problems, whereas men from back pain (16, 17).

Among women the problem could be associated with overtraining or lack of specific training of the shoulder muscles. The sources of these injuries are repetitive movements during attack, so the muscles might be too weak to withstand the force, or they may fatigue from performing the same kind of movement repeatedly (18).

This study also suggests that the position on the court might predispose to trauma. There may be "dangerous" and "safe positions", as previously reported (2, 7). Blockers were the most exposed to injury since they work very hard during the game: they jump in every attacking play; they also block in defensive play, and they quickly move parallel to the net. Setters and opposites are obliged to perform the

**Fig. 3.** *Percentage of injuries by game situations.*

two most dangerous elements of the game-attack and block. Therefore, they are involved in the most crucial situations on field. Women's setters might suffer from overload, because in female league there are not so many experienced players in this position, so the best ones play too many matches without any rest.

Attack and block game situations were the most dangerous elements of volleyball in this study responsible for 65% of injuries. They are the most dynamic and powerful parts of volleyball. Both include three phases: jump, hit and landing. Jump and landing refer to lower extremities. Jump is associated with muscle tears, landing with ligament injuries. Hit is related to all types of accidents among upper extremity. Moreover, both elements are performed by all players except for libero. Thus, attack and block should be of special interest to coaches and physiotherapists because the improvement in technique might result in lowering the number of injuries.

The duration of rehabilitation was alarming, shorter and more dynamic than in other leagues (2, 14). Yet another interesting difference between this study and the others is that the injuries resulting from contact with another player represent a small minority, while in other studies the number of these accidents is much higher (2, 14).

Due to widespread use (68% of practise time is spent by player) of the Taraflex™ surface more accidents will take place on this field. Other types of surfaces are mixtures of Taraflex™ and concrete, or concrete with another surface above. Yet, the types of surface should be considered in future investigations, especially in the leagues, where league's authorities do not require Taraflex™.

This study has some limitations: the data collection depended on contact established with club's doctors. There were also a few clubs (4 from women and 2 from men) leagues that were not included in the study. The previous medical history of players was not taken. The study is not comparable to other studies when different methods of data collection were used.

The risk of injury during a league season is higher than previously reported during the tournaments. On average, 56% of male and 26% of female players reported injuries and musculoskeletal disorders

during two seasons. The risk and the pattern of injuries vary according to the player's sex, phase of the season and position on the court. Match injuries rates were 3 times higher than practise rates. Over 50% of musculoskeletal problems, however, were reported during practise. Almost 50% of musculoskeletal problems occurred in the first phase of the season. The blockers are the most affected players in both the sexes. The differences between the sexes were real and should be taken into serious consideration.

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One-stage Bilateral Total Hip Arthroplasty in patient with sickle cell disease and previous Girdlestone procedure on the right side: First presentation in Togo

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80% of Sickle Cell Disease cases are estimated to be in Sub-Saharan Africa. It can lead to various acute and chronic complications and osteonecrosis of the femoral head is one of these. Girdlestone procedure is an option to treat osteonecrosis in patients who could not afford arthroplasty. We report here the first case of bilateral total hip arthroplasty in a patient with a previous Girdlestone procedure on the right side and an osteonecrosis of the femoral hip on the left side.

Resection hip arthroplasty, commonly known as Girdlestone procedure, was first described in 1928 and then in 1942 by Gathorne Robert Girdlestone (1) as a radical excision to remove diseased and devitalized tissues in tuberculous hips. Nowadays, Girdlestone Resection Arthroplasty (GRA) is a surgical procedure, more sparing than the original, to remove the head and the neck of the femur without replacing them. It is indicated in non-ambulatory patients, in whom a total hip arthroplasty or an arthrodesis is not indicated, and in the cases of impossible reimplantation (2).

Since 1984, GRA has also been used in the management of peri-prosthetic infections that dictate the removal of the prosthetic implant (3) as part of a two-stage revision arthroplasty, though in some instances a GRA may be the final procedure situation (4).

In unfavorable socio-economic contexts, such as in low income African states, the indications of Girdlestone resection are broader (5). Indeed, in those countries, GRA is still a valid option to manage painful hip osteoarthritis, and it is an alternative to hip arthroplasty because of the economic status of the patient or the lack of adequate technical skills.

Key words: Total Hip Arthroplasty (THA), Girdlestone Resection Arthroplasty (GRA), Sickle Cell Diseases (SCD), Direct Lateral Approach (DLA), Direct Anterior Approach (DAA), Quality of Life (QoL).

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About 80% of the global population with Sickle Cell Disease (SCD) live in sub-Saharan Africa (0.74% of births), and about 90% of them could die before the age of 5 (6, 7). Indeed, 171,600 Togolese people are estimated to suffer from major SCD (8). The prevalence of osteonecrosis, especially of the femoral head, affects from 10% to 30% of patients with SCD (9, 10). We reported the short-term result of bilateral Total Hip Arthroplasty (THA) in a SCD patient with a previous GRA on one side.

Case presentation

At 38-years old a Togolese female with SCD experience progressively worse right hip pain from osteonecrosis of the right femoral head for two years before receiving a GRA at her local hospital. The GRA was undertaken through posterolateral approach. A few months later, the patients began to report progressive pain in the contralateral hip and was managed conservatively. Seven year later, she attended another local hospital where plain radiography evidenced osteonecrosis of the left femoral head. On the right, proximal migration of the femoral shaft was apparent (Fig.1. A). At clinical examination, the patient had a positive Trendelenburg on the right, with shortening of the right lower limb of 2.5 cm. There was profound atrophy of the right gluteal and thigh muscles, and

bilateral hip pain with minimal range of motion.

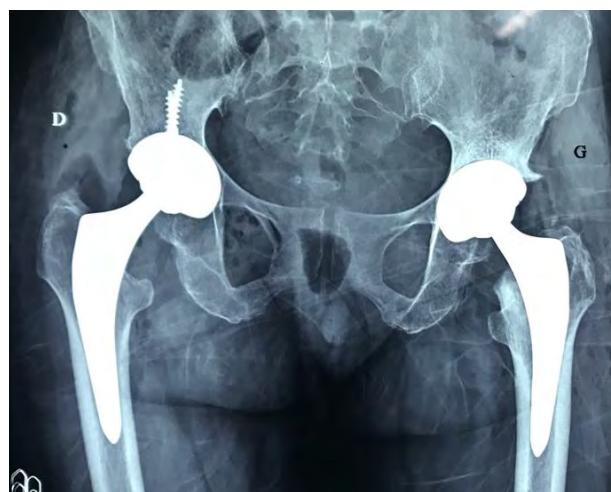
The patient was selected by local doctors for an orthopedic consultation with our visiting orthopedic team in the context of a humanitarian mission, which confirmed the above findings at the age of 47. The patient underwent bilateral THA under spinal anesthesia. We used a Direct Lateral Approach (DLA) for the right side and a Direct Anterior Approach (DAA) for the left side. The right side was treated first in the supine position using a DLA to obtain a wide surgical field and to be able to use an extensible approach in case of complications, as we had no intraoperative imaging facilities.

Intraoperatively, we found widespread muscle atrophy, and no muscles inserted on the lesser trochanter. We only had implants with metaphyseal grip stems, donated by a manufacturer (Medacta). We implanted a lateral offset stem and an acetabular cup with two screws to obtain the maximum stability of the implant. For the left hip, we used a Direct Anterior Approach (DAA) (11).

At the end of the procedure, both hips were stable and had an acceptable range of motion. The right limb was about 1 cm shorter than the left one. Postoperative radiographs showed acceptable position of both implants (Fig. 1. B), and the patient was encouraged to mobilize her hips on the same day of the surgery.



A



B

Fig. 1. Pre-operative plain radiographs (A) and post-operative plain radiographs (B).

The day after, she could stand and walk a few steps with crutches (Fig. 3). The patient reported almost total resolution of her bilateral hip pain, and five days after surgery she was able to walk without aids for few steps. She left the hospital 10 days after surgery with a progressively improved walking autonomy and without any complication.

DISCUSSION

Osteonecrosis of the femoral head is frequent in patients with SCD, and it is a major social problem in young adults. A THA procedure with careful handling of the soft tissues favors rapid recovery and produces optimal stability. Unfortunately, THA is an expensive and unusual surgery in some low-income countries, and in these situations, GRA becomes a viable alternative.

A GRA normally produces a limb length

discrepancy, muscle weakness with atrophy of the gluteal and thigh muscles and decreased hip range of motion (4, 12, 13). Residual pain may be present, with 85% to 100% of patients reporting satisfactory pain relief, though but no authors described total absence of pain (2).

Patients with a GRA after an infected THA have a significantly impaired Quality of Life (QoL) comparing to normal population and to patients with lower limb amputation or myocardial infarction (14). These results are described in the Netherlands, but they can be also easily translated into the patients of some African countries, where having some sort of disability imposes an even greater reduction of the QoL.

In this report, we operated on an adult female patient with a severe bilateral hip pain and a GRA on the right side. We had understandable concerns about the implant stability and the possible retraction or weakness of soft tissues, but a bilateral THA was planned when considering her QoL. Intraoperatively, stability was satisfactory bilaterally, and in the post-operative period, the patient showed an almost complete resolution of pain and a progressive improvement in walking. She did not have any intra and post-operative complication and she is satisfied with the result. Obviously, the early result must be confirmed in the middle and long-term.

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Fig. 2. One day after surgery.

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Reliability, repeatability and comparison to normal of a set of new stereophotogrammetric parameters to detect trunk asymmetries

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Aesthetic impairment is a crucial issue in Adolescent Idiopathic Scoliosis (AIS), but to date no objective measurements are available. The aim of the study is to evaluate the repeatability of 17 parameters measured by surface topography in a group of AIS subjects and verify their diagnostic validity. The paper is divided into three cross-sectional observational studies. We evaluated 17 selected surface topography parameters that could be good predictors of scoliosis' impact on the patients' trunk. We analysed short-term (30 seconds, 38 subjects) and medium-term (90 minutes, 14 subjects) repeatability of surface topography measures and their diagnostic validity in AIS (74 subjects, 33 AIS patients and 41 healthy subjects). All examined parameters were highly correlated as far as short and medium-term repeatability is concerned. We found a statistically significant difference between the scoliosis group and the control group in 3 surface rotation parameters, 1 shoulder parameter and 3 waist parameters. In conclusion, surface topography showed a good repeatability. Moreover, some of its parameters are correlated with AIS, enabling us to find differences between pathological and healthy subjects. Thanks to these findings, it will be possible to develop a tool that can objectively evaluate aesthetics in AIS patients.

Adolescent idiopathic scoliosis (AIS) is a fairly common disease: epidemiological studies estimate that 1%–3% of the at-risk population (children aged 10–14) has a curvature of at least 10° (1) and approximately 3 in 1000 adolescents require specific treatment (2). By definition, AIS affects patients from the age of 10 years until bone maturity; it is more common in girls than in boys (3). AIS does not usually cause clinically important pain during growth. Nevertheless, the deformity has a significant impact on the quality of life of scoliotic patients and, in some cases, important psychological consequences (4-7). Many orthopaedic surgeons agree on the importance

of aesthetic deformity in the treatment of scoliosis despite the well-known complication rate of spinal surgery (8). Aesthetic deformity due to scoliosis and its impact on the patient is considered by the members of SOSORT (International Society on Scoliosis Orthopaedic and Rehabilitation Treatment) as the most important reason for treating AIS. Unfortunately, only a few of scoliosis studies were available in PubMed on this topic (9).

Some of the above-mentioned studies report on tools for self-evaluation. For instance, some questionnaires included a domain for the evaluation of the aesthetics of the scoliotic patient, like the SRS-

Key words: Adolescent Idiopathic Scoliosis; Aesthetics; Trunk deformity; Surface Topography

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22 (10). Other tools were specifically developed for the assessment of the aesthetic deformity perceived by scoliotic patients (or scoliotic patients' relatives). These tools are the "Walter Reed Visual Assessment Scale" (6), the "Spinal Appearance Questionnaire" (11) and the recent "Trunk Appearance Perception Scale" (12). They can be used to assess subjective perception of the aesthetic deformity but cannot describe the objective aesthetic deformity. They are more concerned with psychological damage due to scoliotic deformity than with the deformity itself. However, it is important to find a method to objectively assess the deformity caused by scoliosis, being one of the possible resulting impairments (13). There are a few methods, for example, the Posterior Trunk Symmetry Index (POTSI), the Anterior Trunk Symmetry Index (ATSI) (14) or the Trunk Aesthetic Clinical Evaluation (TRACE) (15). However, the POTSI and ATSI are difficult to use in everyday clinical practice, and the TRACE is operator dependent and does not have good repeatability.

A possible more objective way to assess the deformity is the surface topography, such as rasterstereography (16). A set of parameters can be measured by rasterstereography regarding waist, shoulder and scapulae asymmetries; surface rotation and sagittal measures, but so far, its reliability has not been documented (Fig. 1). Moreover, we do not know if these correlate with the deformity, although they are an instrumental evaluation of the parameters usually applied in the clinical assessment of the trunk. This tool could not, of course, replace

the role of x-rays for diagnosis, but it can give us a completely new measure of asymmetry.

To validate this instrument for clinical practice, the first step and aim of this study is to evaluate the repeatability of the parameters measured by surface topography in a group of AIS subjects and to test if they can distinguish healthy subjects from AIS patients in order to develop an objective tool for deformity evaluation of the trunk in AIS patients.

MATERIALS AND METHODS

This was a cross-sectional diagnostic study that included the short-term (30 seconds) and medium-term (90 minutes) repeatability of surface topography measures and their diagnostic validity in AIS. We analysed different samples because we wanted to investigate different characteristics of the surface topography parameters considered. For the repeatability evaluation, 38 consecutive AIS subjects with no other concurrent spinal pathologies were included (34 females) by convenience sampling from among patients attending our institute. All the patients participated in the short-term repeatability study, which were based on two sets of measures, with a 30-second rest between them. Fourteen of them were retested 90 minutes after the first assessment to evaluate the medium-term repeatability and to take into consideration the possible postural reassessment that probably do not occur in the short-term. We collected the sample during May-June 2013.

For diagnostic validity, we used a database of 398 adolescents who underwent a surface topography

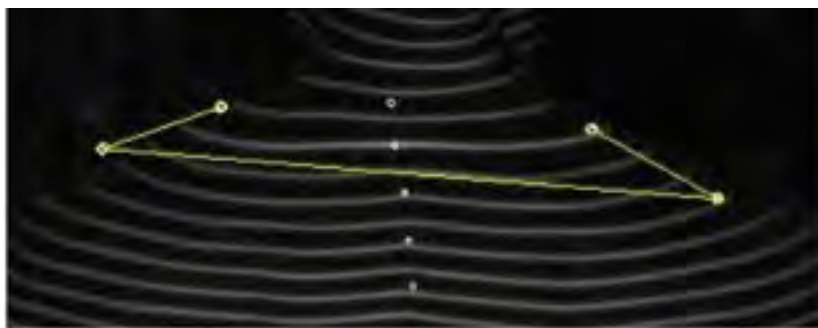


Fig. 1: An example of parameters we can measure using rasterstereography: Shoulders slope and Shoulders height differential.

examination at our institute between January 2012 and June 2013. We excluded those with a diagnosis of spinal pathology other than scoliosis (Scheuermann's disease, spondylolisthesis and spondylolysis) and those under treatment with a brace. In clinical practice rasterstereography is regularly used for sagittal spine issues and only seldom for scoliosis; thus, after this selection, only 74 patients were included in the study; we further divided them into two groups. In the scoliosis group (SG, 33 patients) we included all patients who had a scoliotic curve (measured on an x-ray) of 11° Cobb or more and with 5° or more of the Bunnell angle of trunk rotation (ATR). The control group (CG) consisted of the other 41 participants. Participant anthropometric characteristics are reported in Tables I and II.

We used a device for surface topography based on the principles of rasterstereography. This device (Formetric™, Diers Biomedical Solutions) can digitally reconstruct in three dimensions the spine. It does not require radiation nor reflective markers, as it can find anatomic markers using a “touchless” technique without manual intervention. For

Table I: Demographic data, Cobb degrees and hours of brace of our samples.

	Age	Height (cm)	Weight (kg)	BMI	Distance to Menarche (years)	Cobb Max	Hours of bracing
Short term repeatability							
N	38	38	38	38	24	38	25
Min	10	143	32,0	12,98	,12	11	8
Max	20	181	71,5	24,59	6,82	70	23
Mean	14,5	161,4	51,2	19,5	3,1	28,8	16,7
STD	2,5	9,0	10,1	2,7	2,0	13,1	5,2
Medium term repeatability							
N	14	14	14	14	10	14	11
Min	12,7	153	33,0	13,56	1,08	10	12
Max	19,6	179	63,0	24,59	6,82	70	23
Mean	15,1	161,5	52,2	19,9	3,5	33,1	19,1
STD	2,3	7,2	8,9	2,8	2,0	14,7	4
Diagnostic validity							
N	74	74	74	74	41	41	NA
Min	10,0	30,0	138,0	14,0	0,0	11	NA
Max	16,4	79,0	186,0	27,0	4,4	71	NA
Mean	13,4	49,9	162,5	18,8	1,5	25,8	NA
STD	1,6	9,9	10,3	2,5	1,2	14,7	NA

Table II: Trace and Risser data of our samples.

Short term repeatability		
Median	4	2
Min	1	0
Max	9	5
Medium term repeatability		
Median	3	3
Min	1	0
Max	9	5
Diagnostic validity (scoliotic group)		
Median	6	2
Min	1	0
Max	12	5

the data collection, we used a standard machine. Data were then elaborated with a specifically designed software and currently not implemented in other machines.

This device allows for the analysis of a broader number of parameters compared to standard techniques. We selected 15 parameters that we consider good predictors of the aesthetic impact of the scoliotic patient's spine. They can be divided into four main groups: parameters that examine the whole back of the patient and parameters which analyse the patient's shoulders (Fig. 1), thorax or waist (Appendix 1).

To assess repeatability, the same operator, trained in the use of the device, performed all the tests twice in a clinical setting. The short-term repeatability test required an immediate repetition of the exam after some trunk movements (30 seconds), whereas for medium-term repeatability, the second exam was repeated after an exercise therapy session (90 minutes).

Concerning short- and medium-term repeatability, we applied the Pearson's correlation analysis and checked the dispersion of the data obtained by measuring the R-squared. We also used the Bland and Altman statistics (17) for each of the surface topography parameters in order to identify the minimum change in a parameter required to determine with certainty a real change (repeatability coefficient).

As far as diagnostic validity is concerned, we tested for a statistically significant difference in the personal and

Table III: *Repeatability correlations and coefficients of the rasterstereography parameters.*

	Short term				Medium term		
	Pearson	R square	Repeatability coefficient		Pearson	R square	Repeatability coefficient
Cyphotoc Angle Max	0,924	0,855	10,06		0,873	0,762	13,97
Lordotic Angle Max	0,872	0,760	10,67		0,559	0,313	20,12
Surface Rotation Rms °	0,661	0,437	4,13		0,685	0,469	3,87
Surface Rotation Max °	0,619	0,246	23,99		0,330	0,109	29,33
Surface Rotation Amplitude °	0,781	0,657	6,74		0,804	0,646	6,98
Shoulder slope difference R-L °	0,766	0,587	8,17		0,840	0,706	8,30
Shoulder height difference R-L °	0,815	0,665	2,97		0,865	0,749	3,39
Thorax scapula angle difference R-L °	0,694	0,481	15,80		0,855	0,732	11,38
Thorax thoracic torsion °	0,338	0,114	9,18		0,678	0,460	9,82
Thorax axilla height difference R-L °	0,612	0,374	3,50		0,276	0,076	6,68
Waist opening angle difference R-L °	0,724	0,524	20,25		0,912	0,833	12,82
Waist top angle difference R-L °	0,862	0,743	5,94		0,646	0,417	13,22
Waist bottom angle difference R-L °	0,620	0,384	17,08		0,925	0,856	6,77
Waist triangle area (normalized) difference R-L %	0,842	0,709	22,49		0,917	0,840	19,69
Waist waist-arm distance difference R-L %	0,534	0,285	45,01		0,916	0,839	25,80
Waist height difference °	0,596	0,355	9,94		0,882	0,779	5,27
Waist lumbar torsion °	0,622	0,387	3,21		0,572	0,327	4,61

anthropometric parameters between the two groups with a *t*-test for independent samples (age, weight, height, BMI, time since menarche). We then compared the two samples using a χ^2 test and tested for a statistically significant difference between the two groups in the surface topography parameters by using a *t*-test for independent samples. All the patients or their parents (in the case of minors) gave written informed consent, and the local ethical committee authorized this study.

RESULTS

The 38 patients who performed the short-term repeatability test, 18 were performing regular specific exercise therapy (18) and 25 were wearing a

brace for an average of 16.7 hours per day (SD 5.2). Patient characteristics are reported in Tables I and II.

For the medium-term repeatability test, all patients were performing exercise therapy, and 11 of them were wearing a brace for 19.1 hours a day on average (SD 4.0). Patient characteristics are reported in Tables I and II.

As far as diagnostic validity sample is concerned, the scoliotic group had a mean Cobb angle of 25.8° (SD 14.7), Tables I, II and III. Using a *t*-test for independent samples we could not detect any significant statistical difference between the group of scoliotic patients and healthy subjects in the anthropometric parameters (age, weight, height, BMI, time since menarche).

Table IV: Results of t-test for independent samples between the group of scoliotic patients and healthy subjects for the rasterstereography parameters.

		N	Mean	STD	T-test (sig.)
Kyphotic Angle ICT-ITL max	Control group	41	42,93	12,16	0,21
	Scoliotic group	33	46,06	8,13	
Lordotic Angle ITL-ILS max	Control group	41	39,59	9,91	0,14
	Scoliotic group	33	42,79	8,21	
Surface Rotation Rms	Control group	41	5,61	2,41	0,00
	Scoliotic group	33	3,70	1,57	
Surface Rotation Max	Control group	41	10,61	3,96	0,00
	Scoliotic group	33	7,27	2,49	
Surface Rotation Amplitude	Control group	41	16,27	6,12	0,00
	Scoliotic group	33	9,24	2,84	
Shoulder slope difference R-L	Control group	41	5,29	3,69	0,03
	Scoliotic group	33	3,45	3,54	
Shoulder height difference R-L	Control group	41	1,63	1,13	0,75
	Scoliotic group	33	1,55	1,25	
Thorax scapula angle difference R-L	Control group	41	8,41	9,65	0,52

All examined parameters were highly correlated. In short-term repeatability analysis, we found a strong correlation for each value ($r > 0.5$) except thorax thoracic torsion, where we found a good correlation ($r = 0.338$). In the medium term, only two parameters had an $r < 0.5$: surface rotation max ($r = 0.329$) and thorax axilla height difference ($r = 0.275$). Nevertheless, the data were skewed ($R\text{-square} > 0.5$) for 8 out of 17 parameters in short-term repeatability and 10 out of 17 in medium-term repeatability (Table III).

Concerning short-term repeatability, we found high values (less clinically reliable parameters) for surface rotation max, thoracic torsion, axilla height difference, waist bottom angle difference, waist-arm distance difference and waist height difference.

Concerning medium-term repeatability, we found high values for lordotic angle, surface rotation max, thoracic torsion, thorax axilla height difference, waist top angle difference and waist lumbar torsion (Table III).

We detected a statistically significant difference between the scoliosis group and the control group in the parameters that measured the surface rotation (surface rotation root mean square (rms) deg, surface rotation max deg, surface rotation amplitude deg) (Table IV). Regarding the shoulders, there was a significant statistical difference only in the shoulder slope difference, whereas for the thorax, there were no statistically significant differences. Waist parameters showed a statistically significant

difference in the waist bottom angle, waist lumbar torsion and waist height difference.

DISCUSSION

The aim of this paper was to verify the repeatability and diagnostic validity of a newly developed set of surface topography parameters. This is a basic requirement in the clinical practice to objectively evaluate the deformity of scoliosis patients. The repeatability at short and medium-term was sufficient for almost all parameters. We also found that some parameters could distinguish healthy subjects from scoliosis patients: these are related to surface rotation (standing humps) and waist shape, in contrast to shoulder and upper thorax characteristics.

Theoretically, the most important reason why aesthetic parameters could have a low repeatability are the following: 1. The error due to the device used; 2. The error due to the way the exam is executed; 3. The error due to postural changes of the patient. There are no critical issues with the execution of the surface topography: in fact, the patient indications for the exam are few and simple, and the exam is rapid to perform. Although this last aspect could have influenced our work, postural changes are the main issue that we should consider.

The ability (or incapability) of the patient to maintain posture over a short or medium time span is one of the main issues not only for our work but also for all devices used to assess surface topography of the spine and, in general, for all postural exams (13). It is interesting to note that some parameters have better medium-term than short-term repeatability. This probably implies that it is easier for the patient to assume the same original relaxed posture after 1.5 hours than after rapid mobilization of the spine. Although some parameters have a high repeatability coefficient (measured using the statistical method of Bland and Altman), correlation between the first and the second measures and R-squared were good. Two examples are the shoulder slope difference and shoulder height difference.

In 2012 a paper measured the repeatability of

another surface topography device for the evaluation of the trunk in scoliotic and non-scoliotic patients (19). To verify the repeatability of the device, the authors used the correlation between the values obtained in two different sessions; their correlation analysis results were similar to ours. They concluded that their device had a good repeatability.

The population considered in this study was rigorously selected, focusing exclusively on scoliosis; this reduced the sample size, but it gave more strength to the results. Unfortunately, this precluded the possibility to analyse at different subpopulations of scoliosis patients. It is possible that the diagnostic validity would be higher in higher degree scoliosis and/or subpopulations with different topographic classifications. This aspect should be investigated in future studies. A comparison with a normal population has not been performed for other objective aesthetic evaluation tools like TRACE (15) and POTSI (20).

Although an improved aesthetic is considered as a possible outcome of scoliosis treatment (8, 9), the currently existing tools are only subjective and consequently they reflect the psychological attitudes of patients more than the objective reality. This is a serious limitation for clinical studies.

This study has some limitations: first, the sample size was quite small; nevertheless, it was large enough to demonstrate that our hypothesis was correct. Moreover, we could not perform a subgroup analysis to test if some curve patterns are more correlated with surface topography findings; therefore, we probably missed some relevant information. Lastly, we used dedicated software for the analysis, that still needs some testing and fine-tuning being this first clinical test so far. The patients with a low r-factor are related to new selected and not verified parameter. In a clinical trial and iteration process this result can be improved.

Surface topography showed a good reliability. Moreover, some of its parameters are correlated with scoliosis, showing that this device may thoroughly evaluate deformity due to this pathology. Thanks to these findings, it will be possible to develop a tool that can objectively evaluate aesthetics in AIS patients.

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All-inside repair of meniscal bucket handle tears: a retrospective study at mean 4-years follow-up evaluation

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Bucket-handle tears represent approximately 10% of all meniscal tears. Despite the common treatment is subtotal meniscectomy, repair is technically feasible although complex, and represents a key strategy to avoid severe meniscal tissue loss that could accelerate joint degeneration over time. The aim of this retrospective study was to determine the outcomes of arthroscopically-assisted bucket-handle tear repair, and to identify factors correlating with clinical results. Fifty-four patients affected by meniscal bucket handle tear were included in the present retrospective analysis and evaluated up to mean 4-years follow-up. All patients were treated by arthroscopic-assisted all-inside repair. The primary outcome was considered the need for a re-operation due to failure of meniscal repair. Patients were also evaluated by the following items: KOOS, Lysholm, Tegner, IKDC-subjective and Quadruple-VAS score. Subgroup analysis was performed to identify whether concurrent ACL reconstruction, side of the lesion, age at surgery and time from injury to repair could influence clinical outcome. Ten out 54 patients (18.5%) were considered failed and needed reoperation, mainly within one year from surgery. Overall, there was a significant increase in all clinical scores considered and patients were able to get back to previous sport activity level. Patients with concurrent ACL reconstruction presented a lower risk of failure ($p=0.025$). Patients with lateral meniscus repair showed better clinical outcome compared to medial meniscus. Timing from injury and age at surgery did not correlated with clinical outcome. Our series showed fair results in bucket handle repair up to middle term evaluation. Concomitant ACL reconstruction was associated with lower failure rate whereas lateral meniscus involvement was associated with higher functional scores at final follow-up evaluation.

Key words: meniscal suture; bucket handle tear; all-inside repair; arthroscopy

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Meniscal tears are the most common knee injuries, with an incidence in the United States of 61/100000 per year. Over 636000 knee arthroscopies are performed annually to treat meniscal pathologies (1, 2). The role of the meniscus has been widely evidenced: in addition to the key role in load bearing and shock absorption, it also acts as a secondary antero-posterior stabilizer of the knee, has a role in proprioception and helps in nutrition and lubrication of articular cartilage (3, 4).

The high frequency of meniscal tears, particularly in young people and athletes, encouraged the research in this field with special attention to preservation of the meniscus. Since 1948 Fairbank reported that the majority of 107 patients who underwent total meniscectomy, had progressive flattening of the condyle, narrowing of the joint space and ridge formation; subsequent studies have shown that the amount of the residual meniscus is directly correlated with knee function (5).

Benefits of preserving the meniscus, especially in preventing degenerative changes of the knee joint, have been suggested by several pre-clinical and clinical trials and therefore current indications suggest to saving meniscal tissue as much as possible through repair, especially in young and active patients (6, 7, 8). Location, type, length and stability of the tear influence the healing potential: partial and stable

vertical tears are more eligible to heal in particular if located in the peripheral vascularized zone.

Bucket-handle tears (BHT) represent approximately 10% of all meniscal tears, and medial meniscal tears are three times more common than lateral (9). Severity of the bucket handle meniscal tear is due to its large size and frequent dislocation of the fragment, which causes tenderness, swelling and locking. Its treatment is often challenging and the majority of orthopaedic practitioners perform a total or subtotal meniscectomy, causing a significant deficiency within the joint. Anyway, despite being technically complex, repair can still be attempted with the aim of preserving meniscal tissue.

The aim of this retrospective study is to determine the outcomes of arthroscopically assisted bucket-handle meniscal repair, using the need for reoperation as primary outcome measure. Secondary purpose is to evaluate the influence of different variables such as age, meniscus involved, time elapsed from injury to surgery, ACL deficiency and number of sutures on the results of meniscal repair.

MATERIALS AND METHODS

Patient selection and evaluation tools

Sixty-five consecutive patients who underwent arthroscopic meniscal bucket handle repair with all inside

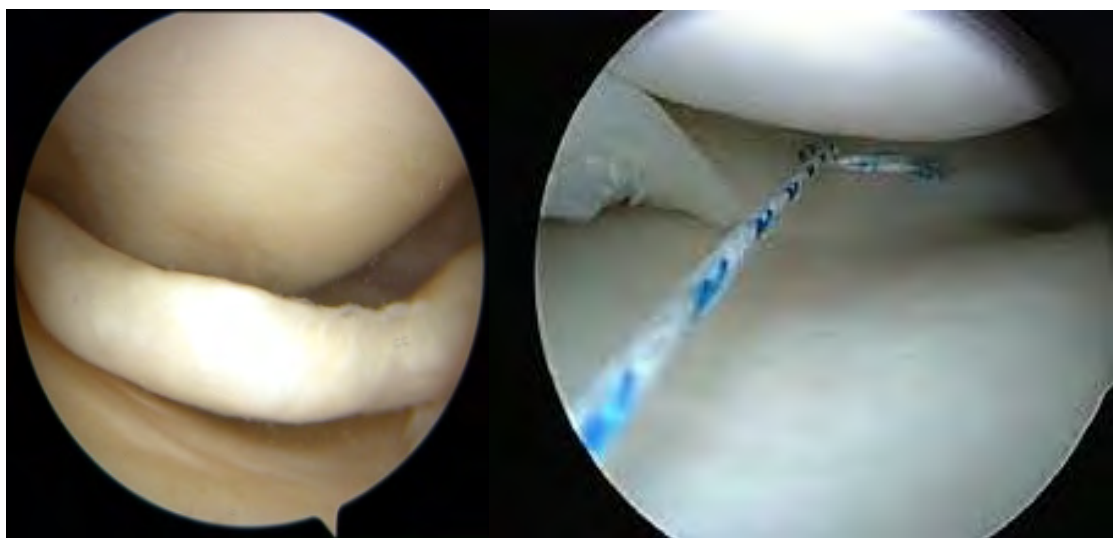


Fig. 1. Intra-op images showing all-inside suture of a medial meniscus bucket handle tear.

technique were identified for this retrospective study. The inclusion criteria were the presence of bucket handle meniscal tear MRI enhanced and clinically confirmed; no previous knee surgery; presence of no more than one associated ligament injury. All patients, when signing the informed consent for the surgical procedure, gave also their consent to the use of their clinical data, after being anonymized, for scientific purposes. Our Institutional Ethic Committee approved the present retrospective trial.

All procedures were performed by the same senior surgeons. Meniscal repair was carried out with all-inside sutures using FasT-Fix devices (Smith & Nephew, Andover, MA) alone or in association with outside-in sutures, mainly used for the anterior meniscal horn (Fig. 1). Fifty-four out of 65 patients included in this investigation had undergone clinical examination at mean 4.1 years follow-up (range 3 to 6.5 years); 11 patients were lost at follow-up so were excluded from the evaluation. The meniscal “bucket handle” tear was located in the medial meniscus in 35 cases and in the lateral meniscus in 17 cases. Both medial and lateral menisci were injured in 2 cases. All tears interested the “red-red zone” or “red-white” zone of the meniscus.

Average patients age at surgery was 25.8 years (range 13 to 53). The mean number of sutures used was 4 (range 2 to 6). In case of concomitant anterior cruciate ligament injury, we proceeded to ACL reconstruction using hamstrings tendon at the same surgical time: 25 of the 54 patients underwent ACL reconstruction in combination with bucket handle repair. Time elapsed between knee injury determining meniscal tear and surgery was estimated in average 106 days. The primary outcome measure was failure of repair, as defined by the requirement for reoperation of the meniscus (meniscectomy).

All patients included in the study underwent clinical evaluation at mean 4.1 years follow-up (range 3 to 6.5). All patients were administered the following questionnaires to assess clinical outcome in the post-op period: Tegner scale, Lysholm Scale, International Knee Documentation Committee Subjective (IKDC Subjective Knee evaluation form), Quadruple Visual Analogue Scale and Knee injury and Osteoarthritis Outcome Score (KOOS score).

Post-op management

All patients were supplied with a hinged brace limiting knee flexion to 0° for the first week and then

gradually increase up to 90° was allowed until the fourth week. Within this range, weight bearing according to pain was allowed from the third week, physiotherapy with isometric exercises was started from the fifth day postoperatively, and gradually increased. Return to sport activity was allowed after at least 6 months after the surgical intervention, after a final evaluation by the senior surgeon.

Statistical Analysis

All continuous data were expressed as mean and standard deviation; categorical variables were expressed as frequency and percentages. The Wilcoxon nonparametric test was used to evaluate the variations at different follow-up times. The Mann-Whitney nonparametric test was performed to assess between-group differences of continuous data. The Spearman rank correlation was used to assess correlation between rank and continuous data, and the Kendall tau ordinal correlation was used to assess correlation of ordinal data. Fisher's chi-square test was performed to investigate the relationships between dichotomous variables. Pearson's chi-square test evaluated by exact methods for small samples was performed to investigate the relationships between grouping variables. All nonparametric tests were evaluated by exact methods for small samples. For all tests, $P < .05$ was considered significant. All statistical analysis was performed with SPSS, version 19.0 (IBM, Armonk, New York).

RESULTS

Ten out of the 54 patients (18.5%) included in the study underwent reoperation (meniscectomy) and therefore they were considered as failure of primary meniscal repair. One failure occurred 4 months after repair, 7 cases failed within one year from the surgical procedure, whereas 2 cases after 18 months and 22 months respectively. In all the failed cases, failed patients had resumed physical activity and complained about persisting pain on the index side and/or locking and/or swelling with knee functional limitation. Based on these clinical findings, they were scheduled for revision surgery. Considering the group of patients who did not need reoperation, clinical scores up to the final evaluation at mean 4 years have been summarized in Table I.

SUBGROUP COMPARISON

Failed vs not failed

The comparison of the two groups did not show statistically significant differences in terms of age at surgery time, side, meniscus involved, and number of sutures used. However, there was a significant difference between isolated meniscal repair and failure: patients undergoing simultaneous reconstruction of the ACL had lower risk of failure

Table I. Demographics and clinical scores of the patients included in the present trial (*pre-inj.*=pre-injury; *ADL*=activity of daily life; *QoL*=quality of life). Post-op evaluation was performed at mean 4.1 years' follow-up.

Variable	Mean	Std. Dev.
Age at surgery	25.8	10.5
No of sutures	3.8	1
Injury to surgery time (day)	106.6	121.1
Lysholm pre-injury	96.3	6.5
Lysholm post-operative	94.6	7.8
Tegner pre-inj.	6.9	1.8
Tegner post-op.	6.5	1.9
Quad. VAS pre-inj	12.9	9.6
Quad. VAS post-op	15.3	13.4
IKDC subj. pre-inj	90.3	8.8
IKCD subj. post-op	88.4	11.4
KOOS pain pre-inj	97.1	2.4
KOOS pain post-op	96.4	3.5
KOOS sympt. pre-inj	92.1	8.1
KOOS sympt. post-op	89.6	8.5
KOOS ADL pre-inj	99.2	1.7
KOOS ADL post-op	99.3	1.8
KOOS sport pre-inj	92.9	8.0
KOOS sport post-op	91.3	9.9
KOOS QoL pre-inj	88.7	14.5
KOOS QoL post-op	83.5	18.3

($p=0.025$). No significant differences in terms of failure of the repair were documented when comparing patients operated within 60 days from the trauma to those operated after 60 days.

Medial vs lateral meniscus

When comparing medial meniscus bucket handle tear to lateral ones there were no statistically relevant differences in age at surgery, ACL involvement, elapsed time from injury to surgery and pre-injury Lysholm and Tegner Scale. Looking at outcomes, significant difference was reported in terms of: Lysholm score ($p=0.001$), KOOS pain ($p=0.02$), KOOS sport ($p=0.02$), KOOS QoL ($p=0.001$), all of which were significantly higher in the lateral meniscus subgroup (Table II).

Isolated meniscal repair vs meniscal repair + ACL reconstruction

Patients with ACL deficient knee who underwent ACL reconstruction at the same surgical time of meniscal repair did not show relevant differences in terms of age, side, elapsed time to surgery, number of stitches/sutures compared to patients who received meniscal repair alone. When analyzing clinical outcome, no significant difference was observed in any score between the two subgroups of patients.

Time from injury to surgery (<60 days vs >60 days)

Comparing patients who underwent surgical intervention within 60 days from injury to those treated after 60 days, no statistically relevant differences were shown in terms of age, knee side, involved meniscus, number of sutures, ACL deficient knee, pre-Injury Tegner and Lysholm scale. No significant difference in post-op. Lysholm score, IKDC-subjective, KOOS symptoms, KOOS QoL were documented.

Age at surgery (≤ 25 yy vs >25 yy)

Using patient's age at surgical time as a comparative parameter, statistical analysis showed significant differences in terms of pre-Injury Tegner score between the two treatment groups, with higher value in <25 yy patients (7.5 ± 1.7 vs 6.0 ± 1.5 , $p=0.001$). No relevant differences between the two

subgroups in terms of knee side, involved meniscus, elapsed time from injury to surgery, number of sutures, ACL deficiency, QVAS and KOOS were noticed. Looking at the final outcome, post-op. Tegner score remained significantly higher in the <25yy ($p=0.001$), even if both subgroups of patients were able to resume the same sport activity level compared to the pre-injury status. No significant differences were reported in other scores considered.

DISCUSSION

Meniscal surgery is one of the most common orthopedic procedures worldwide: it has undergone a remarkable development in the last 30 years, moving from an open procedure to arthroscopy, whose primary goal is now the preservation of the meniscus. Biomechanical studies clarified the protective role of the meniscus: several authors have shown that total removal of the meniscus leads to a peak contact pressure increased by approximately 235% with a reduction of the tibio-femoral contact area of approximately 75%, thus promoting early joint degeneration (10, 11). Accordingly, total meniscectomy is indicated only in severe irreparable injuries of the meniscus. Partial meniscectomy, preferable to total, is acceptable in central, unstable tears of the “white-white” zone (avascular) or in case of irreducible, displaced bucket handle tears (BHT) or flaps (12, 13).

Meniscal repair provides a biomechanical advantage represented by preservation of the meniscus rim: Baratz et al. (11) have shown that the contact pressure after meniscal repair decreases almost down to the intact level, with reduced

incidence of degenerative changes and better long-term outcome compared to meniscectomy. Indications for meniscal repair are still controversial: the ideal lesion for repair is an acute, longitudinal tear of the peripheral meniscus (red-red or red-white zone), in young patients. Nevertheless, some authors reported good clinical results after repair of meniscal tears extending into the avascular zone; other investigators performed meniscal repairs in older patients with good results: healing potential of meniscal tears depends on several factors including vascularity, lesion type, size, age of patient and chronicity.

Indications for meniscal repair can be extended using procedure that promote healing: meticulous stabilization of the tear, synovial and meniscal abrasion to stimulate angiogenesis and proliferation of mesenchymal cells from the meniscus-synovial junction, use of fibrin clot or platelet rich plasma as chemotactic factors (avascular zone tear) and micro-pick technique at the intercondylar notch to provide bone marrow cells and growth factors (14, 15, 16, 17). The aim of our retrospective study was to investigate the outcome of meniscal repair in case of bucket handle tears (BHT), that are usually treated by subtotal or total meniscectomy. As widely carried out in literature (18), high costs of MRI and invasiveness of arthroscopic second-look led us to use rate of re-operation as the primary outcome measure; moreover we analyzed the influence of various factors (age, chronicity, knee side, meniscus involved, ACL deficiency, number of sutures) on the success rate of bucket handle meniscal repair.

There are a few scientific reports focused on the repair of BHT: Espejo-Reina et al. (19) analyzed 24

Table II. Comparison of clinical scores between medial and lateral BHT repair at mean 4.1-years follow-up evaluation (only significant differences shown in the table).

MENISCUS	Lysholm	KOOS Pain	KOOS Sport	KOOS QoL	IKDC-subj.
MEDIAL	89.6 +-8.9	90.5 +-5.3	87.4 +-11.2	79.5+-20.2	86.0 +-12.5
LATERAL	98.4 +-2.5	98.0 +- 2.5	95.0 +- 6.2	91.2+- 12.4	95.6 +- 8.1
p	0.001	0.02	0.02	0.01	0.01

cases of BHT of the medial meniscus reporting a failure rate of 17%; Jin Hwan Ahn et al. (20) observed 13 patients with BHT of the lateral side reporting excellent results in terms of Tegner, Lysholm score and HSS, and no need for reoperation. More recently Moatsche et al. documented satisfactory results with low failure rate at two years evaluation after repairing BHT with multiple vertical mattress sutures using an inside-out technique (21). Conversely to the previously mentioned studies, the paper authored by Moses et al. (22), found less-encouraging outcomes, with a failure rate over 23% and lower return to pre-injury sport level, thus confirming that BHT repair represents a challenge even for experienced surgeons. To the knowledge of the authors, this is currently the study with the largest number of BHT repairs included: in fact, in our series, 54 patients were included and evaluated at an average 4 years' follow-up: 10 patients underwent reoperation (meniscectomy) with a consequent failure rate of 18.5%. To this regard, data from available literature are inconsistent, with estimates of failure ranging from 5% to 43.5% (23).

The variability of these results is due to the heterogeneity of the population studied and the different surgical techniques adopted. Comparative analysis of the two groups of patients (failed vs not failed) showed that the only significant difference was the association between ACL reconstruction and the success of BHT repair, although considering the "not-failed group" we did not observe a significant difference in terms of IKDC, KOOS, Tegner, Lysholm, Q-VAS scores between patients who underwent isolated meniscal repair or ACL reconstruction plus meniscal repair.

These results are comparable to those previously reported in literature: several authors believe that concomitant ACL reconstruction is associated with a better outcome of meniscal repair as it determines hemarthrosis, that provides autologous growth factors in the articular space, favoring meniscal healing; furthermore ACL reconstruction is often associated with a prolonged and more careful rehabilitation that could play an essential role in promoting also meniscal healing.

In our series, variables such as patient's age,

meniscus involved (medial vs lateral), knee side and number of sutures did not influence significantly the failure rate, as well as the time elapsed between trauma and surgery. In 2013, Lyman et al. (23) carried out a review to measure the frequency of revision surgery after meniscal repair and elucidate risk factors for subsequent meniscectomies using a large study population (9529 patients) from multiple surgical centers. The authors found the following prognostic factors: older age of patients; reduced activity level; simultaneous ACL reconstruction; lateral meniscus involvement; and surgical volume of the surgeon. As widely described in literature, the medial meniscus undergoes greater biomechanical loads than the lateral and this could be the reason of higher risk of failure in case of medial meniscus repair (24). Our analysis did not demonstrate significant differences in terms of failure between medial and lateral meniscus, but patients with BHT of the lateral side showed better results when compared to medial meniscus in terms of post-op. Lysholm, IKDC-subj., KOOS pain, KOOS sport and KOOS qol.

Considering the chronicity of meniscal tears, we also divided "not failed" patients into two groups based on the elapsed time between trauma and surgery (<60 days vs >60days). Interestingly, no significant difference in terms of failure rate and postoperative Lysholm, IKDC-subj. and some KOOS scales were detected. This finding might support the fact that meniscal repair could be attempted even in a "delayed" time setting, despite the available literature suggests that acutely treated injuries have a better clinical outcome (25).

Finally, considering the age of patients at surgery, results appear to be contrasting: Noyes and Barber-Westin asserted that meniscal repairs healed equally well in younger and older patients, even when the injury was in the avascular zone, where healing should be less likely (14, 24). Conversely, Lyman et al. found that patients under the age of 30 years' experience significantly higher rates of subsequent meniscectomies than older patients, probably due to their higher functional requests, which increases the risk of a re-injury during sport activities (21). Other studies have previously suggested that the best candidates for meniscal repair are young patients who may have a greater capacity for healing (26). Our

series, in line with Noyes and Barber-Westin, does not prove significant differences between patients younger or older than 25 years in terms of failure rate and both groups were able, after BHT repair, to get back to their usual sport practice. Younger patients, as expected, presented higher sport activity level both at pre-injury and post-op evaluations. The present study has some flaws that should be acknowledged: firstly, the relatively small number of patients included at variable follow-up times, due to the retrospective nature of the present trial. Secondly, the lack of imaging evaluations during follow-up, which prevented the authors from identifying asymptomatic, partially healed meniscal tears.

Preservation of the meniscus is the goal of meniscal surgery, in particular for those tears that could lead to total or subtotal meniscectomy, such as bucket handle tears. Our series showed encouraging results after all-inside meniscal bucket handle tear repair up to middle term evaluation, with a cumulative failure rate of 18.5%. Concomitant ACL reconstruction was associated with lower failure rate, whereas lateral meniscus involvement was associated with higher functional scores at final follow-up evaluation.

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Total hip replacement: a retrospective multicentric analysis on re-intervention rate after single component revision

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Total hip arthroplasty (THA) revision is a procedure consisting in the replacement of a single or multiple implant components and could take place once or more times (re-revision). The aim of this multicentre study is to evaluate the benefits of single component revision in respect of the principles that define implant stability. Two hundred and forty-two patients underwent THA revision at Orthopaedic Clinic of Pisa and Versilia (ITA) from January 2007 to December 2016. We have systematically excluded revisions due to septic or traumatic prosthesis loosening, revisions of both implant components (cotyle and stem) and replacement alone. To evaluate implant stability, we used preoperative X ray and intra-operative mechanical stress tests, applying accredited criteria. Two hundred and twenty-six patients (93%) underwent a single procedure of THA revision: 193 had cotyle replacement and 33 had femoral stem replacement. The remaining 16 (7 %) underwent at least two procedures: 10 of them had consecutive failure of the same component, while the other 6 had revision of the other component after the first procedure. Considering our cases series, we can assert that single component revision is the best choice when no signs of loosening are present on the remaining component. Nevertheless, an accurate evaluation with unanimous radiological criteria and intraoperative testing is essential for the surgeon to choose the most suitable treatment.

Revision of total hip arthroplasty (THA) can be performed on different indications such as liner degradation, septic or aseptic loosening, metallosis, instability, periprosthetic fractures. In each single case the orthopaedic surgeon will consider the substitution of a single component (acetabular shell or femoral stem) or both. The aim of the treatment is to restore stability and a good range of movement. The surgical procedure is usually performed using the former approach, enlarged for more complex cases.

A specialized team and a wide range of instruments are required for this kind of surgery, given the higher

risk of intraoperative complications, sometimes unpredictable; this is the reason why it should be performed only in tertiary care hospitals. Depending on the case, hospitalization is higher compared to first implant THA with consequences on hospital economic balance: in Italy the cost for the revision of an infected THA seems to be 4.8 times higher than that of a standard total hip replacement (1).

Every year more than a million hip prosthesis are implanted all over the world (2); the number of revisions consequently increases. Italy too follows this trend: the 2018 annual report of the

Key words: hip; hip arthroplasty; hip revision surgery; single component revision surgery

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Italian Arthroprostheses Register recorded 38.498 hip prosthesis, including 72.8% THA, 22.1% hemiarthroplasty and 5.1% revisions (3). The population considered ranged 65 to 74 years old with a higher female sex prevalence.

The aim of our multicentric study is to evaluate, with a mid-long term follow up, the utility of a single component revision and to assess the validity of the criteria used to define implant stability.

MATERIALS AND METHODS

Data were collected using the electronic surgical database of each center, selecting patients who underwent THA revision from January 2007 to December 2016 in Pisa Hospital (I and II Orthopaedic Clinic) and Versilia Hospital. Patients with revision of

both components, revision of liner only and patients with septic or traumatic prosthesis loosening were excluded. The following data were recorded: the date of the first revision, the date of re-revision (if performed), the range of time between the two procedures and which of the two components was changed.

Implant stability was assessed on X ray considering as definition criteria the absence of temporal modifications, of lucent zones and periprosthetic bone loss. Intraoperative mechanical stability was assessed too.

RESULTS

Two hundred and forty-two patients were included in this study; 226 (93%) underwent revision surgery once, of them 193 had acetabular component

Table I. *Patients who underwent a single revision procedure.*

	Males	Females	Total
Acetabular component	47	146	193
Femoral component	17	16	33
Total	64 (28%)	162 (72%)	226

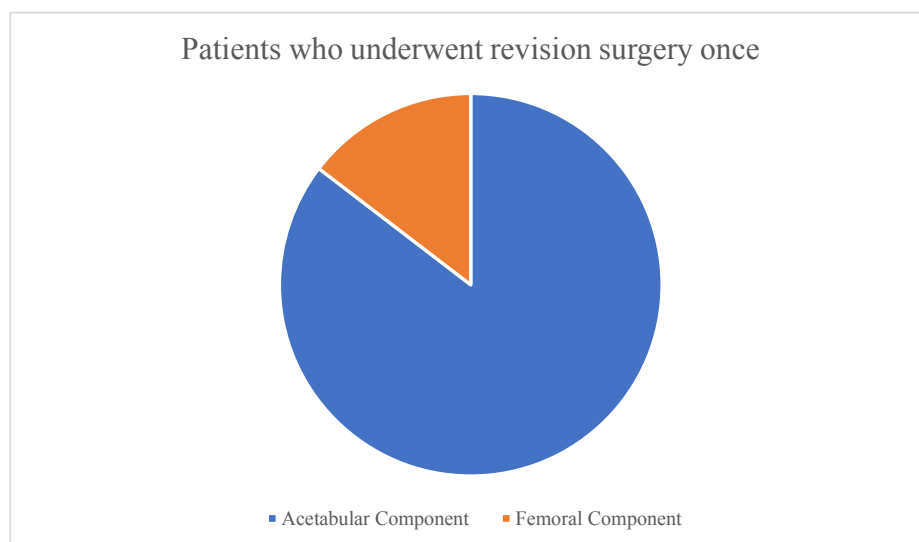


Fig 1. *Distribution between the two components revision.*

substitution while 33 had femoral component substitution (Table I) (Fig. 1). The remaining 16 patients had at least two re-revision procedures, 10 of them due to the failure of the same prosthetic component. Therefore, 6 patients required further re-revision with substitution of the other component after single component first revision. Patients who underwent a single time single component revision

surgery were mostly women (72%); the average age was 72.4 years old.

Regarding acetabular shell revision, in 25 cases (13%) a cemented implant was employed and 135 cases (70%) required the use of screws for better fixation (Fig. 2). Thirteen patients (5%) needed a re-revision surgery; the average age at first revision was 66.5 years old and the average time between the first

Table II. *Re-revision details and average time between first and second procedure.*

Patient	First revision	Second revision	Average time
1	Acetabulum	Complete	20
2	Acetabulum	Acetabulum	7
3	Acetabulum	Acetabulum	16
4	Acetabulum	Acetabulum	26
5	Acetabulum	Acetabulum	1
6	Stem	Stem	20
7	Stem	Acetabulum	23
8	Stem	Stem	24
9	Stem	Acetabulum	1
10	Acetabulum	Acetabulum	1
11	Acetabulum	Stem	10
12	Stem	Stem	30
13	Stem	Stem	14

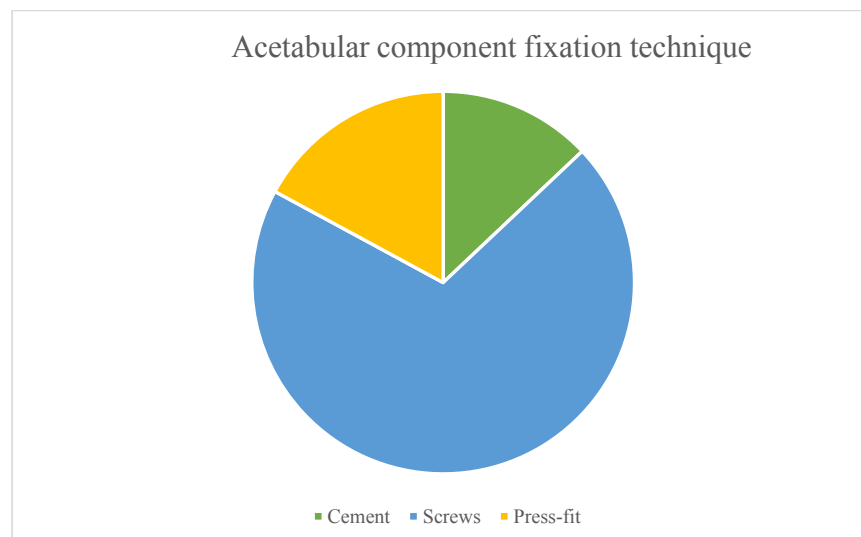


Fig 2. *Fixation techniques for the acetabular component revision.*

and the second procedure was 14.85 months (Table II).

Definitely, 9 patients underwent repeated revision of the same prosthetic component, the remaining 4 underwent revision of the component considered as stable at first revision. Of the 242 patients considered, only 3 needed more than 2 revision surgery (Table III).

DISCUSSION

Every year over a million total hip arthroplasties are performed all over the world with the number of revision surgery procedures increasing because of the improvement of life expectancy and longer follow up (4, 5). The Italian Arthroplasty Register recorded in the 2018 annual report 38498 total hip arthroplasty (THA), of them 5.1% were revisions and their number is estimated to duplicate in 2026 (3).

Arthroplasty revision surgery is gaining importance both as surgical challenge and as economical issue. Managing such a complex surgery requires a highly specialized team provided with a wide range of surgical instruments. Regarding the costs, revision and re-revision have a greater hospitalization time thus having consequences on the economical balance: for example in Italy the cost for the revision of an infected THA seems to be 4.8 times higher than the cost of a first implant (1).

The decision to revise a THA is not as simple, especially when there is no clear radiological evidence of loosening but the patient experiences pain and an unsatisfactory articular function. Even when the indication for revision is clear and fulfils

adequate criteria, it is complex to establish if both components need to be revised. Of course, when the surgeon works only on the acetabular side, the presence of a stable non modular femoral stem makes things harder, with a higher risk of complications, such as periprosthetic fractures, increase of surgical times and blood loss (6-8). Therefore, the chance to remove the femoral stem when revising the acetabular component offers a better surgical exposure and facilitates the surgeon (6). On one hand, the presence of a stable femoral stem provides a good reference for limbs length and femoral neck anteversion (9), on the other hand obliges the surgeon to use only compatible components in order to maintain stability itself (10).

From a biomechanical point of view, in patients with THA have an altered load transmission being determined by prosthesis geometry, by the mechanical features of the implanted materials and the bonds between them. That is why the life expectancy of a prosthesis is strictly related to the interaction between materials and components: to optimize prosthesis endurance good primary stability is mandatory. Nonetheless final integration will be influenced by bone remodelling due to secondary stability. An altered distribution of forces could lead to relative micro-movements affecting integration at the interface bone-prosthesis; macrophages seems to play a role in this phenomenon, being, activated by the presence of micro-particles of cement or debris, that release chemical transmitters activating osteoclasts.

Table III. *Patients who underwent more than 2 revision procedures.*

	Intervention dates	Type of revision
Patient n.1	19/11/2007	Acetabular
	16/07/2008	Acetabular
	26/02/2009	Complete
Patient n.2	13/10/2008	Acetabular
	04/10/2012	Acetabular
	07/11/2013	Acetabular
Patient n.3	11/03/2009	Femoral
	07/12/2009	Acetabular
	12/02/2010	Acetabular

From an accurate analysis of our data we can state that 85% of the patients considered underwent revision of the acetabular component literature (11, 12). A reason for the trend could be the greater use of cement for acetabular component fixation, being femoral stems provided with specific threads for anchorage (13-15).

As regards materials, considering the physiopathology of bone reabsorption, the coupling metal-metal, currently abandoned, has proved to be a risk factor for implant failure causing metallosis. It is also true that the use of a polyethylene liner, independently on the head material (ceramic or metal), has caused in the last years a higher number of revisions of the liner only. The Italian Arthroprosthesis Register shows that hybrid implants (with non-cemented acetabulum and cemented stem) or implants with press fit acetabular cup represent the group less affected by revision interventions performed in Italy in 2018 (3).

Moreover, our study underlines that just 2.5% (6 patients) underwent subsequent re-revision in order to change the component considered as stable at first. This justifies the utility of single component revision if the other is assumed to be stable and corroborate the validity of the criteria used to define prosthesis stability. Finally, the type of component revised at first, acetabular or femoral, does not seem to affect the risk of re-revision of the other component.

Arthroplasty life expectancy is strictly dependent on its stability, both early and late, and it is related to the biological and mechanical features of the materials used, to the geometry and the bonds between implant components.

Revision of a single component can be considered as an effective surgical approach when no signs of loosening are found on the other component. Our casuistry show that the percentage of patients undergoing a new procedure to change the other component is low, especially when compared to the higher risk of complications related to the substitution of a stable component.

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Clinical anatomy of the meniscus in animal models: pros and cons

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Nowadays, despite the possibility to use in vitro or computer models in research, animal models are still essential. Different animal models are available for meniscal repair investigation. Although a unique perfect model for the structure of the human's knee does not exist, the choice of the proper animal model is crucial for a correct research. The principal animal models in the meniscal repair are sheep, goats, pigs and dogs. Each of these has pros and cons for their utilization. Analysing each pro and con is essential for optimizing the choice of the animal model, which depends on the experimental question, avoiding unnecessary waste of resources and minimizing the animal suffering, according to the Russell and Burch's three "Rs" principles (Reduce, Refine and Recycle). In this concise review, we resume the meniscus anatomical features of the main large animals, to help choose the most suitable animal model for subsequent studies on meniscal repair.

Despite the promising results of alternative procedures such as cell, tissue and organ cultures, animal models are still essential for scientific, economical, ethical, and regulatory reasons in many research fields, and orthopaedics is one of them. In fact, animal models are a unique tool for testing tissue repair and regeneration solutions, as well as for validating specific tissue engineering methods after in vitro testing and before moving to clinical application. The meniscus is a challenging tissue from the healing point of view, since it often undergoes a time-dependent degeneration and

exhibits a very low healing potential. On the other hand, it is frequently affected by injuries, especially tears. These lesions are extremely frequent and represent the most common cause of surgical procedures performed by orthopaedic surgeons (1). They are also often responsible for the consequent development of osteoarthritis. The functionality of different therapeutic devices and the efficacy of engineered tissues for meniscal healing have been also evaluated in different species. Since the goal of research is achieving a functionally efficient clinical outcome, species-specific features must be

Key words: meniscal repair, animal models, meniscus

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Table I. Pros and Cons among different animal models for meniscus studies.

MODEL	PROS	CONS
Sheep	Similar anatomy, vascularization and mechanical properties; Possibility to utilize like chronic models; easy to handle and not aggressive.	Difficult post-operative immobilization; Different force distribution.
Goat	The most similar anatomy; Joint easy accessible by arthroscopy; Less expensive than other large animal models and quite easy to handle.	Difficult post-operative immobilization; Small dimensions of the knee.
Pig	Similar vascularization patterns, cell density, collagen structures and biomechanical properties; Similar weight; Possibility to fast translate the information to human field.	Expensive and difficult to host; Can be aggressive.
Dog	Anatomy, histology, and biochemistry similar to that of the human knee; Joint easy accessible; Causes, symptoms, and therapies for osteo-arthritis similar to those in people; Easy handling; Different available sizes.	Strong intrinsic response to tissue damage by deposition of fibrous tissue; Elevated tibial plateau; More ethical issues.

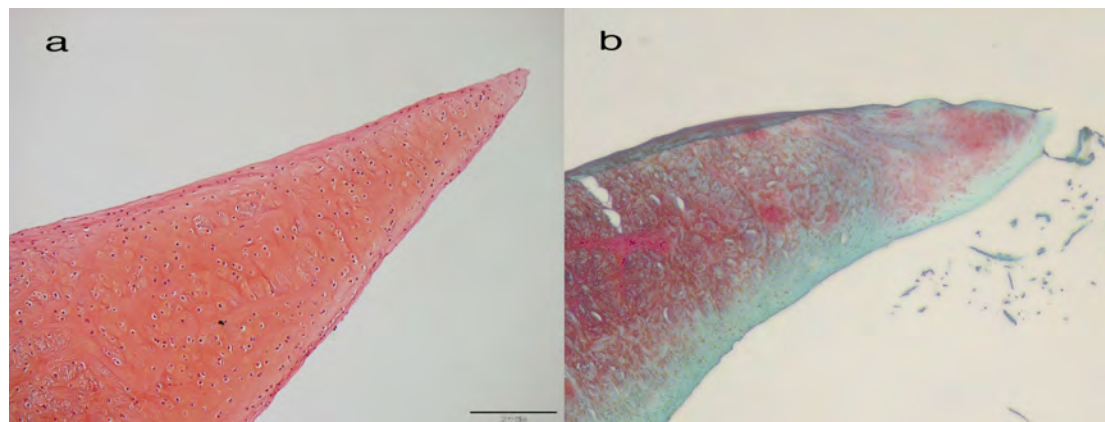


Fig. 1. Safranin-O histochemical staining: orange/pink color for GAGs deposition and green color for fibers. Both pictures have the same scale bar located in Figure 1a. 1a) anterior horn of an adult pig with positive staining for extracellular matrix and chondrocytes (orange); b) anterior horn of an adult sheep with positive immunostaining for extracellular matrix (orange) and negative staining for fibers (green).

considered in the different experimental questions. Therefore, several animal models turn out to be valuable in different scientific issues.

The meniscus: gross anatomy, structure, composition and physiology.

The menisci are fibro-cartilaginous structures

located in the knee joint, in simultaneous contact with the femoral condyles and the tibial plateau. They are C-shaped, and they can be anatomically divided into three different regions: a body and two horns. Each meniscus has a thick convex peripheral margin in contact with the inner capsule of the joint, and an opposite thin- and free-edged margin (2). The

meniscal body is made of a dense scaffolding of type I collagen fibers characterized by circumferential orientation.

Throughout the tissue, a lower number of radial fibers can also be found. Radial fibers seem to hold circumferential fibers together, opposing longitudinal stresses (2). The meniscal tissue is composed of water (72%), collagen (22%), and glycosaminoglycans (GAGs) (0.8%) (2). On a dry weight basis, normal adult menisci contain 78% collagen, 8% noncollagenous proteins and 1% hexosamine (2).

Collagen type I is the major collagen component (90%), followed by collagen types II, III and V (2). Regional variations exist in the distribution of collagens: collagen type I is mostly represented in the peripheral area, while collagen type II is restricted to the inner zone, which shows cartilage-like properties (2). Normal human meniscal proteoglycans contain 40% chondroitin 6-sulphate, 10–20% chondroitin 4-sulphate, 20–30% dermatan sulphate and 15% keratan sulphate (2). The most represented cell type in the meniscus is the fibrochondrocyte (2).

Moreover, the vascularization of the meniscus is provided by a perimeniscal capillary plexus which forms from the lateral and medial geniculate arteries (2). Structure and composition exhibit numerous interspecific differences that will be considered later.

Animal models

The need of using animal models despite the existence of new techniques and resources that virtually seem to allow the non-use of animals in research, is due to the fact that all in vitro studies have some limitations because they focus on aspects that cannot be transferred to the in vivo scenario (3). Unfortunately, a perfect model for meniscal repair in the animal reign does not exist. The principal animals employed in studies on meniscal repair are sheep, goats, pigs and dogs. A few studies have used the cow meniscus which, however, has been proved to be significantly bigger than the human meniscus based on anatomical analysis. Each model has pros and cons for its use, as summarized in Table I, including different anatomy and behavioral habits.

Sheep

Sheep are often chosen as model (2) for the analysis of the effect of a meniscectomy in the joint environment, for meniscal repair (with growth factors) or replacement (meniscus allograft and engineering).

Compared Anatomy

The sheep menisci are shorter than the human ones, but they are the most similar in size among the different animal model species (4). In particular, the lateral sheep meniscus has been found to have a size not statistically different compared to the lateral human meniscus. In fact, except for circumference, dimensions like width, peripheral height, articulating height, superior articular length matched those of the human meniscus. Also, most of the dimensions of the sheep medial meniscus showed no statistical difference in comparison to the human menisci. Both medial and lateral meniscus have smaller average wet weight and volume than human menisci (5).

The medial and lateral menisci have a small connection, which does not hide their anterior insertion sites (4). Microscopically (Fig. 1), the sheep meniscus presents fusiform cells at the surface and round cells in deeper layers (2). The water content of ovine meniscus is 68%, and the remaining dry weight being is largely composed of collagen (75%). Sheep menisci show a deeper Safranin O stain compared to human menisci, but GAGs distribution is similar between the two species. GAGs are present mainly in the inner zone (6). Collagen type I throughout the entire matrix except for the inner tip (2) and collagen type II with an age-dependent distribution: in the young ovine it is located only in the inner zone (7) while in the adult it is located in the inner main body (2).

Pros

Sheep have the most similar meniscal anatomy (4) with vascularization patterns similar to those of human being (2). Mechanical properties of sheep menisci are comparable to those of men and can be utilized to simulate chronic meniscal injuries that better represent the type of lesions found in human clinical practice (8). This species is handy and not aggressive.

Cons

The distribution of shearing and compression forces during the gait is different between human and sheep (2), because the latter usually loads knee in flexion (2) while human does in extension. Sheep generally do not tolerate the post-op immobilization and, even if immobilized in a cast, the full weight bearing could not be completely avoided (2).

Goat

Goats are used as model for meniscal repair with sutures and cell therapy and for testing new devices or techniques for meniscal replacement with allograft or tissue engineering-based strategies (2).

Compared Anatomy

The goat is an animal model very close to humans. In fact, the medial meniscus size and proportions are extremely similar to those of humans (4). A meniscotibial coronary ligament is also present (4). The main differences are the absence of a full-length fibula/proximal tibiofibular joint, replaced by a fibular head fused to the lateral side of the tibial plateau, serving as an attachment site for the lateral meniscus (4).

Pros

Considering macroscopic anatomy, the goat is the ideal model. The size of caprine knee is similar to humans and the joint, thanks to its structure and dimension, is easily accessible by arthrotomy and arthroscopic procedures (2). Moreover, the proportion of cartilage to subchondral bone and the subchondral bone consistency is closer to those of humans than those of other models (2, 9). Since goats rapidly develop osteoarthritic signs following meniscectomy/meniscal replacement (2), they are considered suitable models for the evaluation of the consequences of meniscal substitution on articular cartilage. Goats are less expensive than other large animal models and quite easy to handle (2).

Cons

Despite the ideal dimension of the knee (very similar to human), the size of the caprine tibiofemoral joint is still significantly smaller compared to human (2). Functionally, it is recognized that the fused

tibiofibula in the goat could potentially make its bony anatomy more stable than the human knee in a posterolateral knee injury (10). Moreover, the goat meniscus has been considered too small to provide a realistic model for arrow insertion (11). Behavioral factors limit the use of this model due to rehabilitation concerns. Goats are browsers, not grazers like sheep, so they often stand on their hind legs while foraging. Thus, excessive weight bearing may lead to early damage to meniscal implants or sutures (6). Finally, despite the favorable cost, very few studies on meniscus replacement/repair have been performed on goats compared to sheep: this probably also reflects a partial lack of facilities for goat housing and surgery.

Pig

Swine models (2) are usually employed for testing meniscal sutures and cell therapy (12, 13).

Compared Anatomy

The two menisci present a small connection between the two anterior insertions that, however, does not hide the distinct anterior insertion sites (4). Furthermore, the lateral porcine meniscus is longer than the medial one (4). The meniscal weight and the meniscal volume in pig are significantly larger than those of humans. The pig meniscus is bigger in size than the human meniscus in most of the dimensional aspects (5).

Microscopically, the pig meniscus present chondrocyte-like cells in the inner and middle zones (2). Collagen type I is organized as circumferential fibers and mainly located in the external zone while collagen type II is organized as radial fibers and is principally located in the inner and intermediate zones (2).

Pros

The porcine meniscus is similar to the human meniscus in its shape and structure (2), and, in particular, it is comparable to the young adult human meniscus. The pig model, like human, is characterized by the absence of spontaneous healing (2). The miniature swine bred are also able to maintain an adult weight and size comparable to adult men (2).

This model features allow the reasonable translation of the results to clinical applications (14).

Cons

Porcine menisci have higher mechanical properties than adult human menisci, displaying minimal deformation and equilibrium displacement in response to the visco-elastic creep response compared to human menisci (2). For these reasons, the clinical relevance of the data originating from this species must be carefully considered. In addition, pig breeding involves high costs and the facilities that can host this large and potentially aggressive animal are limited (2).

Dog

Canine models are often utilized like models in meniscectomies, cell therapies and meniscal replacement techniques (2). The dog model has been used in many reports because of the high animal compliance which allows better control in postoperative care, but it is getting more and more unpopular due to the pressure coming from the animal rights organizations.

Compared Anatomy

Dogs have a relatively high tibial slope (range: 19-28°) with respect to human (range: -1°-19°) (15). The insertion areas of the medial meniscus are smaller than those of men (2). Microscopically, meniscus cells are round shaped and, particularly in the anterior and posterior horns of the inner third, chondrocyte-like while in the outer third fibrocytes are present (2). Aggrecan, as an organized network, is more concentrated in the inner zone (16). Collagen type I forms circumferential fibers throughout the matrix from the peripheral to the inner area but not radial ones (2). Collagen type II is markedly deposited in the inner body in an organized network composed of both radial and circumferential fibers (2).

Pros

Anatomy, histology, and biochemistry of the dog's knee are very similar to those of human. Furthermore, causes, symptoms, and therapies for osteo-arthritis in dogs are like those in people (17).

The dog model is characterized by easy handling, a variety of available sizes and increasing information on meniscal repair and replacement. Dogs have an exposed stifle joint that makes the arthroscopic approach easier with respect to the other large animal models.

Cons

This animal model is characterized by a strong intrinsic response to tissue damage by deposition of fibrous tissue (2). The elevated tibial plateau can compromise the translation of the results to men. Finally, there are more ethical issues when dogs are utilized in the research, because of the domestic relevance that this animal has conquered in the course of human history.

DISCUSSION

Animal models are fundamental in meniscal repair and regeneration studies. Large animal models are more suitable for anatomical and biomechanical studies, as they are very similar to humans as far as these characteristics are concerned. Moreover, they proved to be excellent models for the evaluation of surgical biomaterials and procedures. Nevertheless, further aspects besides the anatomical one, should be considered when choosing the animal model for exploration of new strategies and clinical translation of novel techniques. For example, the innate regenerative capacity shown by menisci of some animal models, could jeopardize the outcome, thus representing a limitation in their use. Menisci in dogs, pigs, and sheep, like in humans, do not have innate regenerative capacity which makes them suitable animal models. Furthermore, as the vascularity and cellularity of the meniscus decrease on maturation, the animals used must be skeletally mature. The different gait pattern compared to humans and the difficulties in postoperative weight bearing management in these species make them still unsuitable for the evaluation of the short-term efficacy of fragile materials (18).

This review may serve as a guide to help choosing the most suitable animal model among different large animals for meniscus studies, considering

remarkable anatomical similarities to humans and reasonable handling costs.

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Bilateral osteochondritis dissecans of the patella in an adolescent skier with patellofemoral maltracking treated with pulsed electromagnetic field therapy

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Juvenile osteochondritis dissecans of the knee typically occurs in young athletes, and usually localizes on the medial femoral condyle. Bilateral localization is uncommon. Patellofemoral involvement is rare, mainly found in basketball and soccer players, and never related to patellofemoral congenital problems such as trochlear dysplasia. We report here the first case, to our knowledge, of bilateral juvenile osteochondritis dissecans with patellar localization in a young skier with patellofemoral maltracking and trochlear dysplasia.

Juvenile osteochondritis dissecans (OCD) of the knee is an idiopathic disease affecting the subchondral bone and secondarily the articular cartilage in patients up to 16 years old (1). It typically occurs in young children and adolescents, and the medial knee condyle is the most common localization (2). The most supported theory regarding its pathogenesis involves repetitive microtrauma, with a local reduction of blood supply (2). Osteochondritis dissecans in fact is relatively frequent among young athletes, and its reported incidence is 15 to 29 cases per 100000 every year (3). Nevertheless, the patellofemoral joint is involved rarely, with only in 7% of cases affecting the patella (4). Patellofemoral localization is more frequent in patients playing weight-bearing sports, most of all, basketball and soccer, while its prevalence among skiers is lower, reaching the 6% in case of trochlear lesions (5).

To our knowledge, bilateral simultaneous juvenile patellar OCD presentation has been described by only three reports in literature (6–8), and no cases associated with patellofemoral joint diseases exist.

We report here a case of bilateral simultaneous juvenile patellar OCD occurred in a young skier with patellofemoral maltracking.

Case presentation

A 13-year old male came to our attention complaining of anterior knee pain for two months. He was an agonist skier (slalom specialty).

The pain increased during weight-bearing activity, especially in those requiring up to 60° knee flexion. At the clinical examination, the patient showed slightly valgus knees, both presenting patellar maltracking, positive camel hump and J signs. Both knees showed no signs of either lateral or anteroposterior knee instability or patellar instability. Both quadriceps muscles had an overall good strength at manual test, but a muscular imbalance was found with a relatively weakness of the vastus medialis obliquus compared to the vastus lateralis.

The CT scan showed a trochlear dysplasia (Dejour type A), with bilateral depressed lesions on the articular surfaces of the patella. MRI showed a bilateral OCD

Key words: *osteochondritis dissecans of the patella, bilateral osteochondritis dissecans, pediatric osteochondritis dissecans, OCD, ski*

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of the patella (Hefti class 3 for the left knee and 2 for the right knee, Fig. 1). Both lesions were approximately located on the median patellar ridge, extended on the medial aspect of the lateral patellar facet on the left knee and on the lateral aspect of the medial patellar facet on the right knee. The Tibial Tuberosity - Trochlear Groove distance on CT scan was 15 mm for the right knee and 17 mm for the left knee, while the Caton-Deschamps index (measured on MRI) was 0.85 for right knee and 1.07 for the left knee.

A conservative treatment was started, with a 3-month stop from sport activity, together with Pulsed electromagnetic field therapy (PEMF) 6 hours per day and physiotherapy for isometric quadriceps strengthening.

After 3 months the patient was asymptomatic, a new MRI scan showed absence of bone edema, with a minimal residual osteochondral damage only on the left patella. He returned gradually to the normal physical activity after 6 months. At 1-year follow-up the patient showed no recurrence of pain or other symptoms. Nevertheless, the patient and his parents were informed about the possibility of future surgical treatment for the OCD and the patellar maltracking, in case of recurrence.

DISCUSSION

Juvenile OCD of the patella is a relatively rare

condition, and a simultaneous bilateral presentation is even rarer. Kleinberg first reported bilateral patellar OCD in 1949, and the diagnosis was performed through histologic exam of the lesion, treated through knee arthrotomy (7). More recently, Arandes-Renu et al. reported 3 bilateral cases among a series of 12 patients with patellar OCD treated with physical therapy and limitation of activities, and finally with drilling of the lesion in case of failure of the conservative treatment (8). Arnold et al. instead reported a case of bilateral juvenile OCD involving both elbows and knees in a 12-year old female, managed conservatively except for one knee (arthroscopic treatment) (6).

The association between sports and patellofemoral joint OCD has been described by Price et al (5). In their series of 30 patients with 34 trochlear lesions, they found an association with basketball and soccer, suggesting a role of a sport-specific mechanical repetitive microtrauma in the OCD pathogenesis; no associations were found for skiing. Nevertheless, ski-slalom activity requires a prolonged standing on flexed knees approximately from 60° to 90°, so causing stress on the patellofemoral joint. In our case, we hypothesized that the sport-specific mechanical stress, acting on a pathological patellofemoral joint with trochlear dysplasia, caused the bilateral lesion. Giving the stability of both OCD lesions,

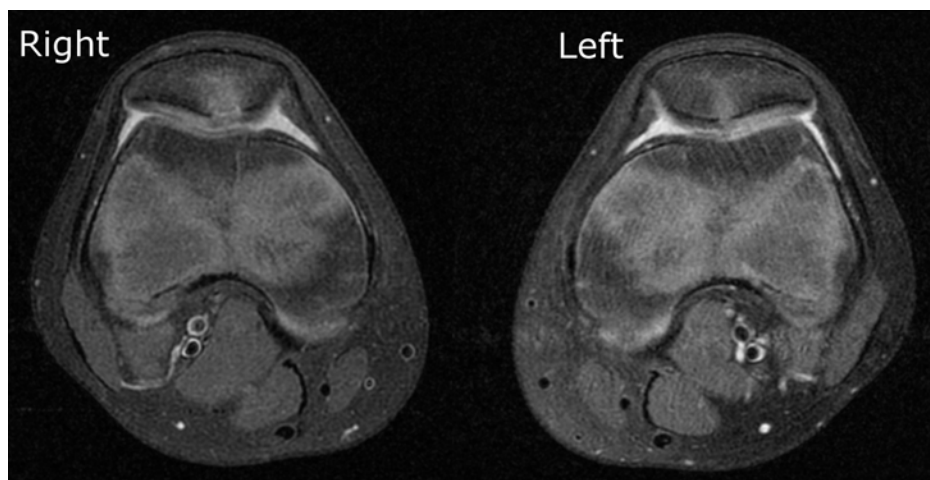


Fig. 1: Axial MRI of the right and left knee showing the OCD lesions.

a conservative treatment was preferred. Knee immobilization was not performed, because of the increased risk of stiffness, considering the high sport participation level (international competitions) of the patient (9). The choice of using PEMF therapy, even if not suggested by guidelines or previous articles, was due to its beneficial effects both on subchondral bone and cartilage healing, and to its effectiveness on other disease affecting those tissues, as osteoarthritis, avascular necrosis of the femoral head and chondral and osteochondral lesions (10). The patient was not treated with shock wave therapy (11) due the young age and the risk of growth plate damage. Furthermore, his parents refused the treatment with local injection of autologous Platelet Rich Plasma (12). Nevertheless, the patient fully recovered and he is still asymptomatic at 1-year follow up.

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Allograft versus autograft in forearm aseptic non-union treatment

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Non-union in forearm fractures is an uncommon challenging clinical condition for orthopaedic surgeons. The complex anatomy and biomechanics of the upper limb make this surgery very demanding. The accurate restoration of the normal anatomy is mandatory to obtain bone healing. Infections and important bone loss further reduce the therapeutic success. The use of bone graft in atrophic non-union may significantly reduce the bone healing time with good clinical results. The aim of the study was to compare fresh-frozen bone (FFB) allograft and autograft in the treatment of forearm aseptic non-union. Inclusion criteria were patients aged between 18 to 75 years old with forearm aseptic shaft non-union treated with plating and bone grafting. The Authors retrospectively evaluated minimum 12-month follow-up with standard X-rays and clinical outcomes. All non-unions were classified according Association for the Study and Application of the Method of Ilizarov (ASAMI) classification for long bones. The sample size was divided in two groups: patients treated with FFB allograft (Allograft Group) and patients treated with iliac crest autograft (Autograft Group). The mean patient age was 33.58±16.72 (18-75) years old in Allograft Group and 33.28±17.24 (18-75) in Autograft Group. The mean follow-up was 62.6 months (±12.3, range 12-160) in Allograft Group and 64.4 (±12.4; 12-160) in Autograft Group. The mean bone union time after the surgery was 101.6 (±14.6; 82 -156) days in Allograft while 117.6 (±14.6; 90 -180) days for autograft. The Radiographic Union Score was 26.8 (±2.2; range 24.3-30) in Allograft while 26.9 (±2.8; range 24.1-30) in Autograft. A correlation between clinical and radiographic outcomes was found (Cohen κ : 0.86±0.11 in Allograft Group; Cohen κ : 0.85±0.10 in Autograft Group, $p=0.051$). The preoperative surgical planning is essential to apply this technique: the adequate cortical graft length is the key point to gain adequate implant stability. A meticulous surgical technique is mandatory to obtain good clinical and radiological outcomes. The study reported a good reliability of FFB allograft for large non-union bone defects. This technique may represent a feasible alternative to bone transport

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or amputation, as it allows the return to daily life activities. Further studies are needed to assess the long-term clinical results of this surgical procedure.

Key words: non-union; forearm; bone loss; trauma; allograft; autograft; bone healing

Non-union in forearm fractures is an uncommon challenging clinical condition for orthopaedic surgeons (1). Non-union of the forearm is also intimately associated with a significant pain and functional disability (1, 2, 5, 7).

The complex anatomy and biomechanics of the forearm make this surgery very demanding (2–4). Indeed, the anatomical restoration of length, axis and rotation of ulna and radius are essential to preserve the stabilizing effect of the soft tissue (5–7).

Recently, the non-union rate has been reduced to less than 5% and good to excellent functional outcomes were achieved thanks to the dynamic or locking compression plates proposed by the AO Foundation. Compact bone allograft has been demonstrated to be fundamental in aseptic non-union reconstructive surgery of the upper limb (8, 9). However, good results were reported in bone autograft associated with plating (2, 5). The aim of the study was to compare fresh-frozen bone (FFB) allograft and autograft in the treatment of forearm aseptic non-union.

MATERIALS AND METHODS

Ninety-three skeletally mature patients were analysed in this retrospective study. Inclusion criteria were patients aged between 18 to 75 years old with forearm aseptic shaft non-union treated with plating and bone grafting. The Authors retrospectively evaluated minimum 12 months follow-up with standard X-rays and clinical outcomes. All non-unions were classified according Association for the Study and Application of the Method of Ilizarov (ASAMI) classification for long bone (10).

Exclusion criteria were haematological or oncological patients; Acute or Chronic infections; ASAMI non-union classification's type A and C; age under 18 or over 75 years old, bone metabolism disease, elbow osteoarthritis, rheumatoid disease. All patients were treated according to

the ethical standards of the Helsinki Declaration.

A total of 52 patients satisfied these criteria and were included in the study (Table I); the sample size was divided in two groups: patients treated with FFB allograft (Allograft Group) and patients treated with iliac crest autograft (Autograft Group).



Fig. 1. Aseptic non-union two years after the first surgery. X-Ray (A): 3D-CT; (B): Plating with Allograft; (C, D): 6-months follow-up.

Surgical Technique

The patient in supine position with the arm on a radiolucent support. The Henry and dorsal approaches were used to expose the forearm non-union site of the radius and ulna, respectively. The orthopaedic surgeon,



Fig. 2. Aseptic non-union two years after the first surgery. X-Ray (A-B): Plating with Autograft; (C, D): 6-months follow-up.

soon after performing the failed implant removal and surgical debridement, needs to surgically stabilize the graft. The different surgical steps could be summarized as followed:

- 1) Removal of the previous implant and accurate surgical debridement;
- 2) Intramedullary drilling during bone graft preparation;
- 3) Graft positioning and stable fixation of the fracture with a Locking Compression Plate (LCP - DepuySynthes™, Oberdorf, Switzerland).

Cortical screws were used to stabilize the FFB Allograft strut (Fig. 1), while in Autograft Group the iliac crest bone chips and Putty Biocollagen Crunch bone pasta (Biogen®, Biotech™, Arcugnano, Vicenza, Italy) were placed inside the humeral shaft to fill the cortical gap (Fig. 2).

A resin postoperative long arm cast was applied for three weeks to better control soft tissue oedema. A rehabilitation protocol was performed with passive and active ROM exercises after the cast removal. Full forearm range of motion and progressive strength and proprioceptive training were allowed in 6-8 weeks.

The Non-Union Scoring System (NUSS) was used to evaluate the bone healing process (11). The surgical time, elbow, forearm and wrist range of motion (ROM), pain visual analogic score (VAS), Quick Disabilities of the Arm Shoulder and Hand (QuickDASH) and complication rate were evaluated for all patients.

The forearm radiographic alignment was measured. Radiographic Union Score (RUS) was used to evaluate the bone healing process (12). At the final follow-up RUS, patient satisfaction and return to work activity were assessed.

Descriptive statistics were used to summarize the characteristics of the study group and subgroups, including means and standard deviations of all continuous variables. The t-test was used to compare continuous outcomes. The Fisher's exact test was used in these groups to compare categorical variables, as they contain fewer than 10 patients. The statistical significance was defined as $p < 0.05$.

We used the Pearson correlation coefficient (r) to compare the predictive score of outcomes and quality of life. Statistical analyses were performed with SPSS v.15.0 (SPSS Inc., an IBM Company, Chicago, IL, USA). Mean ages (and their standard deviations) of the patients were rounded off to the closest year. The predictive score of outcomes, quality of life, and their standard deviations

were approximated at the first decimal point, while Pearson correlation coefficient (r) was approximated at the second decimal.

RESULTS

The mean patient age was 33.58 ± 16.72 (18-75) years old in Allograft Group and 33.28 ± 17.24 (18-75) in Autograft Group (Table I).

The mean follow-up was 62.6 months (± 12.3 , range 12-160) in Allograft Group and 64.4 (± 12.4 ; 12-160) in Autograft Group. The surgical time was similar between the two groups as well as, patients demonstrated wound healing in 21 days. The mean bone union time after the surgery was 101.6 (± 14.6 ; 82-156) days in Allograft while 117.6 (± 14.6 ; 90-180) days for Autograft. No complications were reported; the allograft patients return to pre-injury work activities in 9.4 ($\pm 2.48^\circ$; 6-15) while the autograft ones

needed 12.6 (± 2.8 ; range 24.1-30) months (Table II).

The VAS was 1.4 (± 0.4 ; range 0-3) in Allograft group while 2.8 (± 0.8 ; range 0-4) in Autograft Group. The Radiographic Union Score was 26.8 (± 2.2 ; range 24.3-30) in Allograft while 26.9 (± 2.8 ; range 24.1-30) in autograft. No significant differences were found, however the allograft showed better clinical outcomes.

DISCUSSION

Forearm non-union is a challenge for both patients and orthopaedic surgeons. Minimal changes in length and alignment, or unstable fracture fixation may distort the distal radioulnar biomechanics. The accurate restoration of the normal anatomy is mandatory to obtain the prerequisites for bone healing. Further infections and important bone loss could reduce the therapeutic success (11).

Table I: *Sociodemography of the study.*

Description of population	Allograft Group	Autograft Group	P value
Number of Patients	26	26	P=1
Mean age $\pm$ standard deviation (range)	33.58 ± 16.72 (18-75)	33.28 ± 17.24 (18-75)	P=0.056
Gender Ratio (male:female)	1.6(16:10)	1.6(16:10)	P=1
Forearm fracture site	Radius: 7(26.92%) Ulna: 6(23.08%) Both: 13(50%)	Radius: 6(23.08%) Ulna: 8(30.77%) Both: 12(46.15%)	P=0.0632 P=0.0512 P=0.0501
Orthopedic device used in the surgery for the osteosynthesis	Plate: 26 K wire or Elastic Nails: 13	Plate: 25 K wire or Elastic Nails: 14	P=0.85 P=0.83
Work activity	Agricultural Industry: 8 (30.77%) Industrial Sector: 12 (46.15%) Tertiary Industry: 6 (23.08%)	Agricultural Industry: 6 (23.08%) Industrial Sector: 12 (46.15%) Tertiary Industry: 8 (30.77%)	P=0.0512 P=1 P=0.0512
Injured Upper Limb Side	Right: 7 (26.92%) Left: 19 (73.08%)	Right: 6 (23.08%) Left: 20 (76.98%)	P=0.0632 P=0.0518
Dominant Injured Upper Limb	Right: 6 (23.08%) Left: 6 (23.08%)	Right: 6 (23.08%) Left: 6 (23.08%)	P=1 P=1
Average Non Union Scoring System $\pm$ SD (range)	36.64 ± 16.67 (15-65)	36.24 ± 19.67 (15-65)	P=0.0523

The use of bone graft in atrophic non-union may significantly reduce the bone healing time with good clinical results (5). Nicoll et al (12) described a surgical technique for forearm bone defects (up to 3 inches long), using cancellous bone graft combined with internal fixation.

Despite the Nicoll procedure, and its technical variants (13), the non-vascularized graft is not always the gold standard in septic non-unions with huge long bone defects (> 6 cm) or in severe soft-tissue damage (13, 14). Shelton and Sage achieved an 87% union rate using the iliac crest graft and compression plate. Several papers reported the 100% success rate (15). The bone transport technique described by Ilizarov leads to bone healing but it requires multiple surgical steps and a good compliance from the patient. The use of a cortical graft combined with a Locking Plate allows for excellent implant stability compared with

the isolated Locking Plate; this stability promotes the bone healing process. Moreover, early passive and active ROM and early recovery of activities could be expected in these patients.

The restoration of the anatomy of the forearm with the iliac crest autograft is more challenging. In addition, high donor site morbidity was reported using this technique. In this study the radius or ulnar shaft were used as FFB graft to reproduce the physiological curvature of the native shaft, avoiding the fibula graft.

Using this technique, the preoperative surgical planning is fundamental: the adequate cortical graft length is the key point to gain the adequate implant stability; the screws should not be placed close to the non-union site or to the allograft.

A meticulous surgical technique is mandatory to obtain good clinical and radiological outcomes. This

Table II: *Clinical and radiological outcomes.*

	Allograft	Autograft	P Value
Follow up in months (SD; range)	62.6 (±12.3; 12-160)	64.4 (±12.4; 12-160)	P=0.072
Average surgical time in minutes (SD; range)	80.72 (±19.7; 70 -126)	79.34(±18.8; 64 -126)	P=0.071
Wound healing in days	21	21	P=1
Average Time Of Bone Healing In Days Registered By X-Rays (SD; range)	101.6 (±14.6; 82 -156)	117.6 (±14.6; 90 -180)	*P=0.048
Pre Operative elbow flexion-extension (SD; Range)	146°(±34.3°; 93°-180°)	148°(±32.6°; 100°-180°)	P=0.072
Pre Operative elbow pronosupination (SD; Range)	118.8°(± 14.6°;92°-180°)	119.9°(± 14.8°;93°-180°)	P=0.068
Post Operative elbow flexion-extension (SD; Range)	172°(±27.7°; 124°-180°)	170°(±28.5°; 119°-180°)	P=0.062
Post Operative elbow pronosupination (SD; Range)	168°(±34.3°; 93°-180°)	169°(±35.1°; 96°-180°)	P=0.051
Pre Operative wrist flexion-extension (SD; Range)	108.6°(±34.3°; 95°-180°)	108°.7(±12.3°; 95°-180°)	P=0.98
Post Operative wrist flexion-extension (SD; Range)	168.7°(±9.4°; 115°-180°)	168°.8(±9.4°; 115°-180°)	P=0.98
Pre Operative Quick DASH of Injury Forearm (SD; Range)	70.6(±8.64; 61.2-80.4)	71.2(±9.22; 62.4-81.2)	P=0.053
Post Operative Quick DASH of Injury Forearm (SD; Range)	86.2(±6.94; 77.2-96.4)	84.2(±6.94; 77.2-96.4)	P=0.051
Average correlation between clinical-radiographic results and patients outcomes (SD)	κ: 0.86±0.11	κ: 0.85±0.10	P=0.051
Patients returned to work activity (n,%)	26(100%)	26(100%)	P=1
Retrun to work activity in months (SD; Range)	9.4*(±2.48; 6-15)	12.6*(±4.21°; 7-22)	P=0.036

study has several limitations: a restricted number of patients, and the retrospective nature of investigation. Nevertheless, the current work represents the first report of such technique with middle-term outcomes. The study reported a good reliability of FFB allograft for large non-union bone deficits.

This technique may represent a feasible alternative to bone transport or amputation, and it allows the return to daily life activities. Further studies are needed to assess the long-term clinical results of this surgical procedure.

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Bone grafting combined with Sauvé-Kapandji Procedures for the treatment of aseptic distal radius non-union

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Distal radius fractures are the most common type of upper limb fractures in adults. Non-union after distal radius fracture is rare, serious and unpredictable. The aim of our paper is to analyse the clinical and radiological outcomes of bone grafting and Sauvé-Kapandji Procedures for the treatment of aseptic distal radius non-union. We enrolled 13 patients with distal radius aseptic non-union. The following parameters were evaluated: The surgical time, elbow, forearm and wrist range of motion, the subjective quality of life and the wrist function measured by Quick Disabilities of the Arm, Shoulder and Hand (QuickDASH), Pain Visual Analogic Score (VAS) and the complication rate. Bone union was measured using the radiographic union score as described by Radiographic Union Score (RUS). The evaluation endpoint was set at 24 months after surgery. All patients achieved fracture union. Grip strength improved by 12.4 kg. There was also improvement in wrist flexion, in wrist extension, and forearm pronosupination. These ranges of motion and grip strength improvements were statistically significant. Only 6 patients returned to full activity. This surgical technique represents a reliable alternative for treatment of distal radius aseptic non-unions. Further studies are needed to assess the long-term clinical results of this surgical procedure.

Distal radius fractures are the most common type of upper limb fractures in adults (1), whereas radius and ulna fractures are the most common long bone fractures in children and adolescents (1-2). Non-union after distal radius fracture is rare, serious

and unpredictable (3), healing problems are related to unstable situations, such as concomitant fracture of the distal radius and ulna, and to an inadequate period of immobilization. Non-union should be questioned if pain is still present after remobilization of the

Key words: wrist; non-union; graft; trauma; injury; bone healing

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wrist (Fig. 1-2) in combination with a progressing deformity (4).

The preferred treatment is resection of the non-union zone followed by open reduction and internal fixation with autologous iliac crest bone graft. When the distal fragment is less than 5 mm high, a dorsal plate, which bridges the radiocarpal joint is recommended. In patients with low functional demands, radiocarpal fusion is the preferred choice. The bone-healing rate is 58% and it can improve with a vascular graft. Non-union after distal radius fracture is a serious problem and the functional prognosis is doubtful (3). The bone grafting's results are usually predictable in achieving union and good function, and this technique can be successfully used in patients with extensive soft-tissue damage or infection (5).

However, failures may occur because of a combination of multiple factors as the large corrective lengthening osteotomy, the use of demineralized bone matrix instead of autologous bone graft, and the inappropriate fixation technique (6). The Sauvé-Kapandji procedure may enhance bone healing and the clinical outcome to avoid wrist arthrodesis (7). The aim of our paper is to analyse the clinical and radiological outcomes of bone grafting and Sauvé-Kapandji Procedure for the treatment of aseptic distal radius non-union (Fig. 3).



Fig. 1. Male, 36-years old, antero-posterior (A), lateral views (B) X-rays: failure of three previous wrist surgery



Fig. 2. Male, 36-years old, failure of three previous wrist surgery. Ulna plus with preserved pronosupination.

MATERIALS AND METHODS

From a total of 21 patients, we included 13 patients with forearm distal radius non-union after evaluating the following exclusion criteria: haematological or oncological patients; Acute or Chronic infections; ASAMI non-union classification's type A and C; bone metabolic diseases, elbow osteoarthritis, rheumatoid arthritis. All non-unions were classified according ASAMI classification for long bone (8). The Non-Union Scoring System (NUSS) was used to evaluate the bone healing process (9-10).

All patients were informed all the possible surgical and conservative alternatives. Patients were treated according to the ethical standards of the Helsinki Declaration, and were invited to read, understand, and sign the informed consent form. The enrolled patients are described in Table I. All patients underwent the same rehabilitation protocol.

Surgical technique

All patients lied on a supine position with the arm on a radiolucent support, or a padded post. The volar Henry approach was used to expose the non-union site of the radius (11). After the isolation of the non-union focus, we removed the previous implant and we surgically reduced the fracture. We performed intramedullary drilling of the radius shaft. The radial or bone allograft or the iliac crest autograft was prepared on a separate table and a modelled



Fig. 3. Postoperative X-rays (A, B): intercalary bone allograft and Sauvé-Kapandji procedure: the distal ulna fixed with 3 screws to the distal radius. The bone healing has obtained at 186 days from the surgery (C, D)

long distal radius plate was temporarily fixed with a K-wire. Cortical screws were used to stabilize the plate, while the autograft was placed into the non-union site. The cortical gap was filled with the Putty® Crunch bone pasta (Tecnoss® s.r.l., Giaveno, Torino, Italy). A modified Sauvé-Kapandji sec. Lluch et al. was performed (12).

A resin postoperative long arm cast was applied for two weeks to better control soft tissue oedema. A rehabilitation protocol was performed with passive and active ROM exercises after the cast removal. Full forearm range of motion and progressive strength and proprioceptive training were allowed after 6-8 weeks.

The surgical time, elbow, forearm and wrist range of motion (ROM), pain visual analogic score (VAS), Quick Disabilities of the Arm Shoulder and Hand (QuickDASH) and complication rate were evaluated in all the patients. The forearm radiographic alignment was measured. Radiographic Union Score (RUS) was used to evaluate the bone healing process (11).

Statistical Analysis

Descriptive statistics were performed to summarize the characteristics of the study group and subgroups, including means and standard deviations of all continuous variables. The t-test was applied to compare continuous outcomes. The Fisher's exact test was used in these groups to compare categorical variables, as they contain fewer than 10 patients. The statistical significance was defined as $p < 0.05$.

We used the Pearson correlation coefficient (r) to compare the predictive score of outcomes and quality of life. Statistical analyses were performed with SPSS v.15.0 (SPSS Inc., an IBM Company, Chicago, IL, USA). Mean ages (and their standard deviations) of the patients were rounded off to the closest year. The predictive score of outcomes, quality of life, and their standard deviations were approximated at the first decimal point, while Pearson correlation coefficient (r) was approximated at the second decimal.

RESULTS

The mean of follow-up was $36.75 (\pm 9.3; 24-96)$ months. The surgery lasted an average of $74.26 (\pm 13.6; 54-136)$ minutes. Patients demonstrated wound healing within 21 days. The average time of bone healing was $143.4 (\pm 24.3; 90-183)$ days. At average day of the bone healing the RUS score was of $27.2 (\pm 1.4; \text{range } 26.7-30)$ points.

Only 6 (46.15%) patients return to full work activity. The average time of return to full Work was $12.3 (\pm 6.98; 9-24)$ in months. In the average day of the return to full work the VAS was $2.2 (\pm 0.8; \text{range } 0-4)$. We found at average day of return to full work the regression between RUS and VAS scores (p value: 0.034).

No statistical difference was found in pre/post-operative of forearm/elbow flexion-extension, while

Table I: *Sociodemographic of the study.*

Table I: Description of population	
Sample Size	13
Mean age, years ± standard deviation (Range)	52.28 ±19.34 (22-80)
Sex (male: female)	10 : 3
Previous wrist fracture	Colles: 7(53.85%) Goyrand: 6(46.15%)
Orthopaedic Synthesis device	Plate: 3(23.08%) K wire or Tension K wire: 3 (23.08%) External Fixator: 7(54.84%)
Job	Agricultural Industry: 5 (38.46%) Industrial Sector: 5 (38.46%) Tertiary Industry: 3 (23.08%)
Injured Upper Limb Side	Right: 5 (38.46%) Left: 8 (61.54%)
Dominant Upper Limb	Right: 2 (15.38%) Left: 2 (15.38%)
Average Non Union Scoring System ± standard deviation (Range)	46.34 ± 16.67 (25-70)

there is statistical difference gain in forearm pronosupination between pre- and post-operative period. Clinical and functional outcomes were reported in Table II.

DISCUSSION

Non-union of the distal radius is an extremely

rare occurrence. It has been reported that comorbidities such as diabetes, peripheral vascular disease, alcoholism, and obesity may increase the risk of non-union (13-14). Smoking may also play a role in the development of non-union (13-14). Non-union of the distal radius may occur after internal fixation, external fixation, or non-operative treatment (13-14). Segalman and Clark suggested that excessive distraction of the fracture during the application of an external fixator is one of the causes of non-union, because excessive distraction can create bony defects. Hollevoet et al. reported that radiographic parameters, including the palmar tilt, radial inclination, and ulnar variance, have no significant differences between the right and left wrists. Therefore, volar locking plate fixation with excessive distraction of the fracture may lead to postoperative loss of correction and non-union, although locked plates act as “internal external fixators” and provide very rigid fixation.

Sivashanmugam et al. focusing on non-union treatment, stressed the great osteogenic potential of the periosteum in children and adolescents. Their paper highlights the possibility of stimulating bony union by distracting the minimally disturbed soft tissue and thick osteogenic periosteal envelope to treat paediatric atrophic non-union in selected patients. In general, in these patient's excision of the fibrous tissue followed by compression and stabilization are sufficient to obtain consolidation.

Table II: *Clinical and radiological outcomes.*

Mean follow up in months (SD; range)	36.75 (±9.3; 24-96)
Average surgical time in minutes (SD; range)	74.26 (±13.6; 54-136)
Wound Clousure in days	21
Average Time Of Bone Healing In Days Registered By X-Rays (SD; range)	143.4 (±24.3; 90-183)
Pre Operative Arc of forearm/elbow flexion-extension(SD; Range)	166.4°(±23.4°; 95°-180°)
Pre Operative Arc of forearm/elbow pronosupination(SD; Range)	109.7°(± 13.7°;92°-152°)
Post Operative Arc of forearm/elbow flexion-extension(SD; Range)	171.8°(±18.7°; 134°-180°)
Post Operative Arc of forearm/elbow pronosupination(SD; Range)	164°(±35.8°; 94°-180°)
Pre Operative Arc of wrist flexion (SD; Range)	17.3°(±6.7°; 5°-30°)
Pre Operative Arc of wrist extension(SD; Range)	28.7°(±8.3°; 5°-50°)
Post Operative Arc of wrist flexion (SD; Range)	37.3°(±6.7°; 15°-50°)
Post Operative Arc of wrist extension(SD; Range)	48.2°(±10.6°; 15°-75°)
Pre Operative Quick DASH of Injury Wrist (SD; Range)	30.6°(±19.24°; 0-50.4°)
Post Operative Quick DASH of Injury Wrist(SD; Range)	77.4°(±6.94°; 48.6°-90.2°)
Pre Operative Grip in Kg of Injury Wrist (SD; Range)	3.4(±1.32; 0-10)
Post Operative Grip in Kg of Injury Wrist(SD; Range)	13.6(±8.32; 1-20)
Average correlation between clinical-radiographic results and patients outcomes (SD; range)	κ: 0.78(±0.12; 0.65-0.84)
Patients returned to full Work (n,%)	6(46.15%)
Return to full Work in months (SD; Range)	12.3(±6.98; 9-24)

Debridement of the necrotic bone and bone grafting, vascularised bone grafting, or creation of a single-bone forearm are surgical options and the choice depends on the patient (15, 16).

Removal of a segment of the distal ulna has been suggested by many authors as a treatment for severe radial shortening (12). The best result is obtained if the non-union is done at the level of the ulnar head, removing only 5 mm of bone (12). The axis of rotation of the forearm runs obliquely from the centre of the radial head proximally to the centre of the ulnar head distally (17-20). An osteotomy at a more proximal level will cause a divergence of movements between the proximal ulna stump and the head of the ulna, which has already been fixed to the radius (12).

In a study of 23 distal radius non-unions, Prommersberger et al. reported unsatisfactory treatment results in six patients. They did not find distal fragment size to influence functional or radiographic results, but they observed more post-operative complications when the distal fragments were small. Crow et al. reported good results by using a vascularized bone flap of a second metacarpal base for treating distal radius non-union in one patient. Saremi et al. (5) treated 9 patients (10 non-unions) by posterior interosseous bone flap combined with Darrach or Sauve-Kapandji procedure (5, 12). They reported that all the patients achieved fracture union at a mean time of 3.8 months. Grip strength improved by 12.4 kg. There was also 36° improvement in wrist flexion, 20° improvement in wrist extension, 60° improvement in forearm supination, and 46° improvement in forearm pronation. The range of motion and grip strength improvements were significant (5).

A meticulous surgical technique is mandatory to obtain good clinical and radiological outcomes. This study had several limitations: a restricted number of patients, and the retrospective nature of investigation. Nevertheless, the current work represents one of the first report of such technique with middle-term outcomes.

This surgical technique represents a reliable alternative for treatment of distal radius aseptic non-unions. Further studies are needed to assess the long-term clinical results of this surgical procedure.

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Total hip arthroplasty for osteonecrosis of the femoral head in sickle cell disease: a case series from our African experience

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Sickle cell disease causes osteonecrosis (20% to 50% of patients) and collapse of the femoral head that result in secondary osteoarthritis. Total hip arthroplasty (THA) is a valid alternative for these patients. We define the difficulties that can be encountered when undertaking THA in sickle cell disease patients and give advice on how to deal with these technically demanding procedures. We undertook total hip arthroplasty procedures on 12 patients (4 females and 8 males) with osteonecrosis of the femoral head. Two bilateral prostheses were performed. We had only one type of stem, only one type of acetabular cup and only 28 mm cobalt chrome heads. The procedures were performed through either an anterior or a direct lateral approach. The average size of the Cup was 46 (Versafit, Medacta), the average size of the femoral stem was 0 (Amistem, Medacta), the most used size of the modular head was a S. Standard stem that was used in nine patients, while three patients received a lateralizing stem. Three patients had periprosthetic fracture, treated by cerclage. Total hip replacement is an excellent alternative for patients with osteonecrosis from sickle cell disease. The preparation of the acetabulum and the femur is difficult and requires attention, time and appropriate equipment.

Sickle cell disease is an autosomal recessive hemoglobinopathy widespread especially in sub-Saharan Africa (1). It is caused by a point mutation on the sixth codon of beta-globin that leads to a replacement of the glutamic acid with a valine. Sickle cell disease causes osteonecrosis and collapse of the

femoral head that result in secondary osteoarthritis. Osteonecrosis is noted in 20% to 50% of patients, and bilateral involvement is common (2) (Fig.1). We reported our experience in total hip arthroplasty in sickle cell patients accumulated in our medical expeditions in Afagnan, Togo. We reported the

Key words: sickle cell disease, hip arthroplasty, osteonecrosis, avascular necrosis of femoral head

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difficulties encountered in this type of surgery and give advice on how to deal with the most complicated cases.

Clinical cases

Total hip arthroplasty was performed in Hospital Saint Jean de Dieu, Afagnan, Togo, on 12 patients (4 females and 8 males) with necrosis of the femoral head. Two bilateral procedures were performed. We had only one type of stem, only one type of acetabular cup and only 28 mm cobalt chrome heads, all donated for the humanitarian mission. The procedures were performed through either an anterior or a direct lateral approach. The anterior approach was used for thin patients and in less severe cases of osteonecrosis. The direct lateral approach was used for the most serious cases and for overweight/obese patients. The anterior approach was performed without the use of traction beds or operating beds that would have allowed an extension of the lower limbs. We compared our results with the published evidence on total hip arthroplasty in sickle cell anemia patients.

The average size of the Cup was 46 (Versafit, Medacta), the average size of the femoral stem was 0 (Amistem, Medacta), the most commonly used size of the modular head were S. Standard stems that were used in nine patients, while three patients received a lateralizing stem. Two patients required



Fig. 1. *Severe cases of bilateral cephalic necrosis.*



Fig. 2. *Osteonecrosis with narrow femoral canal.*

acetabular screws. Three patients had periprosthetic fracture, treated by cerclage.

DISCUSSION

We used two surgical approaches to the hip: anterior approach and direct lateral approach. These approaches were preferred in order to reduce the postoperative risk of dislocation (3), which could be resulted increased in Togo, where the postural behavior of many patients is characterized by an extreme hip flexion; a risk worsened by the lack of compliance of some of our patients to respect the anti-dislocation indications.

The anterior approach is intermuscular and allows a rapid post-operative recovery and a faster return to work, which in some rural areas of Africa is essential for the survival of the individual. We used the anterior approach for the simplest cases, and the direct lateral approach for the most complicated hips. We stress that surgical management of patients with sickle cells disease is challenging and should only be performed by experienced orthopedic surgeons.

The absence of extensive screening programs for early diagnosis and the strong appeal of traditional medicine are the reasons why we have seen extremely serious clinical presentations in Togo. Our patients presented with an extremely advanced femoral head necrosis, so that the non-operative management was

no longer a possibility. Non-operative management may provide benefit in the early stages of the condition, prior to collapse of the femoral head (4). Stem cell transplantation, core decompression and core decompression combined with autologous bone grafting are useful in the initial states, and therefore they were not applicable in that setting (5, 6, 7).

Compared to cephalic necrosis due to other causes, in sickle cell disease we found an important involvement in the proximal third of the femur. The medullary canal appeared narrow and cancellous bone was replaced by cortical bone (Fig. 2). This increases the risk of intraoperative fracture, which suggest, especially when using the anterior approach, the use of tailored off-set tools. With the anterior approach, it is difficult to work on the femur and identify the medullary canal an even more difficult task in overweight patients. We therefore advise against the use of this approach in these patients and recommend a direct lateral approach.

Once we found the canal, we had to ream it; at this point, it was difficult to use even the smallest stem available. Katchy et al. (8) encountered these difficulties: we implanted the smallest stem size available; we recommend to stock small-sized femoral stems when planning a mission for total hip replacement in patients with SCD. Despite the

difficulty in inserting the femoral stem, Ilyas et al (9) have published excellent results regarding the long-term follow-up of the femoral stems, with excellent integration results.

We had only one type of uncemented stem available, as all the material was donated by a single manufacturing firm for the humanitarian mission: these stems have long term results comparable with cemented ones (Fig. 3) (10, 11).

Given the anatomical characteristics of the femur of patients with sickle cell disease and taking into consideration the difficulty in inserting the stem of the smallest size, it is advisable to use conical stems, which allow for acceptable siting of the femoral stem and an optimal femoral anteversion. The acetabulum in the advanced stages of the condition is dysmorphic, oval and sclerotic: these features can lead to eccentric reaming. The acetabulum may also appear very deep, and care should be taken to avoid breaking through the floor of the acetabulum.

Hip osteoarthritis in patients with sickle cell disease requires experienced surgeons. Total hip arthroplasty is an excellent alternative for patients with osteonecrosis associated with sickle cell disease, and, in advanced cases, it is probably the only possible treatment. The preparation of the acetabulum and femur is difficult, and requires attention, time and appropriate equipment. Furthermore, it would be important to consider having small femoral stems and, if possible, consider the use of conical stems. The local costumes and activities of daily living in Togolese patients make the anterior and direct lateral preferable to posterolateral approach.

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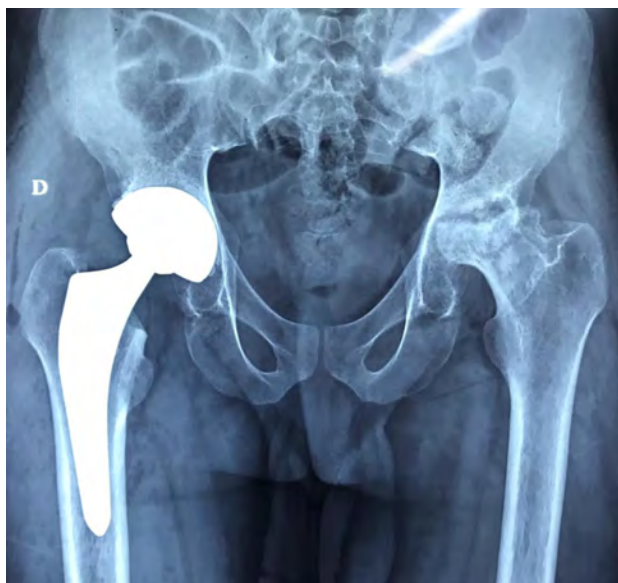


Fig. 3. Post-surgery result.

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Reliability of S.A.R.A. (sterilization and reimplantation autograft) technique in long bone open fractures

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The reimplantation of small or large extruded bone segments is one of the most complex clinical management scenarios in the treatment of open fractures. No consensus exists regarding the efficiency of this technique. The aim of the study was to analyse the clinical and radiological outcomes of Sterilization and Reimplantation Autograft (S.A.R.A.) technique in open fractures. Therefore, fifteen skeletally mature patients with Gustilo-Anderson –IIIB type fractures treated with autograft reimplantation, were included in this study. The sample size was divided in two groups: patients with a loss of small segments (Group A - less than 5 cm) and those with large segments (Group B - greater than 5 cm). Eight patients belonged to Group A and seven to Group B. The treatment of contaminated bone may be performed by the following protocols: saline rinse, povidone-iodine scrub and saline rinse, retain periosteum, immersion in antibiotic solution (clindamycin and gentamicin and metronidazole), washing with physiological solution, acute reimplantation in Group A or reimplantation after 21 days in Group B after a bone freezing at -80°C. The Radiographic Union Score (RUS), pain visual analogic score (VAS), patient satisfaction and return to work were assessed at a mean follow-up of 24 months. No cases of superficial or deep infection were reported at 2-year follow-up. The fractures achieved a complete union in 14 patients; one patient belonging to Group A had a malabsorption of the replanted bone. Furthermore, povidone-iodine scrub, antibiotic solution immersion, and washing with physiological solution preserved the articular surface morphology. This study suggests that reimplantation of extruded short or long segments may represent a reliable alternative to amputation in open long bone fractures. Further studies are needed to define the most efficient technique for sterilizing the bone autograft to reduce the complication rate.

Extruded bone segments are a rare complication of high-energy fractures. These severe injuries are predominant in male, particularly in young adults

between the ages of 20 to 30 years (1-6, 14, 16). Road traffic accidents are the most common trauma mechanisms, followed by gunshot wounds and

Key words: bone loss; long bone; open fractures, re-implantation; trauma; autograft; bone healing.

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falls from great heights (14). The segment may be severely contaminated in road traffic accidents, farm accidents, war-related injuries, or industrial accidents. The gold standard treatment of these fractures is a two step-surgery: wound debridement followed by bone loss management (bone transport, free fibula transfer, or allograft) (11, 14, 16). The treatment of open femur fractures with reimplantation of large extruded segments is one of the most complex clinical scenarios (11, 14, 16). The most intricate clinical scenario is the osteoarticular segment and the greatest difficulty is the management of this type of patient.

No consensus exists about the efficiency of the sterilization method (11). There are very few reports in scientific literature about reimplantation of extruded segments of bone and there are no clear guidelines regarding the surgical timing of bone reimplantation and stabilization. The secondary infection, that can lead to a limb resection, is a possible complication of this salvage surgery (11, 14, 16).

The aim of this preliminary study was to analyse the clinical and radiological outcomes of Sterilization and Reimplantation Autograft (S.A.R.A.) technique in Gustilo-Anderson –IIIB type long bone fracture patients (Fig. 1-4).

MATERIALS AND METHODS

Skeletally mature patients with Gustilo-Anderson IIIB type fractures treated with autograft reimplantation, were included in this study. The exclusion criteria were open fractures according Type I, Type II, Type IIIA and Type IIIC's Gustilo Anderson Classification, hematological or oncological patients, acute or chronic infections, under 18 years, or bone metabolism disease. The 15 patients who were included in the present study were divided in two groups: eight patients with a small bone loss (Group A - less than 5 cm) and seven patients with a large one (Group B - greater than 5 cm) (Table I).

All long bone fractures were classified according to the AO classification (8). All patients underwent intravenous antibiotic therapy with gentamicin and metronidazole before and after surgery, until 7 days after the last procedure. Patients were treated according to the ethical standards of the Helsinki Declaration. They were invited to read, understand, and sign the informed consent form.

S.A.R.A. Technique: the segment of the long bone is provided by the emergency service, who has rescued the bone tissue from the scene of the accident. The bone is wrapped or covered in saline-soaked gauze and placed in saline solution. The orthopaedic surgeon, while performing debridement and/or limb damage control,

Table I: *Sociodemographic of the study.*

Patient	Sex	Age (yrs)	Side	Follow-up (mo)	Occupation	Associated Injury	Injury Mechanism	Site of Bone Loss Extrusion	Size in cm Of extrude segment	AO classification[6]	Damage Control	Neurological Injury	NUSS[7]	Group
1	F	24	L	84	Shop Seller	Spleen Floating knee	MVC	Femur	18.7	3.2-C1	YES	NONE	42	G2
2	M	54	R	72	Public Employ	Brain Blow Spleen; Chest	MVC	Femur	21.3	3.3-C3	YES	NONE	52	G2
3	F	25	L	32	Psychology	R Forearm, R Tibia L Floating knee Leg Extensors Broken Spine	MVC	Femur	19.4	3.3-C3	YES	NONE	72	G2
4	M	23	R	31	Unemploy	Floating knee	MVC	Forearm	3.6	2.2-B3	YES	NONE	42	G1
5	M	26	R	30	Refugee	L Femur R Kidney	Cyclist Hit by Car	Tibial	4.8	4.2 C3	YES	NONE	50	G1
6	M	29	R	30	Track Driver	Cest; Brain; Spleen Blow	MVC	Forearm	4.5	2.2-B1	NO	NONE	55	G1
7	M	54	L	29	Professor	Multiple	Fall From High	Tibial	4.3	4.2-C1	YES	NONE	45	G1
8	M	39	R	28	Track driver	R Humeral Head L Wrist	MVC	Femur	14.9	3.2-B3	YES	NONE	56	G2
9	M	28	L	28	Student	R Wrist	Fall from Motor Bike	Femur	12.6	3.2-C1	YES	NONE	45	G2
10	M	56	L	28	Carpenter	Brain Injury Left foot II R Forearm	Fallen From high	Tibial	5	4.2-B2	YES	NONE	45	G1
11	M	44	L	24	Dancer	L Floating Knee, Brain	MVC	Femur	12.6	3.2 B3	YES	NONE	49	G2
12	M	43	R	24	Car Driver	R Floating Knee, Spleen	MVC	Femur	15.3	3.2 C1	YES	NONE	56	G2
13	M	34	R	24	PC Programmer	Floating Elbow	MVC	Humerus	18.6	1.2-A3	NO	Ulnar Nerve	48	G1
14	F	41	R	24	Professor	None	MVC	Tibial	4.8	4.2-C1	YES	NONE	42	G1
15	F	52	L	24	Unemploye	R Wrist Brain	High Fall Suicide	Tibial	4.4	4.2-C1	YES	NONE	44	G1

Abbreviations: F, female; L, Left; M, male; MVC, motor vehicle crash; R, Right;

must carry-out the surgical stabilization of the fracture. The different steps could be summarized as follows: 1) Accurate surgical debridement using scalpel/curette and fracture stabilization using an external frame. Placement of the bone segment in saline rinse for 20 minutes (Fig. 1).

2) Abundant wash with physiological solution, povidone-iodine scrub and saline rinse for 10 minutes, retaining the periosteum (Fig. 2).

3) Immersed in antibiotics (clindamycin 600mg/4ml; gentamicin 80mg/2ml; and metronidazole 500mg/100ml) in 500 ml of physiological solution for 30 minutes (Fig. 3).

4) Wound washed with physiological solution for ten minutes and when the soft tissue damage is minimal, it is possible to perform the one-step autograft reimplantation; when there is an important soft tissue injury, it is mandatory to re-implant the bone graft after 21 days. Waiting for the second surgery, a storage temperature of -80°C and the use of a sterile triple plastic bag should be recommended (Fig. 4).

5) When soft tissue heals, the orthopaedic surgeon can perform the second step surgery. Debride the bone

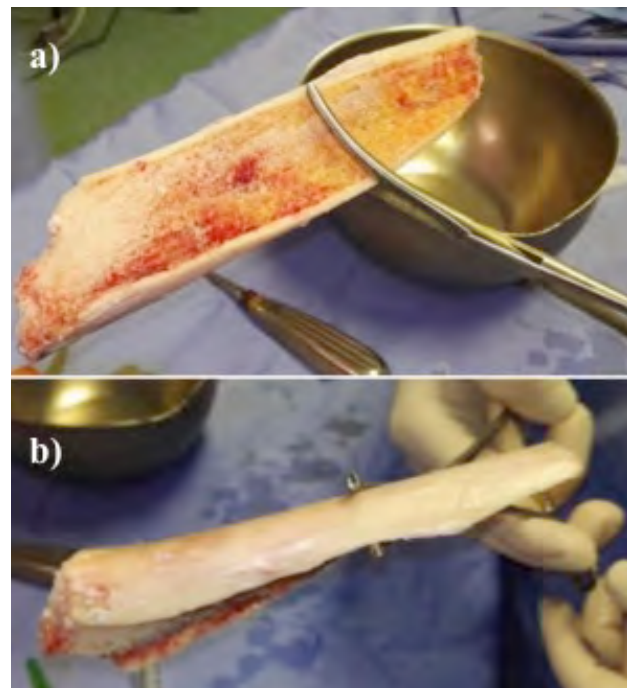


Fig. 2 a-b) Bone brushing and cleaning. Not periosteal removal.



Fig. 1: Female, 25, motorbike crash. **a)** Open left distal femoral fracture with a Floating Knee, Type IIB; **b)** Damage control with accurate surgical debridement and external Fixation; **c)** Postoperative x-ray showing $>75\%$ of distal femoral bone loss.

segment in a solution of 1500ml (500ml of electrolyte solution + 500 ml glucose solution + 500ml physiological solution). The surgeon must carry out the fixation of the fracture using the autologous bone graft to fill the bone gap and a dedicate plate (Fig. 5).

In this study, patients belonging to group A were treated by SARA technique until the fifth step. Patients belonging to group B were also treated by SARA technique until the fifth step. The Non-Union Scoring System (NUSS) was used to study the bone reimplantation healing process (4). Bone union status (using the Radiographic Union Score - RUS), pain Visual Analogic Score (VAS), patient satisfaction and return to work were assessed at a mean follow-up of 24 months.

Statistical Analysis

Descriptive statistics were used to summarize the characteristics of the study group and subgroups, including means and standard deviations of all continuous variables. The t-test was used to compare continuous outcomes. The Fisher's exact test was used in these groups to compare categorical variables, as they contain fewer than 10 patients. The statistical significance was defined as $p < 0.05$.

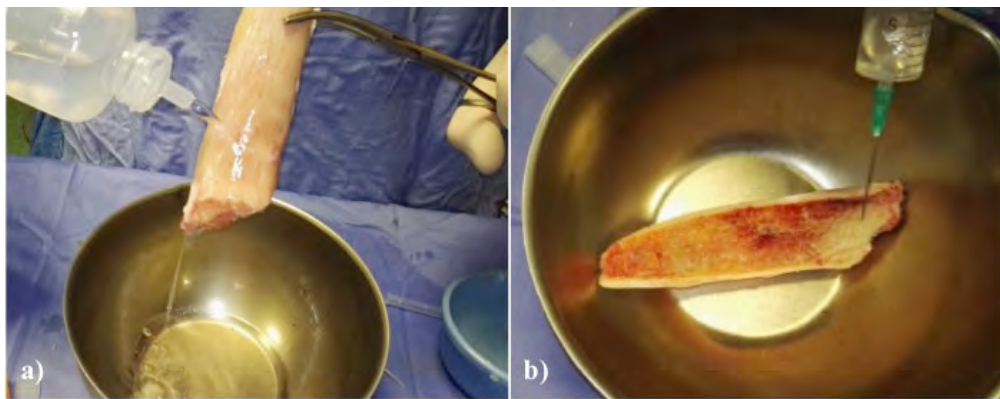


Fig. 3: *a)* Abundant bone fragment wash with physiological solution retaining periosteum; *b)* Graft immersion in 500 ml of physiological solution with antibiotics (clindamycin 600mg/4ml 3 fl; gentamicin 80mg/2ml 3 fl; and metronidazole 500mg/100ml 3 fl).



Fig. 4: *The bone graft storage should be performed in a sterile triple plastic bag at -80° C.*

We used the Pearson correlation coefficient (r) to compare the predictive score of outcomes and quality of life. Statistical analyses were performed with SPSS v.15.0 (SPSS Inc. an IBM Company, Chicago, IL, USA). Mean ages (and their standard deviations) of the patients were rounded off to the closest year. The predictive score of outcomes and quality of life and their standard deviations were approximated at the first decimal point, while the Pearson correlation coefficient (r) was approximated at the second decimal.

RESULTS

The mean patients age was 38.13 (± 12.05 , range 23-56). In Group A the mean age was 39.37 (± 13.28 ; range 23-56), and was 36.71 (± 11.34 ; range 24-54) in Group B. The mean follow-up was 34.13 months (± 18.16 , range 24-84). The average follow-up for Group A was 27.5 months (± 3.02 , range 24-31), and was 41.71 months (± 25.17 ; range 24-84) for Group B. The average fragment size was 19.99 cm (± 6.71 ,

Table II: *Clinical and radiological outcomes.*

Patient	Time in days of reimplantations	Time of definitive Surgery in minutes	Type Of Synthesis	X-Rays Reduction Definitive Surgery	Miscellaneous complication	Recovery from Neurological Injury	Bone Healing in days	RUSH Score at bone healings	Cohen K radiographic union and patient satisfaction	P regression between RUSH and VAS	Return To Full Work	Group
1	21	124	PA	Anatomic	Tibial delay union	-	114	28.3	0.84	0.021	YES	G2
2	23	135	P	Good	Chest problem	-	126	24	0.63	0.64	NO	G2
3	24	236	PAM	Anatomic	Tibial Varus Healing	-	98	30	0.82	0.23	YES with limitations	G2
4	0	63	P	Anatomic	Breakage of radial plate after 4 months And resurgery by PA	-	210	29.2	0.86	0.02	YES	G1
5	0	48	IM	Anatomic	Left Hip recurrent pain	-	123	26.7	0.81	0.042	YES	G1
6	0	54	P	Anatomic	-	-	102	28.2	0.83	0.046	YES	G1
7	0	32	EF	Good	-	-	132	26.9	0.73	0.048	YES	G1
8	22	76	P	Good	-	-	127	28.2	0.69	0.68	YES with limitations	G2
9	25	88	P	Anatomic	-	-	117	27.4	0.82	0.029	YES	G2
10	0	69	IM	Satisfactory	-	-	93	28.8	0.83	0.037	YES	G1
11	24	102	PA	Good	Skin infection	-	112	28.6	0.65	0.19	YES with limitations	G2
12	22	116	PA	Satisfactory	-	-	115	29.3	0.92	0.001	YES	G2
13	0	186	Rush Nail	Satisfactory	Elbow skin Necrosis Radial Shaft MalUnion	Sensitivity function of ulnar nerve	96	28.6	0.71	0.026	YES with limitations	G1
14	0	62	IM	Anatomic	-	-	98	27.9	0.67	0.099	YES with limitations	G1
15	0	43	EF	Good	Ankle algodystrophy	-	135	28.1	0.91	0.63	YES	G1

Abbreviations: P: Plates; PA: Plate + Bone Autograft; PAM: Plate+Allograft+ Mesenchymal Stem Cells; IM: Intramedullary nail; EF: External Fixation

range 3.6-21.3). The average size in Group A was 6.25 cm (± 5.01 , range 3.6-18.6) and 16.4 cm (± 3.43 , range 12.6-21.3) in Group B (Table I).

In 13 patients the damage control with external fixation of the long bones was performed in 6 patients in Group B and 8 patients in group two. In acute trauma, only one permanent neurological injury (ulnar nerve lesion) was recorded. The average NUSS was 49.53 (± 7.97 , range 42-72). The average for Group A was 46.37 (± 4.44 ; range 42-55) and 53.14 (± 9.84 ; range 42-72) for Group B (Table I).

The mean time between first step and bone reimplantation surgery was 23 days (± 1.41 , range 21-25). The surgical time was 95.6 minutes (± 56.56 , range 32-236). The orthopaedic hardware used to perform definitive osteosynthesis was the plate in five cases, plate plus autograft in three cases, intramedullary nailing in three cases, external fixation in two cases, Rush's nail in one case, and plate plus autograft plus mesenchymal stem cell in one case (Table II).

The average time of complete bone healing was 119.87 days after the surgery (± 28.40 , range 93-210): in Group A it was 123.62 days (± 38.70 , range 93-210) and 115.57 days (± 9.71 , range 98-127) in Group B. The Radiographic Union Score was

28.01 (± 1.41 , range 24-30). The average in Group A was 28.05 points (± 0.87 , range 26.7-29.2), and was 27.97 points (± 1.94 , range 24-30) in Group B. The average correlation of radiographic union and patient satisfaction was 'good' according Cohen κ : 0.78 ± 0.09 . The correlation was 0.79 ± 0.08 in Group A and was 0.76 ± 0.11 in Group B (Table II). More complications were reported in Group B than in Group A. Nine patients returned to previous work without limitations, 5 patients with minimal limitations, and one patient retired.

DISCUSSION

Segmental bone loss is a challenging clinical condition for both orthopaedic surgeons and patients. Fractures with minimal bone defects may heal just with a good stabilization (17). Bone loss superior to 3 cm is more frequently encountered in distal tibia. A segmental bone loss larger than 2 cm or involving more than 50% of the bone circumference is unlikely to reach the recovery without any major surgery (18).

There is no consensus on the better surgical choice in this complex scenario. In scientific literature, there are some published reports (Table II) regarding successful reimplantation of a large segment of extruded bone in

open fractures of the femur, tibia, humerus, forearm bones, and talus (10, 11, 14, 16). The therapeutic reconstructive or amputation clinical decision-making changes according to the age as well as to the type of trauma in limbs, without important neurological or vascular deficit. However, scientific literature warns against the introduction of a contaminated devitalized bone fragment back into the wound, which increases the risk of infection, subsequent osteomyelitis, and non-union (10, 11, 14, 16).

There is also no conclusive evidence regarding

the best decontamination protocol for the safe use of the recovered bone fragment (10, 11, 14, 16). The 2016 Afshar's question (1) "What to do with a large extruded segment of bone in an open fracture regarding its safe use to best preserve function?" remains a continuous debate. The third step is always debridement of the soft tissue and washing, soaking, and mechanical agitation by brushing and scrubbing of the recovered bone fragment with copious amounts of normal saline. Different chemical solutions have been used to remove the contaminants and disinfect on the extruded bone fragment to reduce bacterial contamination (9).

To prevent infection, some Authors used boiling or autoclaving for final sterilization of the extruded bone. However, boiling and autoclaving damage the collagen fibres and kills some cells, as well as eliminating the induction properties of regenerating bone. These methods convert the living bone into a scaffold of a mineral matrix (12).

The autoclaved bone is brittle and mechanically weak and requires an extended period for revascularization and incorporation of the graft, which also increases the infection risk (3, 13). Gamma irradiation is very popular in oncological bone reimplantation management (3), it has also been used for the disinfection of extruded bones. However, it is not readily available and adversely affects cell viability and mechanical properties of collagen structure and bone tissue (3).

Regarding satisfactory bactericidal capabilities, 10% povidone-iodine and 2% and 4% chlorhexidine gluconate solutions seem to be the most preferred answers (2, 7, 19). Gentamicin is used for broad-spectrum coverage against gram positive and gram-negative bacteria. Also, against *Escherichia coli*, coliforms, *Pseudomonas aeruginosa*, *Proteus* and for the ability to perform a surfactant function that covers the bone surface and prevents the adhesion of bacterial colonies. Clindamycin is used in treatment of anaerobic infections caused by susceptible anaerobic bacteria, including dental infections, and infections of the respiratory tract, skin, and soft tissue, and peritonitis. Clindamycin is also used to treat bone and joint infections, particularly those caused by *Staphylococcus aureus*. Metronidazole is used

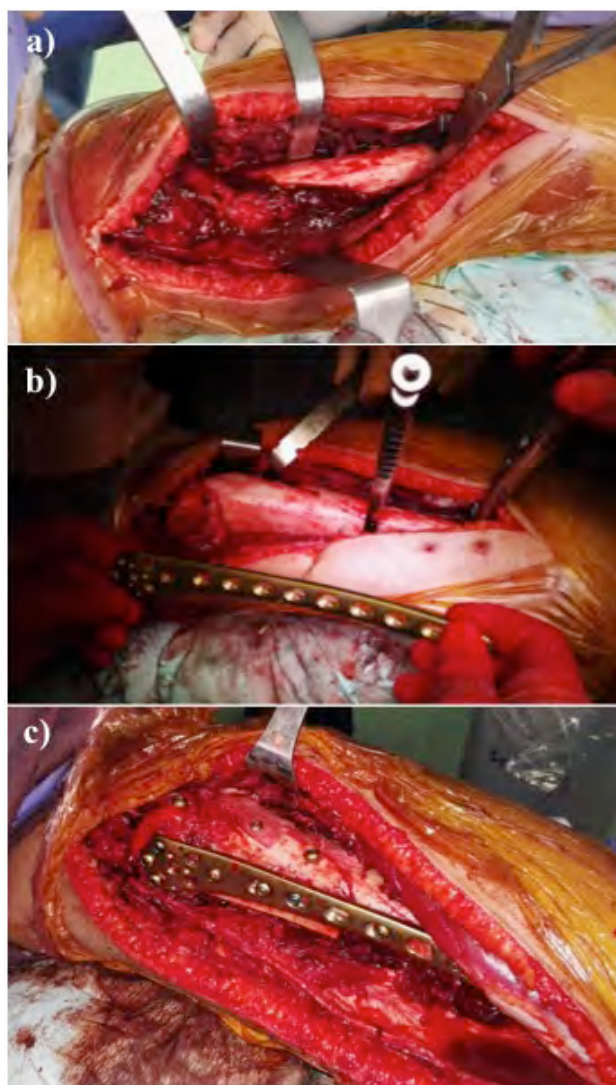


Fig. 5: Second step surgery: **a)** Bone deficit debridement and implantation site preparation; **b)** Autologous bone graft reimplantation; **c)** Stable fixation of the fracture using a dedicate plate.

for the coverage of all anaerobes as demonstrated in Kamal et al. The combination of clindamycin and gentamicin multiplies their effect (5, 6).

The refrigerant was used for the preservation of the autograft. The temperature of the bone bank is usually of -80°C , however the osteoinductive efficacy of the allograft is limited by storage and sterilization techniques. Freezing and freeze-drying methods are implemented to prolong shelf life and decrease rates of disease transmission and to abate the microbial charge.

In 2019, Samsell et al. (15) reported the use of glycerol bone preservation; this technique seems to maintain the tissue biomechanics. The study limitations were a restricted number of patients, and the retrospective nature of the investigation. Despite this, the current work represents the first description of such technique with long-term outcomes. This study suggests that the reimplantation of extruded small or large bone fragments may represent a reliable alternative to amputation in open long bone fractures.

The study reported a good reliability of autograft reimplantation for small or large fragments of long bone, especially if such a fragment is a major portion of an adjacent joint. S.A.R.A. technique may represent a feasible alternative to bone transport or amputation and allows more physiological return to daily life activities. Further studies are needed to assess a better sterilization technique of bone autograft.

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Combined circular external fixation and flexible intramedullary nailing for pediatric bilateral open tibia fractures in blast injury

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Management of blast injuries with open fractures and extensive soft tissue damage in pediatric patients is a challenging task even in experienced hands. This article reports the case of an 8-year-old boy with bilateral open tibia fractures and soft tissue loss due to the accidental explosion of a skyrocket. After the emergency procedures with lavage, debridement and temporary bone stabilization, we performed the definitive reconstruction surgery using a combined circular external fixation and flexible intramedullary nailing technique on both legs. This technique allowed easy access to the wounds for plastic surgery procedures and early bilateral weight bearing. All implants were removed within 6 months, the fractures healed with good axial alignment and the patient returned to his preinjury activities one year after the trauma. In this case, the combined use of circular external fixation and flexible intramedullary nailing ensured optimal fractures stabilization, minimizing the damage to the soft tissues and the obstruction for plastic surgeons. We believe that this technique should be considered in pediatric patients with open fractures of the lower limbs and extensive soft tissue injuries.

The management of pediatric patients with devastating penetrating injuries to the legs due to explosive devices require prolonged treatments of orthopedic and plastic surgery to restore the anatomy and to allow the best recovery of the mangled extremities in the shortest possible time. The goals of the operative treatment include debridement of devitalized tissues, fracture reduction and stabilization, restoration of the limb alignment, minimizing the risk of infection and achieving soft tissues coverage without damaging the periosteal and endosteal blood supply. Any orthopedic intervention should not compromise the access for the plastic

surgeons' procedures to achieve soft tissues coverage.

Each treatment option for management of pediatric tibial fractures has its advantages and disadvantages (1); flexible intramedullary nailing (FIN) is the gold standard treatment for closed transverse fractures, while spiral, comminuted, open or extremely proximal/distal fractures are less suitable for FIN. External fixation is the recommended treatment in polytrauma patients and/or in case of tibial fractures associated with severe soft tissue injury (2).

A 2-stage damage control orthopaedics (DCO) protocol with external fixation followed by definitive fixation has been described as the

Key words: tibia, pediatric, blast injury, circular external fixation, flexible intramedullary nailing

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standard management of open tibia fractures in most trauma centers. Percutaneous reduction and circular external fixation have been described for the treatment of multifragmentary open fractures. The iFixation frame (iFix) (Dial Medicali, Milan, Italy) is a modern multiplanar external hexapod frame that consists of two rings or partial rings connected by six telescopic struts with special universal joints. The iFix offers many advantages including its reliability and the versatility to simultaneously correct rotation, angulation and translation deformities by adjusting the struts' lengths. The aim of this article is to report the clinical effectiveness of combined circular external fixation and flexible intramedullary nailing technique for complex tibial fractures with extensive soft tissue injury.

MATERIALS AND METHODS

In August 2017, an 8-year-old boy was brought to our emergency department after a firework accident in which he was hit on both legs by a skyrocket. Upon arrival, he was intubated and resuscitated according to the Advanced Trauma Life Support (ATLS) protocol, maintaining hemodynamic stability. The fractures were classified according to the OTA and Gustilo and Anderson systems for grading open fractures (3, 4). On the right,

he had open diaphyseal fracture (Gustilo IIIB) of tibia and fibula (AO/OTA 42-D/5.2). On the left, he had open diaphyseal fracture (Gustilo IIIB) of the tibia (AO/OTA 42t-D/5.2), while the fibula was intact (Fig. 1). Computed tomography angiography (CTA) showed no significant arterial or venous injuries in the lower limbs.

The patient started broad-spectrum antibiotics (gentamicin and cefazolin) and was moved to the operating room. Orthopaedic surgeons performed deep debridement of nonviable tissues and extensive lavage with isotonic sodium chloride solution of the wounds. Right leg was stabilized with tibial K-wires and external fixation (rectangular configuration with calcaneal and proximal tibial Steinmann pins); left tibia was stabilized with a unilateral external fixator according to DCO principles.

Then, plastic surgeons performed additional debridement and skin suture to partially cover the soft tissue loss; at the end of the surgical procedures, a large loss of substance in the anterior region of both legs remained. Negative pressure wound therapy (NPWT) was applied the next day on the right leg, and the patient was extubated. Wound irrigation and debridement were performed daily. Plastic surgeons applied a skin graft to cover the left patellar tendon.

Six days after the accident, the patient returned to the operating room: the temporary external fixator was removed from the left tibia, further debridement was

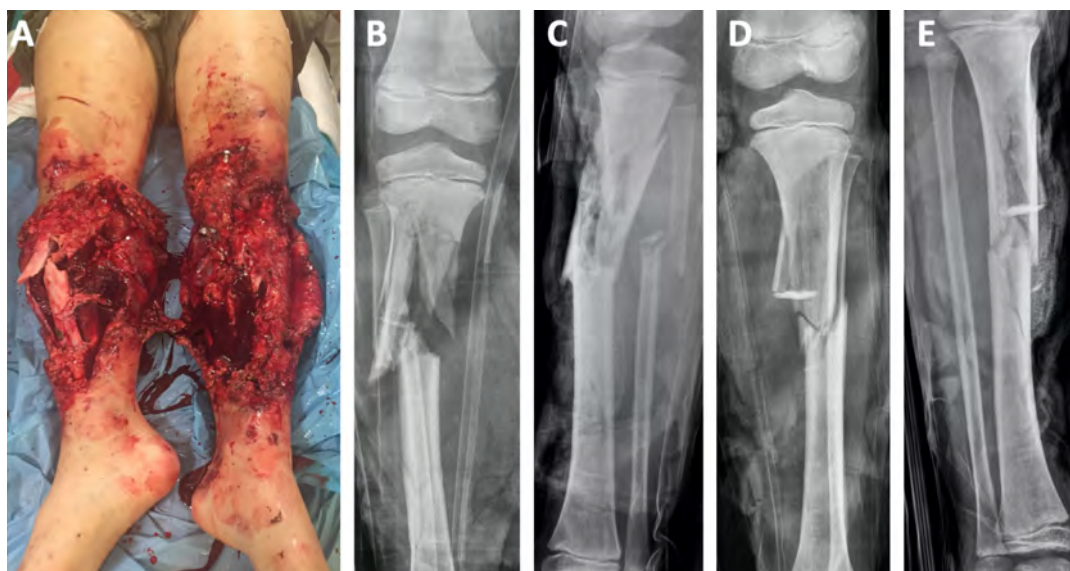


Fig. 1: clinical (A) and radiographic presentation of the patient in the emergency department: anteroposterior (B) and lateral (C) views of the right leg, anteroposterior (D) and lateral (E) views of the left leg.

performed and a spanning femoral-tibial circular external fixator was assembled, using one distal tibial ring with three transosseous tensioned wires and one proximal ring with two femoral hydroxyapatite-coated half-pins. The two rings were connected by three threaded rods. Two titanium elastic nails (TENs) were inserted retrogradely in the left tibia and connected to the distal ring of the external fixator. Plastic surgeons applied NPWT in the anterior region of the leg. Intraoperative samples were sent for culture to the Microbiology Department; the cultures came back positive for *Pseudomonas aeruginosa* and *Enterococcus faecalis*, then antibiotic therapy was switched to ampicillin.

Four days later, a similar surgical procedure was performed on the right leg. Two tibial retrograde TENs were inserted and connected to a distal ring with three transosseous tensioned wires. A proximal ring was assembled with two femoral hydroxyapatite coated half-pins and then connected to the distal ring with three threaded rods. One half-ring with a transosseous wire in the midfoot was assembled and connected to the tibial ring to prevent equinus deformity. The previous DCO external fixator was removed. Debridement of the wound, renewal of NPWT and new samples harvesting for culture were performed.

After 3 days, plastic surgeons harvested split-thickness skin grafts from the anterior thighs and applied them

to cover the anterior region of both legs. After 17 days, NPWT was removed and the patient was transferred to the Pediatric Ward. A psychological support program was set up with periodic interviews.

One month after the initial accident, the external fixators on both sides were modified. In the right lower limb, we removed the femoral ring and converted the Ilizarov fixator into an i-Fix external fixator with two tibial rings; the half ring on the midfoot was kept. On the left, the femoral ring was removed and a proximal tibial ring was assembled, connected to the pre-existing distal tibial ring with three threaded rods (Ring Rod System, RRS, Dial Medicali, Italy) (Fig. 2).

Two and a half months after the initial trauma, the foot component of the external fixator was removed from the right and the whole external fixator from the left leg was also removed, leaving the TENs inside the tibia. The patient was discharged two days later with a rehabilitation program to be performed at home.

We removed the TENs in the left tibia four months after the trauma in our ambulatory surgery center. Two months later, all the implants from the right leg (external fixator, TENs and tensioned wire) were removed and the patient was discharged with a short leg cast and partial weight bearing. The short leg cast was removed after two months and the patient continued physiotherapy with partial weight bearing for the following two months, and

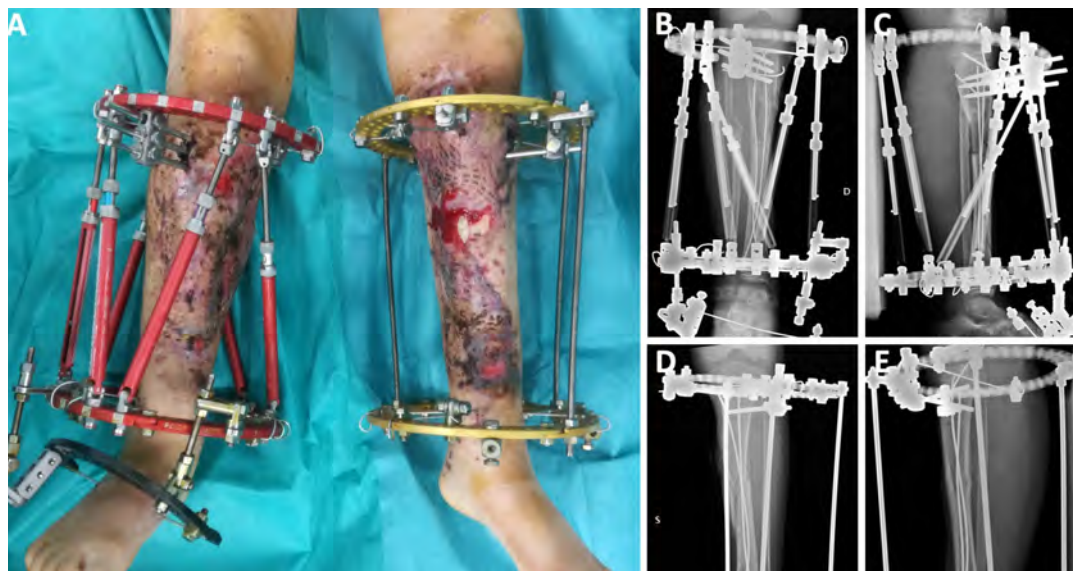


Fig. 2: clinical (A) and radiographic images one and a half months after the initial trauma: anteroposterior (B) and lateral (C) views of the right leg, anteroposterior (D) and lateral (E) views of the left leg.

then full weight bearing was prescribed. Full sport and physical activities were resumed a year after the trauma.

RESULTS

Preoperative and latest (2 years) follow-up radiographic measurements were reviewed for both union and lower limb axis alignment in both the frontal and the sagittal planes. Mechanical axis deviation (MAD) was measured on the anteroposterior view standing radiograph. The results were assessed by using the functional and bone scoring systems described by Paley and Maar (5). Complications encountered intraoperatively and during postoperative treatment were also recorded (6). Based on the outcomes scoring system proposed by Paley and Maar, bone and functional results were excellent in both sides (Fig. 3). The patient returned to his preinjury activities. No complications were encountered intraoperatively and during postoperative treatment.

DISCUSSION

This article describes the use of combined technique of circular external fixation and FIN in pediatric open tibial fractures with extensive soft tissue damage in firework-related blast injury. In our

experience, the flexible nails, assisting the external fixators in maintaining bone alignment, allowed an early weight bearing without altering bone vascularization.

Furthermore, this technique reduced the construct's encumbrance, allowing plastic surgeons to easily work on soft tissues reconstruction and wound care. Several articles in the literature describe the treatment of open tibial fractures in the pediatric population with external fixation or with FIN (1, 7, 8). Some authors have also compared the two techniques by reviewing the literature, concluding that there were no evidence or best practice guidelines due to the poor quality of the available studies (9, 10).

In recent articles, the combined use of monolateral external fixation and FIN for open tibial fractures in pediatric patients resulted in increased fracture stability and was not associated with greater complications than the use of a single technique (11); it also allowed easy access to the wounds and early patients' ambulation (12).

El-Alfy noted that elastic nails allowed for micromotion at the fracture site and did not completely fill the medullary cavity, so endosteal callus formation was not inhibited, while the external fixator maintained the length and controlled the rotation (13). However, these studies on the pediatric population have used monolateral (and not



Fig. 3: radiographic (A) and clinical (B, C, D) images of the patient ten months after the initial trauma.

circular) external fixation. Instead, the combined use of circular external fixation and FIN has been described for the treatment of open tibial fractures in adult patients, showing to decrease the duration of external fixation and the time of bone healing, improving clinical and radiological outcome (14).

Popkov has shown in several studies the advantages of combining circular external fixation and FIN both in fractures on animal models (15) and in bone lengthening and deformity corrections in pediatric patients, with better functional and radiological outcomes (16). In a 2015 article, Bukva also noted that this combined technique in pediatric bone lengthening decreased hospital costs (17).

Recently, McCall reported a case of regeneration of a pediatric radial shaft, after traumatic extrusion from an open fracture, using circular external fixation and one ulnar flexible nail (18). In our case, there were no tibial angular deformities in the frontal and sagittal planes, no loss of reduction or implant failures in both legs.

On the right leg, the hexapodalic circular frame was used in order to easily connect different-sized rings, to allow appropriate wound care and plastic surgery procedures (by temporarily removing some struts) and to achieve correct tibial axial alignment (considering the complex multifragmentary tibial and fibular fractures).

The combined circular external fixator and FIN technique allowed early bilateral weight bearing and versatile limb reconstruction strategies.

To our knowledge, in the literature there are no reported cases of combined circular external fixation and FIN in the treatment of open tibial fractures in pediatric patients. The main limitation of our article is that we described two leg injuries in a single patient, therefore further case series would be needed to confirm our results. We also justify this limitation by the fact that these cases can be considered rare and generally unique, making a comparison very difficult.

In conclusion, we believe that this hybrid technique should be considered as a minimally invasive, safe and valid option for the treatment of open tibial fractures with extensive soft tissue damage in the pediatric population.

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Use of ceramic bearings in hip arthroplasty: correct implantation and review of clinical and radiographic results

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Ceramic materials are widely used in hip prosthetic surgery. Faced with important developments in the design and characteristics of the materials, ceramic-on-ceramic (CoC) are today the bearings in Total Hip Replacement (THR) showing the minimal wear rate. Moreover, ceramic wear debris demonstrated the absence of local and systemic toxicity. This makes ceramic bearing particularly suitable for active patients, whatever their age. The results show excellent survival rates of THRs with ceramic components and excellent clinical and radiographic scores with follow-up close to 20 years. However, the excellent outcomes of THRs with ceramic bearings are depending on appropriate and correctly performed surgical technique.

Total hip replacement (THR) is recognized as one of the most successful surgical practices (1). Introduced in the middle of the last century, it has widespread use and application throughout the world. THR is the solution to problems related to degenerative hip pathology, e.g. pain, disability and limitation of daily activities. Surgical techniques and materials have been improved over the years resulting in long-lasting implants and - especially in ceramic-on-ceramic (CoC) bearings – in extremely low wear rates.

Nowadays, the profile of patients undergoing THR has changed radically. The long duration of the implants has led to increasingly younger patients being eligible for this type of surgery. At the same time, even older patients have higher functional demands and longer life expectancy than in the past. This has put in evidence the need to optimize the implants to ensure low wear, high biological safety of

the debris, stability of the implant and a high Range of Motion (ROM) of the prosthetic joint. Ceramic bearing is the answer for high demanding patients: besides the extremely low wearing, the reaction to the wearing debris is minimal. This led Fisher, et al to qualify the biological functional activity of ceramics as the minimum achievable with new technology (2).

Today the use of ceramic femoral heads in hip replacement bearings is spreading: in some European countries (Austria, France, Germany, Italy, and Switzerland), more than 50% of the hip implants are making use of ceramic ball heads, and in Asian Countries like Korea, where 72% of THRs has an alumina ball head (3). Also, in countries where the introduction of ceramic bearing components took place later (USA, China, India, Eastern European countries), the number of ceramic components used in clinics is increasing. In Italy, the report of the Italian Arthroprostheses' Registry Project (RIAP)

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shows that in 2017 CoC bearings were used in the 21% of the elective THRs (second bearing after ceramic-on-polyethylene (CoP), used in the 67% of elective THRs) (4).

Historical notes on the development of ceramic materials

The first CoC THR bearing was developed by Boutin in France in the seventies. This prototype, implanted in 1970, consisted of a cemented alumina acetabular cup and a stainless-steel stem. The failure of this implant was mainly due to the loosening of the heads, which were fixed to the stem by an epoxy glue. The introduction of the taper connection by Doerre and Semlitsch in 1974 was the solution to this problem and opened the way to implant modularity (3).

Alumina (Al_2O_3 , aluminum oxide) is a polycrystalline ceramic, which molecule contains high-energetic ionic and covalent bonds. This makes the material extremely hard, wear-resistant and not deformable under a heavy load. In addition, the spatial structure of the molecules attracts polar liquids, allowing good wettability of the articular surfaces (5).

Alumina proved to be an optimal choice for younger patients right from the start, with optimal results at a follow-up of more than 20 years. Failures that occurred in the first years of clinical use – especially before 1980 - were mostly due to the design of the implants or to the poor quality of some materials that soon were excluded from the market (6).

Despite the excellent characteristics of the material, the main limitation of Alumina is its intrinsic brittleness that limits the design options of alumina devices. To overcome this limit, Zirconia (Yttria-stabilized Tetragonal Zirconia Polycrystal - YTZP) was introduced into clinic. This ceramic material is characterized by high tensile strength and fracture toughness, but the hardness is about 50% lower than Alumina, a behaviour that limits its use in CoP bearings. This material has never been widely used in orthopaedics and was soon withdrawn from the market for its high cost and less hardness, as well as for fractures (7).

Today, the use of alumina heads in THR bearings accounts no more than 10% of the market. It has been

replaced by Alumina and Zirconia-based composites. The best-known representative of the class was marketed in 2004 by Ceramtec (Plochingen, Germany) under the name “BIOLOX delta”. This material has better tribological properties of Alumina, due to higher mechanical properties and fracture resistance. These materials are composed of a fine Alumina grain, toughened and reinforced by a homogeneous dispersion of Zirconia grains and by strontium hexaluminate platelets. The addition of chromium oxide gives the typical pink colour (3) (Fig.1).

Other composite ceramics are in clinical use in THR bearings: Kyocera (Kyoto, Japan) developed a Zirconia-Toughened Alumina (ZTA) in which Zirconia is stabilized in the tetragonal state by residual stresses that arise during cooling due to thermal expansion coefficient mismatch, known as BioCeram AZ409. More recently, this company presented a further ZTA reinforced by platelet-like alumina crystals (BioCeram® AZUL™) owing its tradename to its characteristic blue colour, due to the presence of cobalt among its additives (8).

A further composite was introduced in the orthopaedic market by Mathys Orthopedie (Bettlach, Switzerland) in 2007 under the tradename Ceramys. As reported by Schneider, et al., large part of this material (80 vol%) is Zirconia. The mechanical behavior of the material are remarkable. Nevertheless, due to the permanence of concerns on materials mostly made of Zirconia, the diffusion of Alumina-Toughened Zirconia (ATZ) in arthroplasty seems limited (9) (Table I). Today, ceramic ball heads can be coupled with a ceramic either to a Polyethylene (UHMWPE, XLPE, Evit-XLPE) acetabular component.

Surgical technique

The surgical implant technique of the CoC bearing must be precise, respectful of the individual patient's joint geometry and joint kinematics. Incorrect positioning of the acetabular cup and/or femoral stem can lead to impingement and component fracture or dislocation. At the same time, excessive verticalization of the acetabular cup may reduce formation of a lubricating film into the joint and may lead the prosthetic neck to impinge on the

rim of the acetabular cup with possible squeaking or liner fracture. Moreover, a shell which is too vertical and with excessive anteversion implies the risk of antero-superior loading of the edge of the insert with consequent wear of the liner and of the femoral head (stripe wear) and increased risk of fracture.

In the first years of use of ceramic femoral heads, the use of small heads (28 mm) was widespread especially in CoP bearings. This was because the smaller the diameter of the bearing (smaller lever arm) the smaller the reaction torque at the cement-bone interface, reducing the risk of mobilization of the acetabular component. The advent of titanium

alloy cups has decreased the importance of containing mechanical stress on the interface and has allowed the use of larger diameter heads (10).

The Norwegian Arthroplasty Register shows that 28mm femoral heads had a 4-fold higher risk of revision for instability than 32mm heads (11). Nowadays, all surgeons specialized in hip prosthetics prefer the implantation of large diameter bearings (36 mm or more). In this way, the stability of the implant is increased because of the increase of the "Jump distance". At the same time, the ROM of the joint is increased (neck diameter unchanged) with reduction of the risk of impingement and luxation.



Fig. 1. Femoral head and liner in white Alumina and CoC bearing in Alumina-Zirconia.

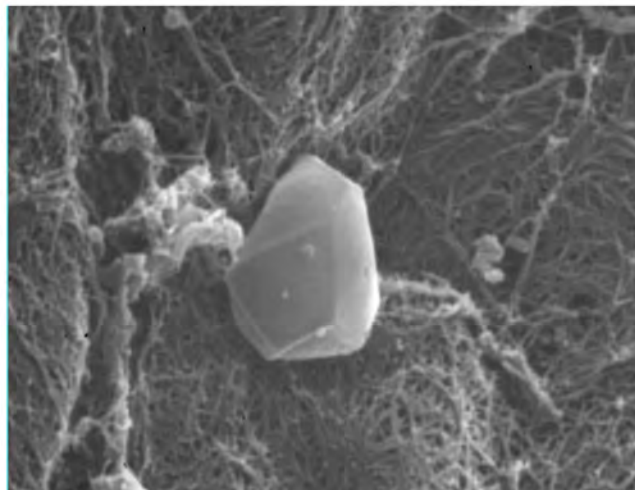
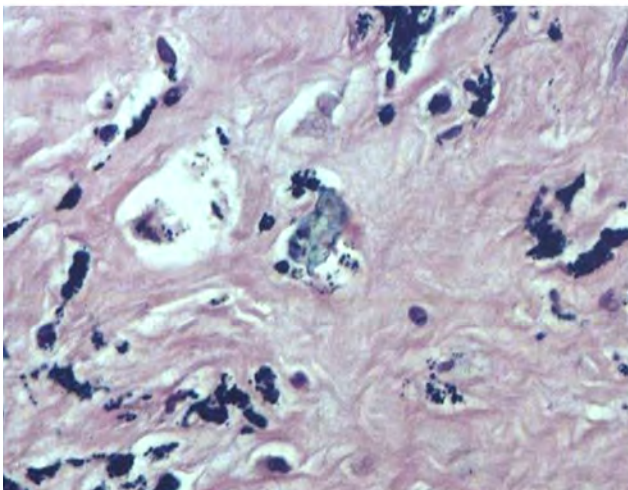


Fig. 2. Histology showing ceramic debris that induce poor inflammatory reaction and electronic microscope detail of them.

Table I. *Mechanical properties of Alumina and of Alumina-Zirconia composites.*

Property	Units	Alumina	Zirconia-Toughened Alumina ZTA	Alumina-Toughened Zirconia ATZ	BIOLOX delta
Alumina content	Vol %	>99.8	75	20	81
Zirconia content	Vol %	--	25	80	17
Density	g/cm ³	3.96-3.98	4.4	5.5	4.37
Flexural strength	MPa	550-630	>700	1050	>1300
Young Modulus	GPa	400	380	300	380
Fracture toughness	MPa m ^{1/2}	4.5	> 5	7.5	7

When installing a ceramic femoral head on the stem, or a ceramic liner in the metal back, it is mandatory to check that these components are suited for the implant selected. Namely, small differences exist among systems of different manufacturers, and among the THR systems made by the same manufacturer whatever the nominal taper size. It is noted that the so-called “Euro Taper” 12/14 does not exist: what exists is a number of tapers “12/14” having different length, diameters, angle, surface status, etc.

At the time of implantation, it is essential to thoroughly clean the taper, wash and dry it, to eliminate contaminants at ceramic-metal interface that can lead to local stress concentrations, and fracture of the ceramic component. The presence of bone cement chips or serum drops at the interface may decrease by 30% the burst load of the head. In addition, scratches on the taper may decrease by 80% the burst load. Then, in case of head removal (i.e. during a revision surgery with stable stem), it must be ensured that sleeves or revision ceramic heads with an inner liner are available. Ceramic heads and liners must be impacted with a special resin toolkit to prevent fractures of the material.

Ceramic femoral head fractures are often occulted during the surgical procedure and may occur even after some years. Different is the case of the ceramic liner, as intra-operative “chipping” can happen during incorrect placement. Likewise, for the reasons explained in detail above, the ceramic liner must be inserted in an acetabular cup with the correct version and inclination according to the Lewinnek’s safe zone, after careful washing and drying of the inside of the shell. Finally, the removal of peri-acetabular osteophytes prevents conflict (12).

Potential risks

Every bearing has benefits, but also potential risks. The most feared complication of CoC bearings is fracture. Today this complication is very rare: it was more common in some materials that have since left the market. From the French National Agency for Medicines and Health Products Safety shows that the fracture frequency of BIOLOX delta ball heads is 0.0013 % (1.3/ 100.000) (13).

Noises, especially squeaking, were object of high attentions during the last years. This is a hip replacement-related complication that was evident especially in some countries, likely due to the prevalence of some devices design in these markets. Acoustic vibrations (noise) due to stick slip friction can be generated in a number of conditions, e.g. ceramic debris in the bearing interface, starved lubrication, and metal transfer onto the bearing surfaces. Results of clinical studies show that there are significant correlations between the positioning of the implant, edge loading, patient body mass index and activity level, implant design. However, squeaking does not appear as a major complication in THR, being in most cases a transient condition only (3).

Ceramic materials, like all others, can wear out, releasing debris. Ceramics have excellent biocompatibility and very low osteolytic capacity. In fact, ceramic debris induces very little macrophage reaction and does not cause local or systemic toxicity. Very few giant cells can be found in the presence of more or less large but inert debris (14) (Fig. 2).

Clinical results

Kim et al. evaluated clinical and radiographic results of their patients with CoC bearing. Patients

had an average age of 38 years, were mainly males with high functional demands. At the last follow-up (11 years) no implants were revised for mechanical failure and there were no signs of osteolysis (15). D'Antonio, et al. reported the results of a multicentre study including 216 hip arthroplasties. They compared clinical and radiographic results at an average follow-up of 12 years between metal-on-polyethylene (MoP) and CoC implants: the risk of revision in the case of MoP bearing was three times greater than in CoC; in addition, the 26% of the latter showed signs of osteolysis, which was completely absent in patients with CoC bearing (16).

In 2019, Kim et al. studied clinical and radiographic results of 266 hips at an average follow-up of 18 years with CoC bearing compared to CoP. They thus demonstrated an implant survival rate of 99% (17). Recently, Chang et al. investigated clinical and radiographic performances of contemporary CoC hip arthroplasties in more than 200 patients, demonstrating excellent implant survival and very low frequency of noise (18). A 2012 meta-analysis showed excellent survival rates of both CoC and CoP bearings, above 90% at an average follow-up of 10 years and above 80% at 20 years follow-up for CoC. The same scientific paper shows that the CoC bearing is characterized by a very low rate of wear and almost no peri-prosthetic osteolysis due to the very low biological reactivity of ceramic debris (19).

THR is one of the greatest successes of orthopaedic surgery. The development and improvement of ceramic materials has allowed their diffusion. CoC bearings are particularly suitable for young and active patients. This is because CoC bearings guarantee very low wear rate and the rare release of debris. Moreover, if this occurs, ceramic debris is inert and does not induce any osteolytic process. Thus, osteolysis of different origins can easily be hypothesized, if periprosthetic osteolysis is found in a patient with this type of bearing (20). The very low wear rates and the excellent biocompatibility ensure that these implants last over time and are safe for patients. For this to be possible, however, the correct positioning of prosthetic components is essential, also thanks to a careful preoperative planning.

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Perioperative case series, qualitative evaluation of gait cycle and ground reaction forces in knee arthroplasty patients using a wearable insole

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Gait analysis using wearable sensors has shown the potential to analyze gait kinetics in an ambulatory setting (1, 2). Historically, gait analysis required expensive and highly specialized equipment and studies were mostly limited to academic research centers, small sample sizes (3) and no large-scale, randomized controlled trials have been performed (4). Furthermore, these experimental setups allowed only momentary views of the patient's gait in a confined research environment.

Several authors have proposed inexpensive and wearable accelerometer-based systems to overcome this situation (5). By applying mathematical transformations, step time and length were adequately measured (6) (7). With these systems, however, only temporal and spatial gait parameters can be recorded. Kinetic gait parameters, such as ground reaction force cannot be measured (7). As these kinetic parameters are important for clinical studies, especially for fracture (8) and rehabilitation research (9), additional methods are needed.

However, even small wearable systems have to be attached to an external apparatus or they are limited by their battery capacity, data storage and other device specific factors (10) (3) (11). Furthermore, the use of these systems was at an early stage and their potential was not yet fully developed (12). As most disease processes are continuous, tools with

long-term, continuous measuring capabilities are needed. For this reason, a new pressure-measuring insole with built in battery and data storage was developed in cooperation with the AO Foundation (AO Foundation, Davos, Switzerland). This system (OpenGo Sensor Insole, Moticon GmbH) offers complete independence from any external measures for up to 4 weeks and monitors a patient step kinematics during this time.

Advanced degenerative arthropathy of the knee ultimately manifests as pain and loss of function leading to impaired gait and activity. Total knee arthroplasty (TKA) aims to eliminate pain, restore the function of the joint and ultimately aims to improve the ability of the patient to move and live an active life. TKA has a history of success, but as the orthopedic and healthcare sectors evolve, a greater level of scrutiny and expectation for success is expected from surgeons and device manufactures alike. In response to these elevated levels of scrutiny and expectation, more advanced methods will likely be required to better capture and understand how TKA affects knee function both on a patient specific basis as well as on a device design and surgical technique specific basis.

In view of these needs, we are aiming to investigate how TKA arthroplasty affects gait dynamics during early and medium phase of rehabilitation and to

Key words: Total knee arthroplasty (TKA), gait analysis, patient related outcomes (PROMs).

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provide objective evidence of the quality and value of the intervention on an individualized basis. Furthermore, we aim to provide advanced insights into the patient's functional recovery and rehabilitation with the potential for health care professionals to intervene earlier and with greater specificity to any challenges encountered by the patient.

This is the first step in this investigation. The present study describes a pilot study aimed to provide preliminary data for effect size and patient numbers estimation as well as to screen for possible reliable markers or surrogate measures of rehabilitation. For this purpose, we used the developed OpenGo Sensor Insole (Moticon ReGo AG, Munich, Germany).

MATERIALS AND METHODS

Study design

Single arm, single centre, prospective, pilot study to measure the pre-operative and post-operative gait dynamics (dynamic ground reaction forces) and gait timing of 6 subjects undergoing TKA. The measurements were controlled by the measurements of the contralateral limb measurements.

Inclusion criteria

For study enrollment, the inclusion criteria were requirement of a primary TKA, age between 45 and 75 years at the time of surgery, skeletal maturity in the primary investigator's (PI) judgement and a BMI below 32. Furthermore, the patient was willing and able to participate in required pre-operative and follow-up visits at the investigational site as well as to complete study procedures and questionnaires. Last, the patient needed to have consented to participating in the study by signing the Institutional Review Board/Ethics Committee (IRB/EC) approved informed consent form.

The following exclusion criteria were used: symptomatic and debilitating concomitant arthropathy of the non-operative joints (e.g. a TKA patient cannot have advanced arthritis of the contralateral knee or ipsilateral hip/ankle), which the PI's judged to interfere the peri-operative gait measurement. Significant comorbidities that would impede the patient's ability to participate in standard recovery and rehabilitation were also used as exclusion criterion.

Patient details and surgery

In this pilot study, six patients (5 female and one male) with an average age of 70.7 ± 4.9 (range: 64 to 75) and average weight before the surgery of 65.5 ± 11.6 kg (range: 50 to 83 kg) were enrolled between November 2017 to December 2108. All patients underwent primary TKA, performed by a single surgeon, using the same standardized surgical technique and all patients received the same implant type (PFC Sigma, DePuy Synthes). All patients were discharged from the hospital on the fifth post-operative day and the patients went to a rehabilitation facility.

Clinical and patient reported outcomes

To validate the methods and correlate the findings with validated outcomes (13, 14) patients were assessed both clinically and radiographically prior to surgery as well as at 3 months postoperatively. The standard clinical data was obtained before surgery (time 0), 12 weeks, and 24 weeks after surgery. Pain was assessed with the numeric rating scale (NRS, 0 points represents no pain and 10 points represent worst pain imaginable). Knee Society Score (KSS) was used to assess pain, knee stability and function (lower scores represent worse outcomes).

The Knee Injury and Osteoarthritis Outcome Score Physical Function Short Form (KOOS-PS) was used to assess the opinion of the patient about the difficulties with physical activity due to knee problems (higher scores represent more difficulties and 100 points represent the maximum). The Short Form 12 (SF-12) was used as generic assessment of health-related quality of life. The score consistent of a physical (PCS) and mental (MCS) component, where lower scores correspond to higher disability.

Gait analysis

Gait analysis was performed with the OpenGo Sensor Insole (Moticon ReGo AG, Munich, Germany) prior to surgery (week 0) as well as 1, 2, 3, 4, 12 and 24 weeks postoperatively. Gait analysis was conducted according to a pre-defined standard protocol provided by the manufacturer of the pressure insole. Data and user feedback were analyzed continuously as they became available throughout the study period. All insole registrations were performed at Istituto Ortopedico Galeazzi IRCCS (Milan, Italy). All data management of the insoles was carried out by a single

researcher. Data analysis was performed by another researcher using the manufacturer's software and Matlab R2018a (Mathworks, Natick, Massachusetts, USA).

The Moticon Science software provides a large number of parameters derived from the acquired data. We used only a sub-set of all available parameters. Some of the most common and easy to understand parameters were used, e.g. maximum force during stance phase (maximum total force), mean force during stance phase (mean total force), gait cycle, step duration and stance phase. Additionally, we evaluated the center of pressure during stance phase (gait line).

Additionally, the software provided averaged ground reaction force curves during stance phase. These were normalized by body weight (BW) and plotted against percent stance phase. BW was only determined before the surgery and at week 12 and 24. Force measurements at week 1, 2, 3 and 4, were normalized with an estimate of BW from the available data and linear interpolation approximate the changing BW, where no measurements were done.

Statistical analysis:

As this is a pilot study, we did not perform an upfront sample size calculation. Based on previous experience, we assumed that six patients would provide enough recordings to allow a proper study plan design and sample size calculation for a future clinical study. Only descriptive statistical analysis was performed. Results were reported only as mean with one standard deviation (1SD).

No statistical interference testing was performed, as applying repeated measures analysis of variance or a two-way Friedman test including post-hoc pairwise analysis would only add limited information when applying to a sample size of 6 that includes missing data.

RESULTS

Clinical and patient reported outcomes:

The average pain score by NRS decreased by 5.3 ± 2.3 from the pre-operative assessment, week 0, to week 12 post-operative and by 6.5 ± 2.1 from pre-operative to week 24. (All patients showed a decrease in NRS pain score at week 12 compared to the pre-operative score. Between week 12 and 24 scores further decreased, remained equal or increased by 1 point. The

latter one is less than what is considered a clinically important changed of 2 points.

On average the KOOS-PS scores decreased by 19.9 ± 14.3 from week 0 to week 12 and by 24.3 ± 18.5 from week 0 to week 24. All patients except patient 6 showed an overall decrease in KOOS-PS score from pre-operative to week 24, indicating fewer difficulties. Patient 6 had an increase by 3.2 from week 0 to week 12 and no further change between week 12 and 24; 3.2 points is close to the minimally clinically important difference of 2.2 (MCID) for KOOS-PS.

All patients showed an increase in their SF-12 scores after surgery at week 12. On average, this corresponds to an increase by 20.8 ± 4.3 points. On average, SF-12 did not significantly change between week 12 and 24, which resulted in an overall increase from pre-operative to week 24 by 18.8 ± 20.2 points. This minimal change was composed by an increase of the physical (PCS) and a decrease of the mental (MCS) component of the test. Only patient 2 showed an overall decrease in SF-12 by 18 points, which is a result of a decrease between week 12 and 24 of 37.4 points. Both MCS and PCS subscale contributed to this decrease.

KSS subscale scores of pain, function and stability were available. Four patients showed a maximal stability score throughout all assessments. Two patients showed an increase from 15 points pre-operative to the maximum of 25 points of all post-operative assessments.

All patients had an increase in pain score (reduction of pain) from week 0 to week 12, resulting in an average increase of 35.8 ± 8.6 points. Scores further increased or plateaued at week 24 for all patients. This resulted in an overall average increase of 38.3 ± 5.2 . Patient 5 showed a decrease by 10 points in the function subscale from the maximum at week 12 to week 24. For all other patients, the function scores increased between consecutive assessments. This resulted in an average increase of 25.8 ± 20.6 from week 0 to 12 and 44.2 ± 15.3 from pre-operative to week 24.

Gait analysis

For each patient measurements were performed at pre-operative (week 0) and at week 1, 2, 3, 4, 12 and 24, post-operative. For patient 1, no data was acquired for the leg that was treated at week 1 and

2. No data was available for patient 3 and 6 at week 24. No data was available for patient 4 at week 3 and no data was available for patient 5 at week 12 and 24. Reasons are not known. Only patient 2 has a complete set of gait data.

Forces during stance phase:

When all maximal forces during the stance phase were averaged over all measurements, the treated leg was loaded $7\% \pm 11\%$ less compared to the control leg. The mean force during stance phase was $11\% \pm 11\%$ lower on the treated leg when compared to the control leg (Fig. 1, 2). Five patients showed lower averaged forces for the treated leg. Patient 1 loaded the treated

leg with more forces (Fig. 3). Example force curves after normalization by BW plotted versus percent stance phase can be appreciated in Fig. 4.

Temporal parameters:

Mean gait cycle periodicity increased after surgery (week 1) and decreased continuously to lower values, reaching similar levels at week 12 and 24 as recorded pre-operatively. Mean step duration did not show a clear trend, but stance phase during gait cycle was lower for the treated leg (Fig. 5).

Double support time was not evaluated as in most measurements the force curves were partly set off in time (Fig. 6). In some cases, this resulted into

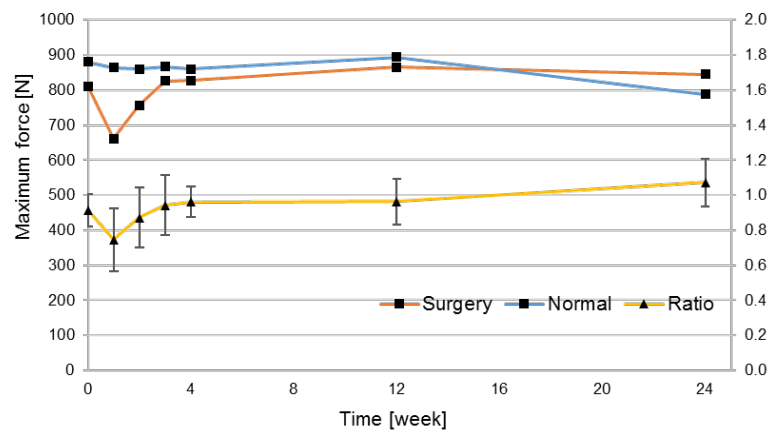


Fig. 1. *Left axis:* Maximum ground reaction forces averaged over all patients. *Right axis:* Ratio of maximum force of the treated leg and normalized by the control leg. 1 SD was only plotted for the ratio to keep a clear view.

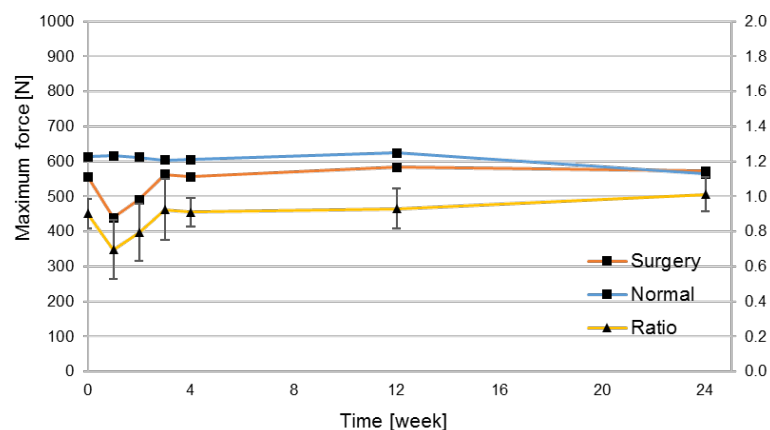


Fig. 2. *Left axis:* Mean ground reaction forces averaged over all patients. *Right axis:* ratio of forces from the treated leg normalized by values from control leg. 1 SD was only plotted for the ratio to keep a clear view.

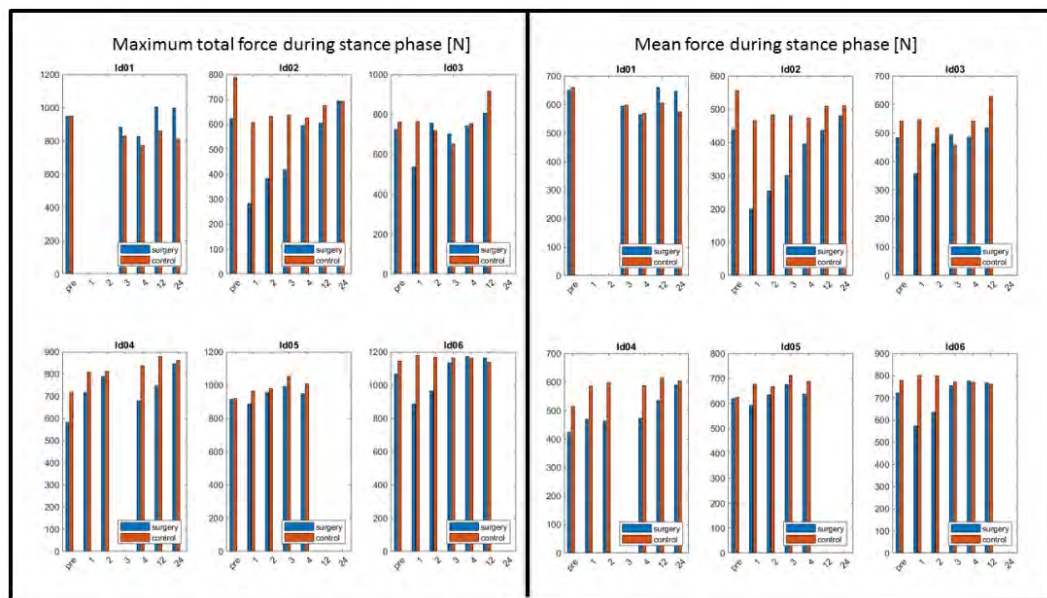


Fig. 3. Maximum total forces and mean forces during stance phase for all patients also showing missing gait analysis data. Patient 2 and 6 showed a clear pattern with approximately constant loading of the control leg and increasing loading after surgery of the treated leg.

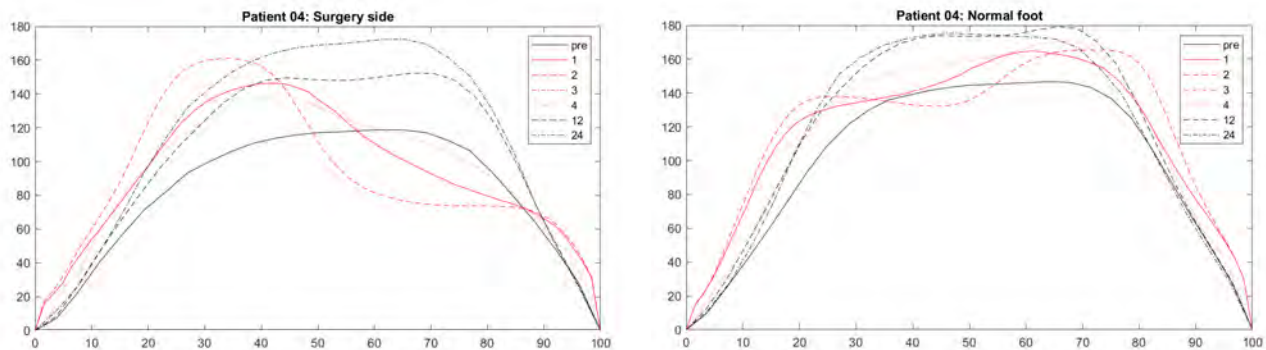


Fig. 4. Example force curve for patient 4. Abscissa: percent of gait cycle. Ordinate: normalized ground reaction force in % BW. The typical bimodal vertical ground reaction force was not always seen or less pronounced as compared to other studies.

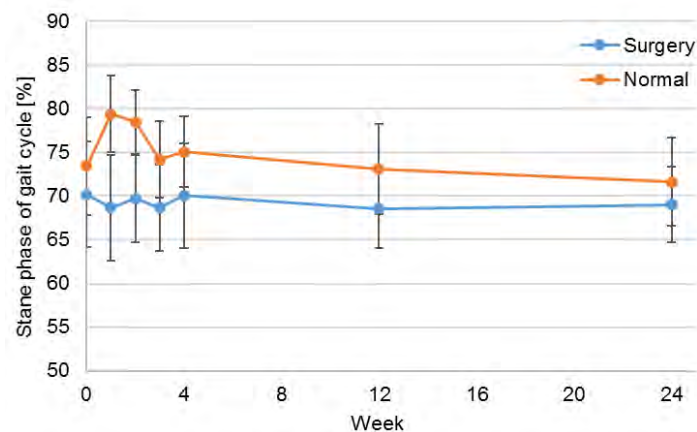


Fig. 5. Relative duration of the stance phase of the gait cycle: the normal leg appeared to be loaded longer when compared to the total gate cycle. Error bars correspond to 1 SD.

simultaneously appearing force peaks (steps) of both feet and in very high forces of up to 328% BW when these forces were summed. All patients showed at least two measurements (data set available at a week) that showed summed ground reaction force larger than 200% BW. This is considered as not plausible and being an artefact of not synchronized data recordings only. Therefore, this parameter depending on correctly synchronized data were not assessed.

Spatial parameters and gait line:

Gait lines, the center of pressure during the stance phase, were on average $16\% \pm 21\%$ shorter for the treated leg, when averaged over all measurements. Out of the six patients, only patient 4 had consistently longer gait lines on the treated side. All other patients showed consistently shorter gait lines for the treated leg. Gait line width showed a similar trend to a narrower gait line for the treated leg, but this was not as consistently observed.

DISCUSSION

The averaged clinical and patient reported outcomes showed reductions in pain (NRS, KSS pain subscale), improvements in function (KOOS-PS, KSS function and stability subscale) and quality of life (SF-12 short form). Typically, the changes

were considerably larger from pre-operative to week 12 than from week 12 to week 24. Overall, these findings can be expected from TKA treatment.

However, patient individual scores were not always reflecting improvements. In some cases, these scores reflected clinically significant decreases or a stagnation, corresponding patterns in the gait data were analyzed to identify possible relevant correlations between both data sets.

The Moticon Science software provided many parameters derived from the acquired data. We used only a sub-set of all available parameters. We used the parameters for our analysis, which were simplest to interpret and widely analyzed, such as the maximal ground reaction force, gait frequency, stance phase and gait lines.

Despite not performing statistical analysis, some trends were apparent. For example, the treated leg was loaded with more weight in 5 out of 6 patients. This difference in force tended to become smaller at week 12 and 24. The mean gait cycle time was more than 0.5 seconds larger at week 1 compared to pre-operative. The gait cycle time decreased at week 2 and 3 and reached approximately the pre-operative values at week 4, 12, 24. The relative duration of the stance phase was slightly smaller for the treated leg, with larger differences at week 1 and 2. The length of the center of pressure (gait line) was on average also smaller for the treated side. Overall, these findings

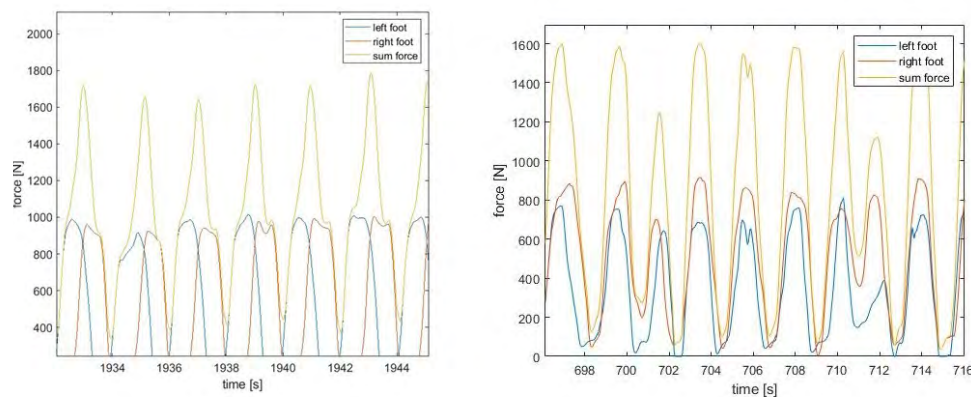


Fig. 6. Example of force curves of patient 1 (BW of 59 kg = 579 N) where the stance phases of left and right partly superimposed (**left**) and completely superimposed (**right**). This would correspond to a kind of jumping movement, which was assumed as not realistic after TKA. Summation of the forces of both legs resulted in peak forces of up more than 300 % BW.

were quite consistently observed in the patients and the exceptions were again used to identify corresponding deviations from an expected rehabilitation as measured by the clinical and patient reported outcomes.

An attempt was made to find possible correlates between gait analysis and clinical or patient reported outcomes. This was limited due to missing data, as insole data was not always recorded for all post-operative time points. Only patient 2 had a complete set of measurements. All other patients had at least one missing measurement. Unfortunately, three measurements were missing for week 24 and one for week 12, the time points when corresponding clinical and patient reported outcomes were available.

In brief, the missing data, some conflicting results of reported outcomes and clinical parameters, make it difficult to find parameters clearly corresponding in both data sets and to choose the best suitable parameters to assess outcomes of TKA. On the other hand, overall trends appear consistent and as expected for improvements in outcome or a successful rehabilitation after the TKA intervention, even with this small sample size.

The acquired maximal ground reaction forces in % BW (overall average for the treated leg: $127\% \pm 33\%$ and for the control leg: $137\% \pm 27\%$) were similar to previously reported values of 130% BW (15). Values also were within the range of other studies investigating gait in healthy and TKA patients at 12 months after surgery (16, 17). Additionally, reduced loading of the treated leg was also seen in these two studies. On the other hand, the typically bimodal ground reaction force (M-shape) seen in the referenced studies, was not always apparent in the present study or it were less pronounced.

Also, a clear correlation between gait analysis and clinical outcome measures is not always shown in the literature. For example, physical activity parameters did not correlate with clinical outcomes after TKA (18). Most patients did not reach the level of physical activity reported for healthy and activity levels after treatment seemed to be influenced by physical activity behavior prior to surgery rather than by the treatment itself. Furthermore, there was no correlations found between KSS and foot pressure-force measurements after knee replacement (19).

One main difficulty for data interpretation was the lack of sufficient available baseline data, e.g. from healthy subjects. A solid knowledge of the experimental equipment and baseline data could allow interpretation of the extreme values (e.g. maximal forces are sometimes very high, absence of the typical bimodal force curves). In addition, such experience with the devices would allow developing strategies to reduce missing data or to avoid errors in time synchronization so that double support time could be assessed. Another main problem for interpretation of the data was the missing data point from the insoles.

Despite all the difficulties, in this pilot study it has been demonstrated the possibility to harvest data related to the gait analysis through a wearable insole. Nevertheless, we believe it is necessary a new study with a larger number of patients to prove the clinical efficacy of the device. Given the efforts and the difficulties to collect data on clinical outcome of patients treated with arthroplasties, particularly at the long-term follow-up, the possibility to use a wearable device opens new perspectives in the development of the clinical research in this particular field.

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Validation of a novel smart drilling system to monitor bone impedance during transpedicular screw placement: a pilot study

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Transpedicular screw placement is a high-risk procedure routinely performed in spine surgery. To decrease the rate of complications, it is necessary to find innovative solutions to assist the surgeon during screw insertion so as to avoid the chance of mispositioning. In this study, we developed a new drilling system able to estimate the mechanical properties of drilled tissues. Several investigations show that cortical bone requires a high level of thrust force and torque during drilling compared to trabecular bone. To implement an algorithm for bony breakthrough detection, a new drilling system has been built together with a mechanical support to drill the pedicle along a pre-planned trajectory. The mechanical support is equipped with a smart rotative drill that embeds force and position sensors. Ten human vertebral segments have been used to test the surgical platform, for percutaneous bone drilling. 10 transpedicular holes from L1 to L5 have been performed bilaterally. The holes were further evaluated by computed tomographic scans to measure bone density in the cortical and in the trabecular layers. To compare bone density with the bony mechanical impedance two new parameters (D_{HU} and D_{PAI}) have been introduced. The results show that in 18 out of 20 cases the D values of bone density and mechanical impedance, related to the same bone transition, differ less than 10%. The proposed system is thus able to evaluate the variation of bone density of the cortical and the trabecular layer using impedance. Therefore, it is possible to use the described system to increase the accuracy of transpedicular screw placement.

Low back pain (LBP) is a common musculoskeletal symptom affecting more than 80% of the general population at least once in their life with significant healthcare, social and financial burdens (1). Although possibly caused by several etiologies, LBP is mainly due to intervertebral disc degeneration (IDD). IDD is a chronic and progressive process characterized by the deterioration of disc tissue integrity (2-5), which ultimately leads to discogenic LBP and additional sequelae, including disc herniations and segmental instability (5-7). When associated with severe neurologic symptoms, the latter may require

a surgical intervention to achieve spinal fusion.

The standard surgical procedure involves the insertion of pedicle screws and metallic rods to obtain a rigid stabilization of the affected vertebral segments. Traditionally, pedicle screws are manually inserted by the surgeon along a trajectory based on specific landmarks that are mentally reconstructed upon preoperative anteroposterior X-ray with the aid of fluoroscopy (8). Although consolidated, such procedure is not free of complications. Indeed, a series of *in vitro* and *in vivo* studies have reported screw misplacement rates of 5-41% for the lumbar

Key words: spine surgery; spinal fusion; transpedicular screw placement; robotic surgery, bone impedance

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spine and 3-55% for the thoracic spine (9). This may result in serious complications including prolonged LBP, myelopathy, radiculopathy and other neurological issues (10). For this reason, innovative robotic automated technologies are currently under development in order to improve surgical accuracy and safety while being minimally invasive, so as to prevent human errors and unintentional damages to vascular or neurological structures (11).

In this pilot study, we describe a novel passive surgical positioning system for guiding pedicle screw drilling along the transpedicular route through a percutaneous access. Bone drilling has been performed using a custom ultrasonic drill equipped with force and position sensors that can identify the specific vertebral bone layers by relying on tissue average impedance, to achieve a safer drilling procedure.

MATERIALS AND METHODS

System description

The drilling platform (Fig. 1A) is comprised of three systems: *i*) a positioning system (PS) previously described (12); *ii*) an end-effector consisting of a custom-made sensorized drilling tool and *iii*) the control and data processing unit. The PS system allows to mount an end-effector for the manual advancement

of the drill, with stable spatial orientation of the drilling trajectory. The surgical drill is equipped with a load cell and an encoder. The main specifications of the rotative drilling system are listed as follows: feed range (axial direction): 0 – 165.5 mm; feed displacement resolution (axial direction): 89.7 μm ; max pushing force (*i.e.* full scale of the load cell): 98 N; rotational speed: 0 – 2360 rpm (13).

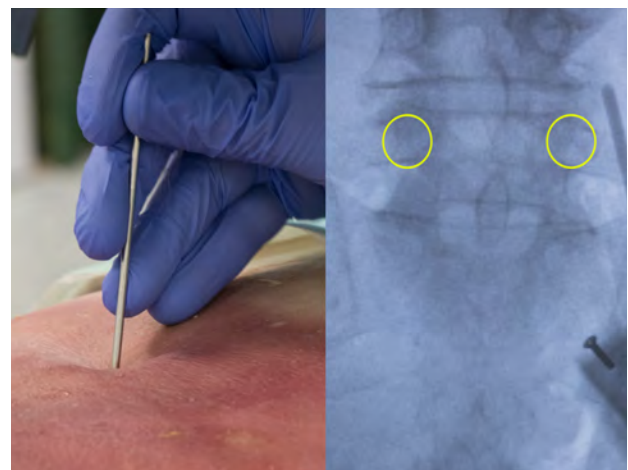
Surgical technique

The validation of the drilling system was performed at the AO Research Institute (Davos, Switzerland) utilizing 10 vertebral segments from two human torsos (male, 88 years old; female, 79 years old) comprising the thoracic vertebrae T11-T12, the lumbar vertebrae (L1-L5) and the sacrum. The specimens was removed from the cold store 12 hours before the experiment and thawed at room temperature. All the perforations were performed by the same spine surgeon. The surgeon percutaneously positioned a Kirschner wire (diameter = 2.5 mm) to locate the pedicle and X-ray images (anteroposterior and laterolateral view) were acquired using a C-arm fluoroscope to verify the correct location of the wire (Fig. 1B).

Subsequently, the wire was advanced under fluoroscopic monitoring to verify the orientation of the wire. The surgeon drilled the bone applying force on the drill knob, being free to perform the



A



B

Fig. 1. A): the experimental setup is composed of the positioning system (blue arrow), the drilling end-effector (red arrow) and the C-arm fluoroscope (yellow arrow); **B):** the Kirschner wire is manually positioned on the skin of the torso; the drilling trajectory is then planned with fluoroscopic imaging.

drilling procedure at his will without any constrain (regarding the thrust force or the feed rate) on the duration of the procedure. Simultaneously, the thrust force and velocity were measured. Bone drilling was performed bilaterally on each pedicle from L1 to L5 level, for a total of 20 holes. Post-operative computed tomography (CT) scans (Siemens CT VA0 COAD, 120 kVp, 330 mA) of the human torso have been performed. A DICOM viewer was utilized (OsiriX Lite, Pixmeo SARL, Geneva) to evaluate length, width and orientation of the bony drilled tunnel and to assess the thickness of the different drilled layers (Fig. 2A).

Moreover, bone mineral density (BMD) has been estimated using the Hounsfield Unit (HU) values calculated in three specific regions of interest (ROI) along the longitudinal axis of significant drilled tunnels (Fig. 2B), as previously reported (14).

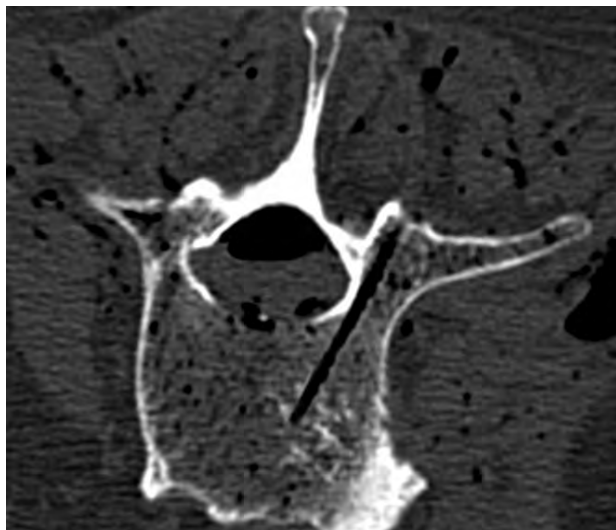
Average impedance

A new parameter has been proposed to estimate bone impedance using the described system. Such parameter has been conceived to address the problem of tissue characterization when neither the force

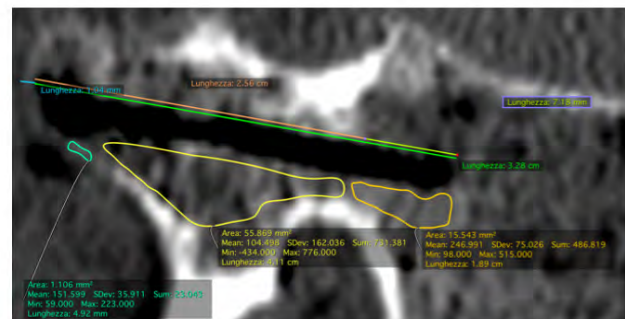
nor the feeding rate are constant (15). Therefore, average impedance (AI), which is capable of binding force and speed together, has been introduced. The mechanical impedance of a linear material is defined as: $AI(f) = \frac{F_d(f)}{v(f)} = \frac{F_d(f)}{2\pi f j S(f)}$ where $F_d(f)$, $S(f)$ and $v(f)$ respectively are the Fourier transforms of the contact force at the interface (drill bit-tissue), the displacement of the drill bit and its velocity. It is then possible to consider the position-referenced average impedance (PAI) as the AI calculated at the exact location of the drill tip, which is directly correlated with the mechanical properties of the drilled bone.

RESULTS

Collectively, 20 different holes were drilled bilaterally through L3, L4 and L5 pedicles. Among these, 2 measurements were excluded due to involvement of the spinal canal. During the drilling procedure, the drill met three different bone layers: the cortical bone of the pedicle, the cancellous bone inside the pedicle and eventually the cancellous bone that fills the vertebral body. Subsequently, PAI and HU values along the drilling route were calculated



A



B

Fig. 2. Representative images showing; **A**): the analysis of length and orientation of the vertebral tunnel; **B**): Measurement of Hounsfield units (HU) from three different regions of interest. The areas indicate (from left to right): the cortical bone of the pedicle, the cancellous bone inside the pedicle and the vertebral cancellous bone.

at each level. Curiously, PAI signal showed characteristic patterns representative of bone tissue mechanical features, as shown in Fig. 3.

Since PAI and HU cannot be directly compared due to different units of measure, the average bone impedance measured by the drill sensors and the BMD estimated at the post-operative CT were correlated by introducing additional parameters, namely D_{HU} and Δ_{PAI} , calculated as follows:

The values referred to the same transitions were

compared as shown in the histogram in Fig. 4, where representative results are depicted. It was assumed that a difference $< 10\%$ between Δ_{HU} and Δ_{PAI} indicated a good correlation between bone strength measurements using CT and the system sensors, respectively.

DISCUSSION

Posterior arthrodesis by transpedicular screw

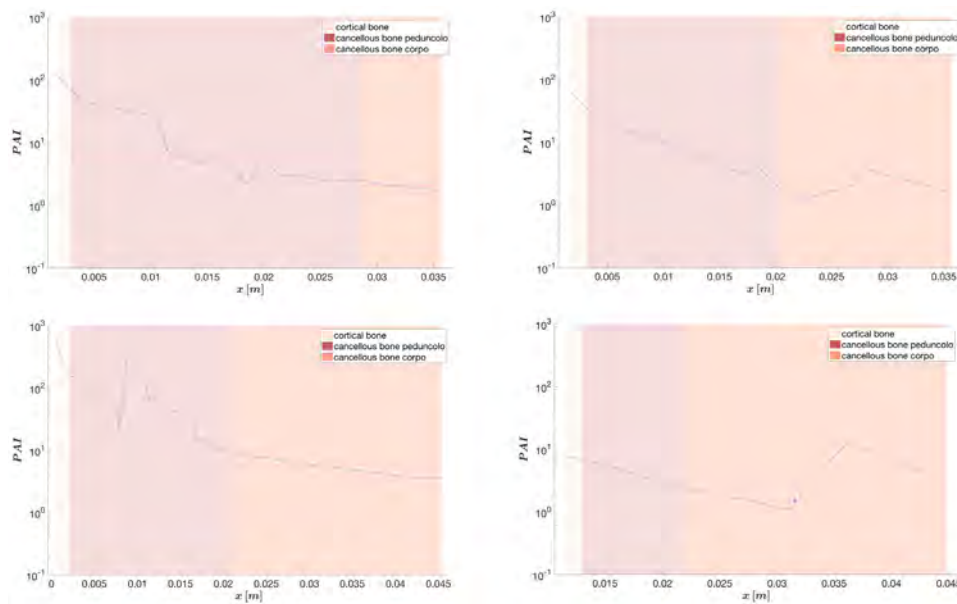


Fig. 3. Representative PAI plot referred to the right L2 pedicle (top left), the right L3 pedicle (top right), the left L3 pedicle (bottom left) and the right L4 pedicle (bottom right).

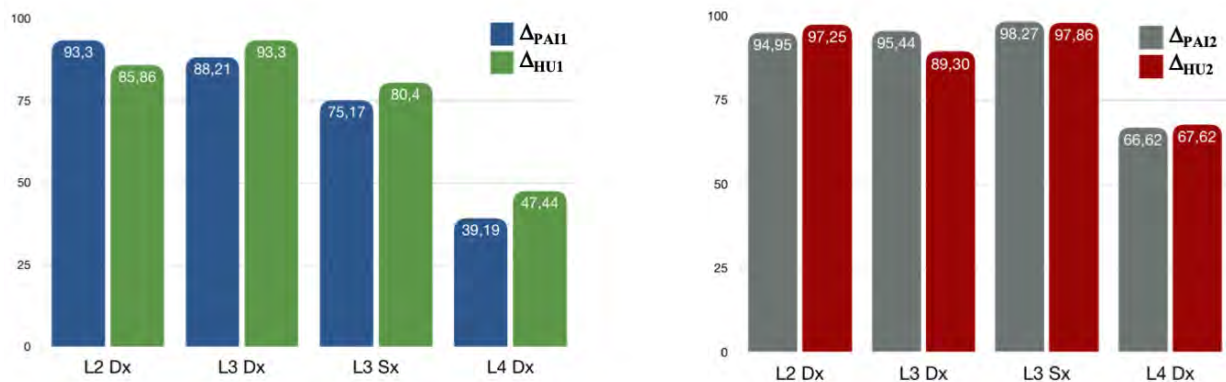


Fig. 4. Representative histograms representing the Δ_{PAI} and Δ_{HU} values related to the transition between the pedicle cortical bone and the pedicle cancellous bone (left chart) and the transition between the pedicle cortical bone and vertebral cancellous bone (right chart).

placement is a common technique to obtain a rigid and stable spinal segment (8), avoiding back pain and neurological problems. The wide use of pedicle screws, together with associated risk and complications (9), have fostered the development of innovative systems to both improve screw positioning and minimize local invasiveness with a “patient-tailored” approach. We presented a passive surgical PS equipped with a robotic arm and customized sensors to evaluate vertebral bone impedance for pedicle screw placement in minimally invasive spine surgery (12). This system has been firstly ideated to perform a transpedicular approach to the disc for delivery regenerative biological agents to the disc minimizing endplate damage (12, 16-19). However, such system can be widely used to implement robotic pedicle screw placement.

Robotic systems are starting to be used in spine surgery, otherwise the major problem around these technologies is the high cost, not affordable for the majority of the hospitals (20). Differently, the described system is characterized by convenient features such as low cost, ease of use and installation, as it only needs to be paired with a C-arm fluoroscope (high compatibility, because no specific C-arm model is required). The choice to design a passive system arose from the fact that surgeons may prefer an assisting device rather than a substituting one in performing surgical procedures. Passive systems preserve the haptic feeling of the surgeon, who remains the only supervisor of the surgical tool advancement along a drilling path.

Meanwhile, the introduction of a PS allows a mitigation of tremor during the orientation of surgical drill enhancing the accuracy of drilling trajectory while reducing the risk of screw misplacement. Such issues may be further overcome by providing the operator with the awareness of the exact location and deepness of the drill tip in real time. In fact, most robot-assisted technologies mainly support the surgeon based on preoperative or intraoperative imaging to guide pedicle screw insertion along a predefined route, without taking into consideration the local characteristics of the bone, which may significantly affect the final outcome. For this reason, a drilling tool embedded

with force and position sensors has been designed and a parameter (named AI) for the evaluation of the bone tissue mechanical properties has been defined. In general, bone electrical impedance is determined by the net result of the ionic intra- and extracellular interactions occurring within the tissue and is hence directly correlated with bone composition. Indeed, past studies have demonstrated that bone impedance is able to predict trabecular bone BMD and strength (21).

In our study, the end-effector of the surgical platform has been used to perform manual drillings in which the operator advances the drill along a predefined path pushing on a knob linked with a load cell. Based on the variation of AI on a moving position window, an algorithm has been proposed to identify the different bone layers encountered during the drilling. It has been possible to conclude that this analysis on the data of thrust force and feed rate can be useful to provide supportive information to the surgeon during manual drillings. In order to verify if AI measured along the drilling route (here defined as PAI) was able to correctly predict the transition between vertebral bone layers, BMD at the pedicle cortical bone, pedicle cancellous bone and vertebral cancellous bone were estimated by calculating HU in specific ROI at post-procedural CT. Subsequently, PAI and HU were indirectly compared using Δ_{HU} and Δ_{PAI} , which proved to be concordant and similar in every transition considered.

This pilot study has several limitations that must be considered. Firstly, human cadaveric vertebral segments used presented with osteoporotic bone tissue which, even considering the distinct pattern of PAI along the drilled layers, may have influenced our measurements. Secondly, we have excluded 2 perforations due to local bone collapse and tunnel misplacement. Lastly, the small number of perforations could be a limit of this study, therefore it is necessary to perform further studies to increase the statistical significance.

A novel smart bone impedance-guided drilling system to guide pedicle screw placement has been tested. The system has proved useful to correctly position the screws along a planned trajectory while implementing a breakthrough detection method

using vertebral bone impedance. Calculated average impedance along the drilled tunnel has shown to closely correlate with bone mineral density, thus resulting predictive of the drill tip location. Furthermore, it may provide the surgeon with further information about the state of bone health which, if poor, may even compromise the surgical outcome.

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The limits and potentials of presepsin in orthopaedic surgery: state of the art and future directions

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Presepsin, i.e. the soluble cluster of differentiation 14-SubType (sCD14-ST), is an emerging biomarker for the diagnosis and evaluation of sepsis and infection. In 2004, Yaegashi et al. originally described presepsin as a potential biomarker; since then, several studies have investigated the role of presepsin in different infectious conditions, including neonatal sepsis, severe acute pancreatitis, infections in patients with haematological malignancies, severe community-acquired pneumonia, pacemaker and implantable cardioverter-defibrillator (ICD) pocket infections, surgical site infections (SSIs) and periprosthetic joint infections (PJIs). Moreover, presepsin has been also studied in the risk stratification in cardiac surgery patients, and as a biomarker in the perioperative management of patients undergoing total hip arthroplasty (THA) or total knee arthroplasty (TKA). This review aims to summarize the current knowledge about presepsin, focusing on the limits and potentials that the use of this biomarker could have in daily clinical practice. Presepsin is could be useful in daily clinical practice in orthopaedic surgery in the diagnosis and prevention of SSIs and PJIs. It is a cost-effective biomarker, but to improve its accuracy, it is important to carefully recalculate presepsin circulating values in patients with chronic kidney disease. However, further studies with larger patients' samples are needed to better validate the use of this biomarker in orthopaedics. In the future, synovial fluid presepsin might be a useful biomarker in the diagnosis of septic arthritis and PJIs.

Presepsin, i.e. the soluble cluster of differentiation 14-SubType (sCD14-ST), is an emerging biomarker for the diagnosis and evaluation of sepsis, originally described by Yaegashi et al. in 2004, (1). Two different forms of the cluster of differentiation 14 (CD14) have been characterized: a membrane-bound CD14 (mCD14) and a soluble CD14 (sCD14) (1, 2).

mCD14 is mainly expressed on cellular membranes of monocytes, macrophages and neutrophils, where it acts as a high-affinity receptor for the lipopolysaccharide-binding protein complex (LPS-LBP)(2, 3). It can also bind to peptidoglycan

and other surface molecules, expressed in both Gram-negative and Gram-positive bacteria, thus triggering the acquired immune response (3, 4).

sCD14, on the other hand, enhances the immune and inflammatory responses, by mediating the activation of CD14-negative cells, namely epithelial and endothelial cells, in the presence of microbes (1). sCD14 is then cleaved in smaller fragments by plasma proteases; presepsin is a specific N-terminal 13 kDa glycoprotein fragment of CD14 (1-4).

Since 2004, several studies have investigated the role of presepsin in the diagnosis of systemic

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inflammatory response syndrome (SIRS), sepsis and neonatal sepsis (5). Currently, it is reported that if presepsin concentration is lower than 300 pg/mL, there is no risk of systemic infection, whereas a value of presepsin higher than 530 pg/mL may suggest a septic state (5).

In recent years, however, other papers have evaluated the role of presepsin in the prognosis of severe acute pancreatitis (6), in detecting infections in patients with haematological malignancies (7), in the risk stratification and diagnosis of severe community-acquired pneumonia (8), in the risk stratification in cardiac surgery patients (9) and in the diagnosis of pacemaker and implantable cardioverter-defibrillator (ICD) pocket infections (10).

In the field of orthopaedic surgery (11, 12), presepsin could be helpful in the perioperative evaluation of patients undergoing total hip replacement (THA) or total knee replacement (TKA) (13), in the diagnosis and management of patients with periprosthetic joint infections (PJIs) (14) and in the prevention and management of Surgical Site Infections (SSIs) in patients undergoing spinal surgery (15).

This review aims to summarize the current knowledge about presepsin, focusing on the limits and potentials that the use of this biomarker could have in daily clinical practice.

Presepsin and sepsis

Sepsis is a life-threatening condition that accounts for about 25% of intensive care unit (ICU) admissions, with a mortality rate that could reach 52% (3, 5, 16, 17). Consequently, the search for a biomarker that could be used in sepsis prediction and management is gaining an increasing importance.

Zhu et al. in a recent meta-analysis including 9 studies and 1,561 patients reported that the receiver operating characteristic curve (AUROC) of presepsin was 0.77 (95% CI, 0.73–0.81) with a pooled prognostic sensitivity (SEN) and specificity (SPE) of 0.83 (95% CI, 0.72–0.90) and 0.69 (95% CI, 0.63–0.74), respectively (18). These authors, moreover, observed no statistically significant difference in the performance of pooled SEN and SPE between presepsin and procalcitonin PCT,

therefore they concluded that both presepsin and PCT are promising biomarkers for the prognosis of mortality in sepsis (18).

Yoon et al. on the other hand, have performed a meta-analysis aiming to assess the overall diagnostic accuracy of presepsin in paediatric sepsis (19). These authors included, in the final analysis, 4 studies and 308 patients aged between 1 month and 18 years. The pooled diagnostic sensitivity and specificity of presepsin were 0.94 (and 0.71, respectively). The pooled sensitivity of presepsin resulted higher than that of C-Reactive Protein (CRP) and procalcitonin (PCT), whereas the overall specificity of presepsin was lower than that of CRP and PCT (19). Based on these findings, these authors concluded that presepsin has higher sensitivity and diagnostic accuracy, but lower specificity, than PCT or CRP in detecting sepsis in children.

Presepsin in orthopaedic surgery

SSIs and PJIs are two dreadful complications in orthopaedics surgery, since they may significantly impact on the postoperative patient's quality of life (20). Consequently, in recent years there is an increasing interest in the prevention of these complications and some studies have focused on the potential role of presepsin in this field (20).

In a recent preliminary prospective study from our Institution, Vicenti et al. assessed the normal perioperative plasmatic levels of presepsin, in 117 patients undergoing primary cementless THA or primary cemented TKA, for primary osteoarthritis of the hip or of the knee respectively (13). Presepsin was found to increase until 72 hours postoperatively, when it reaches its maximum, and starts decreasing at 96 hours after surgery (13). Moreover, presepsin revealed more accurate than CRP in the assessment of post-operative inflammation (13). Based on these data, the authors suggested assessing routinely the plasmatic presepsin concentration in patients undergoing at three different moments: at 24 hours before surgery, at 72 hours postoperatively and at 96 hours postoperatively, when a decrease of presepsin levels should be found (13).

Presepsin has also shown interesting results in the evaluation of PJIs. Marazzi et al., in a prospective

multicentre study on 100 patients undergoing TJR for PJI or septic loosening, observed that presepsin levels in PJI were higher than in aseptic loosening (14). Presepsin showed, in this study, a linear correlation with CRP and IL-6 levels, thus confirming that presepsin increases because of the inflammatory process in response to infection (14). Furthermore, in patients with PJI, presepsin significantly lowered at 48 hours postoperatively and reached values comparable to control patients at one month postoperatively.

Moreover, Imagama et al. have recently evaluated presepsin and PCT levels in synovial fluid and blood in 18 patients with septic arthritis (SA), compared with 28 patients affected by osteoarthritis (OA), to determine whether presepsin would be useful in the diagnosis of SA (21).

These authors observed that synovial fluid and blood presepsin and blood PCT were all significantly higher in the SA group, compared with the OA group. Synovial fluid presepsin exhibited both 100% sensitivity and 100% specificity in the SA group, which were higher rates than those for blood presepsin and PCT (21). Thus, Imagama et al. concluded that synovial fluid presepsin could be a new biomarker of septic arthritis (21).

The role of presepsin in SSIs has been recently investigated by Koakutsu et al., in a prospective observational study evaluating 118 patients undergoing elective spine surgery (15). In this study, presepsin levels were assessed immediately after surgery, on postoperative day one and one week after surgery (15). Three patients out of 118 developed an SSI; in these patients, higher levels (i.e. >300 pg/mL) were observed one week after surgery (15).

In the remaining 115 patients, the presepsin values recorded immediately after surgery and at 24-hours after surgery were significantly higher compared with the preoperative levels. Presepsin values returned to the preoperative level one week after surgery. On postop-operative day 7, the estimated reference value for 95 percentile in patients without SSIs was 297 pg/mL. These authors concluded the presepsin value of 300 pg/mL on postoperative day 7 might be used as a novel indicator for suspected SSI in spinal surgery (15).

Further studies, however, are still needed to

better depict the limits and potential of presepsin in orthopaedic surgery.

Cost analysis and potential limits

Amastha et al. have recently determined the incremental rate of cost-effectiveness of presepsin compared CRP and PCT in detecting severe bacterial infection (SBI) in children aged 29 days to 36 months (22).

The economic analysis of cost-effectiveness, structured using the technique of decision analysis, showed the three different strategies had similar cost-effectiveness for a correctly diagnosed patient with SBI. However, presepsin was the most cost-effective strategy for the pretest probability scenarios between 30% - 90%, ranging from \$911 to \$2685 per diagnosed patient (22).

Moreover, Ulla et al reported similar data in a prospective study recruiting 106 patients presenting to the Emergency, concluding that presepsin is a cost-effective biomarker, able to distinguish septic patients (16).

Presepsin, however, has a potential limit: its concentrations are positively correlated with a few biomarkers of renal function (23). Therefore, it is necessary to consider the effect of renal function on presepsin levels, in patients with renal impairment (23). In these types of patients, the recalculated reference range for presepsin considering kidney function should be used to improve the accuracy of this biomarkers.

Conclusions and future developments

Presepsin is an emerging biomarker that could be useful in daily clinical practice in orthopaedic surgery. It is cost-effective but it should be noted that its circulating values should be carefully recalculated in patients with chronic kidney disease.

Further studies with larger patient samples are needed to better validate the use of this biomarker in orthopaedics. In the future, synovial fluid presepsin might be a useful biomarker in the diagnosis of septic arthritis and PJIs.

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Bridging the gap between serum biomarkers and biomechanical tests in musculoskeletal ageing

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Musculoskeletal ageing is a major public health interesting and strain due to the significant demographic modifications in the population, and it is linked to high risk of falls, loss of autonomy in elderly individuals and institutionalization with small health outcomes. Thus, this pathological status is related to high morbidity and health care rates. Bone mass and muscle mass and strength increase during late adolescence and early adulthood but start to reduce noticeably from the fifth decade of life and are closely linked. Preclinical and clinical data strongly support the muscle-bone cross-talk showing the presence of many tissue-specific factors released by the muscle that modulate bone, such as insulin-like growth factor-1 (IGF-1), IL-6, IL-15, myostatin and irisin. Bone and muscle tissues were increasingly recognized as endocrine target organs and endocrine organs themselves, interacting through paracrine and endocrine signals. It is then plausible that laboratory parameters could be involved in sarcopenia and osteoporosis diagnosis and treatment monitoring. This narrative review raises the possibility of whether this poor correlation between different muscle/lean mass assessment methods and muscle function tests could suggest that each parameter evaluates different aspects of “muscle status” or “muscle quality”. If this is true, no one test can be used to assess muscle status but rather a battery of tests is necessary for a comprehensive assessment. More research is required to provide information for researchers to optimally design studies by using the muscle assessment method that is best associated with selected specific outcomes.

Musculoskeletal ageing is a major public health interest and is strain typical of the demographic changes in the population. It is associated with a high risk of falls, loss of autonomy in elderly people and institutionalizations with small health outcomes. This condition is therefore correlated with high morbidity and health care rates (4). Indeed, the world population is ageing and, worldwide, individuals over 60 are estimated to increase from 841 million in 2013 to more than 2 billion by 2050, with a

proportional gain from 11 to 22%. However, often the increase in life expectancy is not an increase in “healthy life” expectancy, and these additional years are loaded with scarce health and disability (28). Musculoskeletal ageing has many causes, including age-related changes in body composition, inflammation, and hormonal imbalance. Sarcopenia and osteoporosis share these common denominators and are often associated with each other and with the frailty syndrome. A recent work from Greco et al. (36)

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analysed reciprocal pathophysiologic relationships between sarcopenia and osteoporosis and frailty syndrome (34). They concluded that altered cellular and molecular signals and functions leading to sarcopenia, osteoporosis, and inflammation seem to be linked in a circle manner and probably represent the common denominator favouring frailty and unhealthy ageing.

Sarcopenia is one of the most remarkable geriatric syndromes in recent years due to cause of functional decline, increased morbidity and mortality, as well as increased health costs (24, 40). Sarcopenia has been defined as a progressive and generalised skeletal muscle disorder involving the accelerated loss of muscle mass and function (27). It was first described in the 1980s as an age-related decline in lean body mass affecting mobility, nutritional status, and independence (66). The definition has since evolved (3), (25), until a recent consensus paper by the European Working Group on Sarcopenia in Older People (EWGSOP) (26). The EWGSOP2 updated the original definition focusing on low muscle strength as a key characteristic of sarcopenia, using detection of low muscle quantity and quality to confirm the sarcopenia diagnosis, and identifying poor physical performance as indicative of severe sarcopenia (26).

The decrease in muscle mass and strength negatively affect bone mass, which also declines during ageing, causing osteopenia and osteoporosis. Several pieces of evidence suggest that osteoporosis and sarcopenia present common pathophysiological factors and show the correlation between low bone mineral density and sarcopenia in both men and women (22, 46). Osteoporosis is a systemic skeletal disease characterized by a reduction in bone mass and qualitative skeletal changes (macro- and microarchitecture, material properties, geometry, and micro-damage) that cause an increase in bone fragility and higher fracture risk. Diagnosis of osteoporosis and assessment of fragility fracture risks rely on case history, physical examination, laboratory, and diagnostic tests, mostly based on X-ray bone densitometry (DXA) (60).

Preclinical and clinical data strongly support the muscle-bone cross-talk showing the presence of many tissue-specific factors released by the muscle that

modulate bone, such as insulin-like growth factor-1 (IGF-1), IL-6, IL-15, myostatin and irisin (22, 46, 70). Bone and muscle tissues were increasingly recognized as endocrine target organs and endocrine organs themselves, interacting through paracrine and endocrine signals (55,70). It is then plausible that laboratory parameters could be involved in sarcopenia and osteoporosis diagnosis and treatment monitoring. Multiple candidate markers have been proposed including serum myostatin, skeletal troponin T, IGF-1, sclerostin and irisin as they correlate with muscle mass and function in some studies (2, 13, 16, 22, 50, 70). Thus, assessment of potential serum markers for correlation with muscle mass, function, and outcomes is indicated.

Recently, the MRC-Arthritis Research UK Centre for Integrated research into Musculoskeletal Ageing (CIMA) provided an integrated assessment of musculoskeletal function under four headings: biochemical measurements in biofluids or tissue samples, in vivo measurements of body composition, imaging of structural and physical properties, and functional tests. The results of their report suggested as biochemical markers two well-established serum markers of bone turnover and as functional assessments the Short Physical Performance Battery (SPPB) or the Locomotion domain of NIH Toolbox (42). Even though they provided biological basis, and strengths and limitations for common biomarkers for assessing and monitoring musculoskeletal ageing, no relationship among the different systems have been provided.

With this evidence, the objective of this narrative review was to identify and discuss mobility and serum biomarkers that enable the assessment of muscle-bone interactions in ageing adults.

MATERIALS AND METHODS

The first step consisted of a scoping literature search done by two reviewers, IB and DB, using PubMed database to select an initial pool of potentially relevant tests, originally designed to measure either mobility or serum biomarkers in musculoskeletal ageing (sarcopenia or osteoporosis), but that had been shown to be associated which bidirectional changes in both domains.

The second step consisted of revising the literature review to candidate tests based on whether they showed associations with both mobility outcomes and serum level changing, including progression to mobility decline, fracture risk and/or falls and to identify pre-specified criteria to select a final list of core-tests. The list of prespecified criteria identified by the group to aid in the selection of tests is listed in Table I.

Search strategy using PubMed database included the following terms: ((sarcopenia[MeSH Terms] OR “sarcopenia”[All Fields]) OR (osteoporosis[MeSH Terms] OR “osteoporosis”[All Fields])) AND (“weights and measures”[MeSH Terms] OR (weights[All Fields] AND measures[All Fields]) OR “weights and measures”[All Fields] OR measures[All Fields] OR levels[All Fields]) AND ((gait[MeSH Terms] OR “gait”[All Fields] OR balance[All Fields]) AND (marker[MeSH Terms] OR marker[All Fields] OR serum[All Fields])) AND (aged[MeSH Terms] OR aged[All Fields]).

RESULTS

Serum biomarkers in musculoskeletal ageing

Musculoskeletal ageing is a complex process mainly characterized by metabolic and immunological changes, increased inflammatory status and oxidative stress, bone mass reduction, muscular functional

impairment and neurodegeneration (67, 73, 74). As a result of this, several serum biomarkers changes could be depicted, but most of them are not specific for musculoskeletal ageing (67).

Circulating levels of IL-6, Tumor Necrosis Factor-alpha (TNF- α) and C-Reactive Protein (CRP) have been largely employed in clinical trials as potential biomarkers of musculoskeletal ageing (63). However, it should be noted that their usefulness in clinical practice is very limited since these inflammatory markers are as specific as their levels (32).

IGF-1, mainly produced in the liver, plays a central role in musculoskeletal development and in the crosstalk between bone and muscle (9). IGF-1, moreover, can directly enhance muscle mass and bone density: exogenous IGF-1 promotes the growth of longitudinal femoral, whereas IGF-1 receptor deletion hurts growth plate and in the process of the formation of secondary ossification centre (9,75). Sclerostin, a small protein expressed by the SOST gene in osteocytes, is an important negative regulator of bone formation. Sclerostin seems to act a mechanosensor able to detect skeletal loading and unloading, to regulate the bone remodelling cycle (48). It is reported that high sclerostin levels are a strong and independent risk factor for osteoporosis-

Table I. Prespecified criteria to select measures and assessment tools.

Criteria	Description
1	Sensitive to changes in mobility performance
2	No ceiling or floor effects
3	Previously validated in research studies
4	Applicable in both, research and clinics
5	Sensitive to interventions including exercises and treatment
6	Feasibility: Inexpensive, easy to perform, and minimal expertise required

Table II. *Mobility tests appraised to evaluate motor function and abilities in aging.*

Measure	Prespecified Criteria Fulfilled	Advantages	Key Limitations
SPPB	Criteria: 1, 3–6	Good composite measure	Ceiling effect
GS	Criteria: 1–6	Validated Easy to perform Robust predictors of motor decline and health outcomes	
STS	Criteria: 1, 3–6	Easy to perform Sensitive to mobility decline	Ceiling effect
TUG	Criteria: 1, 3–6	Provides info about rising, turning and transferring	Floor effect Difficult to separate components for biological studies
HGS	Criteria: 1–5		Requires instrumented methods
LSM	Criteria: 1–5		Requires instrumented methods
JM	Criteria: 1–5		Requires instrumented methods

related fractures among postmenopausal women (5).

Irisin is a circulating hormone-like myokine, whose serum levels are increased by physical activity (22). Although irisin is produced in skeletal muscle, one of its main functions is to affect bone metabolism. Mice treated with a micro-dose of Irisin have displayed improved cortical bone mass, geometry and strength, resembling the effect of physical activity in developing an efficient load-bearing skeleton (21). In clinical trials, serum irisin levels have shown a positive correlation with bone mineral density (BMD) in soccer players (23), whereas an inverse correlation between irisin levels and vertebral fragility fractures has been reported in older patients (62).

Leptin is a vertebrate-specific hormone, mainly produced by adipocytes and small intestine enterocytes. It is implicated in several physiological processes, including energy expenditure regulation, appetite and bone mass. Leptin can act on bone with both direct and indirect mechanisms (71). Regarding direct mechanisms it is important to remark that bone

marrow adipocytes secrete leptin; leptin receptors could be found in osteoblasts and chondrocytes; leptin impacts on osteocalcin metabolism and it can regulate bone growth by regulating Fibroblast Growth Factor-23 (FGF-23) levels. Indirect mechanisms imply brainstem and serotonergic signalling, by modulating the circulating levels of IGF-1, cortisol, oestrogens and parathyroid hormone (71).

Functional assessment in musculoskeletal ageing

Mobility tests that underlie areas such as gait performance, balance, lower limb function and muscle strength were considered (Table II) based on the resulting analysis showing consistent associations with musculoskeletal ageing.

After restricting the search to last 10 years, 72 unique titles remained, 37 were selected by title, and 35 abstracts of relevant articles were screened. Twenty-one articles in full texts were then studied to identify potentially relevant tests analyzing the relationship between serum biomarkers and physical assessment (Table III).

Table III. Summary of studies included in the analysis with indication of type, cohort, sample number, sex (prevalence), age, measurements related to both domains, outcomes and main findings (only significative *p*-value < 0.05).

Reference	Study Type	Study Cohort	Sample Number	Sex	Age [yo]	Measure	Outcome	Findings (95% CI)
Landi (44)	Longitudinal Clinical-based	iSIRENTE	357	66.9% F	≥ 80	Alb CRP GS SPPB HGS 5STS	MAMC	Mean _{OC} = 0.44(0.02) Mean _{SPPB} = 6.94(0.34) Mean _{HGS} = 31.56(1.24)
Bleicher (10)	Longitudinal Population-based	CHAMP	1122	M	79-97	25(OH)D HGS GS 5STS PSw	BMD	beta _{25(OH)D} = -0.28(-0.55,0.0)
Hwang (38)	Cross-sectional Population-based	I-LAN	532	47% F	≥ 50	ASM HGS GS	FAI FreeT bioT DHEA-S	Mean _{HGS} = 32.0(12.1) - 1.8(1.8) Mean _{HGS} = 7.2(2.3) Mean _{HGS} = 173.5(56.6) Mean _{OC} = 108.5(56.0)-62.6(43.2) Mean _{HGS} = 106.4(70.8)- 61.9(40.8)
Felicio (31)	Cross-sectional Population-based		221	F	≥ 65	GS HGS LMS	IL-6 sTNFR1	ILMS = 0.14 - 0.16
Silva (68)	Cross-sectional Population-based	FIBRA	255	67.8% F	≥ 65	IL-6 CRP	Frailty GS HGS	OR _{CRP} = 3.64(1.060-12.540) OR _{CRP} = 3.306(1.486-7.354)
Gielen (35)	Longitudinal Population-based	EMAS	518	M	40-79	bioT IGF-1 25(OH)D PTH	aLM GS HGS	beta _{IGF-1} = 0.773 (0.126, 1.419)
Meng (54)	Cross-sectional Population-based		1131	52.6% F	≥ 60	GS HGS TUG	CRP IGF-1 DHEA-S	OR _{GS} = 2.84(1.33, 6.33) OR _{TUG} = 2.7(1.34, 5.66) beta _{HGS} = 3.48 - 2.01
Brech (12)	Cross-sectional Clinical-based		63	F	≥ 55	TUG LMS PSw	25(OH)D	beta _{TUG} = -0.07 beta _{LMS} = 0.59
Can (17)	Cross-sectional Clinical-based		72	62.5% F	≥ 65	Sarcopenia (MAMC + HGS. GS)	CRP ESR	OR _{ESR} = 1.156(1.057,1.263)
Landi (43)	Longitudinal Clinical-based	iSIRENTE	332	67.8% F	≥ 80	Sarcopenia (MAMC + HGS. GS) CRP IL-6	CAF	Mean _{CAF} = 91.63 ± 4.31
Wu (78)	Cross-sectional Population-based		344	F	37-55	BMD TUG LMS	25(OH)D	beta _{TUG} = -0.10(-0.16, -0.04) beta _{LMS} = 2.64(0.74, 4.55)
Bulut (6)	Cross-sectional Population-based		403	66.5% F	≥ 65	HGS TUG	Sarcopenia (SMI + HGS, GS)	

F: Female; **M:** Male; **yo:** years old; **MAMC:** Mid arm muscle circumference; **Alb:** Albumin; **OC:** osteocalcin; **ESR:** erythrocyte sedimentation rate; **WBC:** white blood cell count; **PTH:** parathyroid hormone; **25(OH)D:** 25-hydroxylated vitamin D; **B12:** vitamin B12; **CRP:** C-Reactive Protein; **IGF-1:** insulin-like growth factor 1; **sTNFR1:** soluble receptor for tumor necrosis factor- α ; **TNF- α :** Tumor Necrosis Factor- α ; **IL-6:** Interleukine-6; **IL-6R:** interleukin-6 receptor; **IL-10:** Interleukine-10; **TRACP-5b:** tartrate-resistant acid phosphatase-5b; **FreeT:** Free Testosterone, **bioT:** bioactive testosterone; **FAI:** Free androgen index; **DHEA-S:** DeHydroEpiAndrosterone Sulfate; **DXA:** dual-energy X-ray absorptiometry; **TBLH:** total body less head, **BIS:** bioelectrical impedance spectroscopy; **ICW:** intracellular water; **D3-Cr:** creatine (methyl-d3) dilution; **ALM:** Appendicular lean mass; **ht2:** height squared.

DISCUSSION

Seven performance-based clinical tests used to measure gait, balance and/or muscle strength in the elderly population have been identified as reported in Table 3. The HGS (17 articles) and GS (18 articles) were the most used balance tests in our sample. Different variations of STS (e.g. 5STS, 30-sSTS) were most often used to assess muscle strength (6 articles), with the 5STS as the most used test.

Six studies made use of a combination of HGS and GS for assessment of Sarcopenia (according to EWGSOP2) (26) and Frailty (according to Fried et al.) (34) and investigated the relationship between serum biomarkers and overall syndrome. Silva et al. (68) suggest that reduced Hb concentration, reduced Ret Abs count and elevated serum CRP levels should be considered components of frailty, which in turn is correlated with sarcopenia, as evidenced by weight loss. Can et al. (17) demonstrate an association of sarcopenia with inflammatory markers CRP, ESR and adiponectin. Landi et al. (43) showed that elevated serum CAF levels are associated with sarcopenia, independent of age, gender and several clinical, functional, anthropometric, and biochemical variables. The determination of serum CAF concentration may, therefore, be proposed as a simple screening test for sarcopenia in the community. Lustosa et al (53) compared the performance of the knee extensors test (by isokinetic dynamometer) and plasma levels of interleukin-6 (IL-6) and soluble receptors of tumor necrosis factor- α (sTNFR1) between sarcopenic and non-sarcopenic community-dwelling elderly women.

They observed that sarcopenic elder women showed the worse performance of the lower limbs, especially at a higher speed, predisposing these older women to greater vulnerability in functional activities that require agility and postural stability. Plasma levels of sTNFR1 were higher for non-sarcopenic elderlies.

Finally, Suriyaarachchi et al. (33) assessed the potential role of high serum levels of parathyroid hormone (PTH) in osteosarcopenia. Subjects with high PTH levels were more likely to be in the osteosarcopenia group than in the non-

sarcopenic/non-osteopenic group (OR 6.88; CI: 1.9–9.2) thus suggesting an important role of PTH in osteosarcopenia.

The Short Physical Performance Battery (SPPB)

The SPPB is a 15-minute objective assessment tool for evaluating lower extremity functioning in older people (37). It includes repeated chair stands, balance tests and a 2.44-m or 4-m walk. It is widely used and validated, simple to administer, and is considered a good composite measure of mobility. The SPPB score was demonstrated to be the strongest predictor of overall mortality in these very old community-dwelling subjects, even after considering several socio-demographic, clinical, and biological confounders (19). Findings from Landi et al. (44) showed that SPPB was directly associated with Midarm muscle circumference (MAMC), although the association between muscle mass and physical performance is controversial.

Gait speed (usual and fast pace)

Gait speed is expressed as distance/time and is assessed by timing individuals while they walk a measured distance, which has been tested in the literature in the range of 2.4-8 m (1). Some studies have used longer distances (e.g., 20 m), which are required to assess steady-state walking, but shorter distances are more practical in some contexts (eg, clinical). Slow gait speed predicts future fall risk, fracture (52) and low physical performance (49, 51, 72). Gait speed is easy to measure, very sensitive to motor changes, and responsive to interventions. Gait speed measure protocols, normative values, and cut-offs are available, but they are population dependent (18, 57). Gait speed presents ceilings effect only when used in high functioning individuals and it is influenced by non-central nervous system (CNS) factors, including cardiorespiratory diseases. From our analysis, GS decrease has been found related to a decreased MAMC (44).

We also found an association between serum biomarker levels (CRP, IGF-1, DHEA-S and IL-6) and low gait speed in both genders (35, 38, 45, 54). Conversely, low levels of T and 25(OH) D did not

predict loss of GS in Gielen et al. (35). Finally, the erythrocyte sedimentation rate was associated with all three measures of sarcopenia, underpinning the potential role of inflammation in sarcopenia (7).

Sit-To-Stand (STS)

This test includes five consecutive sit-to-stand movements done as fast as possible, without using arms as leverage. Some studies differ in the number of repetitions required (1STS, 30STS) or in the maximum time required to perform the test (30-seconds STS). The STS test assesses the function and strength of the lower limbs (11). It is sensitive to mobility decline (14), although it has a ceiling effect. Instrumented implementation of STS with wearable inertial sensor and surface electromyography (sEMG) may overcome these limitations (41, 56) and provide additional information concerning muscle fatigue development (64), lower leg strength (39) and fall risks (20). Only two studies reported a significant association between worse physical performance in terms of STS and ESR and IL-6R level (7, 45).

Timed Up and Go (TUG)

For this test, individuals are instructed to rise from a seated position, walk 3 m at their usual pace, turn around and return to the seated position. It is validated and reliable, sensitive to mobility impairments, and can provide information about rising, turning and transferring, everyday tasks important for the maintenance of mobility. Limitations of the TUG include the presence of a floor effect and the difficulty in separating gait components from the overall measure since the TUG is a composite measure. Instrumented implementations of the TUG (iTUG) can address many of these limitations (76, 77). All the TUG performed in the included studies were not instrumental.

Four studies reported a significant relationship among the performance-clinical test and serum biomarkers [ESR (7), 25(OH)D (12, 78) and IGF-1 (54)]. In particular, Wu et al. found that in middle-aged women there are thresholds for associations between serum 25OHD concentrations and bone density and most balance measures, suggesting

that 25(OH)D levels of at least 29 to 33 nmol/L are required for optimal musculoskeletal health in this population (78).

Hand-Grip Strength (HGS)

Handgrip strength shows good correlations with lean body mass and the SMI, and with leg strength in frail older people. It is advisable to measure handgrip in both arms, since significant differences between the dominant and the non-dominant side have been observed for handgrip strength, in both sexes, but not for lower limb strength (30). The shoulder was adducted and neutrally rotated with the elbow at 90° flexion and the forearm and wrist resting on the chair arms. Handgrip strength was assessed with three trials on each hand, alternating between each hand, with a rest of 30 s between tests. The highest value was recorded and used for analysis. Almost half of the study reported in this review found a significant association between HGS and several serum biomarkers (10/21).

Two studies reported an association with muscle mass [MAMC (44), DXA-TBLH, BIS-ICW, D3-C (16)], showing how a decrease in muscle strength was positively related to a decrease in muscle mass. Ohlsson et al. (61) explored the association between skeletal muscle mass and muscle function by three different measures of bioactive testosterone (FreeT, bioT, FAI) as well as DHEA-S. The last one was positively associated with muscle mass in men and older women and muscle strength in both sexes. Similar results were obtained from Hwang et al. (38) concerning fall risks in elderly men.

No significant relationship between log-transformed IGF-1 or DHEA-S and muscle strength in either males or females emerged from Meng et al. (54), while muscle strength distinctly showed a significant relationship with log-transformed CRP in male but not in females after additionally adjusting for age. It is difficult to explain the sex-specific association between CRP, muscle strength and physical performance. Gender difference may be related to the tendency of healthier lifestyles in females than males. Moriwaki et al. (58), observed a correlation among serum bone and muscle-derived factors with parameters of physical functions (Sclerostin, OC and IGF-1), however, no observable

obvious relationship between those factors and muscle parameters emerged.

Bulut et al. (6), found that vitamin B12 deficiency seems to be related to lower muscle mass and strength in older adults than sarcopenia in older adults, and both cases might be related to vitamin B12 deficiency. Besides, Dhaliwal et al. (29), indicated a positive relationship of free 25(OH)D with both gait speed and grip strength in older African-American women during a randomized, double-blind, placebo-controlled 3-year trial examining the effect of vitamin D on bone loss and physical performance. Finally, low physical performance has found to be related to ESR and Albumin level in van Atteveld et al. (7).

Lower limb Muscle Strength (LMS)

Lower limb muscle strength (LMS) is assessed using isokinetic dynamometer (8, 59). After a standardized warm-up, the subjects are positioned for the concentric evaluation of extension and flexion movements of the knee joint. The subject remains seated, with the hips at 90° of flexion, and secures to the chair with belts. The test starts with the dominant limb. The limb is evaluated by aligning the lateral condyle of the femur with the mechanical axis of the dynamometer.

After four submaximal repetitions to familiarize with the equipment followed by a 60-second rest interval, two series of five maximal repetitions of knee extension and flexion are performed, starting with the dominant limb, with 60-second intervals between the series. The isokinetic variables are the maximum peak torque, which is corrected for body weight (PTQ/BW) and total work.

Felicio et al. (31) found that plasma levels of IL-6 (0.87 pg/mL) correlated with the power of the knee extensors ($r = 0.14$; $p = 0.03$) and the power of the knee flexors ($r = 0.16$; $p = 0.01$); however, no negative correlation between inflammatory mediators and muscle or physical performance in elderly women, thus suggesting that the cytokine levels did not reach the threshold needed to influence the muscle tissue and functionality of the participants. Brech et al. (12) and Wu et al. (78) investigated the association of serum vitamin D [25(OH)D] and different physical performance in older women. Results showed that

the serum vitamin D levels were independently associated with normalized knee extension strength and functional mobility and depend on cut-points.

Jump Mechanography (JM)

The test consisted of two-leg countermovement jumps on a force platform (15). The jump achieving the greatest height from a sequence of three was used for analysis. Maximal jump height (m), relative power (W/kg), and velocity (m/s) were calculated. The data demonstrate that JM is a highly reproducible and stable functional test over time. JM reproducibility is similar to grip strength. Buehring et al. (16) showed that functional tests assessing maximal muscle strength/power (grip strength and jump power) correlated with all mass measures (DXA-TBLH, BIS-ICW, D3-C) highlighting the necessity for efforts to optimize muscle mass assessment and identify their relationships with health outcomes.

World population is ageing and the increase in life expectancy is often unhealthy. Musculoskeletal ageing, that leads to sarcopenia and osteoporosis, has several causes such as changes in body composition, inflammation, and hormonal imbalance. Sarcopenia, osteoporosis, and more frequently, sarcopenic obesity is commonly associated with ageing and frequently closely linked each other (36).

Since debilitating age-related disorders of the musculoskeletal system have major adverse effects on the independence and quality of life of older individuals which, by limiting physical activity, amplify age-related risks of multiple cardio-metabolic diseases, major cancers and neurodegenerative diseases (47), this underscores the imperative to assess and maintain good musculoskeletal function during ageing (42).

Furthermore, the complexity and heterogeneity of these syndromes require a multidimensional clinical approach based on healthy nutrition, psychosocial wellbeing, regular physical exercise, and pharmacological measures, which seem to prevent and control chronic diseases affecting both life expectancy and quality of life, thereby reducing mortality.

This narrative review raises the possibility of whether this poor correlation between different muscle/lean mass assessment methods and muscle

function tests could suggest that each parameter evaluates different aspects of “muscle status” or “muscle quality”, as previously noticed (16). If this is true, there is no one test that can be used to assess muscle status but rather a battery of tests is necessary for a comprehensive assessment. More research is required to provide information for researchers to optimally design studies by using the muscle assessment method that is best associated with selected specific outcomes.

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Innovations in prevention of infections in oncological megaprotheses: a narrative review

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Infection is a significant complication in oncological megaprotheses. The purpose of our study is to indagate the innovations and new trend about the prevention of infection in this kind of surgery. The research focused on the use of antimicrobial prophylaxis, the defensive antibacterial coating and the use of silver coated.

Infection is a significant cause of failure of primary total knee and hip replacements. Currently, the golden standard for treating prosthetic joint infections (PJIs) is two-stage revision. However, two-stage procedures have been reported to be associated with higher costs and possible higher morbidity and mortality (1). The incidence of infection varies, depending on the location of the implant and could have a heavy impact on quality of life of cancer patients (2). Periprosthetic infections occur in up to 19% of cases in proximal femur megaprosthesis and up to 11% of cases in distal femur megaprosthesis (3). The research is focusing on new methods to prevent the development of megaprotheses infections. The purpose of our study is to review the main methods implemented for this purpose.

Antibiotic Prophylaxis

It is undoubtedly possible to consult numerous international guidelines to administer adequate and effective antibiotic prophylaxis of orthopaedic procedures (WHO organization). Orthopaedic

surgeons and clinical consultants are constantly searching for an optimal prophylactic strategy for elective surgery in orthopaedic oncology.

The prophylactic schemes used between different centres and groups of authors are very different (4). This results in an antibiotic drugs overuse since it is often necessary to prolong the therapy duration, even in the absence of evidence of the efficacy of this decision (5). These behaviours lead to a cutaneous colonization of multi-resistant bacteria instead (5, 6).

Ziranu et al. claim that a single dose of cefazolin 2 g would be sufficient for antimicrobial prophylaxis. In this study, the authors divided adult orthopaedic cancer patients into two risk classes (low risk with cefazolin 2g IV single-shot 30 minutes before surgery and high risk with three doses of cefazolin 2g IV) and did not find no difference in terms of SSI (3 SSI/33 procedures vs 8 SSI/49 procedures) (5). It is evident that antimicrobial drugs cannot influence the intrinsically high incidence of multi resistant surgical site infections (SSI) much more. In fact, it is estimated that antibiotic prophylaxis itself

Key words: infection; megaprosthesis; prophylaxis; defensive antibacterial coating; silver

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can reduce the SSI load by 3-8% (7). However, it is reasonable to assume that prophylaxis should only be a minor part of the overall prevention procedure.

The partial results of these measures ignite the discussion about combination of local and systemic antimicrobial agents; the use of the large-spectrum antibiotics; one-shot prophylaxis vs prolonged antibiotic regimens. More randomized controlled studies about the kind and duration of antimicrobial therapies in megaprotheses in cancer patients will be needed to achieve a more uniform and standardised guideline.

Defensive antibacterial coating

Antibacterial coatings of implants may represent an attractive option to reduce post-surgical infections. In fact, bacterial colonization, from microbial adhesion to an established mature biofilm layer, only takes a few hours. Any antibacterial protection should act at the exact time of surgery and possibly only for a few hours or days thereafter, to minimize the risk of long-term bacterial resistance induction. Any new technology has to demonstrate safety and lack of interference with bone healing and should prove to be effective (8).

The Defensive Antibacterial Coating (DAC®, Novagenit Srl, Mezzo Lombardo, Italy) is a kit for the preparation of novel fast-resorbable bio-absorbable hydrogel containing hyaluronic acid and polylactide acid. DAC can be used for the following indications: uncemented orthopaedic prostheses, osteo-synthesis devices for traumatology, mega-protheses for oncology. This hydrogel coating is designed to undergo complete hydrolytic degradation in vivo within 48-72 hours as well as being able to completely release a variety of different antibacterials at concentrations ranging from 2-10%. The DAC shows synergistic antibacterial and antibiofilm activity with various antibiotics and antibiofilm agents in vitro, while in vivo it has been proven effective in a rabbit model of highly contaminated implant both with and without systemic prophylaxis, without interfering with bone growth.

Biodegradable polymers and sol-gel coatings have been shown to provide controlled antibiotic release on titanium or hydroxyapatite implants,

offering ease of use, versatility, and possible large-scale application (9). Thus, the application of DAC disrupts the ability of pathogens to bind to the implant surface, inhibiting the initial stages of bacterial colonisation that would then result in biofilm formation. The prefilled syringe, containing 300 mg sterile DAC powder, was filled at surgery with a solution of 5 mL sterile water for injection and the desired antibiotic. This allowed the antibiotic-loaded hydrogel with a DAC concentration of 6% (w/v) and an antibiotic concentration ranging from 20-50 mg/mL to be prepared in 3-5 minutes. The surgeons could choose the antibiotic from a list of antibacterial previously tested as being compatible with the hydrogel, including gentamicin, vancomycin, daptomycin, meropenem, rifampicin, and ciprofloxacin.

According to previous studies showing the ability of the hydrogel to resist press-fit insertion, the hydrogel can be directly spread onto the implant surface prior to its insertion into the body, a few minutes after reconstitution. DAC can be used successfully both in orthopaedics and in traumatology, as shown by a clinical trial reporting on the efficacy and safety of DAC coating for internal osteosynthesis. Concerning efficacy, this trial shows that the studied antibiotic-loaded hydrogel coating can significantly reduce early infection after osteosynthesis, at an average 18-month follow-up. To confirm this, Romanò et al. demonstrated clinical efficacy that short-term local prophylaxis with DAC (10) may reduce post-surgical septic complications after joint replacement (11).

Another recent trial shows similar infection recurrence rate after one-stage revision with DAC-coated implants, compared to two-stage revision without coating, with reduced overall hospitalization time and antibiotic treatment duration. In fact, infection recurrence rate after one-stage exchange with cement less, coated implants, compared to two-stage revision is similar (11). These antibacterial protection coatings thus represent an innovative and easy to apply solution for the prevention of bacterial adhesion to osteosynthesis and joint prostheses. However, further clinical trials will be needed to demonstrate its real effectiveness (12). In addition

to this, possible applications of antibacterial coating technologies should be tested to treat implant-related infections.

Silver-coated megaprotheses

One possible approach to minimize the risk of infection is to coat the surface of the prosthesis with an antimicrobial substance. It has been shown that silver has a biocidal effect, therefore it has been incorporated into the surfaces of numerous medical devices (13). Moreover, human toxicity is very low (3). Silver ions bind with bacterial wall protein and cause bacterial DNA precipitation together with formation of reactive oxygen species (14). These mechanisms work if the surgical site remains free from hematoma. In presence of coagulated blood the silver ions bind to albumin and local silver concentration decreases, with a decrease of antibacterial properties (15).

Due to the almost complete degradation of the coating surface, during the years there is a drastic reduction of free silver ions around prosthesis. This could explain why infection risk between silver-coated prostheses and titan ones is comparable for late infection, while the silver coating has a protective role in early infections (16); in fact the infection rate in silver-coated prosthesis was 7.9% but 16.7% in the uncoated prosthesis group (16). Similar rates of infections were found in subsequent studies, with no cases of silver toxicity (3).

A new kind of silver coating has been developed in the last 10 years (PorAg® LINK), composed by 2 layers of silver. Scoccianti et al show how no infection occurred for 2 years in a group of 12 patients with no story of previous infection who received this kind of megaprosthesis (14). The silver release in these cases remained stable from 2 weeks to 3 years after surgery, with no cases of argyria. It remains unclear if silver coating may lead to other implant complications or to more frequent soft tissue infections (16).

Piccioli et al found in their study how infections in silver megaprotheses was related in 80% of patients to a resection larger than 30 cm, prosthetic dislocation and use of Trevira Tube® (15). In a literature review Oliva et al. showed how the use of

Trevira is associated to better tissue adhesion, fastest recovery, reduced risk of dislocation and there is no significant increase of infection rates (17, 18).

Other pathogens involved in prosthetic colonization, even if rare, are represented by fungi which are related to about 1% of orthopedics metalware infections, increasing to 3 % in surgical revisions, especially in immunocompromised patients (18). In a recent in vitro study, D'Adamio et al demonstrate significantly higher antifungal effects of the silver-coated titanium group against any of the different species and strains involved (20).

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The effects of collagenase of *Clostridium Histolyticum* (CCH) in Dupuytren's disease: a histological study on cell mediated mechanisms that allow enzymatic fasciotomy

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Dupuytren Disease is a benign fibromatosis of palmar fascia of the hand, whose pathophysiology is not completely understood. The present study is intended to provide a description of the effects of Collagenase of *Clostridium Histolyticum* (CCH) into an injected cord of Dupuytren. Our experimental study wanted to evaluate the histological effects of injection of CCH in the first 24 hours, without manipulating the specimens. Materials and Methods: Surgical specimens were injected with CCH, and then fixed in formalin every six hours, up to 24 hours. Those specimens were compared to control specimen (non-injected), fixed and analyzed at the same times. Results: In the injected specimens, the number of CD68 positive cells increased into and outside the cords compared to non injected specimens, within the same time from the surgical removal. Conclusion: CCH has a proinflammatory activity and provokes a short ray chemotactic action on white blood cells. The lysis of the cord induced by CCH stimulates the inflammatory response. The role of the inflammatory infiltration deserves to be investigated in a more accurate way, preferably by using in vivo studies.

Dupuytren's disease (DD) is a benign, generally painless connective tissue disorder affecting the palmar fascia that leads to progressive hand contractures. It is characterized by excessive local proliferation of fibroblasts and over-production of collagen and other components of extracellular matrix (ECM) in the palmar fascia (1). Many studies are present in the literature but the aetiology and pathophysiology of Dupuytren's disease remain poorly understood (2, 3). Hyperplasia of myofibroblasts has been demonstrated (1, 2). The origin of myofibroblasts is not fully known (4).

One of the main molecules involved is Transforming Growth Factor- β (TGF β 1, β 2 and β 3 isoforms): it induces the metaplasia of fibroblasts into myofibroblasts and myofibroblasts differentiation

(3). Furthermore, TGF β induces protein synthesis (Extracellular Matrix, Smooth Muscle Actin Alpha, Connective Tissue Growth Factor, fibronectin and collagen) and promotes the contractile phenotype in myofibroblasts (Lysophosphatidic acid, prostaglandins PGE2 α and PGF2 α) (3, 5, 6).

Studies suggested the involvement of both T and B lymphocytes (7–9). DD is described as a T-cell-mediated autoimmune disorder (8), associated with HLA-DR (6). The finding of autoantibodies, against elastin (ELAB) and collagen types I-IV (ACA I-IV), demonstrates the B-cell autoimmune response involvement (10). The role of macrophages appears to be minimal (11).

Research around the involvement of growth factors and pro-inflammatory cytokines is very

Key words: collagenase clostridium histolyticum, dupuytren's disease, enzymatic fasciotomy, cell-mediated mechanisms, histology

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current, and is oriented towards novel targeted drugs, with a view to finding an alternative to the surgical treatment (11). Traditional surgical approach consists in limited fasciectomy and has been the most effective and widely accepted treatment of progressive contracture. Injection of bacterial derived collagenase into contracted fascial cords emerged as a potential therapeutic option in 1996 (12) after inflexible clinical trials (13, 14). CCH, released by the Food and Drug Administration in 2010, has proven to be safe and effective and continues to be studied.

CCH provokes a lysis of the cord, that could be disrupted by tensile strength (forced extension of the finger) (12). Hence a localized inflammatory reaction occurs into the hand, even before forced extension. In fact, in clinical experience, it is true that a wide and bulky hematoma that can be observed along the finger and into the palm 24 hours after CCH injection, which extends far beyond the injection site.

These general considerations led us to investigate if CCH injected into a cord can provokes histological changes within 24 hours from the injection. Given that CCH is an exogenous enzyme, we supposed that macrophages could have played a role in first nonspecific defense. Macrophage is an indicator of early inflammatory activation. Thus we investigated any abnormalities in immunohistochemical pattern of CD68 cells, compared to normal pattern described

by Bianchi et al., that is the complete absence of macrophages and monocytes into the pathological nodule (11).

MATERIALS AND METHODS

In this experimental study, we enrolled 15 consecutive patients. We included in the study: patients with second stage isolated fourth digital ray DD, according to Tubiana classification (total passive extension deficit from 45° to 90°).

In our institution we currently use two techniques for treatment of DD, radical selective aponeurectomy and collagenase injection. All patient included were properly informed about advantages and disadvantages of both kind of possible treatments.

We excluded from the study: breast-feeding or pregnant women, patients in therapy with anti-platelet or anticoagulant drugs, patients with past or recent history of massive use of corticosteroid drugs, patients who suffered from diabetes, patients with hypersensitivity to collagenase or any of the other components of the product. All patients enrolled in the study have expressed their agreement to participate to the study.

For 5 consecutive days, 2 patients per-day underwent radical selective aponeurectomy. Hence, 10 cords of at least 40 mm of total length were taken from 10 patients with DD, who met the inclusion criteria. Five cords were included in group A and five cords were included

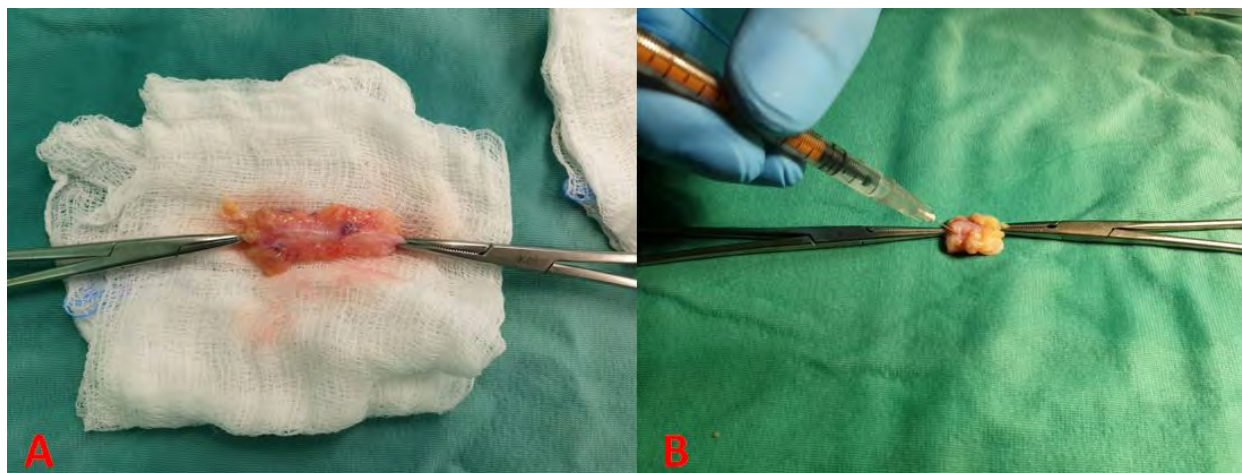


Fig. 1. An extracted cord (A) is divided into smaller specimens and injected according to standard procedure (B).

in group B. Cords were extracted including peripheral fat. Each cord has been divided into 5 specimens of equal length. In Group A, specimens were immediately injected with 0,58 mg CCH Xiapex® (approved for treatment of DD), according to the standard operative technique (13, 15). Specimens were fixed in formalin, in accordance with the timing established (6, 12, 18 and 24 hours after injection) (Fig. 1).

A non-injected specimen, used as a control, was fixed immediately after sampling (time 0). The specimens from group B were sampled and fixed in the same way used for group A. In total, 5 specimens were sampled for each cord. The protocol is resumed in Table I.

Each specimen from group A and B was paraffin embedded. Serial sections of 4 µm were obtained. Sections of the cords were performed transversally to the cord major axis. All specimens were stained for histological examination with HE. Immunostaining with antibodies for CD68 was also performed, to type the inflammatory infiltrate.

Five more histological samples were collected from spontaneous skin lacerations that occurred after forced injected cords' extension, obtained 24 hours after injection. These samples were stained with HE (Group C). Fig. 2 resumes the entire design of study.

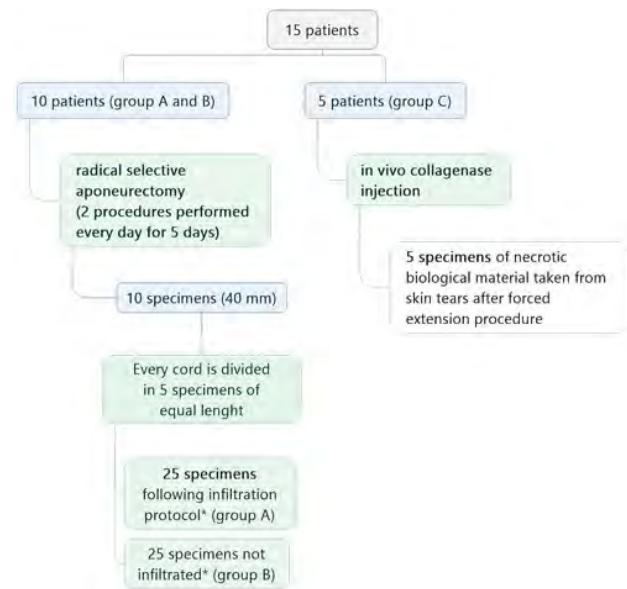


Fig. 2. Design of the study. *: specimens have been treated and analyzed according to what is reported in Table 1.

A qualitative and quantitative analysis was performed by two expert pathologists, who compared specimens at the same time of fixation and decided if there were any differences between group A and B. Quantitative analysis was performed on 10 HPF (20x) for each slice.

Outcomes

Primary outcome was quantitative analysis in CD68 positive cells at any fixation time. Secondary outcome was to assess general qualitative changes in tissue comparing group A and group B for each fixation time.

RESULTS

At time zero, cellularity was similar in specimens from group A and B, no difference was observed comparing the two groups in term of primary outcome and secondary outcome, with a poor quantity of CD68 positive cells.

A difference was noted comparing specimens fixed after 6 hours: cellularity was mildly increased in group A compared to group B. Immunostaining revealed a mildly increased number of CD68 positive cells into the cords in group A, compared

Table I. procedure of injection and fixation of the removed cords. **CCH:** Collagenase of *Clostridium Hystoliticum*.

Group A (infiltration protocol)	Group B (control cord)
1 st specimen – immediately fixed in formalin and then analyzed ("white" specimen)	1 st specimen – immediately analyzed
2 nd specimen – immediately injected with 0,58 mg CCH . After 6h from the removal: fixed in formalin and then analyzed.	2 nd specimen – After 6h from the removal: fixed in formalin and then analyzed
3 rd specimen – immediately injected with 0,58 mg CCH . After 12h from the removal: fixed in formalin and then analyzed.	3 rd specimen – After 12h from the removal: fixed in formalin and then analyzed
4 th specimen – immediately injected with 0,58 mg CCH . After 18h from the removal: fixed in formalin and then analyzed.	4 th specimen – After 18h from the removal: fixed in formalin and then analyzed
5 th specimen – immediately injected with 0,58 mg CCH . After 24h from the removal: fixed in formalin and then analyzed.	5 th specimen – After 24h from the removal: fixed in formalin and then analyzed

with Group B (up to more than 20 CD68 positive cells per HPF) (Fig. 3).

A more striking difference was noted again comparing specimens fixed after 12 hours: cellularity was increased in group A compared to group B. Immunostaining revealed an increased number of CD68 positive cells into the cords in group A, compared with Group B (up to more than 30 CD68 positive cells per HPF) (Fig. 4).

The difference was maintained again comparing specimens fixed after 18 and 24 hours. The number of CD68 positive cells increased significantly with time in group A, whereas in group B the number of CD68 cells does not modify with time.

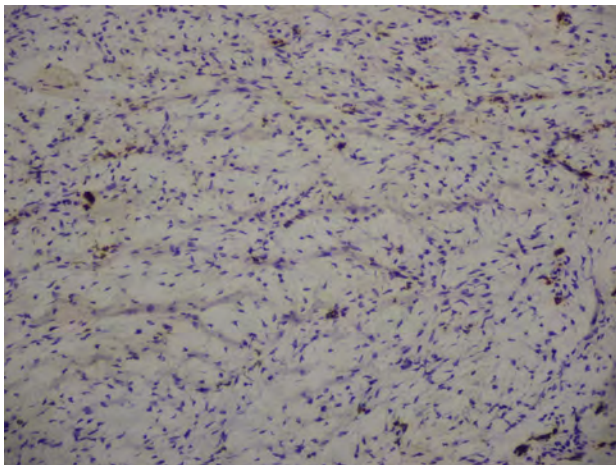


Fig. 3. *Injected cord, CD68 positive cells after 6h (20x).*

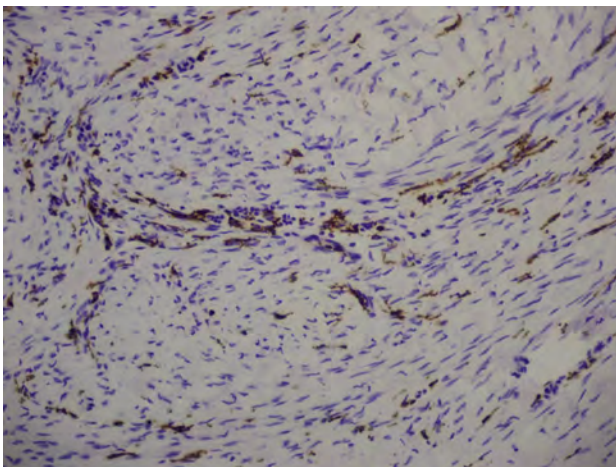


Fig. 4. *Injected cord, CD68 positive cells after 12h. The number of CD68 positive cells is increased compared to 6h (20x).*

In group A, the number of CD68 positive cells increases significantly until 18 hours fixation time. Conversely, the difference between 18 and 24 hours is not significant. Biological material taken from spontaneous skin laceration was stained with HE (group C), and revealed necrotic, hyperemic and inflamed tissue; the fibers are dislocated, separated and disarrayed for the presence of hemorrhage and inflammatory infiltrate of neutrophils and necrosis.

DISCUSSION

CCH works provokes a lysis of the cord. A wide hematoma immediately follows lytic treatment, that probably firstly mediate the inflammatory response to any kind of conventional treatment for DD. From here arises the need to investigate the role of inflammation in the immediate first period after collagenase injection.

Clinical research is now focused on anti-inflammatory and immunosuppressant drugs (anti-TNF), to avoid progression in early stage of disease (16, 17). On the other hand, immunomodulation cannot control stable deformities, characterized by acellular and scar-like tissue. Nevertheless, the inflammatory response plays a crucial role in the period immediately after surgical (radical selective apo-neurectomy) or lytic (collagenase injection) treatment.

Syed et al. with an in vitro scratch wound assay model demonstrated that CCH significantly down-regulated ECM components, cytokines and growth factors in a dose-dependent manner. In fact, at low concentrations, CCH enabled a faster fibroblast reparatory migration into the wound, whereas, at high concentrations, this process was significantly inhibited (18).

Studies which investigate inflammatory reaction after injection of collagenase have never been performed. If we analyze results from group A and B, we observed that inflammatory interfibrous infiltrate increased only after CCH injections, and CD68 cells were revealed in a great number in injected specimens compared with not injected ones.

Both kind of specimen (injected and not injected) received the same inflammatory insults

(surgical ischemia, surgical trauma, blood coagulation, exposition to the external environment). Nevertheless, histological differences were revealed.

Our study suggests that CCH has a proinflammatory activity and provokes a short ray chemotactic action on WBC, which were included in every single specimen at the moment of surgical removal. Chemiotaxis happens in any case of inflammation. Both exogenous and endogenous substances can act as chemo-attractants. Bacterial proteins are chemo-attractants, also because of the N-formyl methionine terminal amino acid, which is a typical exogenous bacterial product (19). In acute inflammation, one mediator can stimulate the release of other mediators.

On the other hand, the histological pattern revealed in group C was very different from what observed in group A and B, revealing that inflammatory activity is different. The exact role of CD68 cells and WBC in vivo after CCH injection is unclear.

We can only speculate on this stage. WBC attracted to the site of injury can produce endogenous collagenases (19-22), thus WBC can contribute to the extracellular matrix lysis in DD. However, we can suspect that they provoke pathologic tissue repair and contribute to recurrence. Indeed, many cytokines, including TGF- β , PDGF, and IL-1, can lead to the transformation of fibroblasts into myofibroblasts (3).

Necrosis, hemorrhage and neutrophils demonstrates that WBC play a role after treatment, contributing to the cord lysis. More studies need to be performed to investigate the role of inflammatory interfibrous infiltrate in DD.

It can reasonably be assumed that the cord lysis induced by CCH stimulates the inflammatory response. The role of the inflammatory infiltration deserves to be investigated in a more accurate way, preferably by using in vivo studies.

This study has several limitations. We conducted a qualitative and quantitative analysis, on a little number of specimens. This problem derives from the high costs of the used drug and the limited availability of the product. Nevertheless, results from our study encourage the research for funds for more studies. A confirm of our results should be obtained from an in vivo study, enrolling patients who would undergo

sampling of an injected cord, at 6, 12 and 24 hours after injection of CCH, under local anaesthesia. CCH could be a mechanism of action beyond the simple and clearly described lysis of the cord.

Very recently, land use of Xiapex® has changed, surprising many stakeholders interested in DD. The new land of use of Xiapex® is cellulite and it will be sold for the need of different kind of patients (23-25).

European Union countries' national healthcare systems cannot ensure CCH injection to patients who need, because of the higher prices charged by the United States producers (about 10 times higher). Xiapex® will be no longer available in Europe for the approved use (Peyronie disease and DD). Considering the proven clinical effectiveness, this has caused disappointment for hand surgeons and patients (23-25). If future studies will confirm the role of inflammatory response in collagen degradation, future research could be channeled towards new drugs, to reduce collagenases' costs and induce and enhance the competition between various drugs.

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Bilateral total hip arthroplasty through minimally invasive direct anterior approach after Legg-Calvé-Perthes disease

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Bilateral secondary osteoarthritis of the hip may affect also young patients following bilateral hip diseases such as slipped capital femoral epiphysis and developmental hip dysplasia. We report the case of an 18-year old male with a previous diagnosis of Legg-Calvé-Perthes disease who underwent a bilateral total hip arthroplasty through minimally invasive direct anterior approach, with optimal results at 1-year follow up.

Bilateral osteoarthritis of the hip (OAH) may occur in up to 42% of patients with degenerative hip changes, especially when osteoarthritis is secondary to developmental dysplasia of the hip (DDH), Legg-Calvé-Perthes (LCP) disease and slipped capital femoral epiphysis (SCFE); also obesity is an important independent risk factor for OAH (1, 2).

On the other hand, total hip arthroplasty (THA) is one of the most successful and satisfactory orthopaedic surgical procedures (3), and some authors demonstrated that high-risk subsets of patients undergoing unilateral THA require a contralateral procedure within 10 years in up to 97% of cases (4). For these reasons the one-stage bilateral THA is becoming increasingly popular in the orthopaedic practice (5, 6).

Different surgical techniques and different implants have been studied to obtain the best clinical results. There is evidence for better short-term

outcomes performing THA through direct anterior approach (DAA) (7), but a gold standard does not exist in literature for one-stage bilateral THA. We report a case of one-stage bilateral THA performed through minimally invasive tissue-sparing direct anterior approach for secondary OAH after LCP.

Case presentation

An 18-year old male came to our attention with strong bilateral hip pain, muscles weakness and significant intra-rotation (30°) of the lower limbs. When he was 9 years old, a diagnosis of bilateral LCP disease was made and due to the strong hip pain and the consequent functional impairment, he had spent the last 3 years in a wheel-chair, and he was totally unable to accomplish daily activities. Preoperative x-rays showed severe bilateral OAH on advanced femoral head deformities after LCP (Fig. 1).

Due to the severity of the symptoms and of the

Key words: bilateral total hip arthroplasty; minimally invasive direct anterior approach; tissue sparing surgery; bilateral total hip replacement; Legg-Calvé-Perthes disease

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Fig. 1. Preoperative x-ray showing the bilateral deformity of the hip following Legg-Calvé-Perthes disease.

clinical and radiological involvement, a bilateral THA through minimally invasive DAA was planned. Total hip replacements were performed using the Medacta Leg positioner, an operator table with a leg holder, specifically designed for DAA (right hip: Mpact cup 56 mm, ceramic liner 36 mm, Amistem-H standard stem size 5, ceramic head 36mm size M; left hip: Mpact cup 56 mm, ceramic liner 36 mm, Amistem-H standard stem size 5, ceramic head 36mm size L, Medacta, Medacta International, Castel San Pietro, Switzerland).

On the first postoperative day physiotherapy was started; the patient was able to walk with two crutches with good pain control. In the following days he became more confident in walking and going up and down the stairs. He was discharged after one week. At 3-month follow-up the patient was able to walk without crutches, limping or pain, and a good improvement of the intrarotation (10°) and of muscle tone of the lower limbs was noticed.

At 1-year follow-up, the patient was in good condition and he had started sport activities including running, despite the persistence of a slight intrarotation (10°) of the lower limbs. The radiological outcome was satisfactory as well, and no signs of implant loosening were found (Fig. 2).

DISCUSSION

The demand of THA and especially minimally invasive approaches is increasing because it results

in fast functional recovery and return to a better quality of life. Compared to other approaches to the hip, minimally invasive DAA is associated with less blood loss and faster recovery (8). In young patients with secondary OAH, especially after LCP and SCFE, the minimally invasive DAA is in our experience the best approach to perform one-stage bilateral THA. Since both one-stage and two-stage bilateral THA have their risks and benefits, these potential complications must be interpreted considering each individual patient's needs.

The advantages of simultaneous bilateral THA are: one-stage anaesthesiological risk, potentially shorter disability and recovery periods and the avoidance of being again in a surgical waiting list. Perioperative complications represent the most significant issues. Same-day bilateral THA reported less major systemic complications, such as deep venous thrombosis, and reduced overall costs, but obviously increased operative times, higher need of blood transfusions and increased hospital length of stay, therefore bilateral procedures are often discouraged in the elderly (9, 10).

Nevertheless, the minimally invasive DAA is especially advantageous in case of one-stage bilateral THA because it is performed on supine-positioned patients, so there is no need of either repositioning or preparing again the sterile field during the surgery. In our experience, specific instrumentation and operator table extensions for minimally invasive DAA are particularly useful to speed up bilateral procedures.



Fig. 2. X-ray at 1-year follow up.

In this case, we obtained an excellent clinical and radiological outcome, with high patient's satisfaction. Nevertheless, further comparative studies are still missing to assess if one-stage bilateral THA could be the gold standard to treat young patients with secondary bilateral OAH. One-stage bilateral THA is a promising safe and cost-effectiveness procedure to treat secondary OAH in young patients.

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Evaluation of PD1 and PD-L1 expression in high-grade sarcomas of the limbs in the adults: possible implications of immunotherapy

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Sarcomas are a heterogeneous group of rare tumours. Improvements in immunotherapy and the important role of PD1 and PD-L1 expression in advancement and prognosis have opened new fields of research for the treatment of these neoplasia. We evaluated the immunohistochemistry of PD1 and PD-L1 expression in 60 adults' patients affected by high-grade sarcomas of the limbs. PD1 expression was 65% while PD-L1 was 68.3%. PD-L1 expression seems to correlate to Ki67 in liposarcomas, fibrosarcoma's and pleomorphic sarcomas, while it does not show any correlation to chondrosarcomas, while in rhabdomyosarcomas there is a correlation but, given the small sample size, it was not possible to perform a statistic analysis. Our study shows positivity among the different subgroups of positive PD1 lymphocytes infiltration and PD-L1 expression in high-grade sarcomas of the limbs.

Improvement of surgical techniques, associated with the improvement of pre-operative and/or post-operative radiotherapy and chemotherapy, brought enhancements in results in localised cancer in the last 30 years (1). Despite these multimodal therapies, survival rate in non-localised disease did not improve in the last 20 years with high grade of metastasis and local recurrence (2). Metastasis is fatal in most patients with an overall survival (OS) of 12-15 months from diagnosis. Therefore, there is urgency in searching for new treatments instead of conventional therapy (1, 2, 3) and targeted therapies, as monoclonal antibodies and immunotherapy may be an option.

Sarcomas were among the first tumours to be considered for manipulation of immune system. Coley reported a case of inoperable small cells sarcoma of the neck in 1891 which completely regressed after a serious episode of erysipelas,

associating the response of the immune system to erysipelas to the response of patient tumour (4).

Improvements in immunotherapy by transferring cells of adaptive immunity, anti-tumoral vaccines and inhibition of immune checkpoints, allowed a better comprehension of how immune oncology may be applied to treatment of sarcomas (5). Immune checkpoints are cell surface molecules which are endogenous regulators of immune response system and are involved in circumvention mechanism of tumour cell in immune response as well.

Programmed cell death receptor 1 (PD-1) is an immune checkpoint receptor expressed on T cells and it is one of inhibitory signals induced during chronic exposition to antigen in external tumour microenvironment which belongs to CD28 family and has a crucial role in tumor immunogenicity. PD-L1 is PD-1 ligand and it is expressed on T cells, B cells, macrophages and dendritic cells (6, 7).

Key words: sarcoma, immunotherapy, programmed cell death receptor, PD, PD-L1

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Interaction between PD-L1 in tumor cells and PD-1 in T lymphocytes negatively controls tumor-specific effector T lymphocytes function and allows tumor cells to evade host immune system. PD-1 inhibitory effect on T lymphocytes activation is mediated by interaction with co-stimulation ligands as PD-L1 and L2-PD.

Interaction PD1/PD-L1 attenuates immune response decreasing cytokines production and induces T lymphocytes to energy and apoptosis (8, 9). PD-1 positive T cells intertumoral infiltration and PD-L1 rate of expression in human malignant tumours has been reported in a range between 19% and 92% and PD-L1 expression has been associated to progression and poor prognosis in non-small cell lung cancer (NSCLC), ovarian cancer and renal cell carcinoma (10, 11).

When considering the important role of PD1 and PD-L1 expression in tumorous progression, especially in malignant carcinomas and melanomas, there is no reason to think that PD1 and PD-L1 expression may not be involved in pathogenesis of sarcomas as well.

Nowadays, there are a few clinical data on efficacy of inhibitors of immune checkpoints in the treatment of sarcomas. The excellent clinical results and the safety of PD1 and PD-L1 inhibitors in melanoma and lung cancer, generated excitement and motivated researchers to exploit power of immunotherapy in searching cures for patient affected by advanced sarcomas, although many sarcomas do not express Major Histocompatibility Complex (MHC) which is necessary for T cell-mediated response. (5).

MATERIALS AND METHODS

Population in exam

We evaluated 60 adult patients affected by sarcomas of the limbs (15 chondrosarcomas, 20 liposarcomas, 10 pleomorphic sarcomas, 5 rhabdomyosarcomas and 10 fibrosarcomas). All patients underwent to complete surgical resection of the lesions between 1st of January 2010 and 31st of December 2014.

Patients were between 20 and 80 years at diagnosis (median age 61 years; mean age 59.9±11.4 years); 33 males, 27 females. A complete resection of the lesion was performed. Tissue samples of sarcoma were collected at

the time of resection and formalin-fixed at 4% and then paraffin-embedded and phenotypically characterized in Pathological Anatomy Department of the same Hospital.

The protocol of the study adhered to the principles of The Declaration of Helsinki by the World Medical Association. All patients, before entering the study, signed an informed consent form. Inclusion criteria for the treatment of relapsing forms were: ≥ 18 years, histologic diagnosis of sarcoma from a previous biopsy.

PD1 and PD-L1 immunohistochemistry analysis

PD1 and PD-L1 immunohistochemistry analysis were carried out on neoplastic tissue sections of 3 mm paraffin-embedded using murine monoclonal anti-human antibody PDCD1/PD1/CD279 (Programmed Cell Death 1, clone NAT105 of ScyTek, Milan) and rabbit monoclonal anti-PD-L1 human antibody PDL-1/CD274, clone RBT-PDL1 of Bio SB, Milan) after adequate preparation of the sections. Sections of healthy human tonsils were used as positive control, while for negative control primary antibody was not used.

Evaluation of PD1 and PD-L1 immunohistochemistry expression

To evaluate PD1 we proceeded in counting the number of positive lymphocytes at 400X on five fields in the peritumoral lymphocytic infiltration, where present. About PD-L1, we proceeded in evaluating its expression on an intensity score and on the number of positive cells. Considering intensity, cases without immunoreaction were classified as 0, low intensity as 1, medium intensity as 2 and strong intensity as 3. Considering the number of positive tumorous cells, we considered as 0 cases with 0-10% of positive cells, 1 with 11-33% of positive cells, 2 with 34-66% of positive cells and 3 with 67-100% of positive cells. Intensity and number of cells results were then added to obtain a score from 0 to 12. We considered as strongly positive those with a score >6 and little positive those with a score <6.

Ethical approval and informed consent

All procedures performed in the current study were approved by IRB in accordance with the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all individual participants included in the study. The study design was approved by the Institute and School Council.

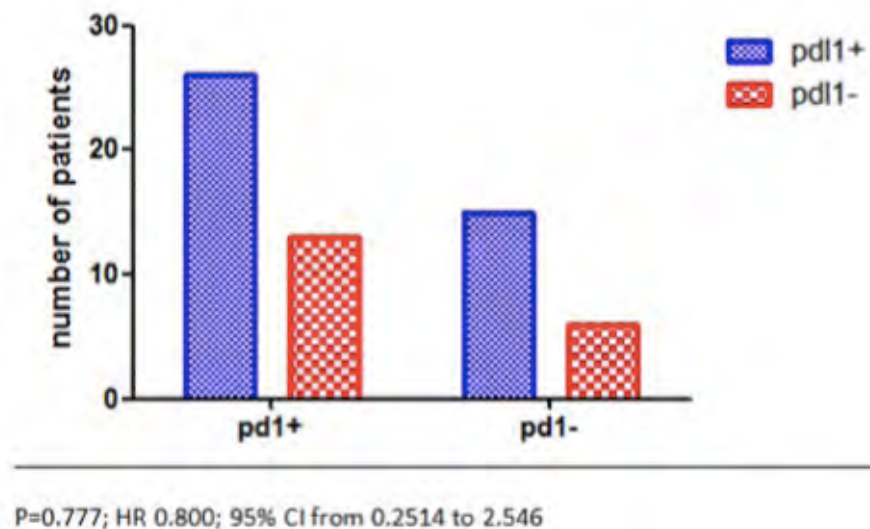


Fig. 1. Number of patients.

RESULTS

All examined samples were high-grade sarcomas. PD1 is expressed in lymphocytes which infiltrate the tumour, while PD-L1 mainly in cancer cells. Intra-tumoral stromal cells showed a weak or absent PD-L1 expression, while intra-tumoral endothelial and inflammatory cells expressed it in some cases only.

In the total of cases, PD1 expression was 65% (39/60 cases) while PD-L1 was 68.3% (41/60 cases); negativity of both PD1 and PD-L1 expression was 10% (6/60 cases), positivity of both was 43.3% (26/60), while positivity of one and negativity of the other et vice versa was 46.7% (28/60). PD-L1 expression seems to correlate in a statistically significant way to Ki67 in liposarcomas, fibrosarcomas and pleomorphic sarcomas, while it does not show any correlation to chondrosarcomas, while in rhabdomyosarcomas there is a correlation but, given the small sample size, it was not possible to perform a statistic analysis. We did not demonstrate any correlation between PD1 positivity and PD-L1 expression both in the totality of cases and in individual subgroups (Fig.1). Moreover, we did not find any correlation between PD1 and PD-L1 expression with mitotic index and tumor necrosis, seeing that values were too variable and the number of cases not very wide.

DISCUSSION

Treatment of bone and soft tissue sarcomas avails of a combination of surgery, chemotherapy and radiotherapy. However, prognosis of these pathologies is stable since 1990 (5, 11). Considering this aspect, a new immunotherapeutic approach may improve prognosis of these patients.

Immune checkpoints blockage is a relatively recent immunotherapeutic strategy in solid tumours which 'removes the brakes' (CTLA4, PD1) to maintain activation and cytotoxic function of T cells and other immune cells which are already present in tumor microenvironment. Clinical studies conducted in melanoma, prostatic cancer, renal cell carcinoma, colon cancer and non-small cell lung cancer showed a high rate of response in tumor regression with an improvement of overall survival (12-18).

Prognosis and clinical aspects on PD-L1 role in sarcomas is unknown. Antibodies against immune checkpoints, not acting directly on cancer cells, theoretically allow their applications in any solid tumour, even in those tumours considered "non-immunogenic" (14).

Maki et al. conducted a pilot study in synovial sarcoma, six patients with advanced disease and NY-ESO-1 positivity received 1 to 3 cycles of

Ipilimumab (anti-CTLA4) (19). Among the six patients, no serological test of an immune response to NY-ESO-1 was proved and all patients presented a progression of the disease after therapy (19). Anti-PD1 therapy represents an alternative strategy.

Recently Kim et al. have analysed PD1 and PD-L1 expression in different subtypes of soft tissue sarcomas. In total, 105 cases of soft tissue sarcomas were tested through immunohistochemistry. The most represented subtypes were leiomyosarcoma (n=20), synovial sarcoma (n=16), undifferentiated sarcoma (n=11) and myxoid liposarcoma (n=10). An intra-tumoral of positive PD-1 lymphocytes infiltration has been observed in 65% of cases while PD-L1 expression in 58% of cases; however, in the different subtypes, there was a significant change of frequency of markers expression.

About PD-1, 100% of undifferentiated sarcoma had positive expression, compared to 10% (one case only) in myxoid liposarcoma. These data suggest that some subtypes of soft tissue sarcomas can experience an immune checkpoint blockage, using anti-PD1 or anti-PD-L1 antibodies (20). The presence of positive PD1 lymphocytes which infiltrated the tumour was significantly associated to the advanced age of patients, high grade of the tumour, distant metastases, histologic grade, tumoral differentiation, mitotic count and tumor necrosis. PD-L1 expression too was significantly associated to advanced stage

of cancer, depth of the tumour, distant metastases, histologic grade, differentiation and tumor necrosis. Authors concluded that positive PD1 lymphocytes infiltration, PD-L1 expression and the pattern of combined expression of PD and PD-L1 in soft tissue sarcomas are independent prognostic factors of event-free survival and lower overall survival.

D'Angelo SP et al. examined immune framework, evaluating PD-L1 expression through immunohistochemistry and the number of tumor-infiltrating lymphocytes (TIL) in 50 patients with sarcoma. They did not show any association of clinical characteristics, overall survival and PD-L1 expression in the tumor or immune infiltrated (21).

Paoluzzi L et al. retrospectively analysed 23 patients with recurrent metastatic sarcomas treated with nivolumab. Clinical benefit was observed in 9 patients giving a reason to explore nivolumab efficacy and other checkpoint inhibitors in soft tissue and bone sarcomas (22). Pydas et al. analysing 65 cases of sarcoma demonstrated a PD1 and PD-L1 expression respectively of 17% and 29% in tumor tissue and of 12% and 30% in tumor microenvironment (23). Kostine M et al. reported an immunochemistry analysis of PD-L1 expression in chondrosarcomas showing absence of expression in classic, mesenchymal and clear cells form and positivity of 41% in dedifferentiated forms

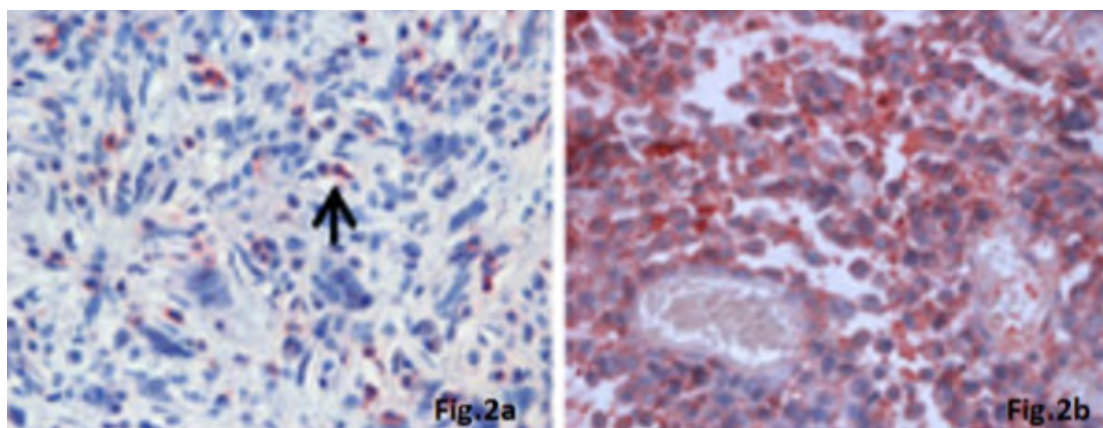


Fig. 2. A, B: rhabdomyosarcomas.

suggesting that this positivity provide a reason to include this kind of patients in clinical trials with therapies that have PD-1/PD-L1 as target (24).

In our study we have showed in some types of high-grade sarcoma of the limbs a positivity of PD1 of 65% and of PD-L1 of 68.3% according to Kim et al. who showed a positivity in soft tissue sarcoma of 58% and 65% respectively, while Paydas et al of just 30% (20, 23). High positivity suggests that in high stage forms the increase of percentage of translocations associated to an increased proliferation can give more antigen expression which lead to more immunoreactivity of the lesion.

In our sample we showed positivity of PD1 and PD-L1 in pleomorphic sarcoma (Fig. 2) respectively of 90% and 80% with a double positivity of 70% and a double negativity of 0% according to Kim et al while Paydas et al showed a double positivity in 50% of cases and D'Angelo a weak positivity (20, 21, 23). In rhabdomyosarcomas (Fig. 2), we showed positivity of PD1 and PD-L1 respectively of 80% and 100% with a double positivity of 80% and a double negativity of 0% according to Kim et al. results (20).

In liposarcomas we showed positivity of PD1 and PD-L1 respectively of 80% and 55% with a double positivity of 40% and a double negativity of 5% in contrast with Kim et al which showed respectively a positivity of 23.5% and 41.1%, maybe due to high stage of all our cases (20). In fibrosarcomas, we showed positivity of PD1 and PD-L1 respectively of 50% and 50% with a double positivity of 30% and a double negativity of 30% partially according to Kim et al results (20). In chondrosarcomas, we showed positivity of PD1 and PD-L1 respectively of 33.3% and 80% with a double positivity of 26.7% and a double negativity of 13.3% partially according to Kostine et al results. Weak PD1 positivity in these forms is partially after decalcification of the sample (24).

This study shows positivity, although variable, among the different subgroups of positive PD1 lymphocytes infiltration and PD-L1 expression in high-grade sarcomas of the limbs, suggesting probable application of immunotherapy directed to PD1 and PD-L1 in some patients, above all those who present high-grade forms.

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Correction of post traumatic tibial varus deviation with hexapodal external fixator

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Physeal fractures are typical in childhood and for their involvement of the germinal layer of the physis they can be followed by growth complications. Axial deviation is one of these. Considering the young age of the patients it is critical to restore articular correct alignment with the least invasive surgery possible. We report here the first case of correction of post traumatic tibial varus deviation with exapodal external fixator.

The epiphyseal fractures represent a common injury during childhood (1). They are divided in 5 types based on a classification introduced by Salter and Harris (SH) in 1963 (2). One of the most involved sites is the distal tibial physis; indeed, it counts for 11% of all the physeal injuries (3) and is the most frequent injured area of the lower limb (4). As these types of fractures can involve the germinal layer of the physis, complications might be associated. The most common complication is the premature physeal closure (PPC), other possible side effects are shortening and/or angular deformity (5, 6), this last situation occurs when a partial but not a complete physeal closure happens. It is vital to correct axial deviations to avoid the onset of early osteoarthritis. In literature, there are only few cases describing the use of external fixators to correct ankle malalignment after these types of fractures. This case report is the first referring to an exapodal fixation system for the correction of the malalignment after a distal tibial fracture.

Case presentation

An 8-year old male was admitted to the emergency

department for a trauma to his left ankle after been hit by a car on a crosswalk. Traditional X-rays were taken and showed an epiphyseal fracture of distal tibia involving the medial malleolus (Fig. 1). The injury was classified as type IV based on Salter Harris classification. A leg cast was applied, meanwhile, reduction and fixation with an intraepiphyseal screw was planned.

The patient underwent the surgery with implant of a 4x32 mm cannulated cancellous bone screw (DePuy Synthes Inc, Raynham, Massachusetts, USA) under fluoroscopic guidance, avoiding the growth plate. Post operative X-rays showed a satisfying reduction and a well-positioned screw (Fig. 2).

The patient was discharged after 3 days with his left leg immobilized in a cast and with indication of no weight-bearing for 30 days. Afterwards, the cast was removed and he underwent a physiotherapy program to regain the range of motion of the ankle and partial weight-bearing was allowed. Full weight-bearing and return to sport activities was reached in two months, without any pain referred to the injured area. After 6 months, the patient underwent a second

Keywords: paediatric orthopedics; Salter-Harris; physeal fracture; posttraumatic tibial valgus; external fixator.

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surgical stage to remove the screw (Fig. 3).

Two years after the hardware removal, the patient started complaining pain in the medial side of his left ankle and limited range of motion, restricting every-day activities and sport practice (basketball). New X-rays were performed (Fig. 4), showing a 13-degrees varus deviation of the distal tibial epiphysis (joint ankle angle: 77.6 °). Subsequently, an MRI was performed to check the growth plate status (Fig. 5).

The images displayed that the fracture had interrupted the growth plate in the medial third part, leading to a growth disturbance. Thus, we decided to treat the malalignment with an external



Fig. 1. Preoperative x-rays showing Salter-Harris type IV epiphyseal fracture.

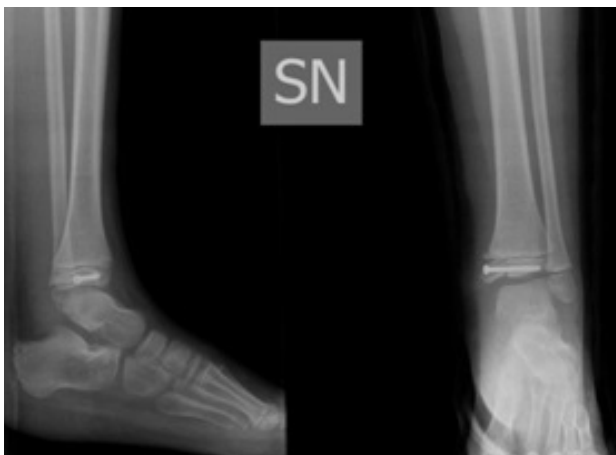


Fig. 2. Postoperative x-rays showing good reduction of the fracture.



Fig. 3. Postoperative removal screw X-rays showing a good bone consolidation.

fixator 1 year after the first surgery. A double tibial and fibular osteotomy was performed and an exapodalic frame (IFIX® by Dial Medicali Srl, Milan, Italy) was positioned (Fig. 6). With a computer assisted program the axial correction was planned: 1 degree per day for 13 days. Immediately after the surgery the patient was allowed to walk with two crutches with no weight-bearing on the left leg. The pain control was successfully obtained. The patient was discharged after 4 days with the indication of a physiotherapy program to restore the range of motion of the ankle and of the knee.

X-rays were performed at one, two, three and four months after the surgery (Fig. 7), showing a progressive correction of the deviation, until the normal axis of the ankle was restored and a satisfying bony callus was present at the osteotomies level.



Fig. 4. Standing lower limb X-rays showing the malalignment of the left ankle.



Fig. 5. Left ankle MRI showing bone dysmorphia and bone edema of the epiphyseal region.



Fig. 6. The IFIX® exapodalic frame.

Five months after its application the external fixator was removed (Fig. 8, 9). After 3 months from the fixator removal, the patient fully recovered: he showed a complete ankle range of motion, he was able to walk normally without crutches, limping or pain, and he returned to his pre-injury sport activity (basketball).

DISCUSSION

Epiphyseal fractures represent the 20-30% of all the fractures in children (1). The most frequent kind of fracture is Salter Harris type II and it is usually associated with few complications (4). Moreover, the growth plate of distal tibia is the most common location for SH type III and IV fractures (7). In case of SH III or IV type fractures, the risk of complications increases: among them, the most important is physeal premature closure (PPC), with an incidence that ranges from 2% to 43% (8). The variability in incidence of complications depends on some factors, such as fracture pattern (SH III and IV), fracture displacement width both initial and post reduction, interposed periosteum, a high-energy mechanism of

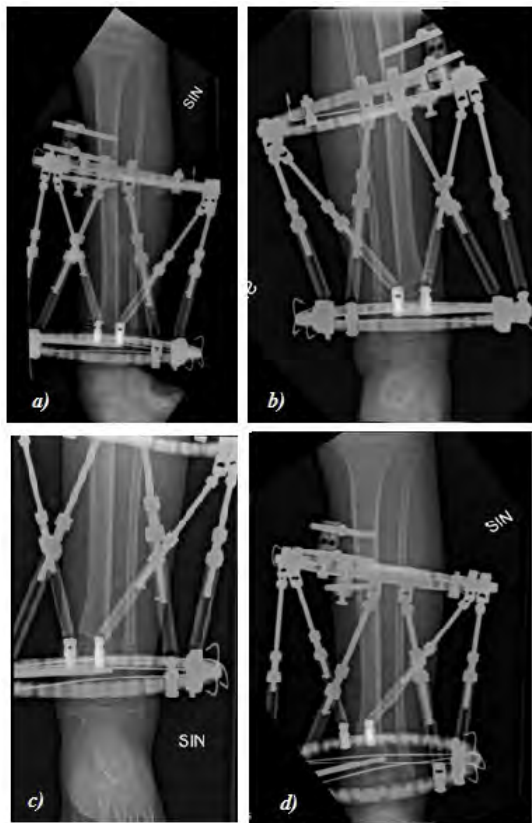


Fig. 7. Radiographic follow up at one (a), two (b), three (c) and four (d) months.

injury and the treatment method (9). Compression forces in some severe injuries (Salter-Harris III or IV) may also cause damage to the growth plate because of the crushing (Salter-Harris V); a bridge in any part of the physis can form, leading to early angular deformities in the younger patients (10).

The prognosis is fundamentally dependent on the biological age of the patient, on the localization in the skeleton and in the specific segment because the growth components of epiphyses are asymmetrically distributed in the bone. In patients aged < 10 years it is more likely to find an overgrowth of the section of the skeleton affected, while in over 10 years old premature closure of adjacent or affected epiphyses is more frequent, causing a possible slight shortening of the limb (11).

Other possible complications may be limb length discrepancies (LLD), axial deviations or both. Those growth disturbances are typically related to the so-called physeal bar, which is a partial premature physeal arrest, resulting in a bony bridge crossing the growth plate, sometimes with a spontaneous resolution (12) but potentially leading to severe bone deformities. It is vital to underline that a physeal



Fig. 8. Final follow-up after removal of external fixator (1).



Fig. 9. Final follow-up after removal of external fixator (2).

arrest can appear even two years after trauma, therefore an extended follow up is unequivocally needed (13).

For all these reasons, nowadays, in a primary displaced physeal separation, a congruous anatomical reduction is compulsory to prevent post traumatic growth arrest (14). Rohmiller et al. (15) showed that patients who developed growth disturbances of distal tibia had a remaining deformity after reduction significantly larger than those who had no consequences. A residual deformity raises the risk of following complications from 17% to 60%, with a peak of 76% if the initial deviation is more than 2 mm (8), thus some authors (16) report this value as cut off for the indication of a surgical treatment.

Textbooks on paediatric traumatology refer to distal tibial physeal separation as a benign injury with an incidence of post traumatic growth disturbances between 5 and 15%.

Other studies (8, 17) reveal different results with far higher percentages of growth alterations, up to 36-39%. However, the consequences are usually described as not severe, since the mean age of patients is 12-13 years old (8, 18), thus near to the age of physiological closure of physeal plates. On the contrary, Berson et al. (19) described varus/valgus deviation to be more frequent the later the growth arrest happens.

Moon MS (20) in 1997 followed nine children who sustained a supination-inversion injury of distal tibial physis until their maturity. He recorded an average varus deformity of 39 degrees (maximum, 80 degrees) with 23 degrees of internal rotational deformity and he found an early closure of the medial distal tibial physis, gradual upward migration of medial malleolus, and eventually medial subluxation of the ankle; these resulted in gradual varus and internal rotational deformities of the injured ankle.

In the same period, Toupin JM (21) studied one hundred and eighty-eight children treated for a fracture of the lower end of the tibia and stated that Mac Farland lesions and Salter and Harris type II lesion drive to epiphysiodesis more often than any other distal tibial fracture, varus deviation (range: 7-20 degrees) is more important in younger children and the procedure of de-epiphysiodesis to deal this

complication has a poor prognosis in more than 60 per cent of cases.

Demopoulos S. (10) reported that in 4 of the 27 patients treated for a fracture-separation (Salter-Harris III or IV) of the medial part of the distal tibial epiphysis, a varus deformity of 10 to 15 degrees developed, while no deformities were recorded in the groups of fractures located in different areas of the ankle (medial malleolus, lateral portion of the distal tibial epiphysis, triplane). The authors suggest that probably this group of injuries are more vulnerable to growth deformities.

Perfect restoration of the anatomy in these fractures is so important that Zhao et al. (22) suggested the application of a printed three-dimensional model of the fracture pattern, based on CT scan, to plan the operative reduction and to choose the internal fixation more appropriate for every single patient. The authors reported excellent anatomic results in all patients with only one displacement of less than 1 mm out of 15 cases, with neither difference in growth length of the limb compared to the contralateral nor varus/valgus ankle deviations. In literature, it is difficult to find descriptions of how to manage these types of complications.

Treatment of a post-traumatic physeal bar depends on the age of the patient and on the size and location of the bar. If the patient is near maturity, no treatment may be necessary or surgical closure of the remainder of the injured physis may suffice. If the patient is young, and especially if he or she is expected to be tall, epiphysiodesis of the remaining open part of the injured physis and of the ipsilateral fibular physis as well as epiphysiodesis of the contralateral distal tibia and distal fibular physes may be considered.

Repeated osteotomies to correct the recurring angular growth deformity can be performed if the bar is left untreated. This method does not correct the ipsilateral tibiofibular length discrepancy or the discrepancy in the lengths of the patient's legs. An alternative to these methods of treatment, all of which have some disadvantages, is excision of the physeal bar, which can potentially allow resumption of longitudinal growth, but results are controversial (23).

Lately, the advent of new exapodalic external

fixators has given the surgeon the possibility to gradually correct triplanar deviations of the bone thanks to a computer-assisted program, to restore the limb length and the pre-injury rotation and alignment of the joint with excellent functional results.

Sabharwal (24) showed a case of a 14-year old girl with a varus deformity of 30°, a recurvatum of 10° and a limb shortening of 2.4 cm nine years after a Salter Harris III fracture of the left distal tibia. The ankle range of motion was limited. Imaging also showed an early joint degeneration due to abnormal mechanical loading. A distal tibial osteotomy with external fixation was then performed and the device was removed as soon as the correction was achieved. At 5-year follow up, ankle range of motion and gait abnormalities significantly improved.

Moreover, external fixation allows an early weightbearing, it avoids a surgical aggression to the growth plate and it reduces the insult to bone and soft tissues. Thus, in the present case an external fixator was applied to correct the deformity.

Distal tibia epiphyseal fractures are frequent in children. Since the injury to the growth plate can lead to severe complications, attention should be paid to the restoration of joint congruency, without violating the physis, to prevent degenerative changes in the joint articular surface, in particular in younger children.

Conservative treatment is recommended in SH distal tibial fractures with an acceptable or none displacement. Tolerability on post traumatic deviations and displacements vary on age: with a range of 10 to 30 degrees for frontal and sagittal planes, but still there are no clear concurring recommendations on what is tolerable or not. In case of the development of an ankle axial deviation due to growth disturbances, the correction using an hexapodalic external fixator has shown several advantages and good results.

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Histological assessment of new bone formation with biomimetic scaffold in the presence of bone loss in trauma surgery

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Open reduction and internal fixation (ORIF) surgery may require the use of bone grafts (usually allogeneic). In the context of traumatology surgeries, the use of autologous grafts is almost never used and allogeneic grafts are not always available. In recent years, bone substitutes have been introduced in clinical practice to overcome these limitations. The purpose of this paper is to report two cases in which the use of a bone substitute was used to overcome the bone loss during surgeries of ORIF. Two patients, one with a tibial plateau fracture (Schatzker 6) and one with a proximal humerus fracture (Neer 4), underwent ORIF surgery. In both cases, due to a loss of bone stock, a synthetic bone substitute (OrthOss®) was used. One year after surgery, the complete osseointegration of the synthetic bone substitute was seen, both radiologically and histologically. This bone substitute may represent a safe and effective alternative to autologous bone grafts, avoiding adverse events related to donor-site morbidity.

Bone graft is the second most common tissue frequently transplanted in the United States and represents a fundamental tool for bone reconstructions in trauma surgery where an important loss of bone stock occurs (1, 2, 3). The qualitatively ideal graft is undoubtedly the autologous tissue, but it certainly exposes to the comorbidities of the donor site and has the limiting factor related to the amount of tissue needed as large quantities of tissue cannot be removed (4, 5). Allogeneic grafts, on the other hand, are not always available (6). For these reasons, the use of synthetic bone substitutes has been increasing in recent years (7, 8). These have the advantage of

being always available and of being indicated even in large quantities.

The objective of this paper was the analysis of the clinical outcome and the quality of the newly formed bone tissue in two patients, presenting a fracture of the tibial plateau and a fracture of the head of the humerus, respectively, where a synthetic bone substitute was used to treat major bone loss.

Open reduction and internal fixation of tibial plateau fracture

A 28-year-old male patient arrived at the emergency room following a high-energy motorcycle

Key words: trauma, bone loss, open reduction and internal fixation, bone graft, bone substitute, fracture

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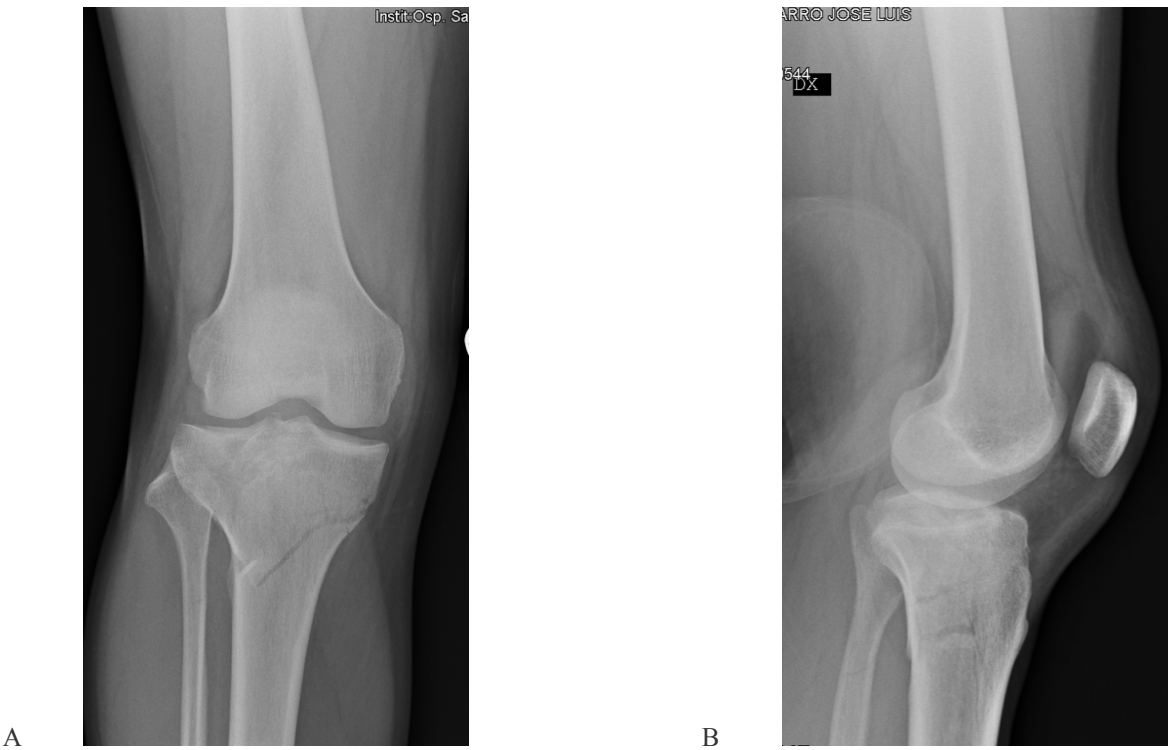


Fig. 1. Pre-operative Rx ray of tibial plateau fracture of the right knee, Anterior-Posterior view (A) and lateral view (B).



Fig. 2. Post-operative Rx ray, Anterior-Posterior view (A) and lateral view (B).



Fig. 3. *Pre-operative Rx ray of humerus fracture.*



Fig. 4. *Post-operative Rx ray of humerus fracture.*

accident conditioning direct trauma to the knee and right leg. A tibial plateau fracture was diagnosed (type 6 according to Schatzker classification) (Fig. 1 A and B).

The ORIF surgery was then performed using an angular stability plate and screws. An important loss of bone substance was found intraoperatively and a synthetic graft (OrthOss®) was used (Fig. 2 A and B). Serial radiographs over time showed progressive fracture healing with good osseointegration of the synthetic bone substitute; the plaque removal was performed after 14 months from the first surgery.

Open reduction and internal fixation of proximal humerus fracture

A 56-year-old female patient arrived at the Emergency Room after a fall from a ladder, leading to direct trauma to the left shoulder. A proximal humerus fracture (fourth type according to Neer) associated with anterior glenohumeral dislocation was diagnosed (Fig. 3) Three days after the trauma, under general anesthesia, an open reduction and internal fixation and reduction of the dislocation surgery was performed. (Fig. 4) Also in this case, the same synthetic bone substitute was used. Serial radiographs showed good bone consolidation and plaque removal was performed after 16 months from the first surgery.

MATERIALS AND METHODS

Formalin-fixed samples were decalcified in a formic acid-sodium citrate solution. After decalcification procedure, samples were rinsed for 10 min in running water and processed for paraffin embedding through a graded ethanol series. Four micrometer-thick sections were obtained and stained with hematoxylin/eosin and Masson's trichrome staining protocols and observed with an Olympus BX51 microscope (Olympus, Italy).

RESULTS

The histological study revealed that the scaffold was not degraded after 60 weeks of implantation and it was still present in the defect area (Fig. 5. a, b). In both cases, the first observation was the presence of

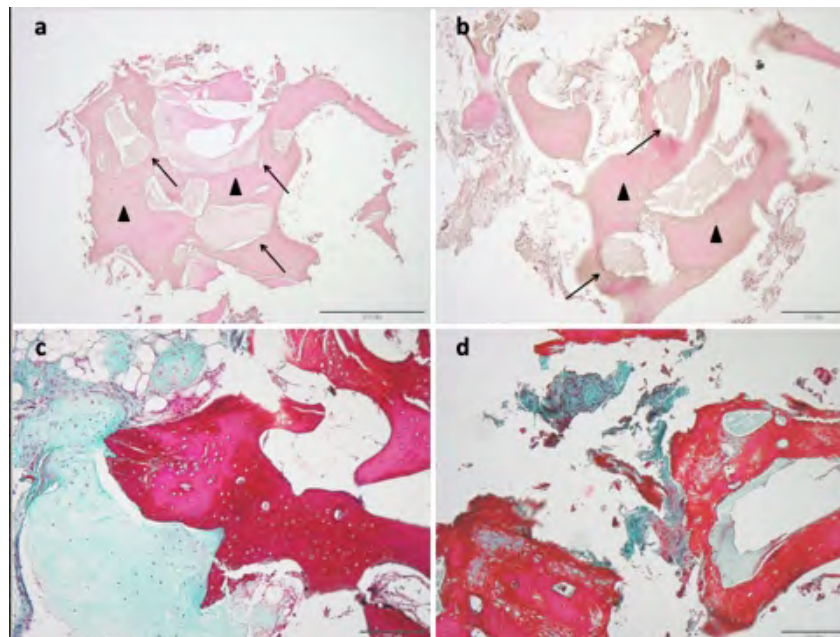


Fig. 5. Histological samples, a,c: shoulder; b,d: tibia; a,b: hematoxylin/eosin, c,d: Masson's trichrome staining. Newly formed bone (arrows) is visible around the scaffold particles (arrowheads). The chondral zones (green color in c and d) is located close to the woven bone (endochondral ossification: red color in c and d). Scale bar 200µm.

newly formed bone: actually, new tissue was only observed around the scaffold particles (Fig. 5 a, b). The Masson's trichrome staining allowed better contrast between newly formed tissues as compared to hematoxylin/eosin stains. Interestingly, the presence of chondral zones (Fig. 5 c, d) adjacent to woven bone revealed that endochondral ossification – typically observed in naturally-occurring bone healing processes (Fig. 5 c, d).

In recent years, thanks to technological developments, the number of synthetic bone substitutes to be used as a graft in case of loss of bone substance or nonunion has increased. On the other hand, having such a broad spectrum of therapeutic or surgical options can be confusing for the surgeon who is facing this type of operation.

Most of the studies in the literature that deal with bone grafts (autologous, allogeneic, or synthetic) result low statistically or are case series. There are no randomized controlled trials comparing these three types of grafting. These studies would serve to create diagnostic and therapeutic protocols that can form action algorithms. Until these studies are done,

the choice of the best bone graft remains based on personal experience, the type of patient and the type of fracture.

The synthetic bone substitute Orthoss® utilized here is manufactured from natural bovine bone, it is a xenogeneic inorganic bone matrix (containing no living cells) and a natural nanocrystalline carbonated hydroxyapatite: $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ and does not contain any soft tissue or organic material. It demonstrated good osteoconductive and biotolerance abilities and may be used in case of large bone losses in the context of trauma surgery.

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Do radiolucent lines and stress shielding of the humeral shaft really matter in shoulder arthroplasty?

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The purpose of this study is to evaluate at a mid-term follow up, the radiological survival of an uncemented humeral stem in shoulder arthroplasty. One hundred and twenty-six replacements including hemi (HA), total (TSA) and reverse (RSA) implanted from 1999 to 2008 were reviewed at a mean follow up of 7.2 years (48-144 months). The same uncemented triconical stem (SMR, Lima Corporate) was implanted. There were: 23 HSA, 43 TSA, 60 RSA. An independent observer evaluated all the patients with Constant Score. A radiologic analysis by an expert radiologist and an orthopaedic surgeon was performed: humeral component-bone interface was divided in seven zones. They judged a mobilisation if a migration or tilt of the humeral implant or if ≥ 2 mm radiolucent line in at least three zones was present. Chi-squared test, Fisher test and analysis of variance were performed and a $p < 0.05$ was considered statistically significant. No major radiological signs of loosening and no tilt or migration of the humeral component were found. Only 23 (18.2%) patients had no RL around the humeral implant. In the remaining 103 (81.7%) implants: 96 (76.1%) presented RL less than 2 mm, particularly 75 (59.5%) in less than 3 zones and 21 (16.6%) in more than 3 zones. Of the remaining 7 (5.5%) implants the presence of RL of 2 mm or greater in only one zone was seen. Apart from sepsis no revision was performed for humeral component loosening. Although a high rate of RL, uncemented humeral stem has an excellent survivorship at a mid-term follow up. Relationship between presence, position and depth of RL and internal stress shielding is commonly observed but does not appear to compromise quality of fixation or clinical outcomes in shoulder arthroplasty.

The history of modern shoulder replacement started with the uncemented press-fit monoblock hemi-prosthesis implanted by Neer in 1951 to treat proximal humerus fractures (1). This implant was first modified by the same author to make it suitable for the use of a polyethylene glenoid component (2) and subsequently the implant was redesigned for fixation with cement (3).

Although early results were good, many failures were observed over time because of different reasons according to the type of the implants.

Glenoid pain, due to bone erosion, was seen in patients with hemi-arthroplasty (4). Whereas in patients with total shoulder replacement, glenoid loosening was the main reason for failure (5). Today we are still debating over cementless metal back glenoid or cemented PE component (6, 7) and furthermore over a keeled or a pegged one (8). Ultimately, in both type of implants many failures were seen because of rotator cuff insufficiency (9).

In 1985 reverse implant was introduced by Grammont (10). Again, we had failure and revision

key words: shoulder arthroplasty; uncemented humeral stem; fracture; implant

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because of instability of glenoid and scapular notching (11). The development of shoulder implants is ongoing with new design and new materials. We are probably far from the definitive type of shoulder replacement.

Many papers analysed complications and survivorship of shoulder arthroplasty. Humeral component complications are essentially grouped in periprosthetic fractures (intraoperative and postoperative), in malposition and in stem loosening (9). Different types of stem-less implants were recently introduced advocating less complications (12). However, a careful operative technique is probably the best prevention for intraoperative fractures and for malposition of the humeral component. Whereas it is quite difficult to prevent postoperative fracture.

Regarding humeral loosening, many papers in the literature discuss the long-term results of the humeral component in shoulder arthroplasty. Only a few papers analysed the radiological results of a shoulder humeral stem specifically designed for uncemented use in a large population at a mid-term follow-up (13-19). The purpose of this study was to evaluate at a mid-term follow up, the radiological survival of an uncemented humeral component in shoulder arthroplasty.

MATERIALS AND METHODS

We reviewed 126 shoulder replacements including hemi (HA), total (TSA) and reverse (RSA), at a mean follow up of 7.2 years (48-144 months), implanted from 1999 to 2008. In all cases, the same uncemented triconical stem (SMR system Lima Corporate, Villanova di San Daniele del Friuli, Italy) was implanted.

All stems are made of Ti6Al4V alloy. They are characterized by an outline with a triple conicity to guarantee the proximal fixation and the correct fit, reducing, in this way, the stress shielding phenomenon, independently of canal morphology. The first conicity fits well into cylindrical canals, while the second one suits the fluted geometry. The last one acts as guide avoiding the distal press-fit in canals with narrow cross section.

They are characterized by a finned design, to allow stable primary fixation of the component in the proximal

part of the humerus during surgery. In addition, the proximal part of the stem is sand blasted to enhance surface roughness and therefore improve osteointegration and secondary fixation. The distal part is polished. Ten different diameters are available for uncemented conical stems (from 14mm to 24mm, increasing by 1mm for each size) with a length of 80mm for all sizes.

All the patients were clinically evaluated by an independent observer pre- and post-operatively with Constant Score (20). The radiological analysis was done with three plain film projections: 1. axillary view, 2. 40° posterior oblique radiograph with the arm in internal rotation and 3. external rotation executed preoperatively, immediate postoperatively and at the last follow up.

Humeral component-bone interface was divided in 7 zones (Fig. 1) as validated in the literature (17). Any change of position of the implant and the presence of radiolucent lines (RL) between the humeral component and the cortical bone interface, were analysed by an expert radiologist and an orthopaedic surgeon.

We specifically looked for radiological signs of loosening as follows: the component was judged at risk if at least one of the observers noticed a migration or tilt of the humeral implant or if both observers found ≥ 2 mm radiolucent line in at least three zones (21). In case

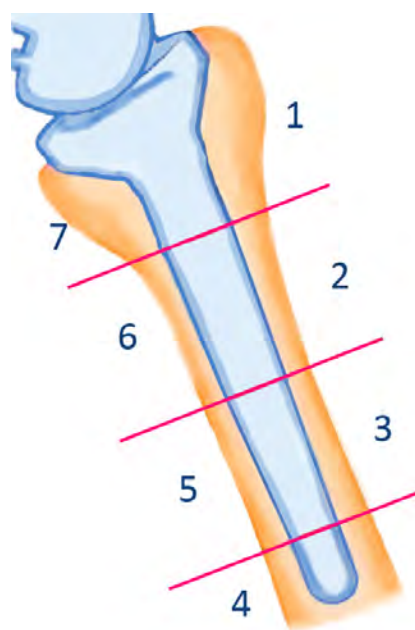


Fig. 1. Humeral zones for radiographic analysis. The humeral stem is divided into 7 zones. Zones 1 and 7 are proximal to the junction of the metaphyseal component.

of persistent pain or loss of motion or function with no radiological sign of loosening, a bone scan was performed.

Statistical analysis

A statistical analysis of the data was undertaken to evaluate the results with chi-squared test, Fisher test and analysis of variance for the comparison. We also performed the Wilcoxon's rank sum test, two sample t-tests and paired t-tests. A $p < 0.05$ was considered statistically significant.

RESULTS

HSA was implanted in 23 cases; TSA was used in 43 cases and RSA in 60 cases. The indications for surgery were varied. These included proximal humeral fractures, osteoarthritis, rheumatoid arthritis and cuff tear arthropathy. The mean age at the time of surgery was 69.8 years (42-82 years) and there were 47 men and 79 women.

All patients were treated *via* a deltopectoral approach, subscapularis tenotomy (and then reattached at the end of the procedure with non-resorbable transosseous sutures). Osteotomy of the humeral head was done with the aid of an intramedullary guide. The humeral canal was prepared with increasing trial stems and stable fixation was assessed with traction manoeuvres. Then the remaining part of the procedure was completed according to the choice of the implant (HSR, TSR or RSR).

No patients had major radiological signs of loosening and there was no tilt or migration of the humeral component. However only 23 (18.2%) patients had no RL around the humeral implant.

In the remaining 103 (81.7%) implants, RL were seen as follows: in 96 (76.1%) implants, there was the presence of RL less than 2 mm, particularly 75 (59.5%) in less than 3 zones and 21, (16.6%) in more than 3 zones. Of the remaining 7 (5.5%) implants the presence of RL of 2 mm or greater in only one zone was seen.

There was no relationship between the presence of RL with type of implants (HA, TSA, or RSA) (Fisher's exact=0.829) or with sex (Fischer's exact=0.205). However, we did find a correlation between the presence of RL and increasing patient age at time of surgery (two-sample Wilcoxon rank-

sum/Mann-Whitney test).

At the final follow up, Constant Score increased from a mean preoperative value of 27 points (range 7-38) to 58 points (range 24-78) ($p < 0.0001$). Importantly, there was no relationship between the clinical results (Constant Score) and presence of RL (two-sample Wilcoxon rank-sum /Mann-Whitney test).

Apart from sepsis no revision was performed for complications associated with the humeral component. Revision surgery was performed in 21 (16.6%) cases: 14 implants (11.1%) were converted from HA or TSA to reverse prosthesis, due to rotator cuff failure or recurrent instability, 7 implants (5.5%) were retrieved due to sepsis and treated with a spacer and then revised with a two stage procedure to a RSA in 5 cases (3.9%) and to a HA with a special Cuff Tear Arthropathy Head in 2 patients (1.5%).

Seven (5.5%) patients reported persisting pain not related to any evident reason. They were all in the group with RL less than 2 mm and particularly 5 had RL in three zones and 2 in two zones. These patients were further investigated with three-phase bone scintigraphy using technetium (22) to better investigate the cause of pain. We found 4 (3.1%) patients with a positive bone scintigraphy for aseptic loosening of the humeral implant, but the patients declined a revision surgery.

DISCUSSION

Boileau, analysing the complications in a multicentric series of 1842 anatomical shoulder prosthesis with a cemented humeral component, had 1.5% of humeral loosening and a 0.3% revision rate due to stem loosening (22). Complications and survivorship of shoulder arthroplasty are treated in many papers published in literature (9, 23). Bohsali in a large review of the literature regarding complications in TSA found a prevalence of 1% humeral component complications in 2540 total shoulder arthroplasties, which represents 7% of all complications (3).

It appears that humeral loosening is not a frequent occurrence in evaluating shoulder replacements results. Very few papers specifically analysed the survivorship of the humeral component in shoulder

replacement (3, 13-19, 24).

Maynou reported the presence of RL in 50% of 40 humeral implants in TSA and the evidence of radiological loosening in two implants (5%) even if none required revision (25). This study included different types of implants with different types of fixation (29 cemented and 11 uncemented). It is quite difficult to make a comparison with other papers, but it was the first study to focus on humeral component results. Mayo Clinic group, produced many studies on humeral stem assessment in shoulder replacement.

In 2000, Sperling analysing 62 ingrowth Cofield TSA (Smith & Nephew, Memphis, TN, USA) found the presence of RL in 17.7% of the implants while six stems (9.7 %) were judged to be at risk of loosening (21). These results may be affected using a metal back glenoid which has been associated with a high risk of loosening (17).

Sanchez-Sotelo in 2001 analysed 72 Neer II (3M St Paul, MN, USA) implanted without cement and he found the presence of RL in 50% of the implants and 55.6% were judged to be at risk of loosening (18). It is important to underline that Neer II prosthesis was designed to be used with cement and that this group of patients were treated with HA or TSA. Therefore again, glenoid loosening could be an influencing factor in the high rate of humeral component judged to be at risk (17). Sanchez-Sotelo found a relationship between the presence of a glenoid component and presence and thickness of humeral RL (3). In fact, polyethylene particles resultant from wear of the glenoid component could be responsible for the presence of humeral RL.

Matsen using a tapered metaphyseal stem, (Global, Depuy Orthopaedics, Warsaw, IN, USA) implanted 127 shoulder replacements (HA and TSA) without cement and found 61% radiolucency lines around the implant, but only 8.3% of the RL were greater than 1 mm and no differences were seen between HA or TSA. Furthermore, they found no subsidence or shielding of the component and none of the implants were judged to be at risk of loosening according to the criteria by Sanchez-Sotelo (16, 18). Rahme analysing the radiological results in rheumatoid people using both cemented and press fit humeral components in a published randomized

study, found no radiological loosening at 2 years follow up (15).

Verborgt reviewed 37 uncemented humeral stems (Neer II -3M St Paul, MN, USA) and he found 59% presence of RL with 41% greater than 2 mm. 19% were judged to be at risk (14). There was no association between age, sex, diagnosis and type of prosthesis, and there was no difference in term of Constant Score between implants at risk or not (14). Throckmorton reviewed 76 TSA with a press fitted stem with proximal porous coating and a cemented glenoid, 6.5% had RL and no implants was judged to be at risk (19).

Our study reveals a higher rate of RL, 81.7%, compared with literature, but no implant was judged at risk, according to criteria of Sanchez-Sotelo (18). It must be underlined that the presence of RL appears to be not related to type of implant (HA, TSA and RSA) or to sex and the only influencing factor was increasing patient age. We found 4 cases (3.1%) with a positive bone scintigraphy for aseptic loosening even in absence of radiological signs of humeral loosening. Therefore, the importance of RL in correlation with radiological failure should be reconsidered.

Analysing the literature, it seems that humeral loosening is not a major issue particularly with uncemented stems specifically designed to be used without cement. Examining 1584 humeral implants (HA and TSA, Neer II, Cofield I and II, cemented and uncemented), Cil found an 82.8% survivorship at 20 years, with the end point being revision or the removal of the humeral component (13). However, the main reason for revision of the stem in HA appears to be progressive arthritis of the glenoid and rotator cuff insufficiency. TSA glenoid loosening or PE wear were related to aseptic loosening of the humeral component, with only 2.2% of revision (13, 24). Internal stress shielding is commonly observed but does not appear to compromise quality of fixation or clinical outcomes (26). In a recent paper by Cole, stress shielding was found common at midterm follow-up in press-fit TSA but did not appear to affect functional outcomes (27).

In case of arthroplasty revision, it is obviously better to have a stable stem, able to host a reverse implant rather than to change the whole humeral component resulting in longer operative time,

increased duration of open wound (with a higher risk of sepsis), higher operating room costs, more difficult procedures, with need for bone osteotomy and a higher risk of periprosthetic fracture (28).

This study has some limitations. Although the data were prospectively collected, the consequent limitations of a retrospective review are present. When evaluating for radiolucent lines on radiographs, we did not perform our reliability analysis. Strengths of this study include a large sample size, blinding of reviewers to radiographic changes and clinical outcomes and a quite long follow-up.

Our results prove that although a high rate of RL, uncemented humeral stem has an excellent survivorship at a mid-term follow up. Relationship between presence, position and depth of RL and internal stress shielding is commonly observed but does not appear to compromise the quality of fixation or clinical outcomes in shoulder arthroplasty.

Compliance with ethical standards

All procedures performed for this study were in accordance with the Ethical Standards of the Institutional and National Research Committee and with the Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the Institutional Review Board of our Institute. Written informed consent was obtained from all people included in the study.

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Osseointegration for lower and upper-limb amputation a systematic review of clinical outcomes and complications

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The conventional use of prosthetic custom-design socket is affected by discomfort related to well-known problems: sweating, sores or skin irritation, excessive weight and harness, impaired body image, that lead to a high rate of abandonment. Osseointegrated prosthetic implants for limb amputation are progressively evolving to overcome limitations of socket. The aim of this article is to present a systematic review of the use, safety in terms of rate of infection and complications, and reported outcomes of upper and lower limb osseointegrated prosthetic implants. A systematic search was carried out for studies that evaluated outcomes of osseointegration technique in case of upper and lower limb amputees according to the PRISMA guidelines with a PRISMA checklist and algorithm. MINORS score was used for methodologic assessment. 17 articles about the treatment of patients with upper or lower limb amputation treated with an osseointegrated prosthesis were included. The overall rate of infections was 32%. All the clinical outcomes reported were related to lower limb. No clinical data for upper limb was found. The postoperative mean value of MCS and PCS SF-36 and Q-TFA was 55.1, 45.4 and 73.8 respectively, while six minute walk test (6MWT) and the timed up and go (TUG) test scored an average value of 388 meters and 11.5 seconds respectively. MINORS score ranged from 5 to 13, with a median of 11 [interquartile range (IQR), 9-11]. The osseointegration is associated to a high rate of postoperative complications but, significant improvement in clinical outcomes compared to preoperative time are shown. The data available from the literature are limited but suggest good clinical outcomes and significant survivorship of the implants. Further clinical studies are needed to establish which kind of implant is associated to higher clinical performance and lower rate of postoperative complications and infections.

A limb amputation is a catastrophic event that affects the mobility, quality of life and daily activities of patients. The more common causes for a lower-limb amputation in developed countries are chronic diseases, such as atherosclerosis and diabetes, often associated. Whereas in developing countries, traumatic aetiology related to pollution and wartime injuries are predominant (1). The amputation rate associated to military conflicts in the United States

army ranges from 7.4% to 19% of all major extremity injuries sustained, that should potentially shift the prevalence of amputations to younger individuals (2, 3). On the other hand, upper limb amputation occurs following high-energy trauma, involves young males in good health (4-6), affecting severely occupational ability and the possibility to return to work (7).

The conventional use of prosthetic custom-design socket is affected by discomfort related to

Key words: osseointegration, prostheses, interfaces, amputation surgery

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sweat in the prosthetic socket, sores or skin irritation from the socket, inability to walk in woods and open fields, inability to walk quickly (8, 9). Therefore, osseointegrated prosthetic implants for limb amputation are progressively evolving to overcome limitations of custom-design socket.

The osseointegration surgical technique for the attachment of prosthetic limb has been used since the 1990s, but nowadays its applied in various fields such as total joint replacements, dental implants, the edentulous mandible, craniofacial deficiencies, maxillofacial reconstruction, orbital prostheses and bone-anchored hearing aids (10). Osseointegration is a promising alternative that provides direct structural and functional connection between the bone and the artificial metal implant (1).

Furthermore, osseointegrated implant may be a reliable option to achieve a bidirectional human-machine interface, especially in upper limb. For instance, “e-OPRA” (Integrum) system allows perimysial and perineural electrodes to pass within the implant, obtaining an advanced motor control of the prostheses and achieving a sensory feedback stimulating the peripheral nerve (11). The latter is paramount to obtain better control and coordination of the robotic prostheses (12-15). However, the osseointegrated transhumeral implant demonstrated its efficacy also in interfaces which do not require electrodes, such as Targeted Muscle Reinnervation (TMR) (16, 17).

Moreover, Lundberg et al. (18) has demonstrated that the bone-anchored prosthesis contributes to the phenomenon called prosthetic “embodiment” namely that, so the patient has a higher acceptance of his/her artificial limb that may lead to a sense of independence. Several countries in the world are now performing osseointegrated prosthetic implants. Over the years, changes in implant design, surgical technique, perioperative and postoperative care, and rehabilitation protocols have resulted in improvements in functional outcomes and health-related quality of life. However, the rate of stoma-associated infections, remains a concern (19). Less common risks are: deeper soft-tissue infection, fractures from falls, and loosening of the implant (10). The aim of this article is to present a systematic

review of the use, safety - in terms of rate of infection and complications - and reported outcomes of upper and lower-limb osseointegrated prosthetic implants.

MATERIAL AND METHODS

A quantitative synthesis of all clinical studies of the osseointegration technique in case of upper and lower limb amputees was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines with a PRISMA checklist and algorithm (20). The article’s search was performed using Medline, Embase, PubMed, Cochrane, CINAHL, and Ovid databases. The combinations of keywords we used was: “Osseointegration”, “Upper”, “Lower”, “Limb”, “amputees” and “clinical outcome”. Articles published from inception of database to 2020 were selected. Two independent reviewers (M.C. and L.D.B.) conducted the search separately. All journals were considered, and all relevant studies were analysed. To be included in the study, articles had to be published in a peer-reviewed journal.

Articles without an abstract, were excluded from the study. Screening of the articles was done considering the relevance of titles and abstracts and looking for the full-text article when the abstract provided insufficient information about inclusion and exclusion criteria. The two investigators (M.C. and L.D.B.) separately reviewed the abstracts and then performed a close reading of all papers and extracted data, to minimize selection bias and errors. To obtain other articles, the investigators performed a cross-reference search of the selected articles. The last search was performed on 06 February 2020.

According to the Oxford Centre of EBM, Level I-IV articles were found in the literature and included in our study. Articles in Italian, English, Dutch, Spanish and French were included. The criteria used to select articles were:

- 1) articles about upper or lower limb amputations treated with an osseointegrated prosthesis.
- 2) articles with a detailed description of the surgical procedure, clinical outcome and complications with an adequate follow-up period.

Literature reviews, case reports, studies on animals, biomechanical reports, technical notes, letters to editors, cadaver, or *in vitro* investigations and instructional were

excluded from the review. Moreover, articles with insufficient details of surgical intervention, clinical postoperative outcomes, clinical examination, statistical analysis, age of patients, and follow-up were excluded as well.

To reduce and avoid bias, the authors reviewed and discussed all the selected articles, the references, and the articles excluded from the study. If any disagreement was present among the reviewers about the inclusion and exclusion criteria, the senior investigator (V.D.) made the final decision.

Quality assessment

The quality of included studies was evaluated using the MINORS (Methodological Index for Nonrandomized Studies) score. The following domains were assessed: a clearly stated purpose, inclusion of consecutive subjects, prospective data collection, endpoints appropriate to the purpose of the study, unbiased assessment of the study endpoints, follow-up period appropriate for the study, loss to follow-up of less than 5%, prospective calculation of the study size (Table III). The items analysed were 8, scored 0 (not reported), 1 (reported but inadequate) or 2

(reported and adequate) therefore, 16 is the maximum value for non-comparative studies.

RESULTS

The literature search and cross-referencing resulted in a total of 124 articles (Fig. 1). Eleven duplicates had been identified and removed, leaving 113 articles. Out of these, 89 were rejected because of off-topic abstracts (47 articles), failure to fulfill the inclusion criteria (14 articles) or both (28 articles). After reading the remaining 24 full-text articles, another 7 articles were excluded because of insufficient details and uncertain diagnosis and outcome measures. Finally, 17 articles focused on the treatment of patients with upper or lower limb amputation treated with an osseointegrated prosthesis were included (19, 21-36). Fig. 1 shows, the search algorithm according to the PRISMA guidelines.

Demographics

A total of 634 patients with 669 implants were

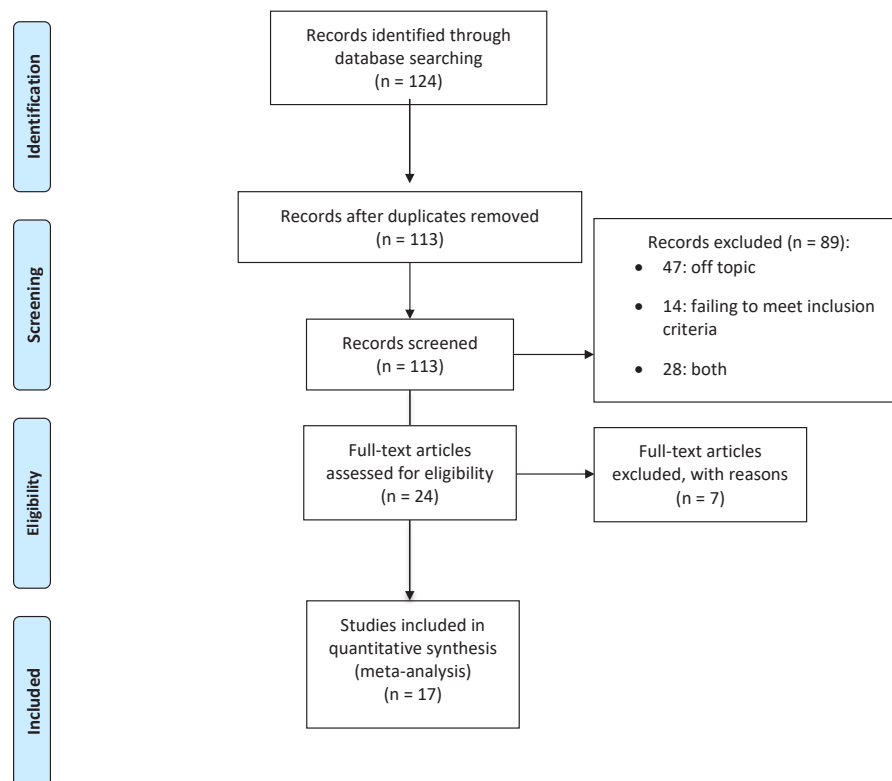


Fig. 1. PRISMA 2009 Flow diagram.

included, with a median age at surgery of 44.7 years ranging from 17 (23) to 84 years (24). Several levels of amputation were analyzed: 586 transfemoral, 37 trans-humeral, 24 trans-radial/ulnar, 12 thumb or partial hand and 6 transtibial. The major cause of amputation was trauma for 419 patients (65%). Other

less frequent reasons are tumor (15%), infections (4%), vascular diseases (2%) and other causes such as congenital and 4th degree burn (16%). Patients were assessed at follow-up for an average 61.4 months, ranging from 10 months (22) to 228 months (19) (Table I).

Table I. *Demographics data.*

Authors	Study Design (level of evidence)	Number of patients (limb)	Mean Age (years)		Level of amputation	Cause of amputation	Type of implant	Follow-up (months)
Tillander J et al 2010 ³⁴	Case series (IV)	39 (45)	-	49.3 (74-28)	Transfemoral (33), Transradial (4), Transhumeral (3), Transtibial (1)	Either trauma or neoplasia	Not reported	36
Muderis M. et al 2016 ²¹	Case series (IV)	86 (91)	32 ± 14	48 ± 14	Transfemoral	Trauma (65), tumor (11), infection (8), congenital (1), other (1)	OPL implant system	34 (24 - 71)
Muderis M. et al 2017 ²²	Retrospective study (III)	22 (22)	-	46.2 (67 - 20)	Transfemoral	Trauma (16), Tumor (4), Infection (2)	OPL implant system	14 (10 - 30)
Aschoff H. et al 2010 ²³	Retrospective study (III)	35 (37)	33 (14-56)	44 (17-69)	Transfemoral	trauma (30), tumor (4), other (3)	Endo-Exo-Femurprosthesis	-
Bränemark R. et al 2014 ²⁵	Prospective study (II)	51 (55)	32 (13 - 64)	44 (20 - 65)	Transfemoral	trauma (33), tumor (12), other (6)	OPRA	24
Juhnke D-L. et al 2015 ²⁹	Retrospective study (III)	69 (73)	-	Group 1: 46 (17 - 69), Group 2: 45 (24 - 76)	Transfemoral	Trauma (51), Tumor (7), Infection (3), 4th Degree Burn (1), Other (7)	Endo-Exo-Femurprosthesis	Group 1: 74 (6-144), Group 2: 32 (1-59)
Atallah R. et al 2017 ²⁴	Case series (IV)	5 (5)	-	67 (56 - 84)	Transtibial	Vascular diseases (4), Trauma (1)	customized 3-dimensional-printed ti-tanium implant (AQ Implants)	12 (-)
Hagberg K. et al 2008 ²⁶	Prospective study (II)	18 (18)	-	45 (22 - 62)	Transfemoral	Trauma (12), Tumor (5), Vascular diseases (1)	OPRA	24 (-)
Hagberg K. et al 2014 ²⁷	Prospective study (II)	39 (39)	31 ± 14.8	44 ± 12.4	Transfemoral	trauma (23), tumor (11), other cause (5)	OPRA	24 (-)
Jonsson S. et al 2011 ²⁸	Retrospective study (III)	48 (48)	-	40.9 (18 - 64)	Transhumeral (16), transradial (20), thumb (10), partial hand (2)	Trauma (32), Congenital (3), Tumor (2)	OPRA	180 (-)
Tsikandylakis G. et al 2014 ¹⁹	Retrospective study (III)	18 (18)	-	42 (19 - 69)	Transhumeral	Trauma (16), Tumor (2)	OPRA	96 (24 - 228)
Tillander J et al 2017 ³⁵	Case series (IV)	96 (102)	-	43.5 (19-65)	Transfemoral	Tumor (20), Trauma (71), Ischemia (5), Infection (5), Other (1)	OPRA	125.5 (64 - 192)
Van de Meent H. et al 2013 ³⁶	Prospective study (II)	22 (23)	-	46.5 (23 - 67)	Transfemoral	Trauma (20), Tumor (2)	OPRA	12 (-)

Infections and complications

Infections and complications were evaluated in 16 (19, 21-26, 28-36) and 13 (19, 21-23, 25, 26, 28-33) studies respectively. The overall rate of infections was 32% (201/626 patients). All the articles included had specified the gravity of infection distinguishing superficial (163/201 patients), localized at the skin,

by a deep infection localized at the bone or causing septic disease (38/201 patients) (Table II).

Other postoperative complications were analyzed in 13 studies (19, 21-23, 25-33) with an overall rate of 75% (164/216 implants). The most common complications were stoma hyper granulation and implant related complication, including breakage,

Table II. *Complications and clinical outcome.*

Authors	Infections	Complications	Clinical Outcomes				
			SF -36	Q-TFA	6MWT	TUG	Others
Tillander J et al 2010 ³⁴	5/45: Femur (4), Humerus (1)	-	-	-	-	-	-
Muderis M. et al 2016 ²¹	21/91	stoma hypergranulation (17), soft-tissue redundancy (14), proximal femoral fracture (3), inadequate osseointegration (1), implant breakage (2), and breakage of the pin used as a fail-safe mechanism (25)	Significant improvement in SF-36 physical component summary (p, 0.001)	Significant improvement in Q-TFA global score (p, 0.001)	Significant improvements (p, 0.001)	Significant improvements (p, 0.01)	-
Muderis M. et al 2017 ²²	15/22	None	-	-	significant improvements, with a mean increase of 128%	mean reduction of 30%	-
Aschoff H. et al 2010 ²³	14/37	Of 37 patients, 17 had no complications or minor complications and 20 had >1 revisions; of these 20 patients, 4 required explantation (1 due to intramedullary infection, 2 due to chronic soft-tissue problems, 1 due to failure 7 yr after surgery), 2 successfully reimplanted; 14 of 37 patients had minor revision due to stoma, 12 of which were exchange of coupler	-	-	-	-	-
Brånemark R. et al 2014 ²⁵	32/55	46/51 patients >1 complications with a total of 101 complications: 49 classified as "serious" complications in 39 patients; implant removed in 4 patients (1 infection, 3 aseptic loosening); 5 patients had episodic pain during rehabilitation, without loosening; 4 patients with 5 fractures, 3 in the ipsilateral hip, 1 below the elbow, and 1 vertebral compression; no peri- implant fractures reported; 9 mechanical abutment complications in 4 patients (6 in same patient), replaced with no long-term effect	SF-36 showed significant improvement in general quality of life (p, 0.0001)	Q-TFA scores improved (p, 0.0001); prosthetic use, prosthetic mobility, global situation, and fewer problems	-	-	-

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Juhnke D-L, et al 2015 ²⁹	Group 1: 23/30 (early infection: 13, late infection: 10); Group 2: 0/39	Structural Failure of Implant (1), Periprosthetic or Pertrochanteric Fractures (5), Implants Explanted (4), Unplanned Intervention Due to Soft Tissue Problems at Stoma (24), Any Unplanned Intervention (29).	-	-	-	-	-
Atallah R. et al 2017 ²⁴	1/5	-	SF-36 MCS: 57,4 (41,2 - 70,3); SF-36 PCS: 40,8 (38,9 - 44,4)	Global: 63,2 (58 - 83,3)	311 (144 - 433) m.	18,65 (6,28 - 26,8)	-
Hagberg K. et al 2008 ²⁶	2/18	loosening of the implant (1), broken prosthetic components (1), phantom limb pain and pain in stump muscles (1),	SF-36 MCS: 50; SF-36 PCS: 44	Global: 72,1 (33 - 100)	-	-	-
Hagberg K. et al 2014 ²⁷	-	loosening of the implant (3)	SF-36 PF: 60 ± 21,4; SF-36 PCS: 40,5 ± 9,8;	Global: 76 ± 17,4	-	-	-
Jonsson S. et al 2011 ²⁸	1/48	Loosening of fixtures (3), fracture (1), non - user (2)	-	-	-	-	-
Tsikandylakis G. et al 2014 ¹⁹	16/18	Loosening of fixtures (2), Incomplete distal fracture (8)	-	-	-	-	-
Matthews D. J. et al 2019 ³⁰	17/18	Fractures (1), persistent pain (1)	improved significantly between pre-operative status and 2 and 5 years post-operative time points	significant improvements in all of the main scores, and in two out of the three sub-scores for prosthetic mobility, between the pre-operative period and 2 and 5 years post-implantation	-	-	-
McMenemy L. et al 2020 ³¹	none	broken dual cone (1), periprosthetic fracture (1)	SF-36 MCS: 58,19; SF-36 PCS: 54,5	-	402 m	10,6 (7,4 - 12,1) s.	-
Al Muderis M. et al 2016 ³²	21/50	periprosthetic fractures (4), failure of osseointegration (2)	SF-36 PCS: 47,29 ± 9,33	Global: 83, 52 ± 18,4	419 ± 31,44 m.	8,74 ± 2,81 s.	-
Sullivan J. et al 2003 ³³	2/11	Mechanical deformation with periprosthetic fractures (2), mechanical deformation (3)	-	-	-	-	-
Tillander J et al 2017 ³⁵	16/102	-	-	-	-	-	-
Van de Meent H. et al 2013 ³⁶	8/23	-	-	Global: 75 (42 - 100)	423 ± 21 m	8,1 ± 0,7 s.	-

SF-36, 36-Item Short Form Health Survey; MCS, mental component score; PCS, Physical component score; Q-TFA, Questionnaire for Persons with a Transfemoral Amputation; 6MWT, six minutes walk test; TUG, Timed up and Go; s, seconds.

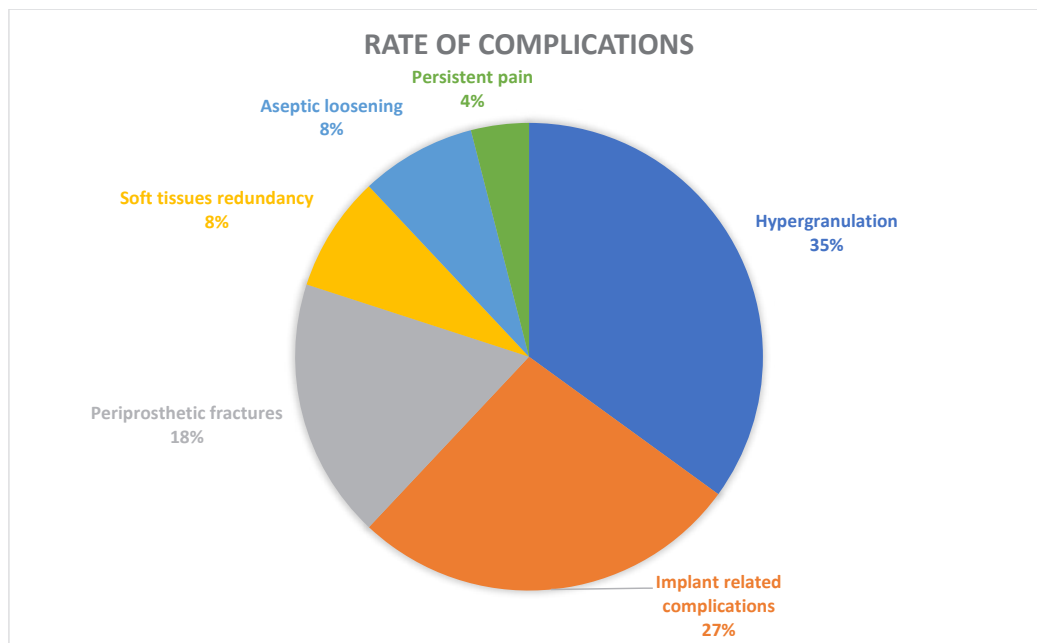


Fig. 2. Rate of complications.

with a rate of 35% and 27% respectively. Other less frequent postoperative complications were periprosthetic fracture or fracture above the implant (18%), soft tissue redundancy (8%), aseptic loosening of the implant (8%) and persistent pain (4%) (Fig. 2).

Outcome Scores

All the clinical scores reported in the included studies were related to lower limb. No clinical data for upper limb was reported. The most common clinical scores used were the mental component score (MCS) and physical component score (PCS) of 36-Item Short Form Health Survey (SF-36) (21, 24, 27, 30-32) and the Questionnaire for Persons with a Transfemoral Amputation (Q-TFA) (21, 24-27, 30, 32, 36).

The postoperative mean value of MCS and PCS SF-36 and Q-TFA was 55.1, 45.4 and 73.8 respectively. Other less reported clinical outcomes were a six minute walk test (6MWT) (22, 24, 31, 32, 36) and the timed up and go (TUG) (22, 24, 31, 32, 36) test, with an average value of 388 meters and 11.5 seconds respectively (Table II).

Quality Assessment

The MINORS score for all non-comparative included studies ranged from 5 to 13, with a median of 11 [interquartile range (IQR), 9-11]. Details are reported in Table III.

DISCUSSION

The most important findings of this review are that the osseointegration technique is associated to a high rate of infection (32%) and other postoperative complications, (75%) underling the fact that this kind of surgery is high demanding and requires an important expertise by the surgeon. Actually, the most common infections reported are superficial and they rarely needed an implant removal (19, 21-26, 28-36). Otherwise, major postoperative complications include breakage of implant, periprosthetic fracture, aseptic loosening, requiring one or more additional surgeries, up to the removal of the implant (19, 21-23, 25-33). However, the data available from the current literature show that the rate of complications associated to bone anchored prosthesis are similar

Table III. *MINORS score.*

Authors	A clearly stated aim	Inclusion of consecutive patients	Prospective collection of data	Endpoints appropriate to the aim of the study	Unbiased assessment of the study endpoint	Follow-up period appropriate to the aim of the study	Loss to follow up less than 5%	Prospective calculation of the study size
Tillander J et al 2010 ³⁴	2	2	2	2	1	2	2	0
Muderis M. et al 2016 ³²	2	2	2	2	1	2	2	0
Muderis M. et al 2017 ²²	2	2	2	2	1	2	2	0
Aschoff H. et al 2010 ²³	1	1	0	1	1	1	2	0
Brånemark R. et al 2014 ²⁵	1	2	2	1	1	2	2	0
Juhnke D-L. et al 2015 ²⁹	2	1	1	2	1	2	2	0
Atallah R. et al 2017 ²⁴	1	1	1	1	1	1	2	0
Hagberg K. et al 2008 ²⁶	2	1	2	2	2	2	2	2
Hagberg K. et al 2014 ²⁷	2	2	2	2	2	2	2	2
Jonsson S. et al 2011 ²⁸	1	1	1	1	1	2	2	0
Tsikandylakis G. et al 2014 ¹⁹	2	1	1	2	1	2	2	0
Matthews D. J. et al 2018 ³⁰	2	1	1	2	1	2	2	0
McMenemy L. et al 2020 ³¹	2	0	0	2	1	2	2	0
Al Muderis M. et al 2016 ²¹	2	2	2	2	1	2	2	0
Sullivan J. et al 2003 ³³	0	0	0	1	1	1	2	0
Tillander J et al 2017 ³⁵	2	0	0	2	1	1	1	0
Van de Meent H. et al 2013 ³⁶	2	2	2	2	1	2	2	0

to those of traditional socket ones which includes: skin issues (in 40% of patients), residual pain (in 30% of patients) (37, 38) restricted limb movement and excessive weight of the socket, especially in case of upper limb amputees. All of these problems mentioned, are related to a high rate of prostheses abandonment (39).

Since the distal side of prosthesis is in direct contact with environment, it is very difficult to distinguish between a simple skin reaction and a bacterial superficial infection. To diagnose a true skin infection, signs of inflammation have to be correlated with the positive bacterial cultures and a good response of inflammation, with the use of antibiotics (19). In this way, skin motion around the abutment, seems to be a predisposing factor for superficial infections and/or skin reactions of the skin penetration site (24). However, bacterial contamination (commensals, mutualistic, or

pathogenic and potential “pathogens”) has been found in half of asymptomatic patients with this kind of prosthesis (34). Therefore, some skin reactions are probably recorded as superficial infections and vice versa in the included studies. For these reasons, a classification system of the skin reactions would be useful, to quantify the risk, of developing a superficial infection, helping the clinician to distinguish a real skin infection or a simple inflammatory skin reaction.

Periprosthetic fractures (18%) and aseptic loosening (8%) are important postoperative complications. Therefore, it is important to perform a close radiological follow-up to detect prognostic signs(40). The studies regarding upper limb amputees showed that the radiological modifications of trans humeral amputees are like those in transfemoral. However, the distal bone resorption in the humerus is often to a lesser extent than in the femur and the proximal buttressing is localised at the side above the

fixture (40). This seems to be associated to different forces that act in the femur (compressive forces and bending moments) and humerus (tensile forces and bending moments). All these radiological changes with endosteal bone resorption are potential factors associated to periprosthetic fractures or reduction of the fixture's stability.

Even if the high rate of complications and infection seems to discourage those procedures, most of the studies included, reported significant improvement in clinical outcomes compared to preoperative time (21, 24-27, 30, 32, 36). These findings are in agreement with the current available literature showing an enhanced comfort, increased range of motion, improved mobility compared with socket-suspended prostheses (23, 33, 41, 42). Regarding upper limb osseointegrated prosthesis, none of the included studies report clinical outcomes.

Nevertheless, as above mentioned, trans-humeral amputation achieves good results especially in terms of full freedom of motion of shoulder joint compared to traditional socket prosthesis (28). This demonstrates that this procedure helps the patient to become more independent during their daily activities and avoids the discomfort of prosthetic custom-design socket (1). Moreover, the osseointegrated prosthesis has less maintenance costs over a long period of time, since being bone-anchored, there is no need to modify the socket periodically in relationship to the residual limb volume, which could change over time (28, 42).

Whereas these procedures are associated to a high percentage of complications, the right selection of patient is crucial. The indications and contraindications for this surgical technique are not always stated in the current available literature. Generally, patients have demonstrated discomfort with the conventional socket prosthesis and they must have an adequate bone stock in the residual limb and must be in good overall health and able to comply with the rehabilitation protocol (23, 33, 35). The contraindications are represented by the clinical conditions associated to an increased risk to develop a postoperative infection, fracture or loosening, such as active infection, peripheral arterial disease, diabetes mellitus, current chemotherapy or immunosuppressant drug use, smoking, osteoporosis,

metabolic bone disease, or untreated skin disease of the residual limb (10, 21, 25, 26).

The osseointegrated implant, besides giving a mechanical stability and avoiding socket issues, can provide a sort of sensory feedback, called "osseoperception". This may be a further component that could explain the good postoperative clinical outcome of these implants. During last decades, few psychophysical tests have been performed on osseointegrated prostheses confirming a better tactile function that leads to a better physiological integration of the limb (43). This seems to be realized thanks to a partial sensory substitution of vibrations and torques (44). Which kind of receptor groups involved in this so-called "osseoperception" is still debated in the scientific community. Non-invasive analysis such as Somatosensory Evoked Potentials (SEPs) and functional Magnetic Resonance Imaging (fMRI) are currently being used to help visualizing the activity centres involved in the pathway from the stimulation site to the cortex. Both these approaches provide new standpoints for osseoperception research and would try linking the anatomical and histological background to the clinical observations. If such links are present, osseoperception might help in physiologic and functional integration of implants in the body (43).

This paper presents several limitations: the studies included are all case series and retrospective with except of two studies (26, 27), and was no randomized and comparative showing a low level of evidence, as stated with MINORS score. Moreover, the population included varies widely in age range and several types of implant was used with a relatively short follow-up, making difficult to point out which is better. Only one study (29) have reported the timing of development of infection. Furthermore, studies regarding upper limb did not report clinical outcome results.

The bone-anchored prosthesis is associated to a relatively high rate of postoperative infections and complications, but good postoperative clinical scores are highlighted. Furthermore, the osseointegration technique is not related to important socket – related problems (skin sores, excessive sweating, fitting issues etc.) that can often lead the patients to abandon the use of a prosthesis.

Therefore, it is a promising technique that would help the patients to carry out a life, as close as possible before the amputation, including the possibility to have a better embodiment and to apply a bionic prosthesis. At the same time, it is a high demanding surgical technique that require important expertise by the surgeon, therefore this kind of surgery should be carried out only in specialized centres.

The data available from the literature are poor, therefore we encourage to perform more clinical studies to report and clinical data, to establish which kind of implant is associated to higher clinical performance and lower rate of postoperative complications and infections.

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Frailty of the elderly in orthopaedic surgery and body composition changes: the musculoskeletal crosstalk through irisin.

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In recent years, scientific interest has been developed towards irisin, a novel molecule of the family of myokines, which is directly involved in body mass composition balance, chronic diseases susceptibility and physiologic resilience to stressful events, including surgery. In the context of musculoskeletal disease, the role of this molecule has been associated to the balance of lean and fatty mass, and the production of irisin is subordinated to a healthy lifestyle and exercise. The mechanism of action of irisin on tissues is complex, and several studies described the molecular pathways in animal model and human subjects. In particular, in adipose cells, the key-role of irisin is to stimulate the differentiation of white adipose tissue to brown adipose tissue, through the action on the uncoupling protein 1. Furthermore, in the bony tissue, irisin stimulates osteogenesis through expression of *Sost* and *Opn* genes. These features make irisin a suitable molecule to use as a biomarker of the overall musculoskeletal health of the elderly, before undergoing orthopaedic surgery. Further research on this topic should be carried out to highlight the possible clinical role and predictive value of irisin in a multidisciplinary approach to the elderly before musculoskeletal surgery.

Ageing of the European population is the present main concern of scientists and institutions. Public expense is markedly burdened by the health of older people (1), and institutional funding to research is strictly focused on the ageing and health of the elderly. Several recent reports showed that Italy is one of the older countries in terms of average life and most of data concerning ageing are supplied by clinical and epidemiological research from this Country (1, 2).

From the comprehension of the mechanism of ageing with the deepening knowledge about senescence of tissues (3), nowadays the attention is more focused on those biomarkers, which could guarantee the understanding on *how* ageing develops

and on the identifications of the molecules that are associated to well-being in older age (4). Special interest has been developed towards irisin, a molecule of the family of myokines, which is directly involved in body mass composition balance, chronic diseases susceptibility and physiologic resilience to stressful events, including surgery (5). In other words, it seems that the multimodal frailty of the elderly, could find a common denominator in irisin.

It has been reported that irisin, the product of *FNDC5* gene (Fibronectin type III Domain-Containing protein 5) translation, plays a major role in reducing the risk of developing metabolic syndrome and obesity, diabetes, and cardiovascular events (6, 7) and to improve vascular function and

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muscular mass preservation, as well as bone health (5). In the context of musculoskeletal disease, the role of this molecule has been associated to the balance of lean and fatty mass, and the production of irisin is subordinated to a healthy lifestyle and exercise. Furthermore, it has been hypothesized that irisin is associated to exceptional longevity, as shown by results of recent studies, evidencing that irisin levels were significantly higher in healthy centenarians than in adults with precocious myocardial infarction (4). However, contrasting evidence is available within the present literature.

From the perspective of the orthopaedic and trauma surgeon, irisin could be of potential interest in the response of the patient to major surgical procedures, since the decrease of muscle mass, defined as sarcopenia, plays a significant role in post-surgical rehabilitation and complete recovery of the patient (8). Only few studies concerning the role of irisin in humans are available within present literature, and even fewer concern the role of this molecule in a context of frailty of the elderly and response to surgery. The present review aims to collect the full available evidence concerning the role of irisin in the multidisciplinary approach to the elderly and specifically focuses on the musculoskeletal tissue modifications which seem to be led by the action of this molecule. Although a relevant part of literature concerns animal model trials and *in vitro* studies, this review has been focused on human subject research.

RESULTS

Basic science of irisin - Molecular basis and functioning

Firstly discovered in 2012 (9), irisin belongs to the family of myokines, a group of proteins that are released from skeletal muscle as a part of its relevant endocrine function. Indeed, irisin should be properly considered as one of the latest discovered hormones (10). It is the product of cleavage of the peptide encoded by the FNDC-5 gene (Fibronectin type III Domain-Containing protein 5), located at the band 1p35.1 of the chromosome 1 in humans. The release of this peptide, among the other pathways, is induced in response to the production of PPAR- γ coactivator-1

α (PGC-1 α) (9) (see Fig. 1), which is a well-known molecule released after physical exercise.

One year later, in 2013, Roca Rivada et al. demonstrated that FNDC-5 should be considered also an adipokine, as the molecule expression was evidenced also in adipose tissue (11). In adipose cells, the key-role of irisin is to stimulate the differentiation of white adipose tissue (WAT) to brown adipose tissue (BAT), though the action on the uncoupling protein 1 (UCP-1). This transformation allows to switch the function of adipose tissue from storage to energy-production, in form of heat dispersion, thus inducing body weight reduction and increase of insulin sensitivity. Further studies in recent years have demonstrated that FNDC-5/irisin is also expressed in cardiac muscle cells and Purkinje cells of the brain; moreover, circulating levels of irisin peptide can be dosed upon a blood sample through Western blot or ELISA assays (12). For its specific role of crosstalk between tissues, the molecule has been named “irisin”, after the name of Iris, the Greek messenger goddess (13).

The role of exercise in irisin production

Muscular contraction yields irisin secretion, through the intermediate action of PGC-1 α . It has been suggested that different types of physical exercises are related to different type and entity of irisin secretion, although a clear correlation has not been defined yet. The firstly published studies failed to demonstrate a direct association between single bout of exercise or prolonged training and FNDC5 expression; on the contrary, this was hypothetically associated to the indirect effect of PGC-1 α , which is not consistently accompanied by a respective and proportional expression of FNDC5 (14).

However, subsequent investigations showed that aerobic performance is correlated to the expression of FNDC5 and PGC-1 α genes, in male patients affected by heart failure, and in particular a direct positive correlation has been found between aerobic capacity and FNDC5 gene expression (14). A completely different result has been reported on a larger cohort of men and women, in which an inverse correlation has been found between peak oxygen uptake (a validated measure of aerobic threshold) and irisin in

men, while the association was positive in women.

Confirming these sex-dependent results, a study by Scalzo et al. (15) reported that a three-week programme of high-hyperintense repetitive exercises was positively correlated to irisin production increase in females but not in males. This effect has been related to body composition, which is different according to sex (15). In addition, an increase in overall FNDC5 mRNA resting levels has been found in response to regular high-volume interval training for a period of 20 days (16).

Furthermore, a positive correlation has been found between irisin production and isokinetic strength of legs in aged woman. A hypothesis advocated by the authors is that irisin level is a predictive factor associated to muscular function impairment (17). Conversely, chronic resistance and strength exercise have been related to decrease in mRNA levels of FNDC5 and PGC-1 α , with a decrease in circulating irisin levels, after the completion of the exercise programme. The same study reported an increase in irisin level after strenuous exercise, with a rapid decrease 2 hours after training (18).

Irisin and metabolic diseases

Adipose tissue is involved in irisin secretion and is a direct target of irisin itself. As a consequence of, this mechanism, effects of irisin are considered relevant for several diseases involving metabolic pathways, including diabetes mellitus, hypercholesterolemia and obesity (19). Furthermore, cardiovascular benefits are associated to circulating irisin levels (4). The main effect induced by FNDC5 is the increased expression of mRNA encoding for UCP-1, with a direct induction of browning of the adipose tissue (9). The phenotypic change in fat, by uncoupling of oxidative phosphorylation, induces an increase in oxygen consumption, heat loss and energy expenditure (20). As a result of this, a decrease in body weight occurs.

However, a recent investigation demonstrated that irisin levels were directly correlated to Body Mass Index (BMI), due to an upregulation of FNDC5 that can be observed in obese patients and in non-diabetic patients with glucose intolerance (21). In support of these results, Huh et al. suggested a positive

association between irisin levels and obesity, with a down-regulation of FNDC5 occurring subsequently to bariatric surgery (12). Therefore, the actual role of irisin in metabolic syndrome prevention and glucose metabolism improvement is far from being elucidated, in contrast to what was proposed by Bostrom et al. in 2012, when irisin was advocated as a molecule probably able to treat diabetes and metabolic syndrome (19, 22).

Significantly decreased irisin levels have been shown in patients affected by Type 2 Diabetes Mellitus (T2DM) (19, 22), but *in vivo* and *in vitro* studies reported contrasting results (5, 21), with a difficult interpretation of this issue. For patients affected by Type 1 Diabetes Mellitus (T1DM), the trend is rather opposite, with increased irisin levels in T1DM children and adolescents; moreover, a positive effect of irisin in metabolic control when continuous insulin treatment was undertaken has been suggested (23). Differently, in adults with T1DM irisin levels correlated to HbA1c ones (24).

Sarcopenia, osteoporosis and the frailty of the elderly-considerations on musculoskeletal ageing

Independently from demographic variables (i.e. sex, ethnicity), ageing of musculoskeletal system leads to a significant decrease in bone and muscle mass (25). Furthermore, joint cartilage wearing and osteoarthritis (OA), constitutes a significant burden in terms of morbidity and inability to attend daily living activities (26). People affected by OA or rheumatoid arthritis and those with a history of osteoporotic fractures have higher mortality rates, when compared to healthy people (26). Furthermore, it has been demonstrated that depression, loss of independence and well-being and generalised frailty are closely associated with ageing and musculoskeletal disease (26).

These conditions not only yield to a low quality of life but are also involved in early retirement from work and impaired social activities, especially in developed Countries. Muscle mass and osteoarthritis development are closely related as suggested by our study group in 2014 (8), although the causative effects of muscle atrophy and sarcopenia is not clarified yet, especially concerning the possibility to

induce joint wearing. Bone ageing primary involves the decrease of bone mass and mineral content, and the increase of adipose substitution of bone marrow (27, 28). These features significantly increase the risk of fracture and decrease the bone healing potential, configuring a clinical situation of frailty. The biochemical factors associated to this condition are poorly understood in their complex, as most of the evidence is still limited to *in vitro* studies (28) but lacking a comprehensive evaluation of the complex underlying biochemical machine.

The role of sarcopenia and osteopenia

The loss of skeletal muscle mass and atrophy that ineludibly occurs with ageing, yields to an imbalance between lean and fatty body mass, configuring a condition of sarcopenia (29). The reduction of muscle mass and therefore of the muscle lever function lead to a relevant impairment of the entire musculoskeletal system, with a reduction in activity and strength. The close bone-muscle relationship, known as the “Utah paradigm” (30), affirms that resting tension at the musculotendinous junction is directly proportional to the new bone apposition, thus suggesting that muscle mass and resting tone are directly related to bone mass and strength (30,

31). This means that sarcopenia is strictly connected to osteopenia and osteoporosis, leading to a two-fold increased risk of fracture: by one side because of intrinsic bone fragility, and by the other, because of a lack of a robust surrounding muscular structure.

This association has been already suggested by Crepaldi and Maggi in 2005, defining “hazardous” the association between sarcopenia and osteoporosis (32). In the elderly, the cause-effect relationship between sarcopenia and OA is not definitely understood, as the decrease in activity yielded by joint pain often leads to muscular atrophy but also the lack of a robust support to bone and joint (physiologically represented by a fully functional skeletal muscle) increases joint cartilage loading and wearing (8).

A vicious circle is then present in the elderly affected by sarcopenia, with a wide effect over the entire musculoskeletal system. In fact, the main criteria for the evaluation of sarcopenia, according to the International Working Group on Sarcopenia include the physical performance of the patient and gait speed (33). Current literature concerning sarcopenia suggests that obesity, altered metabolic conditions, low exercise rate and joint pain positively correlate with the development of this condition, which remains difficult to assess and treat in the elderly (8).

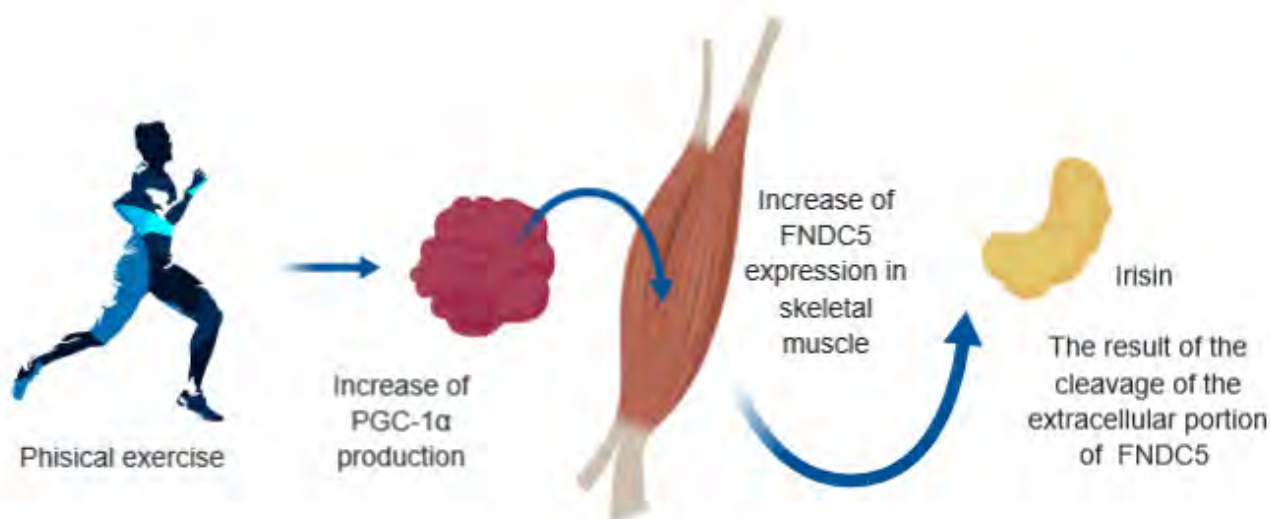


Fig. 1. *Irisin production in response to exercise. PGC-1α (PPAR-γ coactivator-1 α); FNDC5 (Fibronectin type III Domain-Containing protein 5).*

Irisin and musculoskeletal health

Minimal evidence is available concerning irisin and musculoskeletal health, especially in the ageing perspective. Furthermore, the few available studies, often reported contrasting results. A negative association was found between muscle mass percentage and irisin in obese Chinese subjects, and anthropometric studies showed that irisin levels were inversely related to waist and hip circumference (34). Concerning bone metabolism, similar inhomogeneous results were found as well. The association between higher irisin levels and decrease rate of osteoporotic fractures in post-menopausal women was firstly showed by Anastasilakis et al. (35), but not confirmed by Palermo et al. demonstrating an inverse correlation (36).

Nevertheless, both studies failed to stratify results according to bone mass and bone quality, thus limiting the evidence because of the possible role of bone quality indexes in osteoporotic patient outcomes. From a molecular perspective, the studies by Colaianni et al. (37) demonstrated a relevant role of irisin in bone anabolic function, with an increase in osteoblastic genes expression and a decrease in the expression of osteoclastic ones (38, 39) (see Fig. 2). Muscle mass decrease observed with ageing,

yields to a decrease in irisin circulating levels, as demonstrated by Huh et al. (12). Anthropometric measures of muscle mass (i.e. biceps circumference), positively correlated to irisin levels, thus suggesting that amount of muscle in body composition is the main variable associated to irisin production (12). This element is of paramount importance in ageing as sarcopenia of the elderly yields to decreased irisin levels and impaired adipose, glucose and bone metabolism. However, there is a lack of available evidence concerning the effects of muscular atrophy, and consequent irisin decrease in the elderly (40).

The response of the elderly to musculoskeletal surgery

In daily orthopaedic clinical practice, especially in joint arthroplasty department, the average age of patients is high. The clinical management of older patients is often complex, as complex as the patient himself (41, 42). The presence of several comorbidities makes it a mandatory multidisciplinary management, which includes the participation of orthopaedic surgeons together with geriatricians and other specialists (43). Furthermore, an accurate psychosocial evaluation of the patient is mandatory, to understand his personal necessities regarding care-giving and psychological approach to surgery (44).

The perioperative needs of the elderly are significantly different from those of the young adults and expectations and objectives of the surgery may differ (45). If the function restoration is of paramount importance for young, active subjects, often soothing of discomfort and a slight improvement of function can be acceptable for the aged patient (45). Furthermore, there are several orthopaedic procedures that are specific for the geriatric population, including reduction and fixation of femoral neck fractures, vertebroplasty for spine fractures, advanced knee replacement involving hinged prostheses, and arthroplasty revision procedures. For most of these procedures, general anaesthesia is required and the chances that the patients present a high pre-operative risk are very high.

It has been reported that the residual functional reserve of organs in geriatric patients are significantly decreased in comparison to the younger ages, therefore the ability of the organism to face a stressful event,

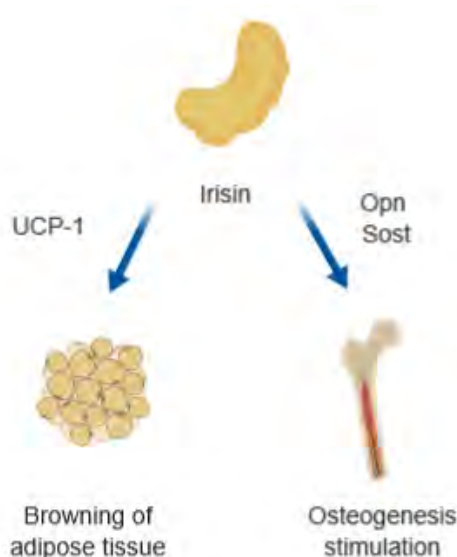


Fig. 2. The hypothesized mechanisms of action of irisin on tissues. Adipose browning (9), Osteogenesis (38). UCP-1 (Uncoupling Protein-1); Opn (Osteopontin gene); Sost (Sclerostin gene).

including surgery, impairs results (46). It has been also reported that anaesthesia protocols, including not only general anaesthesia, but also epidural and loco-regional blocks, lead to a disequilibrium of several metabolites, circulating electrolytes and glucose (47, 48). In addition, the fatigue developed by the patient in the post-operative setting seems to be directly correlated to the stressfulness of the surgical procedure (49), but also to nutritional deficits, pain, depression (50), and inflammatory status (51). It has been reported that depressive tract in the elderly undergoing surgery is correlated to a poorer postoperative outcome (52) and associated to the development of a more marked disability. Moreover, it has been demonstrated that pre-operative cognitive performances of geriatric patients could predict the occurrence of post-operative complications (53) and could influence functional outcomes of surgery and rehabilitation (54, 55).

The modifications of body mass in the elderly with increase of body weight and decrease of active skeletal muscle mass, strictly contribute to the clinical condition of frailty (8). Furthermore, the poor physical performances, significantly affect the post-operative rehabilitation (42), with detrimental effects on functional outcomes of the surgery, restoration of the range of motion and full gait recovery. Since there is a lack of clinically validated measures for general frailty of the elderly, the comprehensive evaluation of all these variables could be of interest in the global assessment of the older patients' in candidate for surgery.

From the available evidence, presented in this review, irisin could be a marker of body composition changes, especially concerning the balance between muscular and fatty tissue. Furthermore, the physical activity status of the patient could be assessed through the evaluation of circulating irisin levels. At present, literature does not present sufficient evidence to formulate a tool for thorough clinical assessment of the elderly before and after orthopaedic procedures. Apart from general assessment concerning the psychological and physical status of the patient, quality of life assessment and patient reported measures, a validated biomarker for the categorization of the status of the patient still lacks.

The main hypothesis underlying the present study

is that the musculoskeletal crosstalk through irisin could be of paramount importance for perioperative outcomes in the orthopaedic patient, especially in the elderly. The study of circulating levels of irisin could be of interest as a relevant marker of different conditions, which the patient may suffer from, including sarcopenia, osteopenia and impaired glucose metabolism. Furthermore, the basal activity level of the patient that seems to influence the circulating irisin levels, is relevant in concern to his ability to face and carry out the prescribed workout for an appropriate rehabilitation.

In conclusion, based on the evidences presented in this review, irisin could be considered a useful marker for identifying frail elderly patients in orthopaedic surgery and a biological predictor of surgical outcomes. Anyway, further studies should be designed to confirm these hypotheses.

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Weil osteotomy for the treatment of grade III hallux rigidus: a case series

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Hallux rigidus (HR) is one of the most common pathologies of the forefoot. The conservative treatment is indicated for early stages, while surgical treatment is required for advanced osteoarthritis and rigidity. Surgical treatment of advanced stages of HR is still controversial and includes joint-destructive procedures such as arthrodesis and arthroplasty, Weil osteotomy for decompression of the joint space may be a safe and effective procedure for the treatment of grade III HR. Twenty-four patients that underwent Weil osteotomy for Grade III HR were retrospectively reviewed. American Orthopedic Foot and Ankle Score (AOFAS), ROM and a subjective 5-point satisfaction scale were evaluated preoperatively, at 1 year, and at a minimum follow-up of 2 years. Joint space width and metatarsal length were assessed through radiographic examination preoperatively, immediately postoperatively and at 2 years follow up. AOFAS score was 45.1 ± 3.9 preoperatively, 84.9 ± 6.4 at 1 year and 73.7 ± 6.2 at two years of follow up. All patients were satisfied with the procedure at 2 years follow up. Mean ROM increased from 35.1° (range, $10^\circ - 50^\circ$) preoperatively to 80.3° (range, $60^\circ - 90^\circ$) at 1 year. Mean dorsiflexion increased from 5° (range 0° to 10°) preoperatively to 15° (range 7° to 23°) at 1 year. Both total ROM and dorsiflexion values remained constant at 2 years. The joint space was 0.5 ± 0.9 mm preoperatively, 2.0 ± 1.9 mm at 1 year and 1.5 ± 1.2 mm at 2 years. The average metatarsal shortening was 2 ± 1.4 mm. Weil osteotomy alone can be beneficial for the treatment of patients affected by advanced HR. It can improve clinical and radiological outcomes at 2 years follow up in a series of patients affected by grade III HR. Therefore, the sliding oblique osteotomy represent a valid alternative to delay more aggressive procedures.

Hallux rigidus (HR) is considered one of the most common pathologies of the forefoot affecting 2.5% of people over 50 years of age. It is a degenerative disease that involves the first metatarsophalangeal joint (I MPJ) joint upon which the whole-body weight is loaded during the propulsive phase of gait (1). HR is characterized by narrowed joint space and dorsal osteophytes which can cause debilitating pain and limited range-of-movement (ROM). If left untreated it may lead to severe impairment in walking and performing daily activities. Main causes of HR

include post-traumatic degeneration, postoperative arthritis, avascular necrosis, excessively long first metatarsal and hypermobility of the first ray with excessive pronation of the hindfoot (2). A widely used classification was described by Coughlin and Shurnas (3), considering ROM, clinical evaluation and radiologic findings (1, 3).

Conservative treatment is indicated in the early stages and it is based on the use of NSAIDs, intra articular steroid injections and partial weight bearing (4). Surgical treatment is reserved to advanced

Key words: hallux rigidus, Weil osteotomy, metatarso-phalangeal joint, osteoarthritis

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stages of HR or in those subjects unresponsive to conservative treatments. Surgical management can be based on salvage procedures such as cheilectomy and osteotomies or destructive technique including arthrodesis and arthroplasty (5). However, there is still no consensus on the appropriate surgical algorithm for the management of advanced HR which remains controversial.

Arthrodesis of the I MPJ has been advocated for a long time by many surgeons as the first-choice treatment (5, 6). However, good clinical and radiological outcomes as also preservation of the ROM have been reported with Weil oblique osteotomy (5) and hemi-arthroplasty (4, 5). Weil oblique metatarsal osteotomy provides a shortening of the first metatarsal (I MT) bone, reducing MT head loading during the passage from the mid-stance to the toe-off phase. Hemi-arthroplasty avoids stiffness and further cartilage fragmentation also providing implementation of ROM, but it does not correct or restore the normal biomechanical function of the first MPJ (7). To achieve better outcomes, these two techniques can be performed simultaneously, associating lower loading with better ROM (5). However, combined surgery is by far more challenging and can lead to a higher rate of complications, first of all prosthesis mobilization (5).

It has been hypothesized that Weil osteotomy alone may result in an effective procedure for the treatment of grade III HR, with good clinical and radiological outcomes and a short rehabilitation period. To support this hypothesis, in the present investigation a series of patients affected by grade III HR treated with Weil osteotomy are reviewed and mid-term follow-up results are presented. Primary endpoints are clinical and radiographical outcomes.

MATERIALS AND METHODS

Study population

The present study was conducted according to Good Clinical Practice and Helsinki declaration statement. Twenty-four patients underwent Weil osteotomy for grade III HR at our institution between 2012 and 2013. Medical records of this cohort were retrospectively reviewed. Inclusion criteria were: 1)

clinical and radiographic diagnosis of symptomatic grade III HR according to Coughlin and Shurnas' clinical and radiological grading system; 2) failure of conservative treatments; 3) minimum follow-up of 24 months present within the medical records; 4) given informed consent to the use of medical records for research purposes. Exclusion criteria were: 1) grade I, II or IV HR according to Coughlin and Shurnas' clinical and radiological grading system; 2) short MT length (shorter than 3 mm compared to the second MT) 3) history of severe trauma on the same foot 4) any previous surgical treatment on the same foot; 5) intermetatarsal angle greater than 10° or hallux valgus angle greater than 15°; 6) septic arthritis or osteomyelitis; 7) neuropathy; 8) inflammatory arthritis.

Demographic data of the patients were collected and analysed. The results were calculated utilizing patient data from postoperative visits.

Outcome measures

The outcome measures were changes in American Orthopedic Foot and Ankle Score (AOFAS) and MPJ ROM measure with a goniometer. Data evaluated preoperatively, at 1 year, and at a minimum follow-up of 2 years.

A subjective 5-point satisfaction scale was used to rate the overall results of surgery (relief of pain, function and appearance of foot) post-operatively at 2 years follow up, where 1 was the lowest satisfaction and 5 represented a full satisfaction.

Radiographic examination was performed preoperatively, immediately postoperatively and 2 years follow up. Standard anteroposterior (AP) and lateral weight-bearing foot radiographs were obtained. We assessed joint space width and MT length. Sesamoid deformity, shape of the first MT head, interphalangeal arthritis, any recurrence of dorsal osteophytes, loose bodies, subchondral sclerosis, and evidence of nonunion were also noted. All complications observed during follow-up were recorded.

Operative technique

Patient was positioned supine and popliteal block regional anaesthesia was performed. Tourniquet was

applied at ankle at a double the systolic pressure of the patient. Dorsomedial incision of the skin and soft tissues was carried out to approach the I MPJ. The capsule was incised, leaving intact the plantar aspect of the capsule and collateral ligaments. Osteophytes of the dorsal and lateral aspect of the joint were removed through a rongeur. The dorsal aspect of the metatarsal bone was freed from overlying tissues through medial and lateral retractors and osteotomy was performed with an oscillating saw. The cut began from the junction between the superior articular cartilage surface and the metatarsal shaft. The cutting trim was directed from dorsal to plantar and from distal to proximal, with an inclination of about 30°, to leave intact the connection of the plantar vessels which supply the MT head. Lateral and plantar soft tissues which remained attached to the MT head, pulled and displaced the bone fragment plantarly and proximally.

A displacement of 1 to 3 mm used to be considered sufficient, although pre-operative evaluation of the deformation was considered to achieve the best decompression and realignment of the joint. The osteotomy was fixated with two mini Herbert screws, also avoiding axial rotation of the MT head. The dorsal aspect of the proximal MT fragment was smoothed to avoid any impingement during postoperative movement and ROM was checked by intra-operative dorsiflexion of the hallux. Capsule was closed through absorbable suture. Skin was sutured, and compressive bandage was applied.

Postoperative rehabilitation

The operated foot was kept elevated and ice therapy applied to the wound. Active and passive ROM exercises began within the first operative day. Full weightbearing in a surgical shoe which concentrate the weight only on the hindfoot was

allowed immediately after surgery and until 4 weeks. Patients were then allowed to wear athletic shoe in approximately 4 weeks based on radiographic evidence of consolidation.

Statistical analysis

Data analysis was carried out using Stata software (ver. 12, Stata Corp, Texas, USA). Demographic data were computed for descriptive statistics. A Shapiro-Wilk test was carried out for numerical variables to assess normal distribution. Once verified normality of the series of data, Student's T test for paired samples was carried out for continuous and discrete variables, assuming discrete variables as continuous in distribution. A significance threshold value was set as $p < 0.05$. No missing data had to be addressed. Continue variables have been reported with mean, standard deviation and/or 95% confidence intervals, discrete variables were reported with median and range. A post-hoc compute-achieved power analysis has been carried out (G*Power software, ver. 3.1.9.4). With an effect size of 0.6 ($\delta = 2.93$, critical $t = 2.07$), the power of the study was of 80%.

RESULTS

A total of 24 subjects and 24 feet, including 11 right feet and 13 left feet, were included in the study. The patient population consisted of were 14 males and 10 females, with an average age of 57 ± 4.7 years (Table I). Follow-up ranged between 24 and 34 months with an average of 28 months.

Mean preoperative AOFAS score was 45.1 ± 3.9 (95% CI 43.5 - 46.7) and improved significantly at 1 year of follow-up, averaging 84.9 ± 6.4 (95% CI 82.1 - 87.6, $p < 0.001$) (Fig. 1). At two years, the AOFAS mildly decrease in confront to the value at 1 year, to a mean of 73.7 ± 6.2 (95% CI 71.1 - 76.3, $p < 0.001$) (Fig. 2).

Table I. Demographic data.

Variable	
Sex (M:F)	14:10
Age (Mean $\pm$ SD)	57 ± 4.7
Follow-up, months (Mean, range)	28, 24 - 34

Evaluation revealed that all patients were highly satisfied (score 5 out of 5), with no patients unsatisfied or mildly satisfied at 2 years follow up.

ROM was significantly improved following the surgical procedure. Mean ROM increased from 35.1° (range, 10°– 50°) preoperatively to 80.3° (range, 60°–90°) at 1-year follow-up ($p<0.001$) and remained constant at 2 years follow-up ($p<0.001$). The greatest increase occurred in the dorsiflexion. Median dorsiflexion of the I MPJ joint improved from 5° (range 0° to 10°) preoperatively, to 15° (range 7° to 23°) at 1-year follow-up ($p<0.001$) and remained constant at the 2-year follow-up ($p<0.001$).

Radiographic evaluation was based on AP and lateral views evaluated preoperatively, immediately

postoperatively and at last follow up. The average preoperative joint space was 0.5 ± 0.9 mm (95% CI 0.2 - 1.9) and significantly increased at 1 year with an average of 2.0 ± 1.9 mm (95% CI 0.8 - 2.9, $p<0.001$). At 2 years follow up the joint space reduced to an average 1.5 ± 1.2 mm (95% CI 0.8 - 3.1, $p<0.001$) (Fig. 3). The I MT was shortened after surgery in all cases (Fig. 4). The average shortening was 2 ± 1.4 mm (95% CI 0.8 - 2.7).

No intraoperative complication occurred during the study. None of the patients underwent hardware removal. One patient reported metatarsalgia at the second metatarsal and was treated with accommodative padding and total resolution of symptoms. There was no correlation between the amount of shortening and metatarsalgia symptom.

DISCUSSION

According to the results of the present case series, Weil osteotomy can be an effective procedure for the treatment of patients affected by grade III HR as shown by the improvement in mid-term clinical and radiological outcomes, in terms of AOFAS score, ROM measurement and radiographic examination.

Surgical treatment for HR is indicated when conservative treatments fail, or as a first-line treatment in advanced HR. The goals of the surgical treatment in the symptomatic HR are the mechanical correction of the deformity, restoration of biomechanics, pain relief, prevention of recurrence to provide the patient with good functional outcomes for a biomechanically correct and pain-free gait.

However, still no single procedure has been proven to be superior in moderate to severe stages of HR. Arthrodesis of the I MPJ is usually considered the “gold standard” in patients affected by severe HR (8, 9). Patient compliance, rigid fixation, adequate bone stock and vascularization are crucial for the success of this procedure which, however, blocks ROM in favor of pain relief. Moreover, the technique is not without potential complications such as nonunion, difficulties in wearing shoes, metatarsalgia and osteoarthritis of adjacent joints and most importantly permanent activity restrictions (10). Therefore, it should be used only as a salvage procedure.

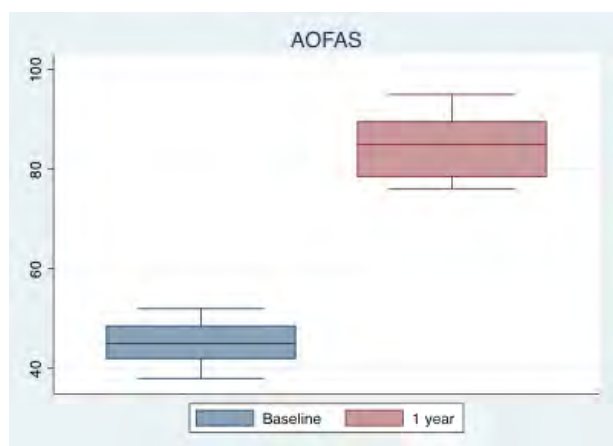


Fig. 1. AOFAS score at 1 year after surgery - compared to baseline.



Fig. 2. AOFAS score at 2 years after surgery - compared to baseline.



Fig. 3. Representative Xray images of grade III HR treated by Weil osteotomy



Fig. 4. Representative Xray images of grade III HR treated by Weil osteotomy.

Total arthroplasty and hemiarthroplasty have been an alternative to arthrodesis since they can preserve joint mobility (7). Nevertheless, the procedure is associated with significant complications such as implant related soft tissue reaction, joint stiffness, subluxation, synovitis and osteolysis, implant failure and poor functional results (11).

Distal oblique sliding Weil osteotomy is characterized by a single, dorsal distal to plantar proximal oriented osteotomy line, beginning just proximal to the articular surface with an osteotomy

angle about 30°. Oblique Weil osteotomy first developed in middle 1990's, aims to shorten the I MT, increase MPJ space while decrease loading, and provide stability of the I ray when instability is the main cause of recurrence. This osteotomy has been widely used in the surgical treatment of different pathologies of the forefoot such as excessively long MT, imbalance of the MT parabola, correction of lesser MPJ subluxation and luxation (12). The osteotomy produces a predictable and programmed shortening of the MT, stable to allow

immediate weightbearing which helps to compress the osteotomy.

In the present study, the procedure was successfully performed on patients affected by advanced HR, proving to be a valid treatment approach for grade III HR. Clinical and radiographic outcomes showed that the osteotomy alone provided good articular ROM, AOFAS score and radiographic outcomes which were significantly improved from baseline. Moreover, the satisfaction score was high in all patients. Clinical improvement can be related both to MT shortening and correction of deformities of the MT head which are able to restore anatomical joint space.

Several clinical studies have also reported optimal results in the use of the sliding oblique osteotomy for the treatment of severe HR. Lundeen et al. initially described the use of the oblique osteotomy for painful HR proving that it is a safe and reliable procedure with excellent results, high patient satisfaction and low complication rates (13). Ronconi et al. evaluated the results of the Weil osteotomy and cheilectomy on 26 patients with excellent results in 84% of patients (5). Malerba et al. retrospectively analyzed 20 patients affected by HR that underwent Weil osteotomy (1). Both AOFAS scores and ROM significantly increased from 44 (range 14–68) to 82 (range 80–100). Good-to-excellent results were achieved in 19 patients.

On the contrary of destructive procedures, the Weil osteotomy is easy to perform and do not have a long learning curve. Moreover, being a sparing procedure preserves ROM and functionality of the joint delaying more aggressive procedures (14). Indeed, although it may not be a definitive surgery it can be a valid alternative to postpone destructive procedures such as arthrodesis and arthroplasty. However, it is not free from complications, including floating toe (most common) (13) transfer metatarsalgia, non-union, postprocedural OA of adjacent joints. The potential complication of lesser metatarsalgia exists with any procedure that is performed on the first ray, but it was not reported on this series of patients.

To achieve good postoperative outcomes, preoperative planning on radiographs is mandatory to avoid biomechanical impairment and transfer metatarsalgia to the other MPJ. The result of the

present study should be tempered with some limitations including the retrospective design, the absence of a longer follow-up and the paucity of the sample. Therefore, further comparative studies of different surgical techniques, through a prospective and randomized design, with a longer follow-up period and involving more patients are needed to assess the most effective treatment for late-stage HR.

Weil osteotomy alone represents an effective treatment for patients affected by grade III HR. Indeed, it improves clinical and radiological outcomes at 2 years follow up in a series of patients affected by grade III HR, in terms of AOFAS score, ROM, patients' satisfaction and radiographic parameters. The sliding oblique osteotomy represent a valid alternative to delay more aggressive procedures.

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Gait analysis in the postoperative assessment of intertrochanteric femur fractures

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Proximal femur fractures (PFFs) are an increasing public health concern. Improving gait and mobility after surgical fixation of intertrochanteric femur fractures (IFFs) is the most important target of research efforts. The purpose of this study is to investigate the role of gait analysis in the functional assessment of over-65 patients with stable and unstable IFFs, at a minimum 6-month follow-up. Fourteen patient's over-65 with IFFs (AO/OTA 31-A) treated with intramedullary nailing (EBA-2, Citieffe Srl, Italy) were enrolled. The patients were divided into two groups according to the fracture stable or unstable pattern, according to AO/OTA classification. At follow-up appointments, clinical outcomes [Harris Hip Score (HHS)], Western Ontario and McMaster University (WOMAC) and gait parameters were assessed. Radiographs were analyzed at the time of surgery and at each follow-up visit. At 3-month follow-up, both groups showed a significantly different gait patterns, compared with control subjects. At 6-month follow-up, a significant improvement of both mean HHS score ($p=0.43$) and mean WOMAC score was observed ($p=0.43$) within groups. Nonetheless, patients with stable fractures showed a comparable gait pattern, compared with control subjects, while patients with unstable fractures still presented a worse gait pattern, compared with control subjects. Therefore, in presence of an unstable IFF, a more aggressive rehabilitative program is needed. The data provided by postoperative gait analysis, therefore, could be useful to customize the patients' rehabilitative protocol, to quickly improve their walking ability and autonomy, thus reducing the post-operative re-fall risks.

Proximal femur fractures (PFFs), affecting around 1.5 million people per year worldwide, have a significant impact on the patients' health status, potentially leading to an increased disability, reduced quality of life and higher mortality (1). In Italy, PFFs have an estimated annual prevalence of 78,000, with 90% of injuries occurring in patients aged over 65 years (2-4). Nonetheless, with the rising life expectancy across the globe, the number of PFFs worldwide will drastically increase in the next few decades, reaching 6.3 million by 2050 (1, 5-7).

Intertrochanteric femur fractures (IFFs), representing approximately one half of all hip fractures, could be managed both with intramedullary and extramedullary implants (8, 9) randomised study was conducted in six level-two trauma centres in our area (Puglia, Italy). However, a recent meta-analysis by Zhang et al. stated the current evidence indicates short intramedullary nails (INs) may be a better choice, than Dynamic Hip Screw (DHS), in the treatment of IFFs (4, 10)^{95% CI: -34.91 - -7.39, $P=0.003$} . Compared to DHS, intramedullary nailing has theoretical advantages of

Key words: gait; biomechanics; proximal femur fractures; osteoporotic fragility fractures; post-operative assessment

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being less invasive and biomechanically superior, providing a buttress to limit fracture collapse (11-13) three, six and 12 months postoperatively, except for nine who died. There was no statistical difference in Parker mobility score between groups. The Gamma nail group had significantly higher Barthel Index and EuroQol-5D (EQ-5D). Moreover, in patients managed with cephalomedullary nails, a better recovery to pre-injury activity level, less blood loss and fewer complications have been reported (10, 12, 13) 95% CI: -34.91 - -7.39, $P=0.003$.

The main aim of the surgical management of IFFs is the recovery of patient's walking ability, in order to reestablish patients into their normal environment (14) among clinical sample of 81 community-dwelling hip fracture patients over 60 years. Perceived difficulty in walking outdoors and 500 meters was assessed before fracture, at discharge to home (3.2 ± 2.2 weeks after surgery). Walking, indeed, is the most essential modality of human life and disturbances of gait have a significant impact on the quality of life. Therefore, the assessment of gait might be a sensitive tool to monitor the progress of fracture healing, as well as success of the treatment in patients with IFFs. The purpose of this study is to investigate the role of gait analysis in the functional assessment of over-65 patients with stable and unstable IFFs, treated with closed reduction and internal fixation with short cephalomedullary nails, at a minimum 6-month follow-up.

MATERIALS AND METHODS

Study Design and Population

The study was designed as a prospective, observational study. After institutional review board approval, all patients with IFFs treated with intramedullary nailing were enrolled in the sample between October 2017 and October 2018 at the Orthopedic and Traumatology Dept, Azienda Ospedaliero Universitaria (AOU) "Policlinico" of Bari, Italy.

Fourteen patients treated with Endovis BA-2 (EBA-2) intramedullary nail, were included, older than 65 and able to deambulate autonomously before hip fracture. Only patients with postoperative reductions that met the displacement criteria (less than 4 mm. of displacement

on either the AP or Lat X-ray) and the angulation criteria (neck shaft angulation normal or slightly valgus 135° and less than 20° of angulation in the Lat X-ray), according to Baumgaertner's method (3, 4), were categorized as good and included in the study. Exclusion criteria were: (1) polytrauma patients; (2) incomplete follow-up; (3) inability to move outdoors without assistance at recruitment; (4) presence of comorbidities liable to influence the patient's mobility; (4) cognitive dysfunctions; (5) concomitant psychological or psychiatric conditions that might potentially influence the subjective evaluation of the outcome, or compliance, with gait analysis; (6) lower limb abnormalities that could be expected to influence gait pattern; (7) previous internal fixation or arthroplasty/hemiarthroplasty of the contralateral hip; (8) previous surgery of the superior and lower limbs.

According to these criteria, all the patients have been evaluated clinically, radiologically and through gait analysis (Table I). All patients received verbal and written information about the study and provided written consent. The Local Ethical Committee provided ethical approval for the study (Prot. n. 5556/2018) and the study was registered on ClinicalTrials.gov (NCT).

All the patients were divided into two groups according to the AO/OTA fracture pattern: patients with AO-31A1 fractures were included in Group-A (stable fractures), whereas patients with AO-31 A2 and A3 fracture patterns were included in Group-B (unstable fractures).

Surgical Procedure and Rehabilitation Protocol

Intramedullary nailing was performed, within 48 h from patients' admission, using the Endovis BA-2 endomedullary nail (Citieffe, Calderara di Reno (BO), Italy). Closed reduction of the fracture was performed, under fluoroscopic control, using an orthopedic traction table for reduction, to restore the anatomical position of fragments. The intramedullary nail was then implanted in distal unlocking configuration, using a standardised operative technique was used following the manufacturer's instructions (3, 15).

Standard antibiotic prophylaxis with 2 g. of Cefazolin – 1 hour before surgical incision and at 6, 12, 18 and 24 hours postoperatively (Fosfomycin in allergic patients)- and thromboembolic prophylaxis with enoxaparin 4000 UI, until full weight bearing recovery, was used.

All the patients followed the same rehabilitation

protocol. After introducing the patient to rehabilitative program, on the first-day post-op., ambulation was allowed with crutches on second or third postoperative day.

Gait Assessment

An eight-camera motion analysis system sampling at 200 Hz (BTS SMART DX-6000, BTS Bioengineering SpA, Milan, Italy) was used in conjunction with two force plates embedded in the walkway, sampling at 400 Hz (BTS Digivec, BTS Bioengineering SpA, Milan, Italy) to collect ground reaction forces during self-selected speed level walking. Each participant was asked to wear form-fitting shorts and a shirt and to walk barefoot during testing, to assess any changes in the ground reaction forces associated with variations in footwear. A standard Helen Hayes marker was used for testing as has been used. Participants were asked to walk at a comfortable speed. For a walking trial to be used in the analysis, the participant had to contact the force plate on the affected side without targeting it and all the marker data had to be collected during the trial.

Spatio-temporal parameters, including stride and length, step width, stance/swing/double stance duration (%), gait speed, walk ratio and cadence, and sagittal - frontal - transverse plane range of motion (ROM) for ankle (A), knee (K), hip (H), pelvis (P) and shoulder (SH) were collected bilaterally during each of the walking trials. Time-synchronized 3-D coordinate data and ground reaction force data were processed in the motion analysis system (BTS SMART Analyzer, BTS Bioengineering SpA, Milan, Italy). Data were normalized to the gait cycle. The variables of interest were extracted from processed data using a custom software developed in MATLAB

R2019a (MathWorks, Natick, MA, USA).

Clinical and radiographic evaluation

Preoperative radiological assessments involved anteroposterior and lateral radiographs of the hip and pelvis. Fractures were classified according to the AO/OTA classification system. All patients were followed clinically and radiologically with mean 3-month intervals for the first postoperative six months. The evaluation of the fracture reduction quality, according to Baumgaertner's criteria (16, 17), was carried out by two independent Orthopaedic surgeons (B.M. and G. V.) using the immediate post-operative standard anteroposterior (AP) and lateral (Lat) radiographs of the hip.

Clinical outcomes were assessed according to the Harris Hip Score (HHS) and Western Ontario and McMaster universities osteoarthritis index (WOMAC) at each follow-up visit. Leg length discrepancy was determined by using a direct tape measurement method; the distance between the anterior superior iliac spine and the medial malleolus on each limb was measured twice and the average value was used to compare the length of the legs between the operated and uninjured limbs. Additionally, body mass index (BMI, kg/m²) was recorded for each patient.

Statistical Analysis

The characteristics of participants were reported as Mean $\pm$ Standard Deviation (M $\pm$ SD) for continuous variables and as frequencies and percentages (%) for categorical variables. The dependent variables included clinical outcomes (HHS score, WOMAC score and T-Score), spatio-temporal parameters (stride and length,

Table I. Demographic Characteristics. *FU*= follow-up; *RLL*=Radiographic Limb Length Discrepancy at the end of follow-up; *CLL*= Clinical Limb Length Discrepancy at the end of follow-up; *n.s.*=not significant.

	Gender ♀, n (%)	FU (Months)	Age (Years)	RLL (mm)	CLL (mm)	BMI (kg/m ²)
Stable (n = 6)	4 (66.7%)	6	75.3 $\pm$ 8.7	81 $\pm$ 9.5	80.8 $\pm$ 10.5	26.3 $\pm$ 4.5
Unstable (n = 8)	4 (50%)	8	80.2 $\pm$ 4.1	83.7 $\pm$ 2.6	84.5 $\pm$ 2.6	23.8 $\pm$ 4.5
p-value	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

step width, stance/swing/double stance duration (%), gait speed, walk ratio and cadence) and kinematic outcomes (range of motion at ankle, knee, hip, pelvis and shoulder). For better interpretation of data, all bilateral variables were summarized as differences between injured and uninjured sides.

Shapiro-Wilk test was used to verify the normal distribution of samples. For unpaired group comparisons, the Mann-Whitney U test was used to verify differences in fracture type (stable, unstable), while Kruskal-Wallis test was used for multiple comparison (fracture type and healthy control). For paired group comparison, has been used the Wilcoxon test (3-month follow-up, 6-month follow-up). All statistical tests were two-sided and p -values < 0.05 were considered as statistically significant.

Table II. Correlation matrix between clinical scores and gait kinematics (for angular kinematics variables are expressed as $d\_joint\_axis\_ROM$, where d stands for difference, axis indicates the axis of rotation). *significant p -value at $p < 0.05$; ** significant p -value at $p < 0.001$.

		HHS	WOMAC	DeXA T-Score
HHS	R	-	.912**	.295
	p-value	-	.000	.351
WOMAC	R	.912**	-	-.319
	p-value	.000	-	.313
GAIT SPEED	R	.719**	.650*	-.022
	p-value	.008	.022	.944
WALK RATIO	R	.692*	.523	-.038
	p-value	.013	.081	.902
dARROM	R	.037	-.323	.652*
	p-value	.765	.657	.016
dAFROM	R	.334	-.245	.674*
	p-value	.720	.934	.012
dHRROM	R	.543	-.682*	.468
	p-value	.078	.015	.125
dSHTROM	R	-.626*	.357	.523
	p-value	.039	.210	.081
dSHKRROM	R	.443	.221	.676*
	p-value	.077	.876	.022

All statistical calculations were performed using IBM SPSS version 23 (IBM, Armonk, New York, USA).

RESULTS

The main data of the study are summarized in Table I. The average follow-up period was 7 months. No statistically significant differences were found among the groups in terms of age, gender, BMI, follow-up period and leg length discrepancy. Analysis of patient-reported outcome scores, including the HHS and WOMAC and DeXA T-Score, revealed significant association with gait variables, as reported in Table II.

Table 3 shows differences in clinical scores and gait kinematics parameters between groups at 3-month follow-up and 6-month follow-up (Kruskal-Wallis test and Mann-Whitney U test) and within groups (3-month follow-up vs 6-month follow-up; paired Wilcoxon test).

DISCUSSION

In the treatment of intertrochanteric femur fractures, it is crucial to employ a technique that combines a minimal invasive operation procedure, one stable implant that allows the possibility of postoperative full weight-bearing and a low complication rate. On the other hand, successful operation does not always correlate with a successful functional outcome.

Recently, Gausden et al. showed that, in patients with IFFs managed with short intramedullary nail, femur shortening is associated with altered gait, specifically decreased cadence, increased double support time, decreased step length and increased single support time asymmetry (18).

In the present study we focused on the fracture stability pattern, to assess any gait difference between stable and unstable IFFs, treated with closed reduction and internal fixation with short cephalomedullary nail, at mean 6-month follow-up. Therefore, 14 patients (female: 8; mean age: 77.9 years old) underwent clinical, radiological and functional evaluation with gait analysis at 3-month and 6-month follow-up. All the patients were

Table III. Differences in clinical scores, spatio-temporal parameters and gait kinematics between and within groups (Mean and Standard Deviation, Significance (p-value). ⁺significant p-value (Kruskal-Wallis test); ^{*}significant p-value (Mann-Whitney U test); [§]significant p-value (Paired Wilcoxon test).

Variable	3-month follow-up						6-month follow-up					3m-FU vs 6m-FU
	Stable	Unstable	Control	St vs Un vs Co	St vs Co	Un vs Co	Stable	Unstable	St vs Un vs Co	St vs Co	Un vs Co	
HHS	58.77±17.1	43.1±6.5	-	0.74	-	-	59.7±39.59	79.35±15.69	-	.643	-	.043 [§]
WOMAC	62.32±15.6	64.05±15.5	-	0.932	-	-	63.47±30.08	83.02±16.55	-	.355	-	.043 [§]
STEP WIDTH	0.17±0	0.17±0.03	0.12±0	.052	.034 [*]	.028 [*]	0.2±0.02	0.19±0.02	.052	.475	.026 [*]	.042 [§]
CADENCE	1.3±0.12	1.18±0.22	1.9±0	.051	.037 [*]	.028 [*]	1.42±0.19	1.37±0.21	.058	.643	.028 [*]	n.s.
GAIT SPEED	0.26±0.1	0.21±0.08	1.39±0	.048 ⁺	.037 [*]	.028 [*]	0.27±0.13	0.31±0.08	.058	.643	.028 [*]	n.s.
WALK RATIO	0.41±0.09	0.42±0.08	0.77±0	.048 ⁺	.037 [*]	.028 [*]	0.38±0.2	0.47±0.04	.060	1.00	.026 [*]	n.s.
LSI STRIDE	97.06±5.88	100.77±3.9	0.9±0	.040 ⁺	.037 [*]	.028 [*]	100.54±0.08	100.24±1.19	.049 [*]	.348	.026 [*]	n.s.
LSI STEP LENGTH	155.5±111.7	102.3±40.7	1.49±0	.047 ⁺	.037 [*]	.028 [*]	115.37±26.4	100.09±7.4	.050	.355	.028 [*]	n.s.
LSI STANCE	90.29±17.14	100.67±13	0.92±0	.047 ⁺	.037 [*]	.028 [*]	98.1±9.73	103.19±2	.061	1.00	.028 [*]	n.s.
LSI SWING	150.92±89.6	108.6±46.7	1.31±0	.051	.037 [*]	.028 [*]	103.31±34.4	90.64±3.93	.061	1.00	.028 [*]	n.s.
LSI DBL STANCE	123.61±26.6	149.1±87.4	6.87±0	.051	.037 [*]	.028 [*]	129.36±19.1	122.32±27.7	.058	.643	.028 [*]	n.s.
dSTEP LENGTH	0.09±0.1	0±0.07	0.01±0	.124	.037 [*]	.266	0.23±0.13	0.28±0.02	.064	.075	.044	n.s.
dSTANCE	-0.06±0.15	-0.08±0.02	0±0	.203	.487	.028 [*]	0.02±0.01	0.04±0.01	.75	.64	.056	n.s.
dSWING	0.06±0.15	0.08±0.02	0±0	.203	.487	.028 [*]	0.03±0.11	0.04±0.21	.54	.62	.063-	n.s.
dAFROM	-19.04±21.88	-4.04±2.51	2.55±0	.047 ⁺	.037 [*]	.028 [*]	-5.34±1.23	-6.22±2.34	.76	.912	.062	n.s.
dHFROM	6.63±1.65	5.75±1.53	7.7±5.9	.050	.056	.067	-7.44±8.57	-4.66±4.3	.058	.643	.028 [*]	n.s.
dHAROM	-2.05±2.8	-1.84±3.69	1.77±0	.212	.037 [*]	.271	-0.56±4.01	-1.64±1	.235	1.00	.028 [*]	n.s.
dHHROM	1.56±2.23	2.76±2.45	0.54±0	0.123	0.072	.065	2.11±0.86	-3.6±6.59	.027 [*]	.064	.028 [*]	n.s.
dPTROM	0.5±0.51	0.08±1.16	1.19±0	.220	.037 [*]	.271	1.78±1.02	2.01±1.22	.88	.062	.073	n.s.
dPOROM	0.02±0.28	-0.18±0.14	0.39±0	.039 ⁺	.037 [*]	.026 [*]	0.33±0.21	0.25±0.25	.92	.77	.825	n.s.
dSHRROM	-1.67±0.1	-0.32±1	-2.1±0	.027 ⁺	.053	.028 [*]	-0.74±0.48	0.02±0.59	.044 [*]	.139	.037 [*]	n.s.

divided into two groups according to the fracture stability pattern: patients with AO 31-A1 fractures were included in Group-A (stable), AO 31-A2 and A3 in Group-B (unstable). Gait analysis reference values corrected per age were also considered, to assess differences between Group-A patients, Group-B and control subjects. The fracture healing was depicted at 3-month follow-up in both groups; no complications were found in the two groups during the study.

At three-month follow-up, both groups showed significantly different gait patterns, compared with healthy subjects (Table III). Moreover, although mean HHS and mean WOMAC scores showed no significant differences between groups, patients with unstable fracture patterns (Group-B) showed a worse gait pattern, compared with Group-A. Several gait

variables, therefore, showed a significant difference between groups, including gait speed ($p=0.048$), walk ratio ($p=0.048$), LSI stride ($p=0.040$), LSI step length ($p=0.047$) LSI stance ($p=0.047$), dAFROM ($p=0.047$), dPOROM ($p=0.039$) and dSHRROM ($p=0.27$).

At six-month follow-up, a significant improvement of both mean HHS score ($p=0.43$) and mean WOMAC score was observed ($p=0.43$) within groups, compared to three-month one. However, Group-A patients showed a significant different LSI stride ($p=0.049$), dHHROM ($p=0.027$) and dSHRROM ($p=0.044$), compared with Group-B patients. Moreover, while patients with stable fractures (Group-A) showed no significant differences compared with control subjects, those with unstable fractures (Group-B) still presented a

worse gait pattern compared with healthy subjects.

Namely, Group-B patients revealed a significant worse step width ($p=0.026$), cadence ($p=0.028$), gait speed ($p=0.028$), walk ratio ($p=0.026$), LSI stride ($p=0.026$), LSI step length ($p=0.028$), LSI stance ($p=0.028$), LSI swing ($p=0.028$), LSI DBL stance ($p=0.028$), dHFROM ($p=0.028$), dHAROM ($p=0.028$), dHHROM ($p=0.028$), dSHRROM ($p=0.037$). These findings highlight that, even if a successful intramedullary nailing is performed, patients with unstable fracture patterns still have an impaired walking at six-month follow-up. Therefore, these patients should follow a more aggressive rehabilitative protocol, compared with patients with stable IFFs, to quicker gain a good walking ability and prevent, at the same time, new falls.

The present study also showed that, although significant correlations were observed with gait parameters and mean HHS and WOMAC scores (Table II), these clinical scores are not specific enough to point out the patients' post-operative recovery. Hence, gait analysis gives the advantage to better assess the patients' walking ability and develop a patient-specific rehabilitative protocol.

From a translational point of view, these data highly suggest gait analysis should be introduced in daily clinical practice, to monitor the follow-up, to customize the patients' post-operative rehabilitation and to improve the patients' functional outcomes. These efforts could reduce the re-fall rate and shorten the return of patients to postoperative social life. The small sample size is the main limitation of the present study. Nonetheless, we applied several inclusion and exclusion criteria to improve its quality. In the present study, patients with unstable fractures (AO-31 A2 and A3) showed a worse gait pattern at 6-month follow-up, compared with stable fractures (AO-31 A1) and with control subjects.

Gait analysis, in this study, revealed a valid tool to assess the postoperative functional outcome in patients with IFFs managed with intramedullary nailing. The data provided by gait analysis, therefore, could be useful to customize the patients' rehabilitative protocol, to quickly improve their walking ability, thus reducing the postoperative re-fall risks and promoting the patients' social life.

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Carbon Ion Radiotherapy for sacral chordoma: a systematic review of the literature

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The aim of the present study is to describe the clinical outcomes and the incidence of complications related to Carbon Ion Radiotherapy (CIRT) in the treatment of sacral chordoma. Through a systematic review of published investigations on CIRT, we collected the local control rates (LC), the overall survival rates (OS) and the post-CIRT adverse effects. Afterwards, we calculated their weighted average, to have a broader perspective. PubMed/Medline and Google Scholar databases were searched to identify studies on Carbon Ion Radiotherapy as a treatment for sacral chordoma. We used Medical Subject Heading (MeSh) terms and keywords. We based our systematic review on the PRISMA guidelines. No data limitations were applied in the search on Pubmed/Medline database; data limitation (from 2000 to 2019) was applied in the search on Google Scholar. Six studies were included in our review. Local control proportions reported in individual studies ranged between 77% and 96% (95% confidence interval), with respect to a 5-years follow-up. Overall survival rates ranged from 52% to 86% (95% confidence interval), with respect to a 5-years follow-up. Adverse CIRT-related events involving bone occurred in 7% of patients. Neurological and skin toxicities affected 20% and 5% of patients, respectively. Nowadays the gold standard of treatment for sacral chordoma is the surgical resection with wide margins. Whenever adequate oncological margins could not be achieved or could be achieved only by sacrificing neurological structures with consequent functional impairment, CIRT is an effective alternative which has been demonstrated to reach optimal local control and overall survival rate. The caregiver, anyway, should be aware of the potential adverse events and complications related to this kind of treatment.

Chordoma is a malignant mesenchymal tumor that shows notochordal differentiation. In 50-60% of cases, it arises in the sacrum-coccyx followed by the clival region (25-30%), the cervical region (10%) and the thoracolumbar spine (5%) (1-3).

Nowadays en-bloc surgical resection with wide/marginal margins is the mainstay of treatment for these tumors. However, surgery with appropriate oncological margins is difficult to be achieved because of the thin pseudocapsule and the huge mass.

Furthermore, en-bloc resection of the sacrum is surgically demanding and associated with severe functional losses, especially for chordomas localized above S3. Unfortunately, in these cases

the achievement of oncological appropriateness of margins requires the sacrifice of the corresponding nerve roots with consequent destabilizing neurological sequela for the patient (paraplegia, sphincter insufficiency and uncontrolled neurological pain) (3, 4).

A recent survey performed on 31 centers in the world with expertise in the treatment of spinal tumors (5) reported the current protocols used for managing chordoma of sacrum and mobile spine, indicating en bloc resection as the first option if it is feasible with acceptable morbidity, frequently associated to postoperative radiotherapy. When en bloc resection would result in significant morbidity, the number of

Key words: Carbon Ion Radiotherapy, sacral chordoma, adverse events

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centers relying more on adjuvant (and neoadjuvant) therapies without attempt to treat patients with en bloc resection, increases. Concerning RT modality, most used a combination that includes stereotactic body RT (SBRT) (49%), protons (38%), photons (36%), and/or carbon-ion therapy (10%). The most frequent combination was photons and protons. Lastly, 74% of respondents have no difficulty accessing proton therapy treatment facilities, and only 15% have access to Carbon Ion Radiotherapy.

The advancement in the fields of high-energy particle therapy provides new opportunities for a less invasive approach, particularly for those patients affected by sacral chordoma too large for en-bloc resection or localized in S1 and S2; those patients are good candidate for Carbon Ion Radiotherapy. In the last years, more data have been published about local control of sacral chordoma showing stable disease or reduction of the tumor volume after CIRT (6-8).

Adrotherapy is an alternative treatment option for patients affected by chordoma of the sacrum. Although most sarcomas were considered radioresistant in the past, this concept has been revised in the last decade. Nowadays things partially have changed with the advent of CIRT, due to its higher rate of reaching

better clinical outcomes as opposed to conventional radiotherapy (9). CIRT's high relative biological effectiveness is to be found in the capacity of a good dose distribution, delivering a high dose to the tumor, while the irradiation to critical surrounding tissues and organs can be minimized (Bragg peak) (7).

The goal of our study is the investigation of Carbon Ion Radiotherapy clinical outcomes and eventual adverse effects or complications in order to give to the caregivers, such as radiotherapists, orthopedic surgeons, neurosurgeons and oncologists, a most accurate possible scenario when facing a sacral chordoma.

MATERIALS AND METHODS

In August 2019 we conducted a systematic review of all peer-reviewed relevant English literature concerning Carbon Ion Radiotherapy as a treatment for sacral chordoma. We collected both clinical outcomes and adverse events related to CIRT from every single paper, and, afterwards, we calculated their weighted average to have a wider vision. We based our systematic review on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The search was conducted

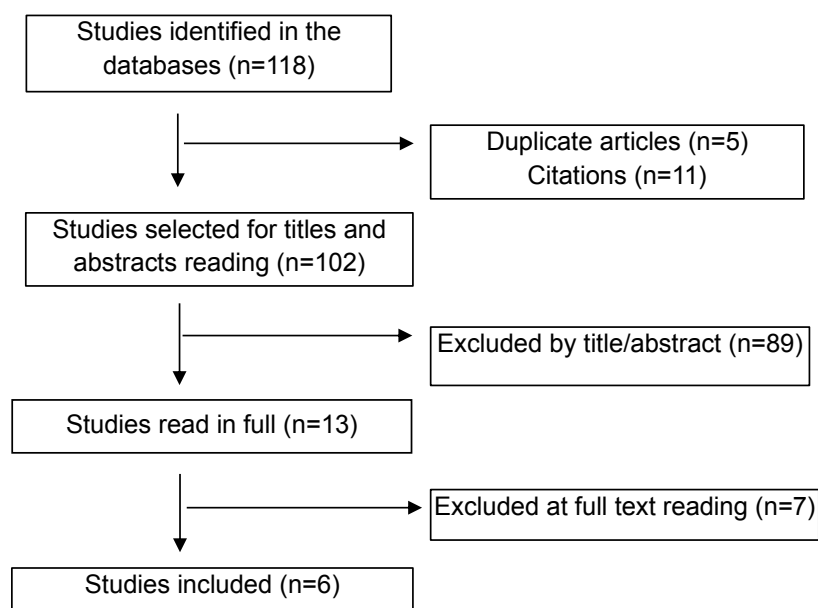


Fig. 1. Flow-chart describing the papers' selection for the review.

Table I. Description of studies about the use of CIRT included in the analysis.

Authors	Study design	Patient characteristics	Most proximal tumor level	Dose of RT	Previous surgery	Median tumor volume in cc (range)	Median duration of follow-up (months)	Inclusion and exclusion criteria
Imai et al. (8)	Retrospective study	Number of patients (30) Age (mean 66) (range 41-85) Gender Male (24) Female (6)	L5 (5) S1 (7) S2 (13) S3 (3) Right iliac bone (1) Pelvic muscle (1)	Mean dose 70.35 GyE (range 52.8-73.6) in 16 fractions. Of which: 52.8 (1) 64 (1) 70.4 (21) 73.6 (7)	No (23) Yes (7)	546 (CTV) (range 25-1468)	Median 30 (range 9-87)	Inclusion: • A Karnofsky performance status score >60 • The tumor had to be grossly measurable. • All patients signed an informed consent form approved by the local Institutional Review Board Exclusion: • Patients had distant metastasis at the time of initial referral for treatment • Patients who had undergone prior radiation therapy at the same site
Imai et al. (7)	Retrospective study	Number of patients 38 Age (median 66) (range 41-85) Gender Male (29) Female (9)	L5 (6) S1 (10) S2 (15) S3 (4) S4 (1)	Mean dose 70.36 GyE (range 52.8-73.6) in 16 fractions. Of which: 52.8 (1) 64 (1) 70.4 (29) 73.6 (7)	Yes (8) No (30)	523 (CVT) (range 135-1468)	Median 80	Inclusion: • Tumor deemed to be medically inoperable by the referring surgeons • A Karnofsky performance status score >60 • The tumor has to be grossly measurable. • All patients signed an informed consent form approved by the local Institutional Review Board Exclusion: • Patients having distant metastasis at the initial referral for treatment • Patients who had undergone prior radiation therapy at the same site
Imai et al. (6)	Retrospective study	Number of patients (95) Age n.r. Gender Male (68) Female (27)	L5 (10) S1 (29) S2 (29) S3 (9) S4 (7)	Mean dose 70.38 GyE (range 52.8-73.6) in 16 fractions. Of which: 52.8 (1) 64 (1) 70.4 (86) 73.6 (7)	Yes (11) No (84)	370 (CVT) (range 47-1468)	Median 42 (range 13-112)	Inclusion: • Tumor judged to be medically inoperable by the referring surgeon • tumor histopathologically diagnosed as chordoma • Karnofsky performance status score > 60 Exclusion: • distant metastasis at the time of initial referral for treatment • prior radiation therapy at the same site
Mima et al. (10)	Retrospective study	Number of patients (23) Age (median 72) (range 35-84) Gender Male (15) Female (8)	n.r.	Mean dose 70.4 GyE: 61% in 16 fractions 39% in 32 fractions Ion type Carbon ion (16) Proton (7)	No (23)	264 (range 94-1037)	Median 38 (range 7-78)	Inclusion: • Histologically confirmed primary sacral chordoma without metastases • ECOG performance status ≤ 3 • Adequate organ function • Written informed consent Exclusion: • Previous radiotherapy • Active concomitant malignancy
Imai et al. (11)	Retrospective study	Number of patients (188) Age (median 66) (range 26-87) Gender Male (128) Female (60)	L5 (11) S1 (49) S2 (77) S3 (38) S4 (13)	Mean dose 68.68 GyE (range 64-73.6) in 16 fractions. Of which: 64 (1) 67.2 (106) 70.4 (74) 73.6 (7)	No (188)	345 (CVT) (range 42-1497)	Median 62 (range 6.8-147.5)	Inclusion: • The tumor has to be medical unresectable • The tumor is histologically confirmed Exclusion: • The tumor has metastasized • Metal instrument action has been applied
Bostel et al. (12)	Retrospective study	Number of patients (56) Age (median 61) (range 34-84) Gender Male (37) Female (19)	L4/L5 (7) S1 (9) S2 (18) S3 (12) S4 (4) S5 (4) Os coccygeum (2)	Mean dose carbon ion only (range 75-82.5 Gy) in 20-22 fractions. Of which: 75 (28.6 %) 78.8 (3.6 %) 82.5 (26.8 %) Mean IMRT + carbon ion boost (range 68.8-80). Of which: 68.8 (1.8 %) 74.5 (1.8 %) 80 (37.5)	Yes (35) No (21)	522 (CTV boost plan) (range 64-1743)	Median 35.5 (range 2-83)	n.r.

n.r. = not reported

on both PubMed/MEDLINE and Google Scholar and, in particular, we used Medical Subject Heading (MeSh) terms (“Heavy Ion Radiotherapy/adverse effects”[Mesh] OR “Heavy Ion Radiotherapy/mortality”[Mesh] OR “Heavy Ion Radiotherapy/statistics and numerical data”[Mesh]) AND (“Bone Neoplasms/radiotherapy”[Mesh] OR “Bone Neoplasms/therapy”[Mesh]) and key words ((carbon ion radiotherapy) AND complications) AND spine. No data limitations were applied to the search on Pubmed/Medline database; limitation data (from 2000 to 2019) was applied to the search on Google Scholar.

RESULTS

Study selection

Overall, 118 studies were identified in the databases and 6 were included in this study (Fig. 1). Studies were considered eligible when either clinical outcomes or adverse events related to Carbon Ion Radiotherapy as a treatment for sacral chordomas were evaluated. Original articles in which clinical outcomes and complications were described without

distinguish between sacral chordomas, spinal chordomas and sarcomas were excluded. Moreover, we excluded review articles from this study.

Studies’ characteristics are shown in Table I. Collected studies were published from 2004 to 2018 and were classified as retrospective cohort studies. A total of 430 patients with sacral chordoma were included in this study. Median duration of follow-up ranged from 30 to 80 months. Median pre-radiotherapy tumor volume ranged from 264 to 546cm³.

Local control and survival

Table II gives an overview of reported local control and overall survival proportions of included studies. Reported treatment success after CIRT was consistently good for both local control and overall survival. Local control proportions reported by individual studies ranged from 77% to 96%, with respect to a 5-years follow-up. Overall survival rates ranged from 52% to 86%, with respect to a 5-years follow-up.

Weighted averages of clinical outcomes were

Table II. Overview of local control rate, overall survival rate and metastasis rate in the studies analysed.

Authors	Local control rate (95% CI)	Overall survival rate (95% CI)	Metastasis rate
Imai et al (8)	96% (89%-100%) (5-year LC)	52% (7%-97%) (5-year OS)	23%
Imai et al (7)	95% (3-year LC) 89% (5-year LC)	95% (3-year OS) 86% (5-year OS)	39%
Imai et al (6)	88% (5-years LC)	86% (5-year OS)	n.r.
Mima et al (10)	94% (83%-100%) (3-year LC)	83% (66%-100%) (3-year OS)	26%
Imai et al (11)	77% (69%-84%) (5-year LC) 52% (36%-66%) (10-year LC)	81% (74%-87%) (5-year OS) 67% (57%-75%) (10-year OS)	29%
Bostel et al (12)	n.r.	n.r.	n.r.

n.r.= not reported

calculated basing on data of all 430 patients included in this study. Average local control rate was 83%, while average overall survival rate was 80%, both calculated on a 5-years follow-up. Average metastasis rate was 29% and the most frequent sites were lung, bone and soft tissues of the pelvis.

Toxicities

Two studies reported on adverse effects CIRT-

related, involving bone (Table III).

Bostel et al. (12) described sacral insufficiency fractures as a radiogenic late effect of CIRT on patients treated for sacral chordomas. After a median follow-up of 3 years, SIF occurred in 52% of patients. Although most of the fractures (almost 80%) developed within 2 years after CIRT, in 22% of patients' fractures occurred later than 2 years after radiation.

It is also worth mentioning that about two thirds

Table III. Incidence of adverse events reported in the studies analysed.

Bone	Incidence of adverse effects	Dosage
Imai et al. (7)	Sacral bone fracture (3%)	n.r.
Bostel et al. (12)	SIF (sacral insufficiency fractures) occurred in 52% of patients after a median follow-up of 3 years	SIF: No statistically significant difference was found between patients treated with surgery + additional RT and patients treated with definitive RT
Skin	Incidence of adverse effects	Dosage
Imai et al (8)	Acute skin reactions grade 3 (10%) Late skin reactions: • Grade 3 (7%) • Grade 4 (7%)	n.r.
Imai et al (7)	Acute skin reactions • Grade 3 (8%) Late skin reactions: • Grade 3 (5%) • Grade 4: (5%)	n.r.
Imai et al (6)	Acute skin reactions • Grade 3 (3%) Late skin reactions • Grade 3 (2%) • Grade 4 (2%)	Grade 4 late skin reactions: 100% of patients who developed grade 4 late skin reactions previously received 73.6 GyE
Mima et al (10)	Acute skin reactions • Grade 3 (35%) • Grade 4 (4%) Late skin reactions • Grade 4 (22%)	Grade 3 acute skin reactions: • 88% of patients who developed a grade 3 acute skin reaction previously received 70.4 GyE/16Fr • 12% of patients who developed a grade 3 acute skin reaction previously received 70.4 GyE/32Fr Grade 4 acute skin reactions: 100% of patients who developed a grade 4 acute skin reaction previously received 70.4 GyE/16Fr
Imai et al (11)	Late skin reactions • Grade 1 (89%) • Grade 2 (6%) • Grade 3 (1%) • Grade 4 (1%)	Grade 4 late skin reactions: 100% of patients who developed grade 4 late skin reaction previously received 73.66 GyE/16Fr

Continue table next page >>>

Neurological	Incidence of adverse effects	Dosage
Imai et al (8)	Neurological complications (including both reversible increase of hypoesthesia and partial paralysis of sciatic nerves) (20%)	n.r.
Imai et al (7)	Temporary or permanent neurological impairments (26%)	Neurological impairment: 40% of patients who developed neurological impairment previously received 73.6 GyE 60% of patients who developed neurological impairment previously received 70.4 GyE
Imai et al (6)	Sciatic nerve neuropathy (16%)	One third of patients who developed sciatic nerve neuropathy received 73.6 GyE
Mima et al (10)	Late grade 3 neuropathies (including motor impairment, numbness and urinary retention) (17%)	Late grade 3 neuropathies: 50% of patients who developed late grade 3 neuropathies previously received 70.4 GyE/16Fr 50% of patients who developed late grade 3 neuropathies previously received 70.4 GyE/32Fr
Imai et al (11)	Peripheral nerve late morbidities - Grade 1 (11%) - Grade 2 (7%) - Grade 3 (3%)	Peripheral nerve late morbidities: 67% of patients who developed peripheral nerve late morbidities previously received 73 GyE/16Fr 17% of patients who developed peripheral nerve late morbidities previously received 70.4 GyE/16Fr 16% of patients who developed peripheral nerve late morbidities previously received 72.6 GyE/16Fr

n.r.= not reported

of affected patients were clinically asymptomatic. With respect to symptomatic fractures, low back pain was described as the most common symptom, leading to mobility impairment. Analgesic therapy was often required.

Although the 5-year fracture-free survival rate was 16% and 5% for patients treated with surgery + additional RT and patients treated with definitive RT respectively, no statistically significant difference was found among the two groups ($p = 0.23$). It

should be noted that both age and gender of patients, as well the volume of the tumors, the bone marrow density prior to RT, the radiation dose and the extent of surgical resection, were examined as possible prediction factors of SIF but none of these emerged to be statistically relevant. A study reported one case of sacral bone fracture 9 months after CIRT (7).

Four studies by Imai et al. (6–8, 11) (Table III) informed on the possibility of skin toxicity after CIRT. With respect to acute reactions, grade 3

Table IV. Overall incidence of bone, skin and neurological adverse events after CIRT obtained from the data included in the study.

Overall incidence of bone adverse events for all the studies included	Overall incidence of skin adverse events for all the studies included	Overall incidence of neurological adverse events for all the studies included
7%	• Grade ≥ 3 acute skin reactions (4%) • Grade ≥ 3 late skin reactions: (5%)	20%

adverse reactions occurred in a range of 3% to 10% of patients. With respect to late reactions, grade 3 adverse reactions occurred in a range of 1% to 7% of patients, such as for grade 4 adverse reactions.

High rate of skin adverse events is shown in a retrospective study by Mima et al. (10). They reported incidences of 35% and 22% for acute grade 3 and late grade 4 skin reactions, respectively, while acute grade 4 complications were seen in 4% of patients.

Four studies about neurological complications after Carbon Ion Radiotherapy are reported (Table III).

In the first study, neurological complications, including both reversible increase of hypoesthesia and partial paralysis of sciatic nerves, occurred in 20% of patients (8). In the second study, temporary or permanent neurological impairment was described in 26% of patients. In particular, 3 patients (8%) experienced serious and irreversible neurological adverse effects. Regarding these patients, the most cranial level of the tumor was L5, S1 and S2 in 3 patients respectively, while for one patient it was S4. After CIRT, no patients got worse with respect to bladder and bowel dysfunctions (7). In the third study, sciatic nerve neuropathy occurred in 16% of patients (6). In the fourth one, peripheral nerve late morbidities involved 11%, 7% and 3% of patients with grade 1, grade 2 and grade 3 neurological toxicity, respectively (11).

A retrospective study by Mima et al. (10) described neuropathies as the second most frequent complication related to CIRT. Late 3 neuropathies, including motor impairment, numbness and urinary retention, occurred in 17% of patients.

Toxicity regarding gastrointestinal tract is described in three different studies. One of them described four grade 1 gastrointestinal tract-late morbidities (11). The other two studies both presented a case of one patient developing temporary and reversible grade 1 rectal bleeding (6, 7).

As performed for clinical outcomes, we calculated the weighted averages of adverse events rates for the entire group of 430 patients (Table IV). The overall incidence of bone complications for all the studies included was 7%. The overall incidence of skin complications was 4% and 5% for grade ≥ 3 acute and late skin complications, respectively. The overall incidence of neurological complications was 20%.

DISCUSSION

Carbon Ion Radiotherapy is an effective treatment when surgical resection could not achieve appropriate oncological margins or could achieve it only by sacrificing neurological structures. Radaelli et al. (13) reported clinical outcomes regarding patients affected by primary localized sacral chordomas and all surgically treated. Overall survival rates, calculated for a 5-year follow-up, were 95% for both wide and marginal margins, as opposed to 70% regarding intralesional margins. Local recurrence rates, calculated for a 5-year follow-up, were 18% and 38% respectively. 28% of patients developed distant metastasis.

In a retrospective case series by Colangeli et al. (14), 33 patients with sacral chordoma were surgically treated. They described an overall survival

rate of 87% and a local recurrence rate of 27% for a 5-years follow-up, and surgical margin was the only statistically significant prognostic factor. Metastasis occurred in 6% of patients.

In this review we analyzed the data from six papers concerning the use of CIRT for the treatment of sacral chordoma and we calculated the weighted average for the local control rate (83%) and for the overall survival rate (80%) at 5-year follow up. The average metastasis rate was 29%.

These data suggest that clinical outcomes reached after Carbon Ion Radiotherapy treatment for patients affected by sacral chordoma are comparable to those achieved by en bloc surgical resection. Above all, CIRT should be considered when margins are not expected to be negative, leading to a poor prognosis.

Therefore, the achievement of appropriate surgical margins is critical. Unfortunately, en bloc surgical resection of sacral chordomas is not always possible due to their anatomic location and to unspecified symptoms. A delayed diagnosis allows the mass to grow, often making it impossible to reach adequate surgical margins. Moreover, a resection of a mass localized in the sacrum above S2 will result in debilitating neurological impairment such as paraplegia, urinary or anal sphincter incontinence and uncontrolled neurological pain (4, 11).

Carbon Ion radiotherapy is typically considered as a safe non-surgical procedure in the treatment of sacral chordoma (6-8, 11) but it is appropriate to assess the possibility of developing toxicities and adverse effects related to CIRT. Our systematic review showed that Carbon Ion Radiotherapy is not exempt from adverse events or complications.

Frequent are neurological toxicities, including reversible increase of hypoesthesia and partial paralysis of sciatic nerves in 20-26% of patients (7, 8) and skin reactions, such as acute grade 1 reactions, reported up to 89% of patients, or late grade 4 reaction, occurred up to 22% of patients (10, 11). Bostel et al. (12) reported a 52% of delayed sacral insufficiency fractures at 3-years follow-up; those events are particularly challenging to manage and often require a surgical fixation: polymethylmethacrylate injection could be a minimally invasive option for not-complicated fractures. When mechanical

insufficiency, especially in S1, or neurological compression arise, a surgical fixation, associated or not to decompression, is required. Moreover, a surgical intervention on an irradiated field is burdened by the high risk of complications such as wound dehiscence and neurological structure damage.

As previously mentioned, surgery as a treatment for sacral chordoma is not devoid of complications. Angelini et al. (15) reported stress fractures of the sacrum as an adverse event in 4% of patients, while wound dehiscence and deep infection occurred in a half of patients. Regarding the neurological status, urinary incontinence was described in 56% of patients, constipation in 46% and fecal incontinence in 28%.

This review has limitations. Firstly, the number of studies included are limited and one of them does not report local control rate and overall survival rate, hence we could not base our assessments regarding clinical outcomes on all the studies. Secondly, loss of follow-up was reported in one study, and it concerned 16% of patients.

Nowadays the gold standard for treatment of sacral chordoma is the surgical resection with wide margins. Whenever adequate oncological margins could not be achieved or could be achieved only by sacrificing neurological structures with consequent functional impairment, CIRT is an effective alternative which has been demonstrated to reach optimal local control and overall survival rate (3, 4). Clinical outcomes described in our systematic review are comparable to those achieved by en bloc surgical resection. The caregivers, anyway, should be aware of the potential adverse effects and complications related to this kind of treatment (4).

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Hamstring grafts are tenogenic constructs for ACL reconstruction and Pulsed Electromagnetic Fields improve tendon specific markers expression. An *in-vitro* study

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Hamstring tendons represent one of the commonest autologous graft used during ACL reconstruction. The harvest of the tendon and the time of tendon processing on the operating table, together with the pretensioning maneuvers and the permanence out of the joint during the time of surgery, might impair tendon derived cells (TCs) viability. The aim of the study was: i) to assess the effective viability of the TCs at the end of the surgical procedure; ii) to investigate if TCs viability and the expression of tendon specific markers may be improved through exposure to prolonged pulsed electromagnetic fields (PEMF) similar to that of clinical practice. Remnants of semitendinosus and gracilis tendons (discarded at the end of the ACL reconstruction) were collected from 13 healthy donors. To isolate TCs, the tendon tissue was minced and digested enzymatically with 0.3% type I collagenase in DMEM with continuous agitation for 15 h at 37°C. The isolated nucleated cells were then plated at 5×10^3 cells/cm² in a complete medium composed of DMEM, 10% fetal bovine serum, 50 U/ml Penicillin, 50 mg/ml Streptomycin, 2 mM L-glutamine, and supplemented with 5 ng/ml basic fibroblast growth factor (b-FGF). They were maintained at 37 °C in a humidified atmosphere with 5% CO₂, changing culture medium every 3 days. When they reached 80–90% of confluence, the cells were detached by incubation with trypsin/EDTA and then cultured at a density of 5×10^3 cells/cm². TCs were cultured in complete medium for 7, 14, 21 days (in chamber slides, to optimize the final immunofluorescence analysis). The following cell cultures were set up: i) TCs cultured with differentiation medium + exposure to PEMF 8 h/day; ii) TCs cultured with differentiation medium without exposure to PEMF. The stimulation with PEMF was generated by a pair of electrical coils, connected with the generator of pulsed electromagnetic fields (PEMF generator system IGEA, Carpi, Italy, intensity of magnetic field = 1.5 mT, frequency = 75 Hz). At day 0, day 7, day 14 and day 21 immunofluorescence analysis was performed to evaluate the expression of tendon specific markers (collagen type I, collagen type VI, scleraxis) and proliferative markers (PCNA, beta-catenin). The TCs from the hamstring tendon fragments at the end of the ACL reconstruction were alive and they expressed markers of proliferation and tendon phenotype at the end of the culture period. The TCs in the presence of PEMF 8h/day showed a greater production of collagen type I, collagen type VI and scleraxis than TCs cultured without PEMF ($p < 0.05$). The expression of these markers increased from 7 to 21 days of culture. The expression of proliferative markers in the presence of PEMF stimulus was significantly lower ($p < 0.05$) than that of TCs cultured without PEMF. Hamstring tendons are not simple “tenoconductive” scaffolds but biologic alive tenogenic constructs rich in cells that can sustain tenogenic

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behavior and tendon matrix synthesis. Prolonged exposure to PEMF improves their phenotype. Thus, from a clinical perspective, the use of PEMF may represent a possible future strategy to positively influence the early phase of graft remodeling and, ultimately, improve the ligamentization process. Following these concepts, further studies might also exploit the anabolic role of PEMF as an adjunctive postoperative strategy in different tendon pathologies.

Key words: hamstring tendons, tendon derived cells, Pulsed Electromagnetic Fields (PEMF), tenogenic commitment

Hamstring tendons are one of the most common autologous sources of grafts for ACL reconstruction. The ease of harvesting and processing makes them very useful for primary and revision ACL surgery. A key point for the success of the procedure is the postoperative intra-articular graft remodeling, namely the ligamentization process, widely described in literature since 1986 by Amiel (3) and more recently by several authors as Claes et al (8) and Pauzenberger et al (19). This process relies on the biological properties of the graft and, more specifically, on the tendon derived cells embedded in the graft structure. These elements have a role in maintaining a “homeostasis” and producing collagen and extracellular matrix proteins that support the *in situ* graft tension and properties required for the ligamentization process to advance toward the later phases. Thus, retaining the anabolic tenogenic commitment is a prerequisite for tendon derived cells to optimize the early phases of graft remodeling.

In literature, different authors have proposed interesting solutions to support and hasten graft maturation. Coating the surface of the graft with platelet-rich fibrin (6) or pre-treating the graft with intratendinous injections of platelet-rich plasma preparation rich in growth factors (23) have shown favorable results. Infiltrating the graft structure with autologous stromal vascular fraction from adipose tissue has shown small positive effects on graft maturation, as well as the intraarticular injection of the secretome from human bone marrow MSC (27). Some authors have advocated the preservation of muscle tissue around the graft (9) during hamstring graft preparation, to enrich the graft with the muscle stem cells that are present *in situ* around the tendon muscle interface.

Preclinical models have also studied a possible

role of connective tissue growth factor (26), postoperative exposure to hyperbaric oxygen or low intensity pulsed ultrasound (15). Nevertheless, none of these solutions have been broadly accepted for several disadvantages, as the cost of the procedures, the lack of strong clinical evidence of efficacy and the ethical concern regarding the use of growth factors and stem cells. Thus, there is still the need for research for postoperative strategies to improve the ligamentization process.

In this perspective, our *in-vitro* study has been focused on two main aspects. Firstly, we evaluated the viability of the tendon derived cells at the end of the surgical procedure. Indeed, the harvest of the tendon, the time needed for tendon processing, the pretensioning maneuvers, and the prolonged exposure of the graft to the external atmosphere of the operating theater might impair tendon cell viability.

Then we investigated if tendon cells behavior and the expression of tenocyte markers may be improved through prolonged exposure to pulsed electromagnetic fields (PEMF) similar to that used in clinical practice. This may have clinical relevance to suggest a possible non-invasive cost-effective strategy that may ameliorate and hasten the early phases of graft remodeling and, ultimately, the ligamentization process.

MATERIAL AND METHODS

Tendon derived cell cultures

The discarded free end of semitendinosus and gracilis tendons were collected from 13 healthy donors (age 18- 40) who underwent ACL reconstruction with autologous hamstrings at San Luigi Hospital, Turin. To isolate tendon derived cells (TCs), the tendon tissue

was minced and digested enzymatically with 0.3 % type I collagenase in DMEM with continuous agitation for 15 h at 37°C (Fig. 1 a-e).

The isolated nucleated cells were then plated at 5×10^3 cells/cm² in a complete medium composed of DMEM, 10 % fetal bovine serum, 50 U/ml Penicillin, 50 mg/ml Streptomycin, 2 mM L-glutamine, and supplemented with 5 ng/ml basic fibroblast growth factor (b-FGF). They were maintained at 37°C in a humidified atmosphere with 5% CO₂, changing culture medium every 3 days. When they reached 80–90% of confluence, the cells were detached by incubation with trypsin/EDTA and then cultured at a density of 5×10^3 cells/cm². TCs were cultured in complete medium for 7, 14, 21 days in chamber slides, to optimize the final immunofluorescence analysis (Fig. 1 d).

The following cell cultures were set up: - TCs cultured with differentiation medium + exposure to pulsed electromagnetic fields (PEMF) 8 h/day (Fig. 1e); - TCs cultured with

differentiation medium without exposure to PEMF.

PEMF stimulation was carried out as previously described by de Girolamo et al (13) (17). It was generated by a pair of electrical coils, connected with the generator of pulsed electromagnetic fields (PEMF generator system IGEA, Carpi, Italy, intensity of magnetic field = 1.5 mT, frequency = 75 Hz).

Immunofluorescence Analysis

Expression of the tenocyte markers scleraxis (Santa Cruz Biotechnology, Dallas, Texas, USA), collagen type I and collagen type VI (Merck Millipore, Milano, Italy), the PCNA and Beta-Catenin marker (Santa Cruz Biotechnology, Dallas, Texas, USA) was assessed by immunofluorescence. Primary monoclonal antibodies were diluted at 1: 200 in PBS-1% BSA and incubated with the sections for 2 h at room temperature. The secondary DyLight 488 antibody (KPL, Kirkegaard &

Study design

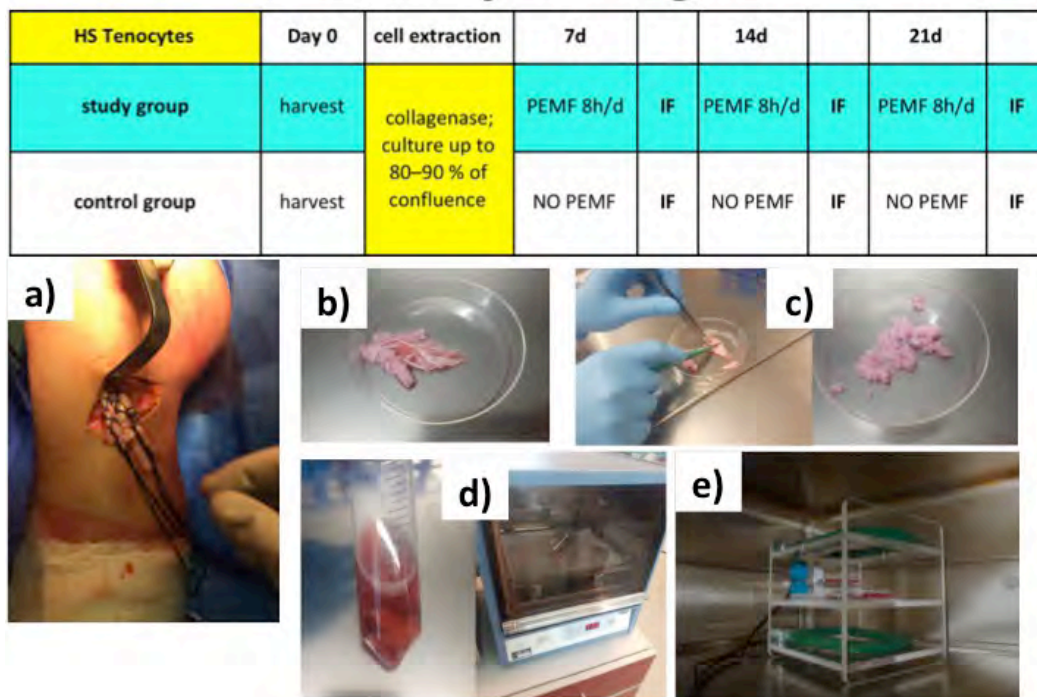


Fig. 1. Design of the study; Tendons processing method: **a)** harvesting of the discarded free ends of semitendinosus and gracilis tendons in the operating room at the end of the ACL reconstruction procedure; **b)** tendon strands on the Petri dish before mincing; **c)** tendon fragmentation; **d)** digestion of minced tendon fragments with 0.3 % type I collagenase in DMEM; **e)** TCs cultured with differentiation medium and exposure to pulsed electromagnetic fields (PEMF) 8 h/day.

Perry Laboratories, Maryland, USA), diluted at 1: 100, was incubated for 1 hr. at room temperature. Stained sections were visualized with an Apotome fluorescence microscope (Zeiss). We collected digital images using a $\times 20$ dry lens within 0–5 days after labeling.

Evaluation of Fluorescence Intensity

We evaluated the difference of fluorescence intensity between study groups using the ImageJ program. This software-generated numerical semiquantitative evaluation corresponding to the mean of fluorescence intensity of each image examined. Ten cellular fields were randomly chosen among the different areas of the cells in each slide. Briefly, a pointed tool enables to mark different points on each image. With each “click,” the coordinates of the mark (xx, yy) and brightness values (0–255) are recorded in the data window. ImageJ brightness units are on a scale where 0 is pure black and 255 is pure white. Brightness values for each image were calculated as the arithmetical mean of all values in all fields recorded for that image. For each group, the mean fluorescence intensity of each marker was calculated and plotted in a graph. The difference in signal intensity allowed for evaluating the change in marker expression between the different culture conditions.

Statistical Analysis

All data in the text and figures are provided as means $\pm$ standard deviation (SD). Statistical analysis was carried

out with the statistical software package Graph- Pad Prism 5.0 (GraphPad Software); $p < 0.05$ was considered statistically significant.

RESULTS

Morphologic characterization of TCs

In primary cultures, spindle-shaped adherent cells were observed expanding after seeding (Fig. 2). When they reached 80–90% of confluence and the cells were detached for culture and subsequent immunofluorescence analysis, cells retained the spindle-like shape.

Immunofluorescence analysis

Immunofluorescence analysis revealed the expression of scleraxis, collagen type I (Col I) and type VI (Col VI), proliferating cell nuclear antigen (PCNA) and beta-catenin in both study group. At day 7, 14, 21 (Fig. 3 a-c) a greater presence of scleraxis-positive cells was observed in culture exposed to PEMF than that of culture not exposed to PEMF. Statistical analysis showed that there was a progressive increase in the absolute values of intensity of fluorescence paralleling the prolonged exposure to PEMF. The maximum intensity on fluorescence occurred at 21 days in culture exposed to PEMF (7 days mean: 13.64 SD:0.65; 14 days mean: 15.46 SD:0.40; 21 days mean: 28.79 DS: 0.65) (Fig. 3 c).

Regarding Col I (see fig 4 a, 4 b, 4 c), on day 7, cultures exposed to PEMF did not show a statistically significant difference in fluorescence intensity values compared to that of the control group (PEMF mean: 10.22 SD: 0.34; NO PEMF mean: 9.80 SD: 0.26). Nevertheless, an increase in the absolute values of FI was observed in the PEMF group at day 14 and 21 (14 days mean: 14.35 SD: 0.61; 21 days mean: 24.16, SD: 0.89) and the differences with the unexposed group were statistically significant.

The expression of Col VI (see fig 5a, 5b, 5c) was similar to that of scleraxis, with an immediate increase in the PEMF exposed group at 7 days and a progressive increase of expression up to the end term (day 21) (7 days mean: 16.59, SD: 0.63; 14 days mean: 18.01, SD: 0.53; 21 days mean: 42.69,



Fig. 2: TCs isolated from tendon tissue during cell culture (magnification 10x). Spindle-shaped adherent cells are easy recognizable seeding.

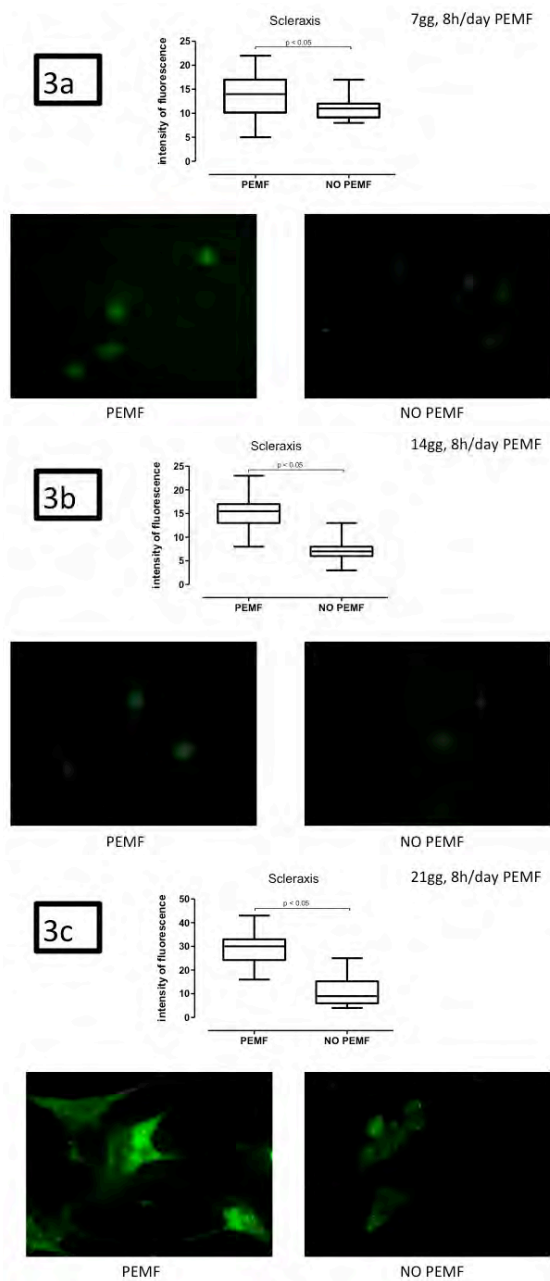


Fig. 3: Scleraxis expression after PEMF exposure for 8h/day and without PEMF exposure. *p* indicates the *p*-value (probability value, statistical significance level <0.05) between two specific groups of study, *ns* indicates a non-significant value; **a)** Immunofluorescence analysis for scleraxis expression and quantification of fluorescence intensity in TCs cultures with and without PEMF exposure for 7 days; **b)** Immunofluorescence analysis for scleraxis expression and quantification of fluorescence intensity in TCs cultures with and without PEMF exposure for 14 days; **c)** Immunofluorescence analysis scleraxis expression and quantification of fluorescence intensity in TCs cultures with and without PEMF exposure for 21 days.

SD: 1.01). The difference between the two groups was statistically significant at any time point (7, 14, 21 days).

In the control group, an increase in PCNA expression (see fig 6a, 6b, 6c) from day 7 to day 21 was observed compared to that of the study group, in which PCNA expression was lower than that of the control group at 7 and 14 days and a decrease in the expression of PCNA was even observed from day 14 to day 21. Indeed, the greater difference between the two groups was observed at the end term (PEMF 21 days mean: 8.40, SD: 0.34; NO PEMF 21 days mean: 24.19, SD: 1.17). In all time points, the differences between the two groups were statistically significant.

A similar trend was observed regarding beta-catenin expression (see fig. 7a, 7b, 7c). PEMF exposure was associated with a lack of increase in beta-catenin expression as observed in the control group and a decrease in the expression was even observed at 21 days (PEMF 7 days mean: 8.46, SD: 0.27; 14 days mean: 8.64, SD: 0.22; 21 days mean: 5.90, SD: 0.24). On the other hand, a progressive increase expression was observed in the control group and the differences between the two groups were statistically significant during all culture period (7, 14, 21 days).

DISCUSSION

This study has two important findings. Firstly, the possibility to obtain an efficient culture of cells derived from the free end of hamstring tendons (semitendinosus and gracilis) shows that the hamstring tendons retain effectively their cellularity and their tenogenic properties during hamstring ACL reconstruction even after the tendon harvesting in the operating theatre, the processing and pretensioning maneuvers on the tendon strands and the prolonged exposure to the atmosphere of the operating theater during the different surgical steps. Thus, far to be mere “scaffold”, they should be considered true tenogenic constructs capable to “competently initiate” the ligamentization process of the neo-ACL. Secondly, the study shows that prolonged exposure to PEMF may provide a positive biophysical stimulus *in vitro* leading to the anabolic commitment

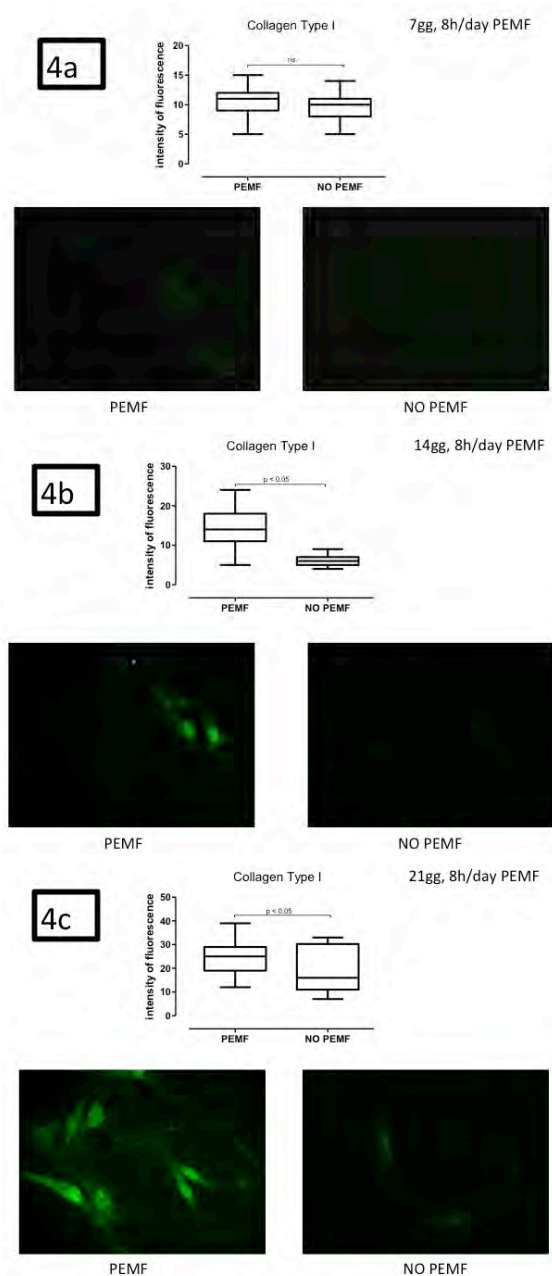


Fig. 4: Collagen type I expression after PEMF exposure for 8h/days and without PEMF exposure. *p* indicates the *p*-value (probability value, statistical significance level <0.05) between two specific groups of study, *ns* indicates a non significant value; **a)** Immunofluorescence analysis for Col I expression and quantification of fluorescence intensity in TCs cultures with and without PEMF exposure for 7 days; **b)** Immunofluorescence analysis for Col I expression and quantification of fluorescence intensity in TCs cultures with and without PEMF exposure for 14 days; **c)** Immunofluorescence analysis for Col I expression and quantification of fluorescence intensity in TCs cultures with and without PEMF exposure for 21 days.

of the cells and an increased tenogenic markers expression related to tendon matrix production, meanwhile reducing tendon cell proliferation. This effect has clinical relevance as PEMF may represent an adjunctive and efficient tool for enhancing and accelerating the physiological ligamentization process of hamstring tendons during the postoperative period of ACL reconstruction. Moreover, our results suggest a possible hypothetical clinical application of PEMF in different settings (i.e. rotator cuff and Achilles tendon lesions) in which the tendon repair process may benefit from the positive anabolic effect of PEMF.

The ligamentization process is, indeed, a complex and long procedure after tendon graft implantation in the ACL deficient knee. This is due primarily to the inherent histological differences between the tendons and the ligaments. Type I collagen and type III collagen together with proteoglycans constitute the framework of the dense connective tissue of both entities, but ligaments seem to be more metabolically active and they contain more type III collagen, more proteoglycans and a different distribution of collagen fibril diameters. Thus a long “road” is needed by a tendon to become similar to the ligament that it is replacing. Nevertheless, since 1986 Amiel et al. (3) showed that a patellar tendon autograft, when transplanted in a rabbit knee, undergoes a progressive remodeling becoming very similar to a normal rabbit ACL. In this study, at 30 weeks, collagen type III was expressed in the patellar autograft in a concentration similar to that of rabbit ACL and the authors observed a parallel increase in glycosaminoglycans content and a pattern of collagen-reducible crosslinks similar to that of ACL. They also noted that the nutrition of the graft depends initially on the presence of synovial fluid but, after 6 weeks, a revascularization process starts to occur. Thus, a real “ligamentization” may be claimed when a tendon is inserted in a different environment as the knee joint space and when it undergoes different biomechanical and biochemical stimuli. The recent work of Claes et al (8) pointed out three different steps of this process, namely “early phase”, “remodeling” and “maturation” but the literature is not concordant in defining the time frame for each phase. It is undoubtedly clear that at 6 months the

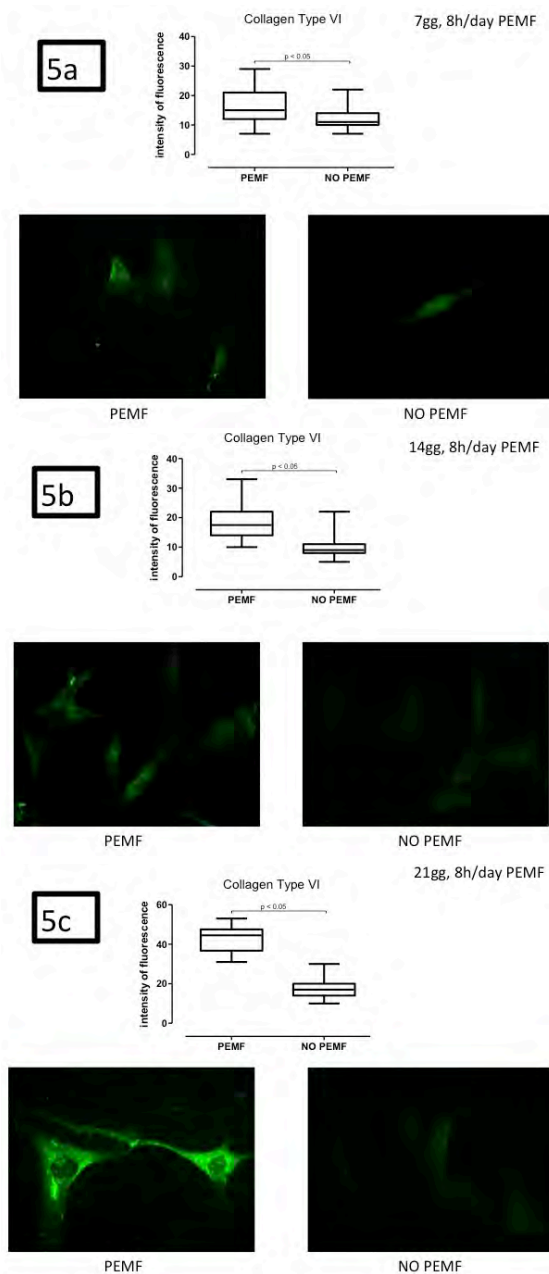


Fig. 5: Collagen type VI expression after PEMF exposure for 8h/days and without PEMF exposure. *p* indicates the *p*-value (probability value, statistical significance level <0.05) between two specific groups of study, *ns* indicates a non-significant value; **a)** Immunofluorescence analysis for Col VI expression and quantification of fluorescence intensity in TCs cultures with and without PEMF exposure for 7 days; **b)** Immunofluorescence analysis for Col VI expression and quantification of fluorescence intensity in TCs cultures with and without PEMF exposure for 14 days; **c)** Immunofluorescence analysis for Col VI expression and quantification of fluorescence intensity in TCs cultures with and without PEMF exposure for 21 days.

graft is still immature, as shown in the recent work of Hofbauer et al. (16) and this may claim caution in resuming the most demanding sport activities after 6 months from the operation. Indeed, in human, Falconiero et al. (12) affirm that the maturity of the graft is reached at 1 year, while Rougraff et al. (22) observed sing of graft remodeling up to 3 years and Sanchez et al (23) observed graft maturity at around 2 years after surgery.

Thus, a clear difference between the animal models and the human situation is the longer time for remodeling needed by the human graft, along with the almost absence of tendon necrosis in situ that characterizes the animal process of ligamentization. Again, we could assume that human is a “slow remodeling mammal” and this aspect may be linked to the increased lifespan of the humans compared to that of the animals used in preclinical models. As reported by Claes et al. (8), neovascularization of the graft occurs from Hoffa fat pad and synovium, likely for the presence of a high number of stem cells that may drive the formation of vessels around the graft.

Moreover, the “continuum” of biologic changes in the human graft can recreate a structure similar to ACL at the end of the ligamentization process, but different authors (1, 29) have pointed out that the tendon is unable to reach a complete ligamentous maturity on an ultrastructural level. Indeed a difference in collagen fibril diameter and distribution persists for many years after implantation, and the “bi-modal” distribution of collagen fibers typical of ACL is never replicated in the tendon graft at the end of the ligamentization. In this context, an interesting study of Marumo et al. (18) showed that in hamstring autograft there is a decrease collagen content in the first phases of ligamentization compared to that of native ACL, and it increases after 7 months from the operation. This discrepancy is particularly evident in the central part of the graft, where collagen synthesis is not very active in the first phases considering the decreased number of viable cells observed end and the lack of vessels. It is conceivable that a biological or a biophysical stimulus enhancing cell metabolism may help accelerate this delicate early phase of the ligamentization process.

This is particularly important when dealing with hamstring grafts that have shown a slower

remodeling process compared to that of the patellar tendon graft in a recent work of Pauzenberger et al. (19), in which the authors claim the need of research studies focused on postoperative care strategies to improve the ligamentization process. Different solutions have been proposed in literature to enhance graft maturation. Beyzadeoglu et al. (6) have recently shown the positive effect of a coating of platelet-rich fibrin on the surface of the graft in patients treated by all inside anatomic single-bundle ACL reconstruction with a semitendinosus tendon graft. The authors have observed at 5 months a superior maturation of the proximal third of the graft, while no differences were detected for the middle and distal part. Sanchez et al. (23) have shown a positive effect of a specific platelet-rich plasma preparation rich in growth factors (namely PRGF) introduced by Eduardo Anitua in early 2000 initially for oral surgery (4). These authors have observed an increased remodeling of the hamstring grafts that were pretreated by several intratendinous injections of PRGF along the graft length and they have also described a newly formed connective tissue enveloping most of the grafts treated with PRGF, compared to those untreated. Alentorn-Geli et al. (2) from the group of Cugat have proposed to infiltrate the patellar tendon graft with an autologous stromal vascular fraction from adipose tissue containing mononuclear cells and a small number of mesenchymal stem cells (MSC). They have observed a slight increase in graft maturation at 12 months at MRI, but their results were not statistically significant if compared to a control group undergoing ACL reconstruction alone.

More promising results come from basic science. The secretome of human bone marrow MSC seems a good candidate to accelerate graft maturation in a rat model of ACL reconstruction, following a recent study of Sun et al. (27). The Croatian research group of Cuti et al (9) suggested the preservation of muscle tissue around the graft during hamstring graft preparation, observing a great number of MSC inside the muscle around the hamstring tendon body and, thus, hypothesizing a positive effect of MSC in hastening the ligamentization process of the hamstring autograft. In an exhaustive recent review of Hexter et al. (15), a positive role in enhancing graft ligamentization has

been observed with the use of growth factors as the connective tissue growth factors (CTGF). CTGF can upregulate mRNA and expression of TGF- β 1, COL1 and COL2, as shown recently by Sun et al. (26). Even in preclinical animal models, the postoperative exposure to hyperbaric oxygen or the exposure to low-intensity pulsed ultrasound (LIPUS) seem able to upregulate genes such as transforming growth factor-beta1, enhancing graft maturation and ligamentization.

From this perspective, the results of our study suggest two important findings. Firstly, the viability and the phenotype of the tendon resident cells after extraction from the hamstring tendon strands demonstrate that no relevant cellular impairment has been provoked by the surgical manipulation of the tendons during the surgical procedure. This is a non-negligible aspect due to the repetitive stress that the tendons receive during the different steps of the operation. The harvesting from the inner distal thigh causes a notable stretching of the tendon structure, and it is followed by prolonged exposure to the external atmosphere of the operating theatre, while manipulation and pretensioning of the tendon are performed to obtain a graft suitable for the introduction in the knee joint. At the end of the procedure, it should be legitimate to investigate if the graft (in our setting represented by the discarded hamstring remnants) still hosts a viable cell population. Indeed, the tendon resident cell (namely the tenocytes and tendon precursor cells) (13) survived out of the knee during the operation. It was possible to extract these cells and to cultivate them in a complete medium with FGF, obtaining a population still committed toward tenocytic lineage, as shown by the “control group” of the study. At different time points (7, 14 and 21 days), the heterogeneous group of cells extracted from the remnants did not lose their original phenotype. Moreover, they continued to proliferate and, in a lesser proportion, to express tenogenic markers, as it can be expected from tenocyte and tendon precursor cells expanding under FGF, *in vitro*. This is in our knowledge the first study showing of immunofluorescence a timeline of expression of tenogenic and proliferative markers in tendon cells from hamstring strands obtained at

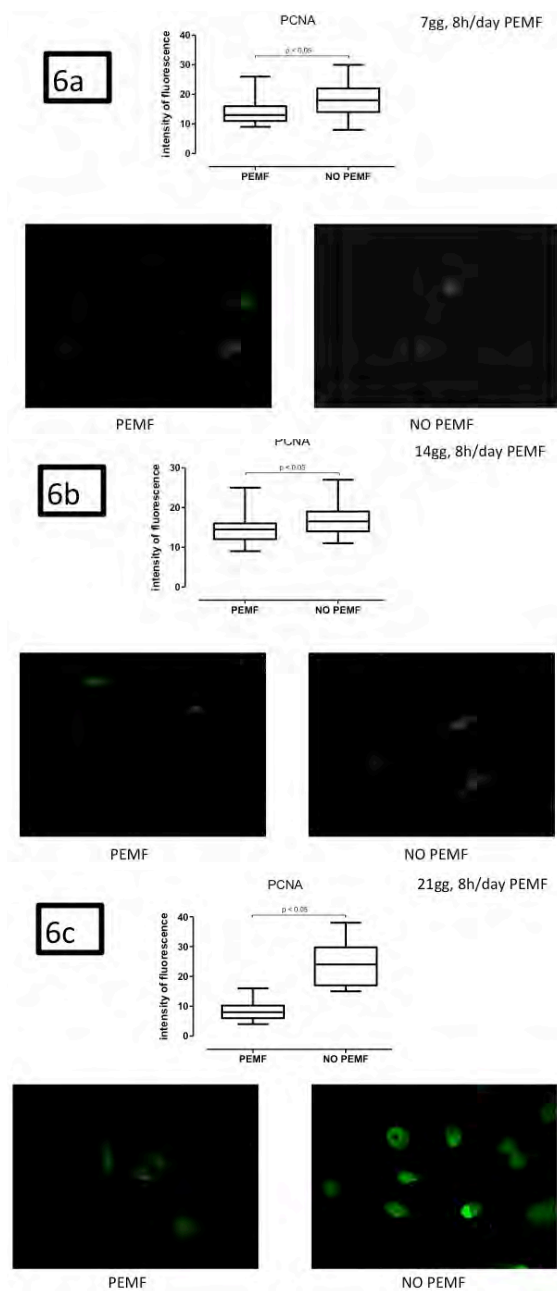


Fig. 6. PCNA expression after PEMF exposure for 8h/day and without PEMF exposure. *p* indicates the *p*-value (probability value, statistical significance level <0.05) between two specific groups of study, *ns* indicates a non-significant value; **a)** Immunofluorescence analysis for PCNA expression and quantification of fluorescence intensity in TCs cultures with and without PEMF exposure for 7 days; **b)** Immunofluorescence analysis for PCNA expression and quantification of fluorescence intensity in TCs cultures with and without PEMF exposure for 14 days; **c)** Immunofluorescence analysis for PCNA expression and quantification of fluorescence intensity in TCs cultures with and without PEMF exposure for 21 days.

the end of the surgical procedure. This is also in accordance with the concepts previously mentioned in the systematic review of Claes et al. (8) and with the work of de Girolamo et al. (13). Thus, hamstring grafts should not be conceived as simple tenoconductive scaffolds, but they are quite rightly a tenogenic construct able to drive a ligamentization process in the proper joint environment.

The second aspect of our study is the positive effect of PEMF exposure on hamstring tendon cells. The previous work of de Girolamo et al. (14) suggested the promising effect of PEMF on the same cell source of our study, but they used a smaller number of exposure cycles (a maximum of 3 cycles). Furthermore, the authors performed the cell analysis at 48 hours after the last exposure. Nevertheless, they observed no apoptotic or necrotic events and they demonstrate an increased expression of scleraxis, VEGF-A, and CO1A1, along with an augmented release of IL-6 and IL-10. These results were similar to a previous study of the same research group (13) who identified the time-lapse of 8 hours as the better length of exposure to obtain tendon-specific marker expressions and the release of anti-inflammatory cytokines and angiogenic factor. In a clinical setting, however, a prolonged PEMF stimulation for several weeks (usually 8 hours per day) is usually performed to obtain a positive effect on the musculoskeletal repair process. In the past, this concept has been presented by Denaro et al. (11) in a study in which tenocytes from supraspinatus and quadriceps tendons were cultivated up to 7 days of continuous PEMF exposure, and the authors observed a positive effect on tenocyte behavior towards the closure of an *in vitro* laceration of a tenocyte monolayer. Nevertheless, even this condition is different from the usual clinical setting in which PEMF exposure is not continuous but limited usually to 8 hours per day. A recent work of Marmotti et al. (17) has introduced an innovative “translation” from the clinical situation to an *in-vitro* setting exposing mesenchymal stem cells (MSC) derived from the umbilical cord (UC) to PEMF (with an intensity similar to that used in clinical practice) for 21 days 8 hour per day. This may represent a suitable “compromise” between an *in-vitro* experiment and the prolonged patients’

PEMF exposure used in different clinical situations. In this study also, the positive effect of PEMF on the tenogenic differentiation of UC-MSC in culture medium with FGF has been shown in the form of increasing expression of scleraxis and collagen type I from day 7 up to day 21 of PEMF exposure.

Following these works, our study also showed an anabolic positive effect of PEMF on tendon derived cells after 21 days of culture. As observed with UC-MSC, the expression of tenogenic markers, namely scleraxis, collagen type I and collagen type VI progressively increased during the time of culture and PEMF exposure and the results were statistically relevant if compared to that of “natural” control group grown only in presence of FGF. Particular attention has to be given to the collagen type VI that, far from being a mere matrix structural molecule, is a full-fledged mechanoreceptor that may be involved in PEMF signal transduction, along with the other well-known mechanism of action of PEMF on cell metabolism. Indeed, the work of Sardone and Traina (5, 24, 25) showed that collagen type VI is non-fibrillar pericellular collagen associated with the cell membrane and it can regulate tissue homeostasis. It is present on both tendon and ligaments and it interacts with different cell membrane proteins as NG2 proteoglycan and integrins (that are considered putative transmembrane receptors of collagen type VI) as well as with extracellular matrix molecules as collagen type I, decorin, biglycan, hyaluronan, and fibronectin. These authors demonstrated that the mechanical perturbation of the collagen VI-NG2 interaction has dramatic effects on the cell, causing cell-cycle arrest. Furthermore, the presence of collagen VI (and its receptor NG2) seems to be important for cell survival and cell behavior, as early collagen fibrillogenesis and tendon matrix assembly. Thus, a pivotal role of collagen type VI in mechanotransduction is so far unquestionable.

Our results show a fascinating and promising increase in collagen type VI expression under PEMF exposure and this may allow for hypothesizing a novel mechanism for the anabolic effects of PEMF on tendon cell, possibly linked to an interaction between PEMF and collagen type VI and leading to a direct action on tendon cell pericellular matrix

structure through the “mechanoreceptor properties” of this molecule. In our knowledge, this is the first study showing the increased expression of collagen type VI on tendon derived cells by PEMF exposure. Indeed, the previously known mechanisms of PEMF on mesenchymal derived cells rely on different pathways involving various cellular mediators (21) as the adenosine receptors A2A and A3, which are linked to the inhibition of the activation of transcription factor NF- κ B, a key regulator of inflammatory responses. Moreover, an interaction between PEMF and the ligand-independent activation of the epidermal growth factor receptor (EGFR) and other members of the receptor tyrosine kinase family leads to the activation of the MAPK (mitogen-activated protein kinase)/ERK (extracellular signal-regulated kinase) pathway. Also, Wnt signaling proteins (Wnt1/lipoprotein 247 receptor-related protein 5 (LRP5)/beta-catenin) seems to be linked to the PEMF mechanism of actions, ultimately leading to an anabolic effect on mesenchymal derived cells.

As a “general impression”, PEMF seems to “aspecifically” interact with some of the basic early mechanisms of stimulation and anabolism on mesenchymal derived cell and, in that, the specificity toward a particular differentiation pathway may be linked to the peculiar microenvironment of the cells. So, it is because of this possible “scenario” that a positive action of PEMF on different setting as bone healing, cartilage regeneration and tendon repair has been observed in the literature. Further studies are needed to better clarify these aspects and the conceivable interrelation between PEMF and specific proto-oncogene activation as c-myc and c-fos, as shown in the study of De Mattei et al (10). In this perspective, a recent work of Chen et al have demonstrated the relevance of fos in promoting tenogenic differentiation of tendon derived stem cells, and, thus, a fascinating connection between PEMF and fos as a new mechanism for promoting tendon anabolism is close to being imagined (7).

In our opinion, it is not surprising that, in our study, PEMF exposure did not impair tendon derived cell phenotype, as cells retained a typical spindle-like shape at the end term of culture. Analogously, a decreased expression of PCNA and beta-catenin

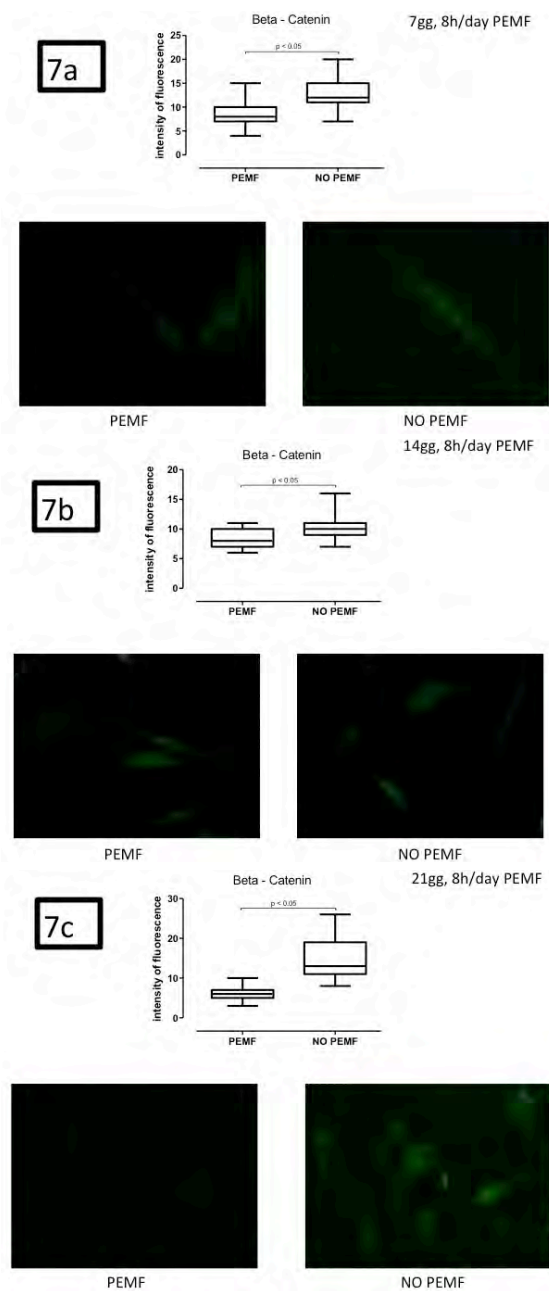


Fig. 7. Beta-Catenin expression after PEMF exposure for 8h/days and without PEMF exposure. *p* indicates the *p*-value (probability value, statistical significance level <0.05) between two specific groups of study, *ns* indicates a non-significant value; **a)** Immunofluorescence analysis for Beta-catenin expression and quantification of fluorescence intensity in TCs cultures with and without PEMF exposure for 7 days; **b)** Immunofluorescence analysis for Beta-catenin expression and quantification of fluorescence intensity in TCs cultures with and without PEMF exposure for 14 days; **c)** Immunofluorescence analysis for Beta-catenin expression and quantification of fluorescence intensity in TCs cultures with and without PEMF exposure for 21 days.

in PEMF-exposed cell culture was not in contrast with the previously mentioned observations. Indeed, we were expecting a notable differentiation effect of PEMF in cells already committed toward a tenogenic lineage, rather than a “generic” proliferative stimulus. Conversely, the group of FGF-only cell cultures shows, in fact, a progressive increase in PCNA and beta-catenin expression, consistent with the prevalent proliferative effect of FGF on monolayer tendon cell cultures, as previously shown in the studies of Qiu et al. (20) and Vigano et al. (28).

In a “wide” perspective, a real clinical relevance of our work can be hypothesized. The tenogenic differentiation promoted by PEMF exposure may allow for facilitating hamstring graft adaptation and maturation, likely shortening the early inflammatory phase and hastening the subsequent steps, in which tendon the cell differentiation followed by neo-matrix production and rearrangement are key elements of graft maturation. Furthermore, the concepts applied to the hamstring tendon graft after ACL reconstruction may be broadened, involving different tendon repair processes that may benefit from the anabolic effect of PEMF, i.e. the Achilles tendon degenerative and traumatic pathologies and the rotator cuff tendinopathy. Thus, future preclinical and clinical models of tendon regeneration and rotator cuff reconstructive surgery may be conceived, based on the results of our study.

Nevertheless, this study has two main limitations. Firstly, the “*in-vitro*” level should not allow for a direct clinical application based on the results obtained. The “*in-vitro*” setting is a very controlled and regulated microenvironment, while “the pathological *in-vivo*” processes at the lesion site and the natural inflammatory reactions that follow any mesenchymal lesions may create a different environment. This may result in possible variations in the positive effects of PEMF exposure. This aspect deserves further preclinical studies before any hypothetical use in humans. Moreover, tendon cell culture was performed *in-vitro* in a monolayer setting while, during any *in-vivo* repair process, cells are embedded in tridimensional structures. Thus, a confirmation of the PEMF positive effect on tendon-derived cells in a tridimensional setting, as

the tendon explant cultures, is mandatory before any direct clinical application.

Hamstring tendon autografts are one the most common sources of graft for ACL reconstruction. The ligamentization process of the graft plays an essential role in the long-term results of ACL reconstruction and improving the anabolic properties of tendon cells may hasten graft maturation. Among the different solutions proposed in the literature (2, 6, 9, 15, 23, 26, 27) the use of PEMF may allow for exerting a positive non—invasive stimulus on the cell microenvironment to “boost” their tenogenic properties.

The two most important findings of this study are: i) the possibility to obtain an efficient culture of tendon derived cells from the free end of hamstring tendons (semitendinosus and gracilis) harvested at the end of the surgical procedure. This shows that hamstring tendon derived cells retain their tenogenic properties after intraoperative graft preparation and, they can be fully considered “true tenogenic constructs” capable to initiate the ligamentization process of the neo-ACL.

Prolonged exposure to PEMF similar to that of clinical practice may provide a positive and efficient biophysical stimulus in vitro leading to the anabolic commitment of the cells and increasing tenogenic markers expression related to tendon matrix production. Thus, PEMF may represent a possible tool for enhancing and accelerating the physiological ligamentization process of hamstring tendons during the postoperative period of ACL reconstruction.

As a consequence, our results suggest a possible hypothetical wider clinical application of PEMF in further studies focusing on PEMF as an adjunctive treatment for different pathologies as Achilles tendinopathy and rotator cuff lesions, in which the positive anabolic effect of PEMF might improve the tendon repair process.

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When math meets surgery: how to improve femoral interference screw alignment in ACL reconstruction. A cadaveric study

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Transtibial femoral tunnel drilling is still an alternative technique in ACL reconstruction. Femoral interference screw divergence is a potential pitfall associated with transtibial tunnel technique, as angles greater than 15° jeopardize graft fixation. Our mathematical model theorizes the proper degrees of knee flexion during femoral screw insertion and the correct screwdriver position to obtain a minimal divergence of the screw in the femoral tunnel. The cadaveric study confirms our method. Mathematical model: using rototranslation matrices, a correlation is demonstrated between the ACL-tibial-guide angle, the knee flexion, and the screwdriver position. A theoretical minimal divergence between femoral interference screw and the femoral tunnel is obtainable following these assumptions: 1) knee hyperflexion during femoral screw insertion is obtained adding a flexion corresponding to the ACL-tibial-guide angle to the flexion while drilling the femoral tunnel; 2) screwdriver position (through the AM portal) is kept parallel to tibial plateau at a rotation of 15° medial to tibial sagittal plane. Cadaveric study: 24 cadaver knees were used. The transtibial tunnel was drilled with an 8 mm drill bit with the help of an ACL tibial guide set at 55°. To simulate femoral tunnel direction, a 2.4 mm K. wire was drilled through the femur with a transtibial 7 mm offset femoral drill guide. To simulate the femoral screw direction, a second 2.4 mm K. wire was drilled from the femoral entry point of the first wire through the femur, with a cannulated screwdriver. Screwdriver direction and knee flexion during the simulation were obtained following two different methods: GROUP A (mathematical model group, 12 knees), screwdriver direction and knee flexion were calculated following the mathematical model; in GROUP B (control group, 12 knees), knee hyperflexion and screwdriver medialization were manually obtained by a senior surgeon. The divergence between the femoral interference screw and the femoral tunnel was identified as the angle formed by the two wires, measured on the plane formed by the direction of the wires. Mean divergence angles between the K. wires were significantly different ($p < 0.05$) between the groups: GROUP 1 (mathematical rule): 7.25° (SD 2.2); GROUP 2 (free-hand technique): 17.3° (SD 2.9). Our study shows that a minimal divergence between the femoral tunnel and the screwdriver can be achieved simply by following a mathematical rule for correct intraoperative knee flexion and screwdriver position without the need for any specialized instrumentation. Namely, during femoral interference screw insertion through the anteromedial portal: 1) the correct knee flexion is the sum between the knee flexion angle while drilling the transtibial femoral tunnel AND the ACL tibial guide angle used during tibial tunnel drilling; 2) Correct screwdriver position is parallel to the tibial plateau,

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engaging the femoral tunnel with a position of 15° medial to tibial sagittal plane. This simple concept has clinical relevance in helping the surgeons in obtaining an optimal alignment between the femoral tunnel and the femoral interference screw during transtibial ACL reconstruction. Furthermore, following the assumptions of this study, a starting knee flexion angle around 70° during femoral tunnel drilling seems preferable for ACL reconstruction when the transtibial tunnel technique is used. Indeed, because ACL-tibial-guide angles range commonly from 50° to 60° and *in vivo*, the maximal intraoperative knee flexion attainable is 130°, a starting knee flexion around 70° is optimal to allows for adding flexion angles up to 60° before reaching the physiological limit value of 130°.

Key words: ACL reconstruction, femoral screw divergence, interference screw divergence; transformation matrices

Arthroscopic anterior cruciate ligament (ACL) reconstruction is a widely used procedure for unstable ACL injuries and various options are available for the choice of the graft, the tunnel preparation, and the graft fixation. The final decision relays on the surgeon's preference. Regarding the femoral tunnel creation, at present four techniques are still available: transtibial, anteromedial portal with rigid reamer (AM-RR) or flexible reamer (AM-FR), and outside-in retrograde (OI) drilling techniques. The transtibial technique is considered a "constrained" approach because femoral tunnel drilling depends on the position of the tibial tunnel, while AM-RR is considered "semi-constrained" alternative as the rigid reamer may create a limitation in the choice of femoral tunnel direction leading in an anterior positioning, thus the AM-FR and OI are considered pure "unconstrained" approaches.

Although the recent "trend" in ACL surgeons is to prefer the "independent" AM approaches for drilling the femoral tunnel, to obtain a more anatomical placement, the transtibial technique is still used for some advantages as the familiarity and less demanding procedures compared to AM techniques, the good long-term outcomes, the possibility to obtain a greater length of the femoral tunnel compared to that of AM approaches and the lesser invasivity compared to that of the 2 incisions of the outside-in technique.

One of the most common femoral fixation methods of the graft in ACL reconstruction is the use of interference screws. The femoral interference screw offers a secure fixation with the ultimate load to failure approximately: 400-500 N) and a "close

to joint line" position (aperture fixation), optimal for the biomechanical role of the graft. In a study of Weiler et al. (28) to increase initial fixation strength, graft harvest with a distally attached bone plug may be advantageous, but biomechanical data do not exist. This study compares the initial pullout force, stiffness of fixation, and failure modes of three strand semitendinosus grafts in 36 proximal calf tibiae using either biodegradable poly-(D,L-lactide, bioabsorbable interference screw showed a higher stiffness (10) of fixation compared to that of the metal screw (57.9 N/mm vs. 39.7 N/mm) and the authors observed also a greater graft pullout strength with a bioabsorbable interference screw than with metals crew (507 N vs 419 N respectively). Thus, bioabsorbable material seems an optimal candidate for the principle of interference screw fixation.

Nevertheless, this procedure bears a non-negligible risk of a divergence between the femoral tunnel and the screw, because in transtibial technique the femur is drilled through the tibia while the screw is inserted through the anteromedial portal. The correct position of the femoral interference screw aiming to obtain parallelism between the screw and the tunnel is fundamental for the initial fixation strength of the graft.

The incidence of femoral screw divergence in literature is reported as high as 36% (8) and the presence of screw divergence can create several problems for the final result such as: i) intraoperative technical difficulties, as screw breakage and femoral posterior wall blow-out; ii) knee pain; iii) reduced pull-out strength, determining a "funnel" effect with the screw acting more as a wedge than a parallel

compressing device and jeopardizing the stability of femoral graft fixation. Divergence is measured as an angle between the axis of the screw and the long axis of the femoral tunnel or the graft. *In vivo*, this corresponds theoretically to a single angular entity in a specific geometric plane (true divergence angle), but, when measured on anteroposterior and lateral radiographs, it corresponds to the sum of the two divergence angles measured in both views.

Our experimental study aimed to describe a method to minimize femoral interference screw divergence in ACL reconstruction with transtibial tunnel technique, through mathematical rules for knee flexion and screwdriver position during surgical procedures, without the use of any specialized instrumentation or technical modifications.

In the first section of the study, we developed a mathematical model representing the direction of the femoral tunnel drilling and the screwdriver insertion. This enabled us to define a mathematical rule to identify a specific knee flexion angle and a specific screwdriver position to obtain theoretical parallelism between femoral tunnel and screwdriver.

In the second part of the study, we performed a cadaveric experiment on 24 knees mimicking transtibial femoral tunnel drilling and femoral screw positioning by using two 2.4 mm K. wires, the first simulating the femoral tunnel direction and the second simulating the screw direction, being drilled through a standard (Arthrex Inc., Naples, Florida) cannulated screwdriver.

Screwdriver direction and knee flexion during the simulation were performed following two different methods:

i) in GROUP 1 (mathematical rule group, 12 knees), screwdriver direction and knee flexion were calculated following the mathematical model.

ii) in GROUP 2 (control group treated by standard free-hand technique, 12 knees), knee hyperflexion and screwdriver medialization were manually performed by a senior surgeon (F.C.), similarly to the procedure that is usually carried out in the operating theatre during a standard ACL reconstruction with transtibial tunnel technique.

The hypothesis was that following the rules derived from the mathematical model, one can

reach a better alignment between femoral tunnel and screwdriver than that obtained by standard manual positioning, thus, ultimately minimizing divergence during femoral screw positioning.

MATERIALS AND METHODS

I section: Mathematical model

To recapitulate the entire surgical procedure, a simple bidimensional geometrical reconstruction was the starting point of the mathematical reconstruction. Indeed, projecting only on the sagittal plane the femoral tunnel drilling, and the screw positioning, we deal with one single parameter namely knee flexion. Thus, a simple correlation is determined. For any starting knee flexion when drilling the femoral tunnel with the transtibial technique: if η is ACL tibial guide angle used in drilling the tibial tunnel and η^1 is femoral tunnel angle referred to tibial plateau plane angle η and η^1 are vertical angles and have the same degree measurement. So to be coaxial with the axis of the femoral tunnel, final knee flexion is the sum of starting knee flexion (while drilling the femoral tunnel) + ACL tibial guide angle η (Fig 1).

However, if intraoperatively the knee flexion in an open kinetic chain lays on a sagittal plane, the tibial guides and, consequently, the tibial tunnel lay on an oblique plane medial to the sagittal one, theoretically intersecting

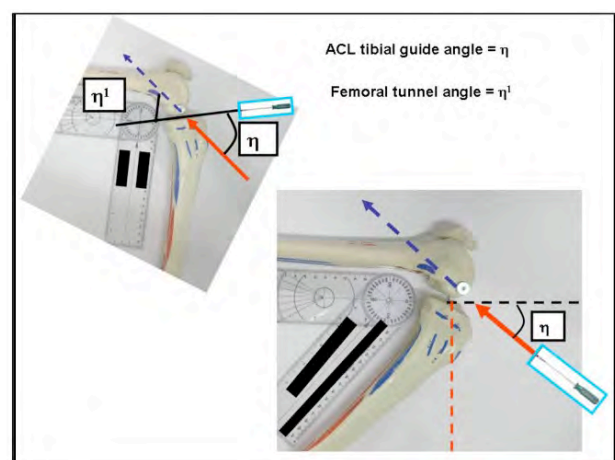


Fig. 1. *bi-dimensional geometrical reconstruction: to achieve parallelism between the axis of femoral tunnel and the axis of the screwdriver, final knee flexion is the sum of starting knee flexion (while drilling the femoral tunnel) + ACL tibial guide angle (see text for further explanation).*

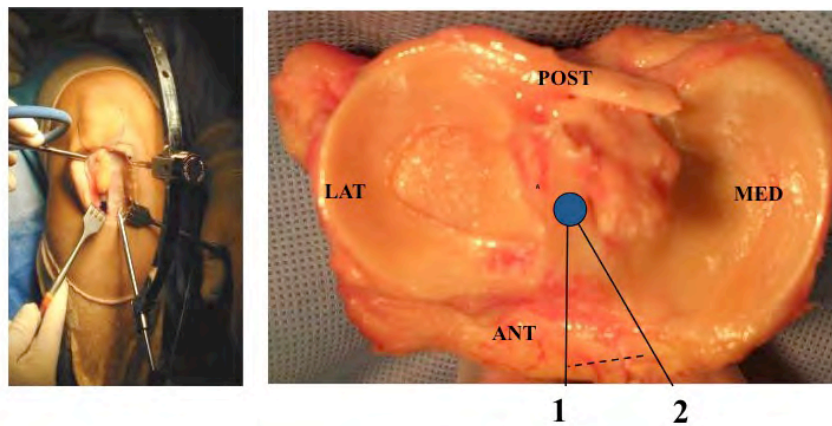


Fig 2. 1) sagittal plane of the knee flexion arc in an open kinetic chain 2) plane medial to the femoral sagittal plane, where the tibial guides and, consequently, the tibial tunnel lay. The two planes theoretically have an intersection in correspondence to the intrarticular opening of tibial tunnel (blue mark).

the sagittal plane at the intraarticular opening of tibial tunnel (usually marked with the hook of the standard tibial guides) (Fig. 2).

Dealing with intersecting planes, a bi-dimensional model shifts necessarily to a theoretical 3D sphere (see Fig. 3), in which the center is the femoral tunnel and in which the previously stated relation is incomplete because: i) the angle η on the tibial guide plane corresponds in 3D to a slightly greater angle when projected on the flexion-extension plane of the knee (i.e. the sagittal plane), ii) tibial plateau plane rotates around the sphere during knee flexion and it determines a different position of the screwdriver, relating to the tibial sagittal plane, to obtain parallelism between the femoral tunnel and femoral screwdriver. This is shown in Fig. 3 where in A: reference frame seated at the center of the sphere, corresponding to the marking hook end of the ACL tibial guide and, subsequently to the direction of femoral tunnel drilled with transtibial tunnel technique.

For every ACL tibial guide angle (i.e. η) and each possible plane medial to the sagittal one, final knee flexion and screwdriver position are then defined with a mathematical approach using rototranslation matrices.

When a reference frame is affixed to each component, the transformations between adjacent components are defined by the rototranslation matrices ($T_{n,n-1}$) which map points and vectors from the n^{th} reference frame to the $(n-1)^{\text{th}}$ one:

$$[T_{n,n-1}] = \begin{bmatrix} [R_{n,n-1}] & \{P_{n,n-1}\} \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

where ($R_{n,n-1}$) is the 3x3 rotation matrix and $\{P_{n,n-1}\}$ is the vector that locates the n^{th} reference frame origin with respect to the $(n-1)^{\text{th}}$ one. It is important to notice that the columns of the rotation matrix ($R_{n,n-1}$) are the unit vectors $\mathbf{i}, \mathbf{j}, \mathbf{k}$ that give the principal directions of the n^{th} reference frame written in the $(n-1)^{\text{th}}$ one, as follows:

$$[R_{n,n-1}] = [\mathbf{i}_{n,n-1} \quad \mathbf{j}_{n,n-1} \quad \mathbf{k}_{n,n-1}] = \begin{bmatrix} \mathbf{i}_x & \mathbf{j}_x & \mathbf{k}_x \\ \mathbf{i}_y & \mathbf{j}_y & \mathbf{k}_y \\ \mathbf{i}_z & \mathbf{j}_z & \mathbf{k}_z \end{bmatrix}$$

In this study, the defined rototranslation matrices are:

$$[T_{1,0}] = \begin{bmatrix} 1 & 0 & 0 & -R \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

$$[T_{2,1}] = \begin{bmatrix} \cos\theta & -\sin\theta & 0 & R \cdot (1 - \cos\theta) \\ \sin\theta & \cos\theta & 0 & -R \cdot \sin\theta \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

$$[T_{3,2}] = \begin{bmatrix} \cos\eta & 0 & \sin\eta & R \cdot (1 - \cos\eta) \\ 0 & 1 & 0 & 0 \\ -\sin\eta & 0 & \cos\eta & R \cdot \sin\eta \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

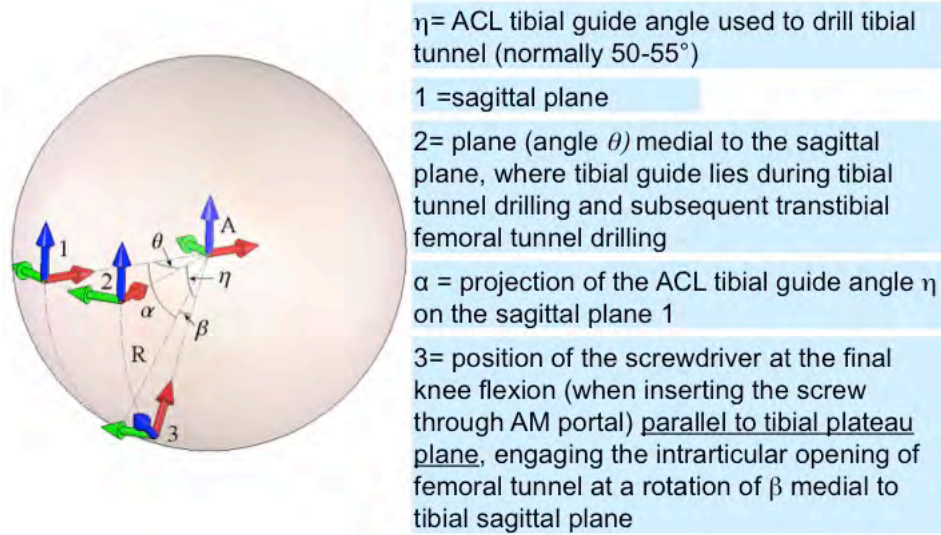


Fig 3. 3D reconstruction of the surgical procedure (tibial tunnel drilling and femoral screw insertion) in a mathematical model; (x-axes are depicted in red color, y-axes are green whereas z-axes are blue); A: reference frame (x,y,z axis) seated at the center of the sphere, corresponding to the marking hook end of ACL tibial guide and, consequently to the direction of femoral tunnel drilled with transtibial tunnel technique; 1: reference frame (x,y,z axis) referring to the sagittal plane; 2: reference frame (x,y,z axis) when drilling the tibial tunnel, angle eta being the ACL tibial guide angle chosen and angle theta being the medial rotation of ACL tibial guide plane; 3: reference frame (x,y,z axis) of the screwdriver, angle beta being the new medial position of the screwdriver on tibial plateau plane to keep convergence with reference frame A; it can be visualized that the medialization angle of the tibial guide when drilling the femoral tunnel (position 2 angle theta) is greater than the medialization angle of the screwdriver inserted through the AM portal (position 3 angle beta) to obtain parallelism between the femoral tunnel and femoral screw. This is due in vivo to the flexion of the knee during the procedure; (see text for further explanation).

where R is the radius of the sphere, θ is the rotation angle about z_1 (medial plane inclination angle with respect to the sagittal one) and η is the rotation angle about y_2 (tibial guide inclination angle on the medial plane). It is important to notice that both each rotation takes place about an axis whose location depends upon the preceding rotations (Z-Y-Z Euler angles representation) and the origins of the reference frame 1, 2, 3 lie on a sphere surface of radius R.

In order to define the position of the reference frame 3 with respect to the absolute one, named “A”, whose origin is located on the marking hook end of ACL tibial guide (in a theoretical projection of femoral tunnel axis) and whose xz-plane lies on the sagittal one, the following rototranslation matrix is defined:

$$[T_{3,A}] = [T_{3,2}] \cdot [T_{2,1}] \cdot [T_{1,A}] = \begin{bmatrix} \cos\theta \cos\eta & -\sin\theta & \cos\theta \sin\eta & -R \cdot \cos\theta \cos\eta \\ \sin\theta \cos\eta & \cos\theta & \sin\theta \sin\eta & -R \cdot \sin\theta \cos\eta \\ -\sin\eta & 0 & \cos\eta & R \cdot \sin\eta \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

To obtain the desired inclination angles

- angle α = projection of ACL tibial guide h angle on the sagittal plane, from which final knee flexion = starting knee flexion + angle α

and

- angle β = medial rotation of screwdriver referring to the tibial sagittal plane (the screwdriver lying on a plane parallel to tibial plateau), when the knee is at

$$\alpha = \arctan \left[\frac{T_{3,A}(3,1)}{T_{3,A}(1,1)} \right] = \arctan \left[\frac{-\tan\eta}{\cos\theta} \right]$$

$$\beta = \arctan \left[\frac{T_{3,A}(2,4)}{\sqrt{[T_{3,A}(1,4)]^2 + [T_{3,A}(3,4)]^2}} \right] = \arctan \left[\frac{-\sin\theta \cos\eta}{\sqrt{(\cos\theta \cos\eta)^2 + (\sin\eta)^2}} \right]$$

Fig. 4 shows the trend of α and β as a function of η and for different values of θ (the value of the angles is expressed in degree). For every value of θ , at the increasing of η up to 90°, the angle α increases till 90° and β decreases till 0°.

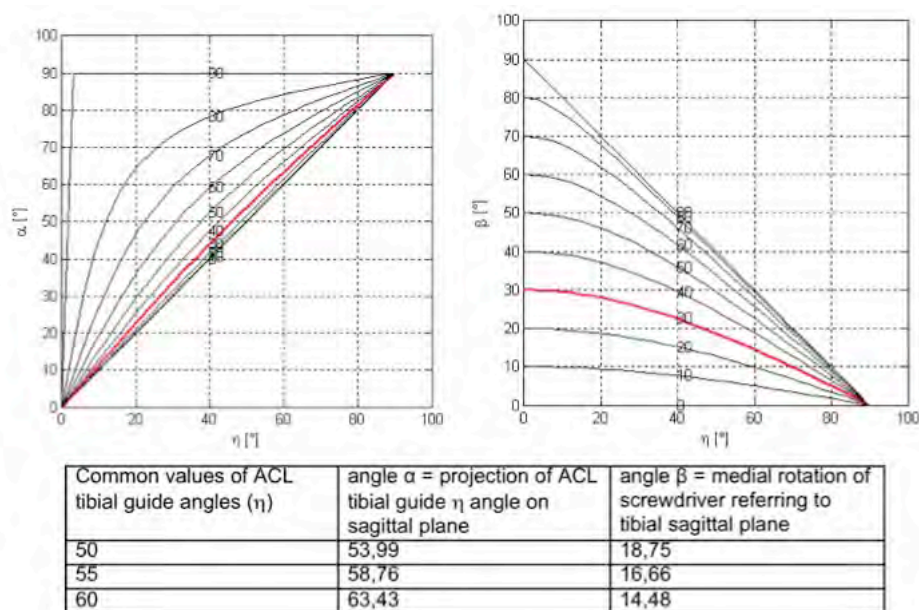


Fig. 4. The trend of α and β as a function of η and for different values of θ (the value of the angles is expressed in degree). For every value of θ , at the increasing of η up to 90° , the angle α increases till 90° and β decreases till 0° . It is important to notice that for $\theta = 30^\circ$ (standard value of θ during ACL reconstruction), α has a value only slightly greater than η (nearly a discrepancy of 3° - 4° degrees); the function can so be considered as an equation of the first order with an inclination of 45° . Conversely, for values of $\theta > 30^\circ$, the discrepancy becomes progressively significant. Thus, for a range of η between 50° and 60° (corresponding to commonly used values of ACL tibial guide angles in ACL reconstruction) angle β has an approximate value of 15° (range 18° - 14°).

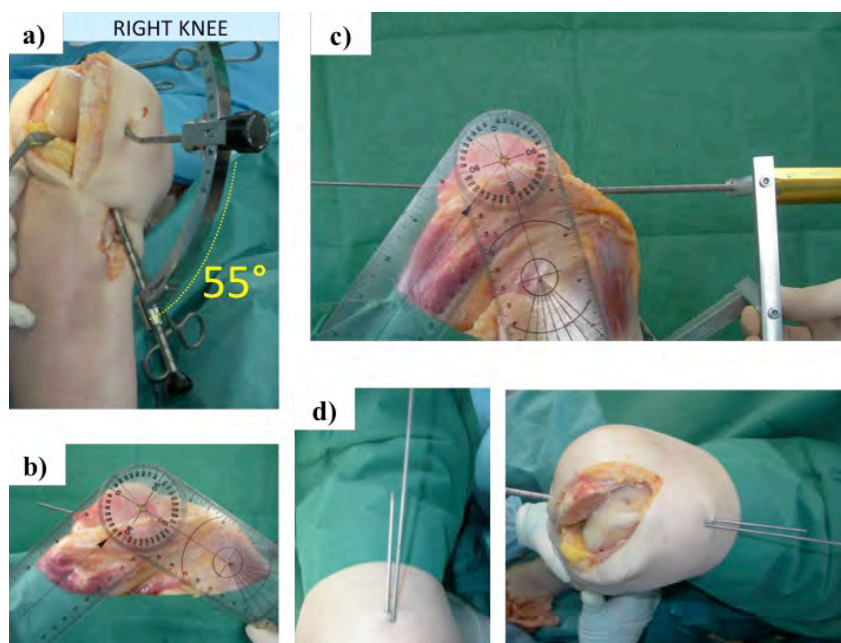


Fig. 5. a) tibial tunnel drilling following standard anatomical landmarks; ACL tibial guide was set at an angle of 55° for both groups; b) a 2,4 mm K-wire simulating the transtibial femoral tunnel drilling with a starting knee flexion of less than 90° (group 1: 70°); c) Final knee flexion and screwdriver direction marked with a second 2,4 mm K-wire; the screwdriver was inserted through the AM portal, engaging the center of the femoral tunnel, parallel to tibial plateau (in group 1: 15° medial to the tibial sagittal plane, in group 2: free-hand technique, parallel to the first K-wire); d) divergence of the 2 K-wires). Screwdriver direction marked with a second 2,4 mm K-wire inserted through the screwdriver and pushed out of the anterolateral surface of the thigh.

It is important to notice that for $\theta = 30^\circ$ (standard value of θ during ACL reconstruction), α has a value only slightly greater than η (nearly a discrepancy of 3° - 4° degrees); the function can so be considered as an equation of the first order with an inclination of 45° . Conversely, for values of $\theta > 30^\circ$, the discrepancy becomes progressively significant, as shown in Table I.

Besides, for range of η between 50° and 60° (corresponding to commonly used values of ACL tibial guide angles in ACL reconstruction) angle β has an approximate value of 15° (range 18° - 14°), i.e.: for $\eta = 55^\circ$ and $\theta = 30^\circ$, $\alpha = 58.76^\circ$ and $\beta = 16.66^\circ$ (see Fig. 5).

From this complex rototranslation matrices model, a simple mathematical rule may be sorted out to minimize divergence between the femoral tunnel drilled with transtibial tunnel technique and screwdriver position through the AM portal. Indeed, when ACL tibial drill guide is placed 30° medial to the sagittal plane of the tibia during tunnel drilling (standard position during ACL reconstruction)

1) the correct final knee flexion when inserting the screw is the sum of starting knee flexion while drilling the femoral tunnel and the value of the ACL tibial guide angle

(usually set between 50° and 60°);

2) for ACL tibial guide angle values between 50° and 60° , the correct position of the screwdriver through AM portal is parallel to tibial plateau plane, engaging the intraarticular opening of the femoral tunnel at a rotation of 15° medial to the sagittal plane

II section: Cadaveric study

The cadaveric study was been performed on 24 knees (12 right knees and 12 left knees) from 12 fresh frozen cadavers (Fig. 5, Table I). Dissection was performed anteriorly, cutting longitudinally the patella along with its tendon and the distal portion of the quadriceps muscle. This enabled us to visualize the anterior half of the tibial plateau and the trochlear space including the medial surface of the lateral condyle, allowing to keep intact articular capsule and patellar tendon. ACL was removed.

In each specimen, the intra-articular entrance of the tibial tunnel has been identified following standard anatomic landmarks. The commercially available marking hook (PCL oriented marking hook, *Arthrex*) was placed flush with PCL, so leaving a 1-2 mm bone bridge between the PCL and the planned intra-articular tibial

Table I: Experimental procedure of the cadaveric study performed on 24 knees; group A (mathematical approach) and group B (standard manual approach); each group was composed of 6 left knees and 6 right knees to eliminate any bias related to performing the procedure in the same side of the specimens.

experimental procedure of the cadaveric study	
Group A (mathematical rule)	Group B (free hand technique)
1. <u>Position of ACL tibial guide: 30° medial to tibial sagittal plane</u> 2. Tibial tunnel drilled with an 8 mm cannulated reamer 3. Center of femoral tunnel identified using transtibial 7 mm offset femoral-drill-guide at 2 o'clock position (left knee) / 10 o'clock position (right knee) 4. <u>knee-flexion-angle during the simulation of femoral tunnel = 70°.</u> 5. Femoral tunnel marked with a 2,4 mm K-wire pushed out of anterolateral surface of thigh 6. <u>knee flexion during screwdriver insertion: 125° ($70^\circ + 55^\circ$)</u> 7. Cannulated screwdriver (through AM portal, engaging the center of femoral tunnel <u>parallel to tibial plateau at a rotation of 15° medial to tibial sagittal plane</u> 8. Screwdriver direction marked with a second 2,4 mm K-wire inserted through the screwdriver and pushed out of anterolateral surface of thigh	1. <u>Position of ACL tibial guide: the tip of the guide pin sleeve set midway between anterior and medial edge of tibia</u> 2. Same as group A 3. Same as group A 4. <u>knee-flexion-angle during the simulation of femoral tunnel: between 80° and 90°</u> 5. Same as group A 6. <u>knee flexion during screwdriver insertion: manual maximal flexion</u> 7. Cannulated screwdriver (through AM portal, engaging the center of femoral tunnel) <u>manually medialized to approximate the direction of the first pin</u> 8. Same as group A

tunnel entrance. 2,4 mm guide-pins were used in all the procedures.

Specimens were then divided into 2 groups. (Table I). In group 1 (6 left knees and 6 right knees), tibial tunnel procedure was performed with standard commercially available instruments, following the mathematical rule. The medial half of the patella, patellar tendon and articular capsule were left intact and an anteromedial portal was established. The tibial tunnel was identified with the help of a standard ACL tibial guide (Adapteur™ Drill Guide System, Arthrex Inc., Naples, Florida) set at an angle of 55°, keeping the guide on a plane approximately 30° medial to the tibial sagittal plane (Fig. 5a). The horizontal arm of the guide was kept parallel to the tibial plateau. The tunnel was subsequently drilled with an 8 mm cannulated reamer. Femoral tunnel was then identified, using transtibial 7 mm offset over-the-top femoral drill guide (Arthrex Inc., Naples, Florida) placed at 10 o'clock position (right knee) or at 2 o'clock position (left knee). The knee was kept at 70° of knee flexion (Fig. 5b); the pin was pulled back proximally until its distal end disappeared from the medial surface of lateral condyle leaving the "footprint" of its entry hole.

Final knee flexion was determined following the aforementioned simple mathematical rule ($70^\circ + 55^\circ$) and the knee was set at 125° degree with the help of a goniometer (Fig. 5c). Through the AM portal, a standard guide pin sleeve (Arthrex Inc., Naples, Florida) was manually driven toward the lateral condyle, as a guide for a second pin, simulating the axis of the screwdriver. With a direct site visualization, the sleeve was positioned through AM portal following the concepts of the mathematical model, namely coplanar to tibial plateau plane, toward the intraarticular entry hole of the first pin (i.e. center of the femoral tunnel), as much as close to a 15° medial angle referring to the tibial sagittal plane. The second pin was then cautiously driven through the sleeve up to the entry point of the first pin and pushed forward out of the anterolateral surface of the thigh. The divergence angle between the pins was measured on the plane formed by the direction of the pins (true divergence angle; Fig. 5d).

In group 2 (6 left knees and 6 right knees), a senior surgeon (F.C.) performed the same procedure as in group A without applying the concepts of the formula. The standard ACL tibial guide was set at an angle of 55° and the extra-articular opening was manually kept medial to

the sagittal plane. As it is performed during the standard intraoperative steps of transtibial ACL reconstruction, the tip of the guide pin sleeve was positioned on the tibial cortex in the middle between the anterior and medial edge of the tibia, one fingerbreadth medial to the tibial tubercle.

The femoral tunnel was identified with a pin, using transtibial 7 mm offset over-the-top femoral drill guide at 10 o'clock position (right knee) or 2 o'clock position (left knee), with the knee at less than 90° of flexion (approximately 70°-80° of flexion). Knee was then manually hyper-flexed (to approximately 120°) and the guide pin sleeve was directed through AM portal toward the intraarticular entry hole of the first pin (i.e. center of the femoral tunnel), manually medializing the sleeve to approximate the direction of the first pin that represents the femoral tunnel that can be visualized intra-articularly during the standard in vivo procedure. The second pin was then pushed through the sleeve out of the thigh and the true divergence angle was measured.

RESULTS

Both group 1 (mathematical rule) and group 2 (freehand standard technique) were homogeneous for the number of specimens and sides of the specimen tested by the procedure. Furthermore, several steps of the experimental design were the same in both groups (see table I). The differences in the techniques were present only in the steps related to the mathematical rule, namely the starting knee flexion, the position of ACL tibial guide for drilling tibial and femoral tunnel, the knee flexion during screwdriver insertion and the orientation of the cannulated screwdriver through AM portal.

A direct method for evaluating the divergence between the pins was used. The authors measured the angle formed by the pins falling out from the anterolateral surface of the thigh. This angle was measured on the plane formed by the intersecting pins and it has an apex corresponding to the intraarticular opening of the femoral tunnel, thus representing the highest spatial divergence shown by the two pins (namely, true divergence angle). The reliability of the method was favored by the decreased bone density of cadaveric specimens, their femoral cortical bone being unable to significantly

interfere with the direction of the pin during drilling maneuvers.

Mean divergence angles were significantly different ($p < 0.05$) between the two groups (see Fig. 6). In group 1, mean divergence was 7.25° (range 4-10; SD 2.2°), in group 2 17.3° (range 12-22; SD 2.9°). This is consistent with an effective improvement in parallelism between the femoral tunnel and screwdriver direction in group 1 compared to 2, demonstrating an advantage of our mathematical method compared to the standard free-hand technique.

DISCUSSION

The femoral interference screw divergence is a potential pitfall associated with transtibial anterior cruciate ligament (ACL) reconstruction. Indeed, angles greater than 15° may jeopardize graft fixation. We describe a method to minimize divergence without the use of any specialized instrumentation or technical modifications but following 2 simple rules

derived from an experimental reconstruction of the surgical technique through a mathematical approach using rototranslation matrices. From this theoretical model, a minimal divergence is obtained if:

1) the knee flexion during femoral screw insertion is the sum of the ACL-tibial-guide-angle (when drilling the tibial tunnel) and the knee-flexion-angle during transtibial femoral tunnel drilling;

2) the screwdriver (aiming at the femoral tunnel aperture through the AM portal) is kept parallel to tibial plateau with a position of 15° medial to the tibial sagittal plane.

A cadaveric study on 24 knees confirms our method. We observed a significant lesser divergence in the group of cadaveric knees treated according to these mathematical rules than that of the group of cadaveric knees treated with a standard “free-hand” technique mimicking the procedure commonly used *in vivo* during transtibial ACL reconstruction. This may have clinical relevance in helping the surgeons in obtaining an optimal alignment between the femoral tunnel and the femoral interference screw

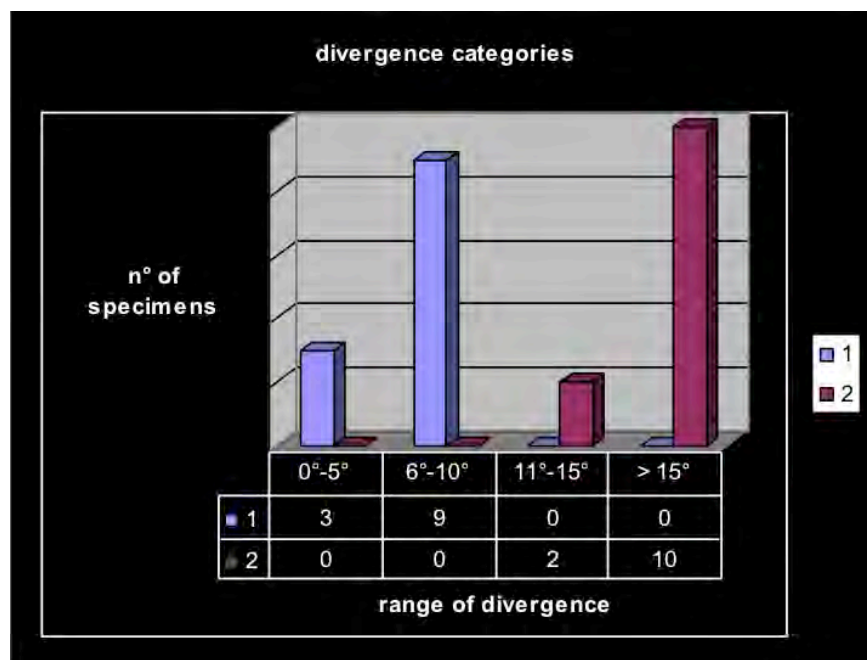


Fig. 6. divergence between the femoral tunnel and screwdriver direction in the cadaveric knee specimens of group 1 and 2; divergence values of each specimen were included in one of the following categories: 0° - 5° , 6° - 10° , 11° - 15° , greater than 15° ; in group 1, all specimens showed divergence equal or less than 10° (range 4-10), 3 of them being between 0° and 5° ; in group 2, all specimen showed divergence greater than 10° (range 12-22) and in 10 specimens divergence was greater than 15° ; $p < 0.05$.

during transtibial ACL reconstruction.

Furthermore, our model indicates that in transtibial-ACL-reconstruction it is preferable to maintain a knee flexion around 70° during femoral tunnel drilling because ACL-tibial-guide-angles ranges commonly from 50° to 60° and a knee flexion around 70° easily allows additional flexion up to 60° (during femoral screw insertion) without exceeding the maximal intraoperative flexion angle of 130° .

The transtibial technique, indeed, may still be considered an alternative to the more anatomic independent approaches for femoral tunnel creation. Besides its simplicity and reproducibility, it has some advantages as the greater length of the femoral tunnel compared to that of AM approaches, the reconstruction of the AM bundle of the ACL, leading to a stable Lachman test, and the fact that the axes of the femoral tunnel drilled by the transtibial technique are similar to the ACL graft axes, which may minimize graft-tunnel orifice impingement and minimize graft-intercondylar notch impingement.

Some studies have also observed that the transtibial technique leads to the creation of tunnels at the optimum isometric point. The recent work by Robin et al. in 2015 (23) has outlined all these aspects as well as the disadvantages of transtibial techniques, as the vertical tunnel placement and the subsequent risk of poor control of tibial internal rotation. Nevertheless, these authors affirm that there is still no specific technique for creation of the ACL femoral socket that may be considered as a “gold-standard”. This is in accord with a recent observation of Rahardja et al (21) in a study that analyzed the New Zealand registry. They observed that no significant difference was found in terms of risk of revision ACL reconstruction between the AM and transtibial femoral tunnel drilling techniques up to 3 years follow-up. Furthermore, these authors affirm that some differences were noted in patient-reported outcomes at 1 year favoring the AM approach, but these differences were not significant and good clinical outcomes may be obtained by both techniques. Comparable outcomes between transtibial and AM portal techniques were also outlined in a study of Minguell et al (17) based on 106 patients with a follow up of minimum 2 years,

in the Chinese study of Geng et al (7) in the study of MacDonald et al (14) in Canadian patients. Even if compared to the OI technique, the transtibial approach yields comparable functional clinical outcomes, although inferior rotational stability, as observed in the study of Ji et al. (12).

The risk of revision rate was also similar between transtibial and AM techniques in the recent work of Desai et al. (3) from the database of the Swedish National Knee Ligament Register and previously, in 2013, in the study of Rahr-Wagner et al. (22) based on the Danish Knee Ligament Reconstruction Register. A recent study of Jamsher et al. (11) also observed a “not so significant” difference in graft orientation when the femoral tunnel is drilled with a transtibial compared to the AM-RR approach, because both techniques do not lead to a satisfying restoration of ACL sagittal angle, and the OI and AM-FR only seem to obtain a perfect result as analyzed by magnetic resonance imaging.

Moreover, it has been observed in the literature that the increased risk of aseptic revision after “tibial independent” methods of femoral tunnel drilling compared to transtibial technique, as shown by Tejwani (26) et al. may be likely due to the higher in situ forces transmitted to the anatomically placed graft compared to those of nonanatomic more vertical grafts. Also, a recent study of Metha et al. (15) outlined these differences in peak contact pressure on the graft at the tibial aperture, possibly leading to stress on the graft and earlier failure, following ACL reconstruction with the AM technique compared to those observed with the transtibial approach.

Additionally, the literature is also controversial about the increased osteoarthritis that may develop in non-anatomically reconstructed ACL graft. Indeed, the study by Tejwani did not show at 5 years any statistically significant difference in the reoperation rate for meniscal and chondral injuries between the transtibial group and AM portal group. So, the transtibial approach may be considered still an option for femoral tunnel creation in ACL reconstruction.

A drawback of the transtibial approach is, however, the divergence between the femoral tunnel created through the tibial tunnel and the interference

screw inserted through the AM portal. Indeed, interference screw divergence was a common and well-debated problem in orthopaedics. Fanelli et al. in 1994 reported a femoral divergence incidence in 46% of their patients, using the patellar tendon defect as the portal of insertion, and in 84% using an inferomedial patella portal (25) and, more recently, the incidence of femoral screw divergence in literature was reported as high as 36% (8).

Divergence is regarded as a complication mainly because biomechanical tests revealed that the initial fixation strength may depend on the screw position and the pull-out is adversely affected by a significant divergence angle. Recent literature agrees that the strength of fixation of the graft decreases if divergence angle exceeds 15° , as reported in the studies of Fineberg et al. (5), Ha et al. (8), Miller et al. (16), Piertz et al. (20), Ninomiya et al. (18), Duffee et al. (4) and Rodin et al. (24). Johma et al. (13) also have even shown that a divergence no greater than 10° is acceptable without compromising the tensile strength provided by interference screw fixation. The “hampering effect” of screw divergence for graft fixation has been well demonstrated in the biomechanical study of Duffee et al. (4), who show a significant reduction of insertion torque, increased displacement and decreased relative stiffness during submaximal cyclic testing, and decreased load to failure and decreased stiffness during load to failure testing. Thus, surgeons should manage to attain the most parallel placement of the screw for the strongest possible construct.

Various techniques have been described to reduce femoral screw divergence, with the help of special instrumentations and substantial modifications of the traditional arthroscopic technique. These include notching the anterior edge of the femoral tunnel with a small curette (so “initiating” screw insertion) as recommended by Fu in early 2000 (6), engaging the screw into the femoral tunnel through an anteromedial portal and seating the screw with a screwdriver placed through the tibial tunnel (1) (5), using intraoperative fluoroscopy to confirm the position of the interference screw (24), using a flexible graft passer allowing direct screw insertion through an anteromedial portal (HAKI technique) (8) or the

tibial tunnel with specific instrumentation as flexible transtibial single-use graft passers [i.e. StraightShot technique (25)]. Recently, Pandey et al. (19) have also proposed a “patellar tendon” portal through the donor defect for interference screw placement obtaining good results. Criticisms to these methods point out several aspects as the potential widening of the tibial tunnel and the risk of graft damage when as the screwdriver is pushed into the limited space between the graft and the tunnel wall, the need of over-reaming the tibial tunnel to accommodate the graft passer, the use of special instruments or portals that lead to substantial modifications of the traditional endoscopic technique, the encumbrance of fluoroscopy for the operating theatre and the difficulties in obtaining clear imaging. In 2006, Chan et al. (2) have described a modified procedure to reduce these complications. In their study, the graft is initially inserted through the AM portal up into the femoral tunnel by lead sutures pulled out the anterolateral thigh; then, the screwdriver is passed through the tibial tunnel and the screw is inserted in the femoral tunnel, while the lead sutures and a probe through the AM portal drive the graft stump parallel to the screw. The graft is finally totally retrieved through the AM portal and pulled retrograde into the tibial tunnel by sutures at the graft tibial free end. This can reasonably lessen tibial tunnel widening and graft damage, but the technique is surely technically demanding and it implies a completely different approach compared to that of standard transtibial technique.

One of the key element of our study is that a minimal divergence between the screwdriver and the axis of the femoral tunnel can be achieved following a simple mathematical rule for knee flexion and screwdriver position during the surgical procedure without any specific tool and any relevant modification of the standard transtibial ACL reconstruction technique. The lack of specific devices or costly instrumentation, or major surgical modifications or new accessory portals make our assumptions readily available for any surgeon dealing with transtibial ACL reconstruction. Indeed, following the standard steps of transtibial tunnel ACL reconstruction, surgeons have just to check

the knee flexion in two phases during the procedure and to slightly force medially the screwdriver during femoral screw insertion, this being possible for the elasticity of the knee joint capsule and the surrounding medial soft tissue.

Our results are consistent with acceptable divergence angles, as reported in the literature. Considering a divergent of more than 15° significant for hampering the final result of the graft fixation at the femoral side, in our study all specimens treated according to the mathematical rules achieved an acceptable divergence angle of less than 15° , while only 2 specimens of the free-hand technique group reached a divergence angle in a range from 10° to 15° . A similar proportion of good results have been achieved by the previously mentioned authors in literature, as shown in the studies of Brodie (1), Rodin (24), Miller (16), Shroeder (25) and Chan (2).

We agree with the experimental studies of other authors that the knee hyperflexion is mandatory for achieving an optimal screw positioning, as described in the past by different authors as Fineberg et al. (5), who suggested a flexion of approximately 120° , and Fu et al. (6) who advised keeping a flexion range of 100° - 120° during femoral interference screw fixation. The difference between the previously mentioned work and our study lies in the specific value of the final knee flexion angle that we advise for each procedure. Indeed, we disagree with the “generic freehand knee hyperflexion” from 100° to 120° , but we advise to obtain a specific value of final knee flexion angle for each procedure, that can be calculated with our simple mathematical rule.

Actually, in our mathematical study, we have shown the great influence of specific final knee flexion on the divergence of the screw. This theoretical concept can be converted intraoperatively, with the use of a sterile goniometer for measuring during each procedure a specific degree of final knee flexion, that will be calculated following the mathematical rules of our study from the starting knee flexion when drilling the transtibial femoral tunnel. Taken for granted that 5° can be considered an acceptable degree of accuracy that a surgeon can obtain with *in-vivo* measurement, in our opinion, this method will allow for a better alignment between the femoral

screw and femoral tunnel, reducing the divergence.

As a practical consequence of that, starting knee flexion when drilling a femoral tunnel must be carefully planned related to the maximal flexion allowed during the operation. Indeed, given patient positioning, the volume of thigh muscles especially in the athletic or obese population and the presence of the tourniquet, no more than 130° of flexion is theoretically obtainable as a final value of knee flexion for femoral screw placement. Thus, following the mathematical rule, the sum of the ACL-tibial-guide-angle (when drilling the tibial tunnel) and the knee-flexion-angle during transtibial femoral tunnel drilling should not exceed the value of 130° and, for this reason, it seems convenient to drill the femoral tunnel at a starting knee flexion angle of 70° . Indeed, knee flexion of 70° will easily “accommodate” any value of aperture of the ACL-tibial-guide in the common range (45° - 60°) without exceeding the physiological limit of 130° of knee flexion at the moment of the femoral screw insertion.

Recently, similar advice has been proposed by Tomihara et al (27) in 2019 in a study about femoral graft bending angle in patients who underwent ACL reconstruction with a transtibial technique with bone-patellar tendon-bone autograft. These authors observed that the femoral tunnel creation should be started at between 75° and 80° of knee flexion to reduce femoral graft bending angle because shallow knee flexion angle during femoral tunnel creation, can reduce femoral graft bending angle and may lead to better clinical outcomes. On the other hand, in our opinion, a starting knee flexion closer to 90° during transtibial femoral tunnel drilling should be kept only for thin patients (who allows for more than 130° of flexion) or when facing short patellar tendon graft and, consequently, lower the ACL-tibial-guide aperture angle (i.e. close to 45°). Besides, we disagree with the study of Hackl et al. (9) who claim to create the transtibial femoral tunnel at 60° , due to impractical posterior cortex engagement by the offset guide and the resulting higher risk of blowing out the femoral posterior wall during femoral tunnel drilling and interference screw insertion.

The main limitation of our study is certainly the cadaveric experimental setting that does not

correspond perfectly to the intraoperative in vivo procedure of transtibial ACL reconstruction. Indeed, simulated surgical steps have been set up to verify the mathematical assumptions of the rototraslation matrices model. Further clinical studies may allow for verifying in vivo the effective reduction of the divergence and the possible clinical relevance to the clinical outcomes of patients who underwent transtibial ACL reconstruction.

Nevertheless, to our knowledge, this is the first time that a rototraslation matrices model is applied to solve a surgical pitfall and, in the specific setting, to optimize the problem of femoral screw divergence in ACL reconstruction. Rototraslation matrices are a fascinating choice for describing the movement of devices around axes and their precise theoretical relationship in a pre-defined confined space. Furthermore, they allow for conceiving theoretical models that may be proposed for clinical use to improve the surgical procedures, as demonstrated in our study. Thus, the study itself may be an example of the interaction between complex mathematical models and surgical procedure and it may also open a new research scenario in which “when math meets surgery”, surprising results may be achieved to improve our clinical practice.

A mathematical model can help solve complex surgical problems. Our study shows that adequate alignment between the femoral tunnel and screwdriver axes can be achieved simply following a mathematical rule for correct knee flexion and screwdriver positioning during transtibial ACL reconstruction, without specialized instrumentation or modification in surgical technique. Namely, when inserting the screwdriver, an additional flexion angle corresponding to the ACL tibial guide value has to be added to the knee flexion while drilling the femoral tunnel, while the screwdriver has to be set parallel to the tibial plateau, engaging the femoral tunnel at a rotation of 15° medial to tibial sagittal plane. This easy and reproducible formula enables to achieve good parallelism between femoral tunnel and screwdriver, as displayed in the cadaveric study. This may allow for reducing screw divergence in both sagittal and anteroposterior planes and, ultimately to improve ACL graft stability.

Furthermore, following the assumption of this study, a flexion angle of 70° during transtibial femoral tunnel drilling is assumed as the most suitable for ACL reconstruction, allowing additional flexion increment as much as 60° before reaching the maximal knee flexion of 130°.

This study is the first example in which rototraslation matrices models are applied to solve interference screw divergence in ACL surgery. Their versatility and the precise approach offered for tridimensional reconstruction suggest a further use of rototraslation matrices in investigating other controversial aspects of knee reconstructive surgery.

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Comparing different approaches in robotic-assisted surgery for unicompartmental knee arthroplasty: outcomes at a short-term follow-up of MAKO versus NAVIO system

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The popularity of unicompartmental knee arthroplasty (UKA) continues to grow among orthopaedic surgeons and robotic surgery may be helpful in obtaining a precise placement of the prosthetic components, thanks to the meticulous intra-operative computer study for simulating the prosthetic positioning. This may lead to longer implant survivorship as well as a reduction in intermediate and long-term prosthetic complications, despite the initial greater costs than those of manual UKA. In this preliminary study, from January 2017 and October 2017, 18 patients underwent UKA with MAKO robotic system assistance and 10 patients received UKA with NAVIO robotic system assistance. The two groups were homogeneous by age, BMI, degree of osteoarthritis involvement, and postoperative program. Patients were followed both clinically (Numeric Rating Scale NRS and Knee Injury Osteoarthritis Outcome Scores KOOS) and radiographically. At the end term follow up (2 years), no significant difference was observed for NRS and KOOS as well as for clinical parameters as an active range of motion. A significant discrepancy was detected regarding the duration of the surgery and time of using the robotic system, that appeared to be longer in the NAVIO group than that of MAKO group, likely due to the specific technical aspects that characterize these two different robotic systems. The main finding of this study is that favorable clinical and radiographical results may be obtained using a robotic approach (MAKO or NAVIO) for UKA positioning at a short follow up. Due to the lack of significant clinical differences observed between the two groups of patients at end term follow up, the “concept” of a robotic approach, more than a specific patented system, may be considered the key element for improving UKA technique and it is likely that in the near future the choice of a single specific robotic system will still be a “surgeon’s preference”. The results of the study add scientific evidence regarding the effective improvement of UKA results using different robotic approaches. They also show possible economic sustainability of this therapeutic strategy related to the optimal patients’ performance obtained at short term follow up, suggesting that the robotic assistance may really become a key element for better long-term survivorship of unicompartmental knee arthroplasty

The popularity of unicompartmental knee arthroplasty (UKA) continues to grow, currently accounting for roughly 10% of all knee arthroplasty procedures; the percentage is anticipated to increase to more than 20% in the future (1, 2, 3). Interest

in UKA continues to expand thanks to lower perioperative morbidity, lower risk of infection, less blood loss, accelerated recovery and improved range of motion compared to total knee arthroplasty (TKA) (4). Nevertheless, compared to TKA, UKA has

Key words: robotic surgery, unicompartmental knee arthroplasty, outcome

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shown inferior results, with revision rates between 10% and 20%, and ten-year survivorship of 85-90% compared to 95% of the (TKA - SKA) (3-5, 6, 7).

These aspects seem to be linked to the intrinsic differences between UKA and TKA. Indeed, dealing with UKA, we do not face a damaged ligamentous apparatus and moreover, UKA implies a less invasive surgery with respect to the total knee prosthesis. Furthermore, UKA allows for a three-dimensional correction of knee unicompartmental osteoarthritis, with, theoretically, few alterations of the patient's specific mechanical axis. However, achieving a consistently accurate alignment of the tibial and femoral component in UKA using conventional approaches is difficult (8, 9). These aspects are extremely important for the success of the intervention and it is precisely in this "operative setting" that robotic surgery may help us, allowing for better final placement of the components thanks to the meticulous intra-operative customization of prosthetic positioning.

The definition of the robot is given to us from the "Robot Institute of America" which defines it as a programmable multifunctional manipulator designed to move materials, objects, tools, or devices through different schemes engines for carrying out certain tasks (10). The use of robots is rapidly increasing in surgery to help physicians improve the results of their procedures, especially those that need more precision and accuracy in positioning prosthetic components, i.e. during the implant of UKA (MAKO (11), Navio (12) and TKA -Tsolution One Surgical System (13), Robodoc (14), iBlock (15). MAKO systems and similar equivalents require a preoperative CT or MRI analysis to decide how (on pre-operative planning) the bone cuts must be performed and thus the final position of the prosthetic components. The disadvantage is therefore due to the costs associated with performing these examinations in addition to the fact that we expose the patient to further radiation (16) (10) (18).

Among the advantages, one of the most important is the concept that the pre-operative study allows the surgeon to keep in mind the result that he wants to obtain even before starting the operation. Unlike most of the robots just described,

the NAVIO and iBlock systems are able to make these assessments without a pre-operative CT planning. Indeed, the procedure takes place directly in the operating room, through surface surveys with special pointers that allow for acquiring the anatomical landmarks. The disadvantage is due to the lengthening of surgical times as well as the lack of a real pre-operative planning combined with the impossibility of assessing if the anatomical landmarks have actually been taken correctly and if the image generated by the system is correct.

The positive results of robotic use in the orthopedic field are appreciable with a reduction in morbidity, complications, overall costs. It should also not be forgotten that an optimal better alignment of the prosthetic components showed a longer duration of the implant due to a better distribution of the forces and consequently less wear, in addition to the reduction of the revision rate (4). These aspects alone are sufficient to justify the increase in surgical times (more appreciable during the first operations due to the normal learning phase) and the costs of the robot. A study has shown that robot-assisted surgery is convenient compared to manual surgery, when the number of interventions exceeds 94 interventions/year, Failure rates are reported less than 1.2% at 2 years and the patient's age is considered an important predictive parameter (19). There are three different types of robots used in prosthetic surgery (11):

- i) Passive systems complete part of the procedure under the direct and continuous supervision of the surgeon;
- ii) Active systems perform the task regardless of any surgeon's intervention;
- iii) Semi-active systems require surgeon involvement but provide restricted feedback, usually tactile, acoustic, or visual, to increase control and operational safety. For example, the surgeon cannot perform an osteotomy that exceeds the pre-established volumetric parameters, limiting the cut only up to the level decided in the preoperative planning.

Another mode of semi-active technology uses the control of certain instrumental parameters, such as the speed and depth of action of a drill: once the bone resection plane has been defined, the robotic

system will evaluate the position of the drill within the operating range. When the drill approaches the edge of the planned resection, the computer system slows down the speed of the drill or retracts it. The objective of our study is, therefore, to analyze the clinical, functional and radiographic results of the implantation of unicompartamental knee prostheses through the MAKO and NAVIO robotic systems, using a “fast-track” rehabilitation protocol and comparing the two operating systems at two years follow-up.

To achieve our goal, we have taken into consideration different objective and subjective parameters. The former includes the duration of surgery and the robotic time, the intra-operative blood loss, the average hospital stay, and the radiographic evaluation of the mechanical knee axis. The second group includes the NRS (Numerical Rating Scale), ROM (Range of Motion) (Active Autoassisted Flexion (FAA) & Active Autoassisted Extension (EAA) and KOSS (Knee Injury and Osteoarthritis Outcome Score).

MATERIALS AND METHODS

The first group was composed of 18 patients, operated with the MAKO robotic system from January 2017 until May 2017. The second group included 10 patients operated with the NAVIO robotic system in September and October 2017. Surgery in both groups was performed consecutively. Surgical procedures of both groups were performed at the San Luigi Gonzaga Hospital in Orbassano, by the Orthopedic and Traumatology Division team.

From 20 January 2017 to 10 May 2017, 18 patients underwent UKA with MAKO robot-assisted technique, with an average age of 68.70 ± 7.70 years (min 55 - max 80). Patients were followed from pre-operative to two years follow-up. No patients enrolled in the study were lost during follow-up. Regarding the general characteristics, the patients examined were 5 men (27.8%) and 13 women (72.2%). The average BMI of the patients is 27.46 ± 3.69 kg/m. In 9 patients (50%) the operated limb was the dominant limb. Two patients (11.1%) used walking aids at the time of admission. The following procedures were carried out: one patellofemoral implantation; one bi-

compartmental implant (medial and patellofemoral); one lateral UKA; 15 medial UKA.

From September 2017 to October 2017, 10 patients underwent surgery with NAVIO technology, with an average age of 69.2 ± 7.1 years (min 54 - max 79). Patients were followed in the pre-operative phase, up to 2 years follow-up. No patients enrolled in the study were lost during follow-up. As for the general characteristics of the patients, the BMI was 28.72 ± 5.25 ; all patients were right-handed, suffering from multiple comorbidities, both orthopedic and general. All patients underwent medial UKA.

Surgical indications and contraindications were unchanged compared to those of UKA implantation without robotic assistance. According to the guidelines of the literature, the indication to perform a UKA is based on the following parameters (13) (21, 22):

- absence of inflammatory arthritis;
- joint degeneration confined to a single compartment;
- the integrity of the anterior cruciate ligament;
- reducibility of the varus or valgus deformity;
- varus deformity less than 15° and valgus deformity less than 20° ;
- flexion contracture of less than $<15^\circ$;
- no previous high tibial osteotomy

Despite the numerous restrictive parameters, we decided to include some borderline cases, such as patients with BMI 36 due to obesity, elderly patients, and those with modest chondrocalcinosis. All patients were asked to sign an informed consent to participate in the study.

The necessary pre-operative X-Ray examinations were A-P (antero-posterior), L-L (latero-lateral) and Rosenberg views, the long-leg standing view of the lower limbs and the sunrise view. MRI of the knee was required to assess the integrity of the ligament compartment and the absence of osteoarthritis in the unaffected compartment. MAKO patients underwent a CT study on average 30 days before the date of surgery. NAVIO patients have not been subjected to this diagnostic procedure, as it is not required for the use of the NAVIO robot. For our study we evaluated several parameters for each patient:

- Perceived pain, through Numeric Rating Scale

(NRS) (23, 24);

- Knee Injury Osteoarthritis Outcome Scores (KOOS) (26);
- ROM (Range of Motion);
- intra-operative blood loss;
- days of hospitalization in the departments of Orthopedics and Traumatology and of Physical and Rehabilitation Medicine;
- Evaluation of mechanical knee axis;
- Time of surgery and robotic time.

MAKO surgical technique

Robotic Arm Interactive Orthopedic System (Rio, Mako Stryker, Fort Lauderdale, FL) is a semi-active system available in clinical practice for robotic THA, TKA, and UKA implantation procedures. Being a system based on the image, pre-operative planning by CT is used to determine the correct positioning and the correct dimension of the components, as well as to establish the level of bone resection. These data are confirmed and regulated during the surgical procedure, based on the patient's specific joint kinematics before any surgical resection. Indeed, during the operation, the patient's anatomy must be mapped, through the location of landmarks, to allow the robot for recognizing the location of points in the articular space. During the procedure, the robotic system provides auxiliary feedback to prevent bone resection outside the established plane. The patient is placed in a supine position, with special support at the level of the calcaneus, which allows for fixing a position during the operation. The next step is the registration of the robotic arm. If the fault tolerance is within the limit value (0.5 mm), the software proceeds automatically to the verification step. A longitudinal incision is then made, and medial parapatellar access is performed. At this moment, two anterior and proximal femoral and tibial screws, with their "arrays" are positioned percutaneously. Possible osteophytes should not be removed until femoral and tibial detection is complete.

With the help of the palpator (probe), the points shown by the software (on the computerized 3D virtual model) are identified. Only after the bone detection procedure, the overlapping medial osteophytes are removed. Then, we proceed to the "gap balancing"

and, to be able to do that, a minimum of 4 different positions are recorded, applying stress in valgus to correct a possible coronal deformity. Registered knee positions are in extension, mid-flexion, flexion, and maximal flexion (hyperflexion).

On the computerized 3D model of the patient's knee, a simulation is performed of knee stability, at various degrees of flexion, with the hypothetical femoral, tibial, and spacer components in place. Based on the position of the components and the thickness of the spacer, which is modified by the specialist in the OR, at the operator's request, graphs of laxity knee stiffness are obtained for various degrees of flexion. Following the execution of these procedures, it is possible to proceed with bone cutting. Depending on the prosthetic components and their position, the software transmits to the robotic arm the area and thickness of cartilage and subchondral bone to be removed with the burr. On the screen, green areas correspond to the tissue to be cut and in red, the surgeon visualizes the areas of excessive cutting. If the cutting exceeds the planned thickness by 2.3 mm, the cutter will stop automatically. Any soft tissue, meniscal residue or excess bone outside the milling area is removed.

After profuse washing, the final components are cemented and implanted. Finally, the knee and the final stability check is performed, to confirm the correspondence with the intra-operative planning previously performed. Before closure 2 vials of Tranexamic Acid are injected intravenously to reduce the risk of bleeding. The insertion of a drain is generally indicated.

NAVIO surgical technique

The NAVIO system (Smith & Nephew®) differs from the MAKO system for the absence of preoperative CT images. The system is designed not only for the UKA and TKA procedures, already seen in the MAKO system but also for patellofemoral arthroplasty (PFA). In a similar way to the system previously seen, it is necessary to map the patient's anatomy, to allow the robot for recognizing the location of the points in the space and for generating the computerized 3D image. The patient is placed in a supine position with the knee flexed at 90° and

the hip bent at 45°. Similarly, to the MAKO system, special support is used to keep the leg firm in place for the entire procedure. The robot has a video camera connected to a computer that communicates the positions of the handpiece and the femoral and tibial markers and connected to a probe that is used for the acquisition of landmarks and subsequently to milling. The procedure begins with the acquisition of anatomical landmarks of the affected limb. Then the surgeon continues the procedure positioning the detectors, which will allow the system for mapping the knee. Bicortical partially threaded pins are inserted percutaneously into the proximal tibia and distal femur and the attachment of optical tracking arrays is performed.

After the surgical incision and exposure of the joint, the presence of osteophyte and bone spurs (both femorotibial and patellar) must be verified and, if present, they must be removed: the objective is to allow the knee to reach 120° of flexion. Peripheral checkpoints are then highlighted using the probe, i.e. the center of the tibiotarsal joint and the center of the femoral head. These points are designed not to be altered during osteotomy procedures.

We then proceed to the verification of the femoral kinematics both through a complete extension, which allows for determining the degree of deformity in varus or valgus of the knee and through a complete flexion and extension to obtain the kinematic rotation axis of the femur. The ligamentous tension is also verified during passive mobilization, by applying persistent stress in varus or valgus to check the stability of the lateral or medial collateral ligament; for lateral or medial UKA, this step quantifies the joint space to be filled. In this phase, several other landmarks are identified at the level of the femur as the point of demarcation, which marks the anterior part of the femoral component and the center of the knee or center reference point of the joint.

Then, through the probe, the entire surface of the condyle is digitalized. In sequence, at the level of the tibia, the center of the knee (insertion of the anterior cruciate ligament), the lower point of the plateau, where the cartilage is more worn, the most posterior and anterior point and finally the most medial or lateral point on the tibial condyle are identified.

Subsequently, by using the probe, the entire surface of the tibial plateau is digitalized including a portion of surface inferior to the plane of the tibial plateau. Then we move on to the planning phase in which the anatomy of the knee is virtually reconstructed as well as the tension of soft tissues and ligaments (for joint balancing), and the points of contact and load transfer at the component level are represented. This allows also for predicting the area in which the wear will be hypothetically more consistently represented. Through a solid surface and cross-sectional view and the views on the sagittal, coronal and transverse planes, it is possible to determine the best size and the optimal position of the prosthetic components.

Postoperative program

On day zero, following the resumption of sensitivity, the physiotherapist suggests the patient to start in the sitting position, to stand up and try to walk with the aid of the walker. The first steps are taken in the room to assess the patient's clinical conditions. If these are favorable, the patient is taken to the hallway. As soon as the patient can walk safely with the walker, the physiotherapist recommends the use of crutches during the kinesitherapy session of work, keeping the walker for independent movements during the day. Subsequently, the walker is abandoned, and the patient is advised to use only crutches. Climbing stairs is started on the second day. The treatment takes into consideration the state of health of the patient and his state of mind. Indeed, the patient's compliance and fitness are essential for a satisfying physiotherapeutic program. When pain or fear prevented the patient from participating in the rehabilitative sessions, he or she has never been forced and the process was then recalibrated daily.

RESULTS

MAKO UKA

The average time for surgery was 91.27±12.24 minutes (max 105 - min 70 minutes). The robotic time was on average 37.55±10.22 minutes. No intervention required conversion to a "free-hand" technique or conversion to TKA. None of the patients

developed intra-operative complications. Blood losses during surgery were on average 122.83 ± 58.13 cc.

The mean hospital stay was 4.5 ± 1.4 days in the Orthopedics and Traumatology ward, while in Physical and Rehabilitative Medicine Division the patients remained 4.55 ± 3.35 days. The evaluation of the NRS demonstrated a reduction from pre-intervention to subsequent follow-up with a significant p-value from the pre-operative value to the follow-up at different time points ($p < 0.001$).

The result of the KOOS questionnaire, submitted to patients both pre-operatively and in all subsequent follow-up intervals, showed an improvement in scores, with a statistically significant p-value between pre-operative value to the follow-up at different time points ($p < 0.001$).

The ROM of all patients was measured with an active-assisted method using a goniometer. The p-value between pre- and final follow-up of the active auto-assisted flexion (FAA) was statistically significant ($p < 0.001$). Even the auto-assisted extension (EAA) showed a statistically significant result ($p < 0.007$).

NAVIO UKA

The average duration of surgical procedures with NAVIO system was 133.3 ± 10.43 min (max 145 -

min 113 min). The robot was used for an average of 95.5 ± 18.78 min. No intervention required conversion to a “free-hand” technique or conversion to TKA. None of the patients developed intra-operative complications. Blood loss during surgery was 73 ± 30.20 cc.

The mean hospital stay was 2.9 ± 1.45 days in the Orthopedics and Traumatology ward, while in Physical and Rehabilitative Medicine the patients remained 9.9 ± 3.38 days. The evaluation of the NRS demonstrated a reduction from pre-intervention to subsequent follow-up with a significant p-value between pre-op. and the follow-up at 1 year and 2 years ($p < 0.001$).

The result of the KOOS questionnaire submitted to patients both pre-operatively and during the follow-up showed an improvement in scores with a statistically significant p-value between pre- and the follow-up at 1 year and 2 years ($p < 0.001$). The ROM of all patients was measured with an active-assisted method using a goniometer. The p-value of FAA between pre- and end-term follow-up was statistically significant ($p < 0.001$); the EAA showed a statistically significant result although lower than the FAA ($p < 0.03$).

MAKO vs NAVIO: results

Comparing the two systems from the statistical

Table I. Study parameters evaluated: **NRS** (numeric rating scale); **ROM** (range of motion); **FAA** (active auto assisted flexion); **EAA** (active auto assisted extension); **KOOS** (Knee Injury Osteoarthritis Outcome Scores).

PARAMETERS	MAKO	NAVIO
Duration of surgical procedures	$91,27 \pm 12,24$ min.	$133,3 \pm 10,44$ min.
Duration of robotic procedures	$37,55 \pm 10,22$	$95,5 \pm 18,78$ min.
Preoperative NRS	$5,5 \pm 2,43$	$6,4 \pm 1,71$
Postoperative NRS	$1,5 \pm 0,82$	$0,3 \pm 0,67$
Preoperative ROM (FAA)	$108,3^\circ \pm 12,24^\circ$	$106^\circ \pm 13,7^\circ$
Preoperative ROM (EAA)	$121,39 \pm 7,96^\circ$	$-4,5^\circ \pm 6,85^\circ$
Postoperative ROM (FAA)	$-4,44^\circ \pm 6,43^\circ$	$130^\circ \pm 12,48^\circ$
Postoperative ROM (EAA)	$-0,28^\circ \pm 1,14^\circ$	EAA $-1^\circ \pm 2,1^\circ$
Preoperative KOOS	$44,8 \pm 10,03$	$58,54 \pm 18,82$
Postoperative KOOS	$92,6 \pm 7,75$	$87,5 \pm 4,49$
Intraoperative blood loss	$122,83 \pm 58,13$ cc	$73 \pm 30,20$ cc
Mean hospitalization days	$9,05 \pm 4,5$	$12,8 \pm 4,1$

analysis (Table I), we observed that the duration of the intervention, the robotic time and the blood losses were different in the 2 groups:

- the duration of surgery was significantly longer in the NAVIO group (133.3 ± 10.44 minutes) than that of the MAKO group (91.22 ± 12 minutes). ($p < 0.001$);
- the duration of the robotic time was significantly longer in the NAVIO group (95.5 ± 18.78 minutes) than that of the MAKO group (37.55 ± 9.94 minutes). ($p < 0.001$);
- blood losses were significantly higher - albeit to a lesser extent than the other data - in the MAKO group (118.61 ± 56.6 cc) than those of the NAVIO group (73 ± 30.20 cc). ($p < 0.02$).

On the contrary, the statistical analysis performed at 2 years between the two techniques was not statistically significant for the following parameters:

- NRS: MAKO 0.44 ± 0.82 ; NAVIO 0.3 ± 0.67 . ($p = 0.81$);
- KOOS: MAKO 93.6 ± 7.75 , NAVIO 95.28 ± 4.49 . ($p = 0.56$);
- FAA: MAKO $121.38^\circ \pm 7.95^\circ$, NAVIO $130^\circ \pm 12.47^\circ$. ($p = 0.20$);
- EAA: MAKO $-0.28^\circ \pm 1.14^\circ$, NAVIO $-1^\circ \pm 2.10^\circ$. ($p = 0.26$).

DISCUSSION

The main finding of this study is that favorable clinical results may be obtained using a robotic approach (namely MAKO or NAVIO) for UKA positioning at a short term follow up. The authors observed a promising increase in patients' performance as well as a significant reduction of knee pain comparing preoperative and postoperative scores for each system. This makes the robotic approach a promising valid alternative for improving UKA results. Moreover, in our specific population, no significant differences were observed between the two systems, suggesting that the "concept" of a robotic approach more than a specific patented system may be considered the key element for improving UKA technique. Although in the future the choice of a single specific robotic system will still be a "surgeon's preference", a study with a

larger population including a comparative subgroup of patients treated by manual implantation technique will certainly add stronger scientific evidence regarding the effective improvement of UKA results using a robotic approach and the economic sustainability of this concept compared to manual implantation in terms of revision rate and patients performance.

The increase in the prevalence of degenerative knee pathologies makes partial knee replacement surgery a widespread procedure in the last decade. Nevertheless, the relatively smaller number of UKA, if compared to that of TKA, still implies for the surgeons a "greater challenge" for an optimal and reproducible result. This concept may be considered the main "present limitation" of UKA. The strategy currently used to overcome the problem is the introduction of robotic instrumentation in the operating room: this may increase the precision in prosthetic implants positioning (27, 28) assisting the entire decisional process through multidisciplinary management of the single patient (29, 30). Even in our national landscape, the small number of UKA (31), compared to the TKA (15.6% and 84.4% in Italy in 2016) is a reality (27). Furthermore, according to the article by Monil K. et al. (13), a difference in the precision of UKA positioning has been observed when performed with or without robotic assistance.

The objective of our study is to analyze the clinical, functional and radiographic results of the implantation of unicompartmental knee prostheses through the MAKO and NAVIO robotic systems, using a "fast-track" rehabilitation protocol and comparing the two operating systems at two years of follow-up. Our study shows some interesting results, mainly in the duration of surgery, but it is important to extend the number of patients. Indeed, we have already started a multicenter study with other hospitals in our region to broaden the number of patients to be treated and followed. Furthermore, our short follow-up does not allow for understanding if this new technology is, nowadays, really a convenient alternative to the surgeons compared to the standard manual procedure. It would be extremely helpful to have a longer follow-up to learn more about the long-term advantages of unicompartmental replacement

through robotic technology.

Another important issues regarding the learning curve of this new system. When dealing with robotic technology, one has to “learn to know” the robotic system at the beginning of his experience, to obtain a reproducible result in the UKA implantation, as observed by Hamilton W.G. et al (33). These authors have shown that, in a series of 445 UKA performed by the same surgeon with a minimally invasive approach, the number of failures and time for surgery was significantly reduced from the second half of procedures. Thus, there is undoubtedly a considerable improvement in the learning curve linked to the greater familiarity between operator and robot. Specifically, some studies claim that a surgeon needs about 13 interventions to reach a “steady state” in the operative times, with an average of 56 ± 20 minutes of robotic time with MAKO technology (34), while Wallace D. et al. (35) state that a “steady state” is achieved in only 8 interventions with the NAVIO system. The use of the NAVIO system, therefore, seems easier and more intuitive than the MAKO system.

Our study showed a different trend of surgical timing compared to those reported in the literature, recording lower values in patients operated with

MAKO system (91.27 ± 12.24 min) compared to those of patients treated with NAVIO system (133.3 ± 10.43 min), even if both were superior to the data reported in the literature. This could be related to the small number of patients (18 MAKO, 10 NAVIO) in our study, that necessarily led to include, for each robotic system, the first group of patients normally “excluded” from the analysis as part of the learning curve. Analyzing in detail our patients (Fig. 1, 2) it is possible to notice how the surgical times have been slightly reduced among the first and last procedures in both study groups. As an exception, nevertheless, there have been some procedures performed at the end of the period with a duration overlapping those of the first surgeries. This could be related to the fact that the operations were performed by different surgeons of the same division. This has hampered the possibility of a single surgeon to improve and to reach the time of surgery comparable to that reported in literature.

Furthermore, we observed that the duration of surgery and robotic time with MAKO system was significantly lower than that of the NAVIO group. This is linked to the fact that the use of the MAKO platform implies a pre-operative TC planning, while the NAVIO system provides for the collection and

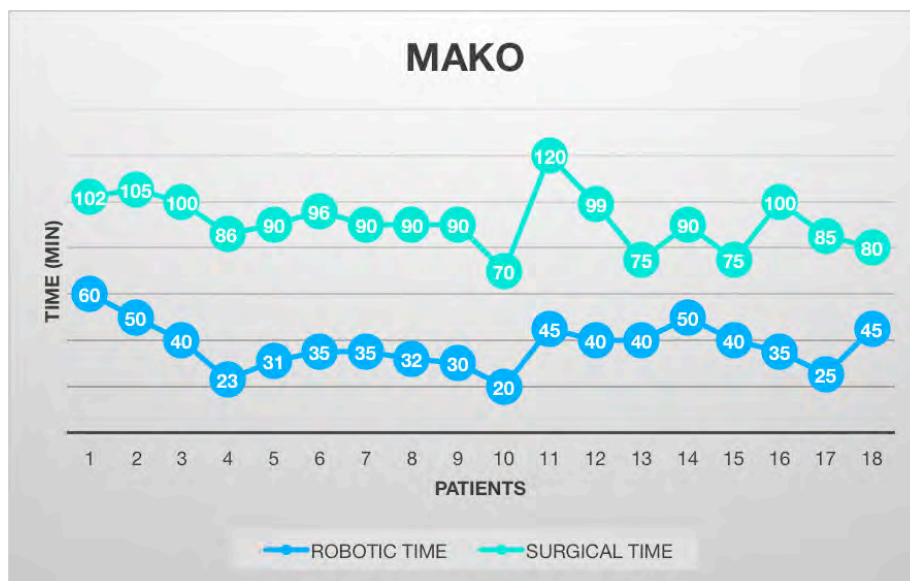


Fig 1. *MAKO* robotic time (blue line and dots) and overall surgical time (green line and dots). On the X axis the time expressed in min; on the Y axis the 18 patients who underwent surgery.

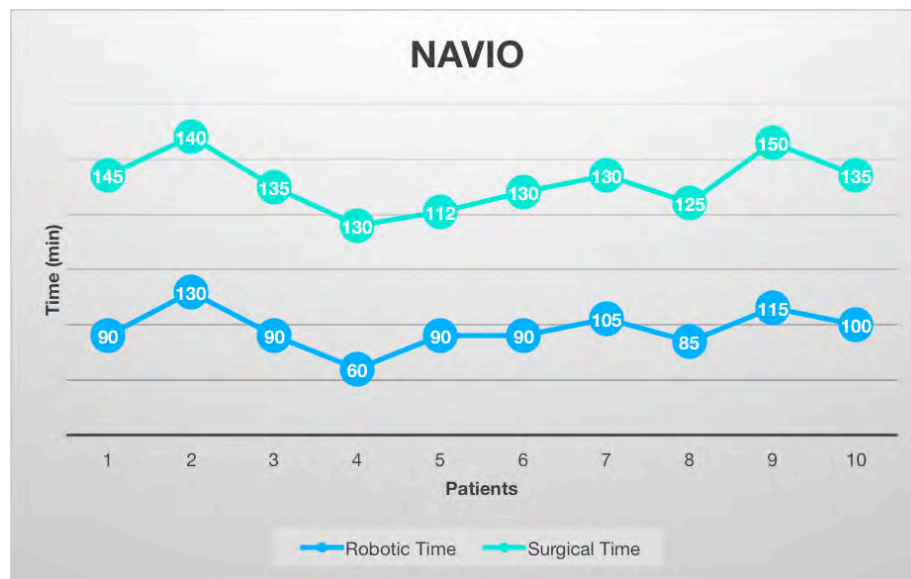


Fig. 2 NAVIO robotic time (blue line and dots) and overall surgical time (green line and dots). On the X axis the time expressed in minutes; on the Y axis the 10 patients who underwent surgery

identification of landmarks during the operation and, thus, it increases the duration of surgery. Indeed, analyzing the duration of surgeries regarding the MAKO system, we found out that MAKO has an average of 91.27 ± 12.24 minutes compared to the NAVIO average of 133.3 ± 10.43 minutes ($p < 0.001$) (Fig. 1, 2). In the literature, we found that the length of the procedure was 104 ± 16.6 min for the Acrobot system (36), 90-100 minutes for ROBODOC system (37) and from 81.4 ± 25.5 to 88 ± 16.3 minutes for the traditional technique.

Overall, a difference immediately emerges between the data in the literature and our results regarding the two systems examined by our study. The difference between the robotic technique (both MAKO and NAVIO) and the traditional technique is most likely due to digital mapping procedures, which can only be performed during the operating session. The second discrepancy could instead be ascribed to the less intuitive NAVIO system and/or to the lack of preoperative CT imaging for the intraoperative planning, requiring to obtain the images necessary for the bone mapping during the surgery and, thus, delaying the surgical times. This should introduce another possible aspect of longer operative times.

Indeed, the price of excluding a preoperative CT irradiation for the patients corresponds to a lengthening of the time in the operating room and, as a matter of fact, a greater risk of infection.

A similar trend was observed in our study regarding the “time of activity” of the robot, which corresponded to 95.5 ± 18 minutes for the NAVIO group and 56 ± 20 minutes observed on average for the MAKO group (35).

Patients of both groups were treated with a local intraoperative injection of 2 vials of Tranexamic Acid (5 mL) before proceeding with the closure and a Redon drain was used for each procedure to better monitor blood loss (39, 40). We observed that the blood losses of MAKO patients (122.83 ± 58.13 cc) were slightly higher than those of NAVIO patients (73 ± 30.20 cc). It is difficult to evaluate blood losses since a copious amount of physiological solution is used during the operation for intraoperative washing. So, it is necessary to have reference personnel that considers how much ml of solution are used and subtract them from the total. We were not able to find such information in similar studies in literature; however, we have observed a statistically significant difference between the two study groups. For this

specific aspect, the information about blood loss is slightly “in favor” for the NAVIO system compared to the MAKO system.

One of the goals of our study was to maintain the mechanical axis of the knee. To evaluate this aspect, a comparison was made between preoperative long-standing x-rays and the x-rays at a 6-month follow-up. For the MAKO patients (9 varus 1 neutral and 8 valgus alignments) the x-ray evaluation at 6 months showed preservation of the preoperative mechanical axis in all patients. Similar results were obtained with the NAVIO group. This further confirms the validity and efficacy of the robotic approach for unicompartmental knee replacement.

This study has some limitations as a low number of interventions and the variability in the surgeons performing the operations. These aspects have impaired the correct evaluation of the impact of the learning curve for both the robotic systems, keeping necessarily for all the patients a higher time for surgery than that reported in the literature. Furthermore, the small number of patients in both groups does not allow for reaching a strong statistical power and the results obtained have to be considered still preliminary, although very promising. The lack of a control group treated by manual UKA implantation is another drawback of the study design and this aspect will be considered in the previously mentioned multicenter study ongoing in our region.

The strength of our study was a prospective design. Indeed, it was possible to choose the objectives of our study and collect data following a protocol standardized for both the MAKO and NAVIO groups, allowing for comparing effectively the two different robotic approaches. Indeed, not only the same parameters were collected, but also the follow-up was set with equal frequency for both groups, thus making the comparison very reliable. Furthermore, we have been able to dismiss all the patients to the Rehabilitation Department of our hospital, allowing to perform the same “fast-track” protocol and the same kind of postoperative rehabilitation program.

It is also noteworthy that it was possible to collect data for all patients up to two years of

treatment, without loss of patients at follow-up. This made the comparison more “correct” between pre- and post-operative as well as between the two different groups.

The study shows how the UKA implantation with MAKO or NAVIO robotic platform along with the postoperative “fast-track” rehabilitation protocol may allow for achieving autonomy in mobilization after a few days, with consequent reduction of the risk of nosocomial infection and, at two months after surgery, good pain control and complete autonomy in primary ADLs, without the need of walking devices. In our study, the results obtained in terms of functional recovery, short duration of hospital stay, reduced number of blood transfusions, and a low number of physiotherapy sessions are promising even if compared to those reported in the literature.

Small differences were observed between the two study groups regarding the time for surgery and the blood loss, but our preliminary results do not allow to favor one system over the other and both robotic devices allowed for reaching similar good results at the end of the short term follow up in all patients. These aspects may have also a hypothetical cost reduction if a high prosthetic survival without revision will be demonstrated in larger population studies with longer follow up and with the presence of a control group of patients subjected to manual UKA.

Indeed, there is an urgent need to carry out long-term multicenter prospective studies to be able to better compare and validate our preliminary results. For that reason, a larger study involving different centers and a greater number of patients is about to start in our region. In this way only, it will be possible to fully ascertain the clinical relevance and the economic and social impact of robotic surgery, in order to demonstrate that robotic assistance may really become a key element for improving the technique and the results of unicompartmental knee arthroplasty.

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42. Fig 1. MAKO robotic time (blue line and dots) and overall surgical time (green line and dots). On the X axis the time expressed in min; on the Y axis the 18 patients who underwent surgery.
43. Fig. 2. NAVIO robotic time (blue line and dots) and overall surgical time (green line and dots). On the X axis the time expressed in minutes; on the Y axis the 10 patients who underwent surgery.

Periprosthetic osteolysis: a narrative review

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Periprosthetic osteolysis is still one of the major limitations of prosthetic joints longevity. The process of this “silent” iatrogenic disease involves both mechanical and biological factors that initiate a local immune response in the periprosthetic tissue that eventually lead to implant loosening and failure. There are many causes of the primary aseptic loosening inside the periprosthetic microenvironment, but the most important elements are the wear debris and the cell-particle interactions. Together with implant position, micromotion, bearings, joint fluid pressure, and increased load on the joints drive the pathogenesis of the disease. This narrative review aims to summarise recent studies describing the biological and mechanical factors in the pathogenesis of osteolysis and some of the current pharmacological attempts to “rescue” a failing implant.

Periprosthetic osteolysis is the principal long-term complication of implant survival, and the major factor contributing to aseptic loosening of the prosthesis. Recent literature predicts a steady increase in revision prosthetic surgery both for knee and hip. Osteolysis has a clinical picture, there are numerous interconnected mechanical and biological factors that contribute to the development of this disease.

The iatrogenic origin of periprosthetic osteolysis after joint replacement surgery has been studied over the past 50 years (1). Sir John Charnley initially identified debris and macrophage populations in periprosthetic tissue, interpreting the histological picture as a septic process, for which identification of the bacteria responsible was impossible (2). McKee, at the same time, ascribed the bone erosion typical of osteolysis to the mechanical impingement between, and 14 years after the first prosthetic implants in

1977, Willert illustrated particulate debris migration to the periprosthetic joint space.

In particular, the evolution of scientific discovery in the last 20 years highlights the tight link between biological processes and mechanical action as the cause of osteolysis. Debris diffusion and cell-particle interaction lead to inflammation in the microenvironment around the implant at the pseudosynovial interface membranes. Mechanical factors also play a pivotal role, such as prosthetic alignment, the pressure at the surrounding bone, micromovements, pumping of synovial fluid around periprosthetic space during cyclic loading of the joint, and prosthetic load, following the principle that “wear is a function of use, not time” (Schmalzried, 2000) (3). Due to a very complex association of these factors, the main and primary cause of osteolysis, or *primum movens*, is still, impossible to be identified at our current level of knowledge.

Key words: periprosthetic osteolysis, growth factors, RANK-RANKL, osteoimmunology

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Pathogenesis of periprosthetic osteolysis

The pathogenesis of osteolysis begins at the time of joint replacement surgery when the microenvironment responds to the operation trauma with a consequent inflammatory process, similar to that of common bone lesions, and a bone and fibrous cell interface is formed around the prosthetic components. Osteoblasts and osteoclasts coordinate to provide prosthesis surface interdigitation, initiating the osseointegration process (Fig. 1).

After implantation of the prosthesis, bone integration is opposed by two elements: i) the demineralization process due to avascular necrosis, that occurs during the prosthesis positioning and ii) the gap between implant and bone that has to

be “bridged” with the addition of new bone tissue (4) At the interface around the prosthesis, cytokine (i.e. BMPs, TGF- β , IL-1, IL-6, M-CSF and VEGF) mediate osteoclast-osteoblast activation that regulates bone homeostasis through a dynamic equilibrium of bone reabsorption and neoapposition (namely the ARF-Activation-Resorption-Formation cycle of activation, resorption and formation) (4, 5).

The process is similar to bone-graft integration and is susceptible to cyclic stress (6). Loads are transmitted to matrix microenvironment as electrical signals and transduced by mechanoreceptors as the transmembrane receptors of the integrins family and they influence cell proliferation through TGF- β activation. Cyclic loading, within a reasonable range,

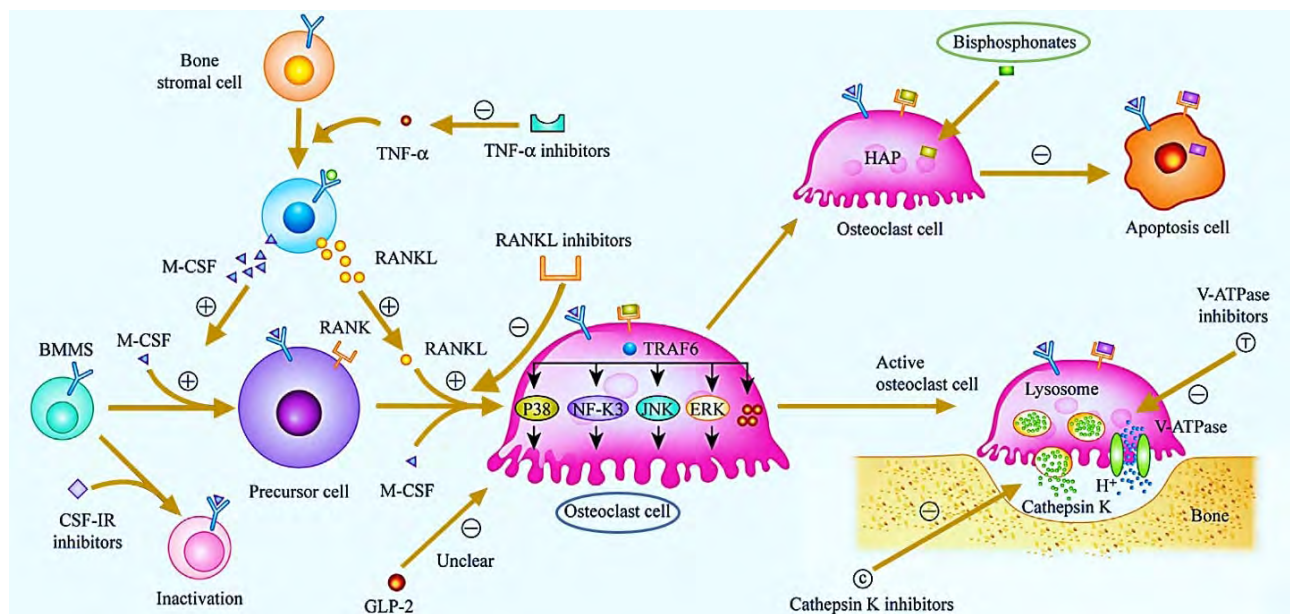


Fig. 1: Biological mechanism of osteoclast differentiation, bone resorption, and effects of current or future therapeutic drugs. Osteoclasts maturation starts from bone marrow hematopoietic stem cells (BMMs) with the stimulation of two critical factors, M-CSF (Macrophage colony-stimulating factor or CSF-1 or colony-stimulating factor 1) and receptor activator of nuclear factor kappa-B ligand (RANKL). Binding to its specific receptors (CSF-1R and receptor activator of nuclear factor kappa-B (RANK)) on BMMs membrane, a series of cascades are activated, and BMMs differentiate into matured osteoclast. GLP-2 (glucagon-like peptide-2) is a negative regulator of osteoclast differentiation. Inhibitors to CSF-1R (colony-stimulating factor 1 receptor) and RANKL are a possible strategy to hamper osteoclast activation. Bisphosphonates are derivative of inorganic pyrophosphate with a high affinity for bone mineral because they bind to hydroxyapatite crystals. After osteoclast-mediated uptake from the bone mineral surface, bisphosphonates become incorporated into molecules of newly formed adenosine triphosphate (ATP) and the intracellular accumulation of these nonhydrolyzable ATP analogs is cytotoxic to osteoclasts, leading to osteoclast apoptosis. Bone resorption is a specific function of osteoclast, and bone matrix degradation is induced by the release of cathepsin K, as well as H⁺, and the release of H⁺ is enabled by V-ATPase on the membrane of matured osteoclast. Thus, V-ATPase and cathepsin K inhibitors (i.e. Odanacatib, Balicatib) are also a potential strategy to impair osteoclasts function. (down-regulated effect, up-regulated effect).

is necessary for periprosthetic environment survival. Bone is a very dynamic tissue and responds to stress by deviating anabolic processes to higher loading areas according to Wolff's law.

While high loading inevitably results in localized avascular necrosis, low loading causes local osteopenia, whose onset depends on mechanical factors such as long-term immobilization. Thus, on a long-term basis, the prosthetic alignment will influence the process as bone reabsorption is also related to the degree of malalignment (7). The coating and implant biomaterial play an important role in the microenvironment around the prostheses. A hydroxyapatite implant coating helps bridge the gap between bone and implant, filling spaces of up to 2 mm, while other materials reach up to only 0,3 mm.

Moreover, its molecular structure guarantees mechanical interlocking and a chemical bone bond that may greatly improve implant fixation, in the femoral shaft. Instead, the acetabulum is a structure subjected to high tensile stress and it does not specifically benefit from hydroxyapatite coating (4). We can divide the many interrelated factors leading to osteolysis onset into three main groups: 1) preoperative (bone quality, pre-existing pathologies, selected biomaterials; 2) intra-operative (sterile procedures, washing, component positioning); 3) post-operative, (stress, debris, metallic ions, micromovement, macrophages, osteoclasts, osteoblasts, fibroblasts of the metastable periprosthetic fibrous membrane). These countless variables make establishing the *primum movens* of osteolysis onset *in vivo* impossible.

In this perspective, the "classic" model of periprosthetic osteolysis implies the release of debris and metal ions derived from the prosthetic implant and, subsequently, the different immunological reactions related to this process. Metal ions (namely Chrome, Cobalt and, to a lesser extent, titanium) are released from the modular metal-metal interface (e.g. head-neck joint, porous surfaces) (4, 8) through electrochemical corrosion in presence of Sodium chloride. These ions are both direct activators of macrophages and haptens that can promote Th1-mediated type IV delayed hypersensitivity when linked to endogen proteins.

The debris of polyethylene and cement as well as titanium and chrome-cobalt debris are released from the periprosthetic surfaces and interact essentially with the monocyte-macrophage system, with the fibroblasts and with the osteoblasts. This deleterious interplay is known with the term "*small particle disease*".

The role of the debris in the pathogenesis of periprosthetic osteolysis

The fundamental role played by the debris (polyethylene, cement, titanium and chromium-cobalt microparticles) makes them the implant's worst enemies. They have profound implications for implant stability, given their ability to activate the osteoclasts and to cause the consequent massive host bone tissue reabsorption. Quantity and quality of wear-generated debris depend on varying factors: the choice of implant biomaterials (Chromium-Cobalt, Titanium), the options for prosthetic couplings (polyethylene, diamond, ceramic, metal coatings) and the different techniques for prosthetic component fixation (PMMA cemented versus uncemented fixation)(9, 11).

Some extrinsic mechanical factors can influence debris production. The medialization of the centre of rotation decreases stress to hip, consequently reducing wear, while, the increase of the femoral offset enhances the abductor lever arm. Vertical orienting of the acetabulum may cause peripheral impingement, increasing third-body wear and osteolytic areas in the ilium (12). Frequent intraoperative irrigation reduces debris that may accumulate in the joint space, particularly PMMA, thus limiting third-body wear in prosthetic couplings.

Debris and host cells accumulate at the interface membrane and pseudosynovial membrane surrounding the neo-articulation; particles such as polyethylene are enveloped by the pseudocapsule pseudosynovium or transported from the joint space by the pseudosynovial fluid to the bone-prosthesis interface. This process progressively extends along the implant surface, inside the periprosthetic bone and into the periarticular soft tissue, by joint fluid diffusion to the less resistant zones. The "effective joint space" is defined as all the periprosthetic regions accessible to the joint fluid and thus accessible to

particulate debris (10). Wear particles trigger a foreign body inflammatory response, their size being the key factor in establishing the potential bioreactivity of wear debris.

For non-phagocytatable debris greater than 15-30 mm (e.g. PMMA particles) (13), macrophages form foreign body-type giant multinucleated cells with cytoplasmic phenotype, similar to that of osteoclasts, and they react by forming a fibrous envelope encapsulating debris, leading to limited cell activation and a reduced immune response (14). RANK and RANKL interaction, at macrophage and fibroblast surfaces respectively, leads to giant multinucleated cell generation (4, 15, 16). Osteoprotegerin (OPG) secreted from vascular endothelial cells inhibits this interaction. However, these cells are situated distant from the RANK-RANKL interaction site, so this inhibiting effect is reduced, and this provides permissive circumstances for foreign-body type giant cells genesis.

For phagocytatable debris of less than 15-30 mm, the inflammatory reaction is greater. Polyethylene particles sizing up to 0.1-1 mm trigger this response through a type I wear-mechanism (17). Macrophages are incapable of digesting debris, lacking the enzymes necessary for synthetic covalent polymer lysis (18). Part of the uniqueness and peculiarity of periprosthetic osteolysis lies in this purely iatrogenic etiopathogenetic principle. Therefore, phagocytosis, which is the inflammatory defense mechanism and the “phylogenetic tool” against pathological agents, is in this context a failure. This “impossible digestion” leads to a chain reaction involving the inflammatory response, through progressive chemotaxis and activation of other cells by macrophage cytokine (TNF- α , IL-1, IL-6, PGE, PDGF, FGF, VEGF) and superoxide release (O₂⁻), this latter being responsible for periprosthetic tissue metallosis observable during revision surgery (4, 19).

Cytokine release in osteolytic processes, however, might also be conditioned by the presence of bacterial endotoxins adhering to biomaterials, in particular to titanium. This mechanism has yet to be clarified but may “turn the tide” of aseptic loosening to favor bacteria as a contributory cause in the final periprosthetic osteolysis development (20-

23). These intercellular “vicious circles” have one common denominator represented by the cycle of “debris formation-cell response-osteolysis – implant mobilization - new debris formation”.

In this respect, the macrophage has a central role. Indeed, macrophages are activated by the presence of wear particles through the surface receptors CD11b, CD14 and the Toll-like receptor), and they exploit different mode of action as i) promoting osteoclast differentiation and activation from the monocyte/macrophage cell lines, ii) secreting MMPs that remodel and degrade extracellular matrix proteins, iii) releasing pro-osteolytic cytokines and iii) directly differentiating into osteoclasts in presence of debris, through the RANK-RANKL system (24-27).

Intracellular MAP kinase (c-Jun, Erk, JNK, p38) activation is essential for osteoclast lineage differentiation; they are Serine-Threonine protein kinases that, in the cell, communicate a signal from a receptor on the surface of the cell to the DNA in the nucleus of the cell. In other words, they are “mediators” between extracellular stimuli and nuclear proto-oncogene activation (28). Furthermore, differentiation of macrophages into osteocytes and the production of resorption bays (namely Howship’s lacunae) may also be independent of the RANKL-RANK system. Indeed TNF- α and IL-1 α are sufficient to induce cell activation in the presence of M-CSF (29, 30).

Anabolic activity of pre-osteoblasts, osteoblasts and MSCs resident in the periprosthetic microenvironment is reduced in contact with wear particle (polyethylene, ceramic, titanium, sizing 1.5-4 mm) following the presence of cytokines and the interaction with their receptor (24, 30-35). Thus pre-osteoblasts and MSCs decrease collagen and matrix synthesis, they secrete PGE₂ and NO (in particular in mature osteoblasts), they release M-CSF and they express RANKL on the surfaces. This may happen even with a minimum quantity of wear particles (36).

As a consequence, M-CSF binds to c-Fms, its receptor and RANKL binds to RANK, promoting macrophage activation and osteoclast differentiation-activation (37, 38). The interaction with wear particles may also induce preosteoblast-MSC caspase-dependent apoptosis and this further contributes to the reduction of bone-forming processes around the implant.

The “freshly” activated osteoclasts display lytic activity on surrounding bone, creating resorption bays and the consequent production of new debris. From debris release, the “vicious circle” of osteolysis is self-powered (39, 40). In this regard, implant surface topography influences osteoclast proliferation because a rougher surface can promote osteoclastogenesis (41).

The previously mentioned fibroblasts are the ideal connection between osteoclast-dependent and osteoclast-independent resorbing processes. Indeed they secrete pro-inflammatory and “pro-osteoclastogenic” factors as Prostaglandin E2 (PGE2) and IL-6, but they promote the formation of foreign body macrophagic giant cells and they also secrete degradation enzymes (42, 43).

Mesenchymal cell and titanium particles interaction further contribute to catabolic processes (44-46). The contact with titanium particles leads both to a decrease in osteoblast differentiation and to apoptosis, which reduces the number of resident precursor cells and, indirectly, the possibility of new bone neo-apposition.

Recently, Tang et al have shown that osteoblast differentiation may also be inhibited by the long non-coding RNA DANCR, which is involved in the differentiation of many cells, such as hepatoma cells, osteoblasts and cartilage cell. Long non-coding RNA is a class of RNA greater than 200 nucleotides in length that are not translated into proteins, but they play a role in epigenetic level regulation as well as transcriptional level, translational level and protein modification regulation.

These authors have observed that DANCR could inhibit osteoblast differentiation by regulating the expression of FOXO1. Indeed, FOXO1 is a member of the fork box transcription factor (FOXO), a subclass of the fork box protein family, which plays a regulatory role in many biological processes as osteoblast differentiation and bone formation. This concept may suggest DANCR as a potential future therapeutic target to reduce periprosthetic osteolysis (47).

Osteoimmunology

Recently, the osteoimmunology field is accruing increasing interest related to periprosthetic osteolysis (48, 49). This branch of immunology studies the inter-relations between the skeletal and immune systems

and the cellular mechanisms and the components that they share. These relationships generate cell signaling are able to reciprocally condition osteoblast, osteoclast and lymph cell behaviour (50). The RANKL-RANK-OPG (osteoprotegerin) axis is an example of an important signaling system, functioning in both bone and immune cell communication.

Indeed, activated T cells express RANKL, generating a reciprocal activation of osteoclasts, osteoblasts and T cells triggered by debris in the periprosthetic environment (51). Metallic debris, in an example, induces local production and secretion of CC17 and CC22 (CCL17/TARC = thymus and activation-regulated chemokine; CCL22 /MDC = macrophage-derived chemokine) and CCR4 (chemokine receptors CC17 and CC22) in T cells. Due to the local increase in CCL17 and CCL22 concentrations, T helper cells, migrate and localize in the periprosthetic tissue and they express IL-17 and RANKL, contributing to the “orchestration” of osteoclast activation. IL-17, in particular, can increase local inflammatory response and boost, indirectly, osteolysis by inducing RANKL production in resident osteoblasts (52).

Moreover, at the local level, both ionic and particulate metal debris may form protein complexes inducing conformational alterations. These complexes can be processed and presented to T lymphocytes by cells expressing major histocompatibility complex class II (MHC II) molecules. This mechanism leads to the formation of a population of activated T cells, able to react against the proteins modified by metallic debris. This biological phenomenon is the basis for reactions similar to delayed hypersensitivity (Type IV) defined generically as “metal allergy” (53).

Even non-metal wear debris are involved in osteoimmunity mechanisms (54). These are presented to T cells by macrophages and osteoblasts, mediated by MHC II, thus initiating a reciprocal chain activation by paracrine induction of cytokine secretion that involves both killer T cells and B cells, differentiating into plasma cells (55). Mediators from the alternative macrophage activation pathways were recently implicated as a clinical biomarker for periprosthetic osteolysis.

CHIT1 macrophage-induced expression was found to increase response to wear debris and it was found in both in the synovial fluid and serum of the patients with implant failure. This finding may facilitate clinical management and prognosis of patients for revision surgery (56).

Genetic susceptibility

Although the genetic basis to the interindividual differences in susceptibility to osteolysis has been observed, a most recent meta-analysis from two large European cohorts found modest heritable contribution to the susceptibility to osteolysis. The evidence points out the suggestive association of several loci of which one has a statistically significant signal in the time-to-revision analysis: LOC105369917 (57). This study paves the way for further research on potential clinical biomarker discovery.

Genetic susceptibility to cellular phenomena also depends on single nucleotide polymorphisms (SNPs) within the genes involved in the inflammatory response and periprosthetic osteolysis. Variations in the DNA sequence determine different genes and different behaviours of the corresponding protein and, consequently, a major propensity to osteolysis development. As an example, carriers of polymorphism in position 238 in TNF- α gene promoter are at high risk of osteolysis, while polymorphism carriers in the frizzled-related protein 3 (FRZB) 200T allele, involved in the regulation of MSC osteogenic differentiation, reduce osteolysis development, but have a higher predisposition to heterotopic calcification (58, 60).

Furthermore, genetic susceptibility appears also to influence antigen presentation mechanisms via HLA class II molecules. Indeed, the HLA-DR2 genotype is linked to a less efficient immune response for debris-triggered macrophage-mediated lymphocyte activation, and individuals carrying this specific class II HLA are therefore denominated “low responders” (61).

From cell involvement to implant loosening

Generalized cell involvement in the prosthetic microenvironment, micromovement on the bone-implant interface, and fluid diffusion into the joint

space lead to the formation of implant bursitis, characteristic of mobilization processes, and, by confluence, to development of large areas of osteolysis. The problem in this phase, albeit developing from biological-type interactions, has essentially “mechanical features”. For the patient, implant mobility, in association with secondary synovitis, generates pain and functional failure.

The onset of this mechanism may derive from an “ab initio” hypermobility of prosthetic components or a prosthetic malpositioning. This latter predisposes to generate a greater quantity of debris than that of well-positioned implants. However, bone is not the only tissue that develops around the implant from the granulation tissue generated from the “surgically induced inflammation”. The presence of relevant size gaps between implant and bone (early post-op micro or macro-instability) promotes fibrous tissue in growth in the areas devoid of bone neo-apposition. Furthermore, due to the different isoelasticity of the prosthetic materials compared to that of bone, micromovement invariably are produced because of the loads that the structure withstands during the normal daily activities (e.g. deambulation) (4). Micromovement induces fibrous tissue formation by fibroblasts around the implant thus hampering osteointegration and biological fixation.

Micromovement is unevenly distributed around the prosthesis for the different directions of the forces around the implant (axial, torsional, oblique). Moreover, mechanical factors such as type and extent of stress, prosthesis rigidity and design, and biological elements as the quality of the host bone, together they may influence micromovement distribution and degree.

The fibrous interface could provide the histological interpretation of radiographic radiolucencies around the prosthesis. If previously considered an inert phenomenon, not being linked to any patient symptoms, this fibrous interface should now be considered as metastable, due to the presence of fibroblasts and macrophages. During cyclic loading, micromovement generates synovial fluid diffusion around the prosthesis towards the implant-to-host interface. From this action, fluid pressure waves transport cell mediators and wear

debris and simultaneously they induce fibrous tissue differentiation into the so-called “synovial-like interface membrane” (SLIM). Fibroblasts and macrophages co-exist within the membrane because they are attracted to this environment for its low oxygen pressure and high lactate concentration. This close relationship is particularly important in light of the recent study, where macrophages were found to be potentially involved in reducing osteogenic capability of fibroblasts treated with wear particles (62).

Fibroblasts carry similar characteristics to those found in rheumatoid synovial tissue; they are activated by cytokines and lead to osteoclast activation and matrix degradation via lytic enzyme secretion (MMP-1, cathepsin K metalloproteinase, facilitated by the acidic environment, and also produced by osteoclasts) (15, 42, 63). Moreover, the acidic environment in the interface membrane leads to the decalcification of hydroxyapatite and fluorapatite, as well as periprosthetic bone demineralization.

Joint fluid pressure also plays a determining role in osteolysis because it interacts with the behaviour of the monocyte-macrophage at the behaviour, stimulating the production of pro-resorption cytokines like IL-6 and TNF- α (64, 65). Eventually, the effect of very high fluid pressure gradients may even lead to osteocyte death (4). Such mechanisms are at the basis of non-osteoclast induced periprosthetic osteolysis.

As it appears from the forementioned concepts, the pathogenesis of the osteolysis is a very complex, multifactorial process. Yet there is still “more” to add to this story. A recently published analysis on gender-specific bone loss mechanisms in periprosthetic osteolysis showed evidence that the female osteocytes are pre-programmed to undergo osteolysis and an altered hormonal status may drive this process. This important finding may be helpful for the future management of periprosthetic osteolysis in female patients although larger longitudinal studies with higher statistical power are needed to better clarify these aspects (66).

Therapeutic perspectives

There have been many attempts over the years to increase implant life span improving the already existing materials (i.e. large-size metal head) or

finding new high- resistance biomaterials (Delta ceramic, cross-linked polyethylene). Despite the improved resistance to wear and the delaying effect toward the onset of osteolytic phenomena, these innovative technologies produce additional complications. Metal-on-metal couplings with large head diameters have revealed slower wear and an increased range of motion, however, they do not resolve the metal ion release problem and therefore are inclined to metal debris induced osteolysis. In a recent study by Ormsby RT et al., ultra-high molecular weight polyethylene, highly cross-linked polyethylene (XLPE), and Ti6Al4V and CoCrMo metal alloys were found to stimulate osteocytes to adopt a bone catabolic state to varying extents (66). Moreover, patient blood evidences a systemic production of metallic ions.

Clinical studies are underway to establish the connection between metallic ion serum concentrations and neoplastic pathology onset, although no certain evidence has yet been presented (67). Recent laboratory studies about cross-linked polyethylene have demonstrated improvements of these new macromolecules in terms of wear resistance compared to that of the old generation polyethylene. However, production processes weaken the material structure with breakage occurring in implants following acetabular component malpositioning. Some doubts remain for the use of cross-linked polyethylene insert in posterior stabilized knee prostheses (68, 69). The new ceramics (delta ceramics) have shown improved resistance and hardness, allowing for using wider diameter heads to further reduce wear, although there are still concerns regarding stripe wear and squeaking phenomena (70).

However, in this “pathological panorama”, early treatment is highly justified and the theoretical possibility to use pharmacological substances for decreasing osteolysis is certainly a fascinating perspective. Without a doubt, early pharmacological treatment may prevent the development of large osteolytic areas and major bone loss, which would require complex and long revision surgery, translating to increased costs to healthcare systems. Basic research has not yet provided a unique suitable and efficient pharmacological solution. At the moment,

there aren't long-term studies proving the efficacy of non-surgical pharmacological treatment for the prosthetic osteolysis. Even if "there is no approved drug therapy to prevent or inhibit periprosthetic osteolysis", there are, nevertheless, promising studies at the experimental level (32).

Traditional drugs such as NSAIDs, the anti-cyclooxygenases, ciprofloxacin, pentoxifylline, misoprostol, interact with and modulate the inflammatory cascade, and in the future, new therapies involving IL-4, IL10 and hIL-1Ra (possibly administered through retroviral vectors) could deal more efficiently with inflammation (71, 74).

Studies have also been carried out on drugs modulating the osteoclast and osteoblast function, such as the bisphosphonates and, at an experimental level, TGF- β , FGF-2 and the direct inhibitors of osteoclast activation such as the recombinant viral vectors for OPG gene transfection or RANKL antagonists, constructed via RANK fusion to immunoglobulin Fc region (72, 75, 80).

Another approach involves NG-R1 (the main compound of *Panax notoginseng*) which was found to suppress RANKL-induced osteoclast formation, bone resorption, and F-actin ring formation in vitro. Animal model studies implicated NG-R1 as a promising therapeutic agent (81). Some agents can directly modulate macrophage function such as acetylcysteine and erythromycin (82, 83). Even direct therapies against TNF- α seem promising, as an example as etanercept, a soluble TNF- α inhibitor, gene vectors for soluble TNF- α inhibitor, vectors for soluble TNF inhibitor constructed by the immunoglobulin Fc region fusion to TNF receptor type I extracellular domain (72, 84, 85).

Nevertheless, a present, patient monitoring and timely surgery are still the current way to avoiding massive bone loss caused by the formation of osteolytic lacunae. It is fundamental to remember that patient monitoring is needed even in asymptomatic, or few-symptomatic cases (1). The follow-up is carried out using a standard x-ray examination, albeit this could be arguable, due to difficulty in early identification of the osteolytic area, pending standardization of new investigative methods (i.e. 3D CT imaging) (32). When revision surgery appears

essential, the surgeon's task is both to identify and to remove particulate debris as well as to substitute mobile prosthetic components and to replace any lytic lacunae with bone grafts (32, 86).

In conclusion, prosthetic osteolysis is a complex, multifactorial disease with underlying genetic background. This disease remains the major limitation of artificial joints longevity and, considering the current trends of increased prosthetic implantation in the population, it translates to a significant burden on the healthcare system. Our understanding of the pathogenesis is still lacking and there is a need for validated diagnostic biomarkers and new pharmacological approaches to early identify the osteolysis phenomenon and thus improve the non-surgical management.

Although there are many potential pharmacological treatments "in the pipeline" (87), at present the surgical treatment is, still the best current solution. However, if early operative intervention is fundamental for osteolysis treatment, so too is continuing promiscuous basic research, that may allow for conceiving the "dream" of a pharmacological approach that can reduce periprosthetic osteolysis and consequently aseptic implant failure. Besides, research is a matter of sharing knowledge to envisage new therapeutic horizons or, in the words of Bruce Springsteen, "Talk about a dream and Try to make it real" (Badlands, from "Darkness on the Edge of Town", Columbia Records 1978).

Abbreviations:

BMPs: (*bone morphogenetic proteins*).

TGF- β : (*transforming growth factor-beta*).

FGF: (*fibroblast growth factor*); FGF-2 (*basic fibroblast growth factor*).

PDGF: (*platelet-derived growth factor*).

VEGF: (*vascular endothelial growth factor*).

(PGE): (*prostaglandin*).

TNF- α : (*Tumor Necrosis Factor α*).

IL: (*interleukin*).

MMP: (*matrix metalloproteinase*).

(OPG = TNFRSF11b): (*osteoprotegerin*).

RANKL: (*Nuclear factor κ B ligand = TNFSF11, tumor necrosis factor superfamily 11 = ODF*).

osteoclast differentiation factor = *TRANCE*, *TNF related activation induced cytokine*).

RANK: (receptor activator of Nuclear factor κ B= osteoclast differentiation factor receptor = TNFRSF-11a, Tumor necrosis factor superfamily member 11a).

M-CSF: (macrophage - colony-stimulating factor): hIL-1Ra: (interleukin-1 receptor antagonist).

NO: (nitric oxide).

MAP: (mitogenic activated protein).

MSC: (mesenchymal stem cells).

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Rehabilitation protocol after simultaneous anterior cruciate ligament reconstruction and high tibial osteotomy: introducing the concept of the individualized approach

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Postoperative rehabilitation after simultaneous anterior cruciate ligament reconstruction and opening wedge high tibial osteotomy is a complex concept. Different osteotomy techniques, extremely selected patients, high expectations in returning to previous sport activities, and the different individual physical profile and performances make traditional chronological criteria impractical and unfeasible. This study presents a novel rehabilitation in which functional objective criteria are considered the key factors for standardizing a 4-step protocol. Each step is “individualized”, based on the patient’s response to the healing processes and to the different training phases, allowing for a safe return to sports competitions. This definitively implies a strict collaboration between patient, surgeon, physician and physiotherapists, as well as thorough and detailed patient education. Due to the high versatility of these new rehabilitation concepts, the application of the “individualized” steps described in this study may be broadened to include different sports medicine knee injuries that may benefit from a specific, detailed and carefully patient-centered rehabilitation project.

“A good outcome depends heavily on thorough preoperative preparation and patient education” (Amendola A, 2010) (1).

Postoperative rehabilitation after simultaneous anterior cruciate ligament (ACL) reconstruction and opening wedge high tibial osteotomy is a particularly challenging task. Patients’ profile and their expectations, multiple available osteotomy techniques and different ACL reconstruction techniques are invariably able to influence rehabilitation timeline, making impractical any chronologically strict and schematic post-surgery protocols for both the rehabilitation specialists and the surgeons.

Thus, individualized rehabilitation protocols are a possible key for the success as well as and for early identification of post-surgery complications

(such as loss of alignment, osteotomy site non-union, arthrofibrosis, leg extension deficit, and muscle atrophy). In our work, we describe a possible rehabilitation approach that implies splitting out the recovery phase into five gradual steps. Passing from one step to the next requires the achievement of precise criteria, which work as a “green light”. In other words, the patient can “go on” to the successive rehabilitation phase only if reaching specific results that provide the proof of completion of the specific step. This approach provides a clear and simple rehabilitation warranty and it allows for “releasing” both the patient and rehabilitation specialist from the time limits imposed by traditional ACL or tibial osteotomy post-surgery rehabilitation protocols.

Moreover, a step-by-step individualized rehabilitation program is therefore independent of

Key words: postoperative rehabilitation; ligament reconstruction; tibial osteotomy; ACL

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the osteotomy technique, from the osteotomy healing time, from the graft incorporation time and, above all, from the patient's response to joint recovery. This concept of an individualized approach simplifies the available protocols for patients who underwent rigid osteotomy techniques with "Tomofix" type plates (Synthes) (2), for patients treated with the "simpler" opening wedge technique with Puddu's (Arthrex)

plate and for patients undergoing the "inherently more stable" lateral closing wedge osteotomy (3, 4). Indeed, the post-surgery protocol is targeted to the patients and their joint functioning rather than to the type of surgery (see table I).

Phase 1: Pre-operative assessment

Both the patient's preparation for surgery and the

Table I. *Green light criteria for progressive rehabilitation phases.*

Rehabilitation phases	Green light criteria
Phase 1: Pre-operative assessment	1. Range of movement (R.O.M.) 0-0-120; 2. Passive extension same as the contralateral joint; 3. Trophic quadriceps muscle to allow for lower limb isometric extension without a knee flexion lag 4. Correct gait cycle
Phase 2: immediate postoperative period	1. Absent or minimal joint swelling (0/+1) 2. knee extension comparable to that of the contralateral joint 3. Good coordination during the gait cycle 4. Minimal pain 5. Quadriceps strength equal to (or greater than) 30% of the strength of the contralateral quadriceps muscle Once these criteria are reached, patients can start to walk without crutches and to move on to phase 3 of the rehabilitation program.
Phase 3: Intermediate postoperative period	1. Absence of pain 2. Absent or minimal joint effusion at rest 3. Active flexion of 120° or more 4. average quadriceps, ischio-crural and triceps surae muscle mass (similar or slightly inferior to that of the contralateral lower limb) Once these criteria have been accomplished, patients are allowed for running on the treadmill and moving on to phase 4 of the rehabilitation program
Phase 4: Functional postoperative period: from the gym to the on-field rehabilitation	a) to move on the "on-field" phase: 1. isokinetic test resulting in strength in flexion and extension equal to (or greater than) 80% of the strength of the healthy contralateral knee) 2. single-leg hop test resulting in a hop distance equal to (or greater than) 80% of the hop distance of the healthy contralateral limb 3. Ability to run on the treadmill for 10 minutes at 8 Km/h; this value indicates that the patient has reached a good resistance to the fatigue over an extended time (10 mins) and it identifies the "aerobic threshold value" of resistance to exertion, under which the patient can maintain an exercise without particular muscle fatigue b) to return to the competitive and/or recreative sports activities: 1. isokinetic test resulting in a strength equal to (or greater than) 90% of the strength of the healthy contralateral knee 2. At the metabolic assessment, AeT S2 greater than 11.5 Km/h and AT S4 greater than 13,5 Km/h 3. single-leg hop test resulting in a hop distance equal to (or greater than) 90% of the hop distance of the healthy contralateral limb

patient's perception of the realistic expectations from the operation are fundamental for the rehabilitation process, for ACL reconstruction with tibial osteotomy. Surgery should come after a rehabilitation assessment that allows for correcting the pathological gaits resulting after lesion of the central pivot and for re-establishing the proprioception and the muscular mass, to address such a complex surgical operation as the ACL reconstruction with tibial osteotomy. Indeed, patients do not normally undergo surgery straight after ACL injury and there is usually the necessary time lapse to prepare the patients for surgery. Goals for this phase are:

- Control of reaction and joint effusion with ice and eventually with the use of non-steroid anti-inflammatory drugs (NSAIDs).
- Checking the ligamentous integrity or the healing of any other associated ligamentous lesions (i.e MCL injury) that may have taken place at the time of the first trauma or in previous traumatic events.
- Checking for injuries of the articular cartilage surface (5) (20).
- Full recovery of both knee extension (comparable to the contralateral joint) and flexion of at least 120°. This may be obtained through gentle manipulation holding the knee in extension with cushioning under the heel and through careful passive mobilization exercises. Reaching this extension level is important for preventing postoperative mobility impairment (6).
- Re-establishment, as far as possible, of voluntary quadriceps activation, invariably compromised by the deafferentation mechanisms and the reflex inhibitions that appear after an ACL injury. This can be done through isometric contraction exercises, electric stimulation of quadriceps muscle in selected cases, and, ultimately, open and closed kinetic chain exercises.
- Flexor muscle strengthening to potentiate stabilizing mechanism in co-contraction.
- Walking re-education for a normal gait cycle.

The patient's emotional sphere has also a central role in this phase. Indeed, psychological factors may influence the rehabilitation and, the long-term resumption of sporting activity. Therefore, it

should be appropriate to evaluate the influence of psychosocial factors with specific and validated scores (such as Knee Efficacy Scale, for example) and to sketch out a stepwise rehabilitation approach, with a gradual progression and goal setting, that may help patients to develop the self-confidence (5).

In this phase, the "green light criteria" can be considered:

1. Range of movement (R.O.M.) 0-0-120.
2. Passive extension same as the contralateral joint.
3. Trophic quadriceps muscle to allow for lower limb isometric extension without a knee flexion lag.
4. Correct gait cycle.

Phase 2: immediate postoperative period

Rehabilitation must begin early in the immediate postoperative period to help the patients in pain management, joint effusion, and passive and active mobility. In this phase, the concept of "patient education" becomes a mainstay and it implies the starting of communication between surgeon and patient and between patient and therapist. This is the moment in which the recovery is planned and directed most efficiently, according to the patient's physiology and abilities.

Surgeons and therapists must keep joint effusion under control. The prolonged presence of blood in the joint can be detrimental both for the new cartilaginous tissue and for the neo-engineered tissue, including the conditions in which the main surgery included chondral repair or regeneration (7, 2). The best method for prevention is still the long-term cryotherapy (at least for 15-30 days after surgery) together with elevation and rest. In this phase, the devices providing both cryotherapy and graduated compression such as the "Knee Cryo Cuff" or similar may be helpful too. The use of NSAIDs should be limited, according to the patient's tolerance, to the initial post-op period, as prolonged use hinders tissue healing and PGE2 inhibition promotes excessive scar formation (8).

Early ROM recovery is a further key point in this phase. Recovery of extension is fundamental during the immediate postoperative period: at the end of the operation, the lower limb is positioned in a full-length articulated knee brace, initially locked at 0°

extension. The patient must be informed that the brace should be kept for 8 weeks at different degrees of freedom following the postoperative rehabilitation progress. Antigravity extension exercises are carried out with cushioning under the heel whilst the patient is at rest. Particular caution must be taken if the contralateral joint has a high hyper-extension (more than 5°): if this is the case, exercises should be limited to reaching neutrality (0°) and exercise to reach the same contralateral joint extension should be done at a later stage to avoid compromising of neo-ligament tension.

Theoretically, neoligament integration time will dictate the time scale to “force” hyper-extension recovery: approximately after fourth weeks for autologous patellar tendon grafts and after sixth weeks, at least, for autologous gracilis and semitendinosus reconstruction grafts. Furthermore, the patient must be educated to reach a 90° flexion within the first days from surgery, eventually using continuous passive motion devices (C.P.M.). Early passive motion is also fundamental for knee extension recovery and it is recommended for 4-6 weeks postoperatively. The patient should be also instructed to passively mobilize the patella in gradual steps in all directions, 4 to 6 times per day to prevent adhesions and arthrofibrosis (5).

From the second day after surgery, the patient should start isometric exercise for the quadriceps and then, within two weeks from surgery, he should also progressively perform four-plane straight leg raises and short-arc quadriceps exercises. Quadriceps tone and control are particularly important in this phase. In some cases, when quadriceps strength deficits are observed, early electrical stimulation can also be used. The exercises together with neuromuscular stimulations have proved effective in the treatment of strength deficiency after ACL reconstruction (9).

The therapist should check for eventual patient's posture compensations, suggesting quadriceps inhibition, such as slight hip flexion-adduction - extra-rotation, knee flexion - intra-rotation, and ankle plantar-flexion. These postures may be due to the long time during which a cushion has been kept under the knee for pain relief and they may further contribute to the quadriceps “misuse” atrophy (10).

In that case, resting supine with straight leg provides a correct initial recovery and it increases articular capsule tension to prevent joint effusion. On discharge from the hospital, the knee brace should be released to a range of 0°-90°, and the patient must be instructed to carry out isometric and non-weight bearing exercises for assisted knee mobilization.

Once sutures are removed and full healing of the surgical scar is verified, the patient should begin non-weight bearing exercise in water (chest height) without the brace, for early recovery of the gait cycle and kinetic control of joint. The exercises may vary from simple open kinetic chain movements to the use of hydro bikes and walk-simulations in deep water with a float jacket. In water, careful close kinetic chain exercises such as walking at different depths, start & stop exercises and step climbing may be also included in this specific phase of rehabilitation depending on patient's pain and compliance.

After four to six weeks from surgery, depending from the type of graft used for the ACL reconstruction (4 weeks generally for patellar tendon grafts and sixth weeks for autologous gracilis and semitendinosus reconstruction grafts), the range of motion of the brace should be increased to a range of 0°-120° (full range) and patients should begin gradual and progressive complete mobilization exercises.

In this phase, weight-bearing on operated limb depends strictly on the surgical technique used to stabilize the osteotomy. This is a fundamental aspect of this first phase because the patient can move on to the second phase of rehabilitation, aimed at complete recovery of joint function only in the presence of full weight-bearing conditions. Weight-bearing allowance is based on the delicate balance between the articular functionality and the need to protect osteotomy site and this principle is an example of how the individualized rehabilitation approach detaches from the time limits imposed by previous schemes. Indeed, weight-bearing can be early or late depending on the entity of correction carried out and, on the stability, reached in the osteotomy site. So, for example:

i) With high stability plates (e.g. Tomofix) (11), partial load (50%) is allowed after 2 weeks from surgery, then gradually the load advances to full

weight-bearing after four weeks from surgery. This time interval may be shortened by one week when small corrections are performed (i.e. 5 mm), related to the implant fixation stability (12).

ii) with staple fixation (both for wedge subtraction and addition), full weight-bearing is allowed at least after eight weeks from surgery (13).

iii) When a Puddu plate is used (14), toe-touch weight-bearing is allowed from the early postoperative period.

Partial weight-bearing (50% of body weight) is permitted only after four weeks and full weight bearing after six to seven weeks. However, when the osteotomy wedge is thicker than 10 mm and/or the gap has been filled with allogeneic graft, it is advisable to postpone full weight-bearing, due to the slow osseointegration process of the allogeneic tissues or the synthetic bone substitutes. In these specific situations, full weight-bearing could be even permitted after the twelfth week post-surgery. In any case, a correct alimentation, rich in calcium and iron (15), and the abstinence from smoking (16) will promote gap filling and healing processes. However, full weight bearing is subordinate to the radiographic evidence of osteotomy stability and the hardware used.

In the case of opening wedge osteotomies, post-op X-rays must be carefully checked for elements suggesting the opening of the osteotomy gap (a sign of instability) or the delay in gap filling. Where non-optimal healing is observed, there should be no hesitation in postponing full weight-bearing, even up to two to four weeks, until x-rays may prove stability, a reasonable progression of the osteotomy gap closure and, if used, initial graft incorporation. At this regard, translational research is providing interesting alternatives for speeding up osteotomy gap healing, including Pulsed Electromagnetic Field Therapy (PEMF), Platelet Rich Plasma therapy and bone marrow concentrate in association with lyophilized bone and pre-operative mobilization of mesenchymal precursors by the subcutaneous administration of growth factors as the granulocyte-colony stimulating factor (G-CSF) (17). In the future, the results of these studies may allow for shortening of weight-bearing times and, consequently, earlier functional recovery.

The introduction of open chain kinetic exercise is still a controversial issue in the literature. A good compromise for these patients who underwent ACL reconstruction associated with tibial osteotomy is to start muscle strengthening exercises using open kinetic chain devices after two months post-surgery. During this initial phase, however, the therapist must instruct the patient to carry out stretching exercises for anterior quads and posterior hamstrings, gluteus, and fascia lata in parallel with quadriceps strengthening exercises. This is done to maintain anterior and lateral elasticity and to re-establish correct muscle co-contraction for future closed kinetic chain exercises.

The second phase ends with the achievement of these "green light criteria":

1. Absent or minimal joint swelling (0/+1).
2. knee extension comparable to that of the contralateral joint.
3. Good coordination during the gait cycle.
4. Minimal pain.
5. Quadriceps strength equal to (or greater than) 30% of the strength of the contralateral quadriceps muscle.

Once these criteria are reached, patients can start to walk without crutches and to move on to phase 3 of the rehabilitation programs.

Phase 3: Intermediate postoperative period

This phase aims to make the patients able to run on the treadmill without difficulty. This goal implies a rehabilitation process in which the patient must obtain a complete flexion, a good thigh muscle strength, and the basic proprioception control of the knee joint. Given the typology of patients undergoing simultaneous osteotomy and restoring of the central pivot, this phase may well be much slower than that of patients who usually undergo ACL reconstruction only. Indeed, for an isolated ACL reconstruction, treadmill running is allowed after approximately 80 days from the operation.

Thus, the first task of the surgeon and the therapist is to gradually achieve a complete range of movement and a correct muscle trophism of the operated limb. This is obtained through standard

closed kinetic chain exercise (mini-squat, lunges, presses with elastic bands) that exert tension and “joint play” on the neo-ACL in a more physiological range compared to that of open kinetic chain exercises. Indeed, if it is true that the closed kinetic chain is less effective for early muscle strengthening, it is equally important to protect the neoligament at the osteotomy site from excessive load.

In this phase, the exercises in water are also very effective. This may be performed through elastic band work on muscle strengthening (both in the open and the closed kinetic chain such as trying to counteract flexion force on the knee maintaining the extension of the knee in standing position in water) and through simulated running movements. Working in decreasing depths is highly useful to accustom the joint to increasing loads and to recover functional movements such as climbing-descending stairs, fast walking, and flat surface light running. Patients who show a deficit in quadriceps strength should continue with electrical muscle stimulation in association with non-weight-bearing (open chain) exercises⁵. Besides, the physician might suggest eccentric muscle training to improve strength and hip performance (18).



Fig. 1. Preparatory running exercises on the elastic carpet (bouncer).

Along with these previously mentioned exercises, the rehabilitation team can promote proprioceptive exercises for joint positioning/re-positioning and balance board training to improve subjective balance control. (Fig. 1).

The last step of preparatory running exercises is represented by exercises on the elastic carpet (bouncer) (see Fig. 1) and by exercises performed with the help of elliptical machines. Cryotherapy at the end of each physiotherapy session is recommended to reduce joint pain and effusion.

The end of phase three involves the attainment of these “green light criteria”:

1. Absence of pain.
2. Absent or minimal joint effusion at rest.
3. Active flexion of 120° or more.
4. average quadriceps, ischio-crural and triceps surae muscle mass (similar or slightly inferior to that of the contralateral lower limb).

Once these criteria have been accomplished, patients are allowed for running on the treadmill and moving on to phase 4 of the rehabilitation program.

Phase 4: Functional postoperative period: from the gym to the on-field rehabilitation

In this phase, the rehabilitation team has the aim of “shifting” from a rehabilitation work performed in the gym to a real on-field re-education practice, to reinforce coordination and specific gestures related to the patients’ sport preference. For sportive patients undergoing such a challenging surgery as simultaneous high tibial osteotomy and ACL reconstruction, on-field training is a fundamental goal for their return to play. In this phase, a great role has the patient’s motivation, grit, and perseverance to ultimate the rehabilitation program and obtaining the best functional results.

However, the on-field rehabilitation sessions should not be misinterpreted with specific training for a sport. On the other hand, they represent a real assisted rehabilitation program that follows the same methods of gym-based rehabilitation except that the physiotherapist provides directly “on-field” a sequence of exercises and he checks the correct accomplishment.

Indeed, the main risk of a “too early” return to a sport is joint overload. For this reason, before starting the “outdoor on-field training”, it is fundamental to complete the “indoor” rehabilitation program with eccentric exercises and isokinetic exercises. These are aimed to strengthen i) the triceps surae and the hamstrings muscles (to potentiate their “breaking” function towards the neoligament), ii) the gluteus medius (to increase hip control), and iii) the knee flexor and tibia internal rotators muscles, specifically in patients who underwent ACL reconstruction with autologous gracilis and semitendinosus graft (19). Proprioception exercises should also be continued to increase neuromuscular control.

Moving on to the rehabilitation “on-field” requires the following rehabilitation criteria:

1. isokinetic test resulting in strength in flexion and extension equal to (or greater than) 80% of the strength of the healthy contralateral knee (Fig. 2).
2. single leg hop test resulting in a hop distance equal to (or greater than) 80% of the hop distance of the healthy contralateral limb.
3. Ability to run on the treadmill for 10 minutes at 8 Km/h; this value indicates that the patient has reached a good resistance to the fatigue over an extended time (10 mins) and it identifies the “aerobic threshold value” of resistance to exertion, under which the patient can maintain an exercise without particular muscle fatigue.



Fig. 2: *Isokinetic dynamometric test for testing the strength in flexion/extension of the knee.*



Fig. 3: *Ear lobe blood test to assess the aerobic threshold (AeT S2).*

The aerobic threshold (AeT S2) is particularly relevant because it represents the personal safety threshold for a prolonged submaximal load and it corresponds to a relatively mild exercise load that can be maintained for extended periods. Indeed, AeT S2 quantifies the patient’s “resistance to the fatigue”. For a specific muscle strain, it coincides with the production of 2 mmol of lactic acid per litre of blood and this can be easily measured by an ear-lobe capillary blood test (Fig. 3). These values can be compared to an “indoor” treadmill running velocity or a heart rate value (measured with cardiometer/heart rate monitor) after a series of outdoor exercises “on- field”.

The aerobic threshold is usually higher in athletes and sporting individuals and it rapidly drops to lower values after a traumatic event leading to interruption of physical activity. Nevertheless, it can increase during the rehabilitation period. Indeed, a correct and continual rehabilitation program increases the general “performance”, thus increasing the AeT S2 value. Thus, if the athlete can start on-field exercise once AeT S2 is equal to 8 Km/h treadmill run, by the end of the program the AeT S2 may have increased to 12 Km/h, corresponding to the value of a well-trained high-level athlete (see table I for further details).

However, the AeT S2 level is not only indicative of a well-performed rehabilitation program, but it is also a sign of its adequacy. Indeed, it indicates

which fatigue threshold should not be exceeded during that specific program. For this reason, the on-field exercises must be carried out without causing muscle fatigue or articular and metabolic overload (i.e. below the AeT S2 level), to allow for gradually improving the metabolic and muscular condition and the cardiorespiratory fitness of the patients. Exercise performed above this aerobic S2 threshold would cause an excessive load that would oblige the patients to interrupt or slow down the physiotherapy program to obtain a full recovery from the fatigue. Ultimately, this may also compromise the result and the achievement of acceptable AeT S2 levels.

In this fourth phase, on-field rehabilitation should bring the patient to gradual global performance improvement. This can be obtained by controlled intensity exercises with progressive load, avoiding metabolic overload to keep the patient below his AeT S2 values through repeated AeT measurements during the rehabilitation period. With this strategy, the patient's performance will progressively improve together with a gradual increase in fatigue resistance level. In this setting, the cardiometer becomes an essential tool for the patients because it may suggest when to reduce the load to maintain the performances inside the "theoretical aerobic working area" or when

to increase the loads in connection with the patient's improved fatigue tolerance.

On-field re-education involves increasing the complexity of the exercises. These can start with running on the spot and in a straight line and then, once weight-bearing symmetry is re-established (Fig. 4), running on a curve, making direction changes, quick starts, and change of pace. At the end of the program, the therapist may start with a specific training simulating specific athletic gestures (i.e. with a ball) similar to that usually observed in real sports competition.

In this phase, the therapist must identify the anaerobic threshold (AT S4) or each patient during fast running performances. AT S4 corresponds to high lactic acid production, more precisely a lactacidemia equal to 4mM/l. S4 is the biochemical expression of medium-high exercise intensity. Lactic acid values beyond that level cannot be metabolized by the patient. AT S4 represents more than 70-80% of the maximum possible intensity of efforts affordable for a specific patient. It is a highly indicative parameter of the submaximal performance and, consequently, of the recovery of performance for the return to play. The AT S4 velocity is calculated using the Mogroni test (20) in which the patient should run for 6 minutes at a constant speed of 13.5 km/h, then the lactate concentration is measured and it is positioned in the formula:

Velocity 4mM (km/h) = $27.94 - 4.86 [\text{lactate acid}] + 0.32 [\text{lactate acid}]^2$.

The result represents the patient's anaerobic threshold (AT S4) speed. Once the patient can carry out correctly the on-field exercises, both the therapist and the surgeon should evaluate the patient to give the "go-ahead" for the return to the competitive and/or recreative sports activities. This collective assessment represents the end of the fourth rehabilitation phase and it requires again to fulfill specific "green-light criteria" that will allow for a safe patient's return to play.

The "green light criteria" to be reached are:

1. isokinetic test resulting in a strength equal to (or greater than) 90% of the strength of the healthy contralateral knee;
2. At the metabolic assessment, AeT S2 greater than



Fig. 4. On-field re-education exercises to improve weight-bearing symmetry.

11.5 Km/h and AT S4 greater than 13.5 Km/h;

3. single leg hop test resulting in a hop distance equal to (or greater than) 90% of the hop distance of the healthy contralateral limb.

For specific sports such as football, additional criteria have been established to integrate the aspecific final “green-light criteria” previously mentioned. These imply more complex functional tests such as the triple leg hop test and the shuttle run test) (21). These tests do not belong to common clinical practice and, to be valuable and reliable, they should be performed under the supervision of a team of physiotherapists able to provide a correct and global assessment of the athlete. Surprisingly, the assessment of knee laxity is not a leading parameter. Indeed, it is commonly observed that a residual laxity is unrelated to a lesser functional recovery of operated knee.

“The days after”

Once sports activities have begun, demanding patients such as those undergoing simultaneous anterior cruciate ligament reconstruction and tibial osteotomy should remain in contact with the therapists and the surgeon. The peculiar pathology and delicate articular balance need periodic assessment and the intervening signs and symptoms, such as synovitis and pain after sports activities should be immediately evaluated. Indeed, these may represent signs of functional stress beyond knee joint tolerance. The follow up should include Xray and MRI in association with AeT S2 and AT S4 measurement upon resuming athletic activities.

Moreover, the possible development and the subsequent evolution of central pivot related pathologies as meniscal and cartilage

Table II. Patient categories according to the aerobic threshold as determined by running speed; *RIGHT* column: patient's physical categories, that are related to (*LEFT* column) the running speed at which the lactic acid in peripheral blood (ear lobe) reaches the concentration of 2 mmol /l (corresponding to the aerobic threshold AeT S2).

Treadmill Running Speed (Km/h)	Patient category
➤ 7	Sedentary with moderate fatigue resistance
➤ 8	Sedentary with good fatigue resistance
➤ 9	Reasonably trained amateur athlete
➤ 10	Well trained amateur athlete
➤ 11	Well trained non-professional athlete
➤ 12	Well trained professional athlete

RIGHT column: patient's physical categories, that are related to (*LEFT* column) the running speed at which the lactic acid in peripheral blood (ear lobe) reaches the concentration of 2 mmol /l (corresponding to the aerobic threshold AeT S2)

lesions may suggest that the patient should be eventually addressed toward sports activities that may be less harmful to the knee joint. We are aware that to be forced to leave a high-level sport for a more recreational activity may have a deep psychological impact. Nevertheless, in such a specific situation, the patient should be persuaded that this limitation may significantly “slow down” the degenerative process of the joint microenvironment. In these difficult moments, the task for the surgeon and the physiotherapist is supporting the patient, through their therapeutic alliance and their communication skills.

In the end, for the patients, the surgeon, and the rehabilitation team, every therapeutic process is like a “journey” aimed to reach the best functional outcome through the “route” that may better preserve joint survival. And in these paths, the versatile concepts of the individualized approach described in this study may help both surgeons and therapists to treat the most demanding sports medicine knee injuries that may benefit from a specific, detailed, and carefully patient-centred rehabilitation project.

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Effectiveness of bone marrow aspirate concentrate (BMAC) as adjuvant therapy in the surgical treatment of congenital pseudoarthrosis of the tibia: a retrospective comparative study

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Congenital pseudoarthrosis of the tibia (CPT) is a rare disease characterised by the onset of bone anomalies or fractures, leading to deformities in paediatric patients. The aetiology of this pathology is unknown. The main theories include the presence of hamartomatous tissue related to Neurofibromatosis type 1, vascularisation deficit of the periosteum and alterations in the numbers and functions of the osteoblasts and osteoclasts *in loco*. Surgical treatment generally requires multiple operations during the patient's childhood and adolescence. The best outcomes seem to occur when using intramedullary nailing, vascularised fibular transplant and external fixation with the Ilizarov technique. The purpose of this paper is to evaluate the effectiveness of in-situ injections of Bone Marrow Aspirate Concentrate (BMAC) as an adjuvant therapy for congenital pseudoarthrosis of the tibia in patients treated with external fixation and that of radiographic healing over time compared to external fixation treatment alone. We performed a retrospective review of clinical and radiographic records of patients affected by CPT and treated in the Paediatric Orthopaedics and Traumatology Department of the Gaetano Pini Orthopaedic Institute with in-situ injections of bone marrow aspirate concentrate (BMAC) on the pseudoarthrosis site, in addition to pseudoarthrosis site excision and application of circular external fixator frame in compression (Group A). The time needed to reach the radiological consolidation of the resection site was recorded and compared to that needed for patients treated with only pseudoarthrosis site excision and application of circular external fixator frame in compression (Group B). There is a statistically relevant improvement of healing time in patients affected by congenital pseudoarthrosis of the tibia treated with external fixation and bone marrow aspirate concentrate compared to patients affected by the same pathology treated with external fixation only. Injection of MSC in the pseudoarthrosis site after focus removal in combination with circular external fixation achieves faster bone healing compared with external fixation only, and the lower refracture percentage may be associated with the better quality and structure of the new bone. However, it would be desirable to have a longer follow-up to determine if the results of the BMC as adjuvant therapy will hold up over time.

Congenital pseudoarthrosis of the tibia (CPT) is a rare disease characterised by the onset of bone anomalies or fractures, leading to deformities in paediatric patients. The literature reports an incidence of 1:140-250.000 in live births, regardless

of gender, typically with unilateral side prevalence (1). Although the average onset age is between 1 and 2 years, the disease can also manifest at birth and between 8-10 years of age (2). The most common site is the middle and distal third of the tibia, followed by

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the proximal tibia and the diaphyseal middle third of the tibia (3).

The aetiology of this pathology is unknown. The main theories include the presence of hamartomatous tissue related to Neurofibromatosis type 1 (4), vascularisation deficit of the periosteum (5) and alterations in the numbers and functions of the osteoblasts and osteoclasts *in loco* (4). In the 60-80% of total cases, there is a correlation



Fig. 1. AP X-ray of spontaneous pathological fracture of the tibia in a 4-year-old patient affected by congenital tibia pseudoarthrosis.



Fig. 2. Lateral X-ray of the same patients in fig. 1, shows the anterior bowing of the tibia.

between congenital pseudoarthrosis of the tibia and neurofibromatosis type 1 (NF1). Although this correlation is quite frequent in patients with congenital pseudoarthrosis, it occurs in only 5% of the patients with neurofibromatosis (4, 6).

The clinical signs are variable, in most cases, the clinical manifestation is a pathological fracture of the distal tibia (Fig. 1-2). In other cases, clinical evidence is limited to a deviation of the anatomical

axis, which may be associated with anterior bowing and external rotation of the tibia. Researchers have developed several classifications; the most widely accepted in the literature are from Andersen (7), Boyd (8), Crawford (9) and El-Rosasy-Paley-Herzenberg (10). The natural history of this pathology is characterised by recurrences, poor outcomes and frequent complications during treatment.

Surgical treatment generally requires multiple operations during the patient's childhood and adolescence. Surgery aims at good bone healing with a minimal degree of axial deviation, the best functional outcomes, less bone length discrepancy, minimisation of complications and providing patients with the highest quality of life possible (1).

The literature describes a vast number of surgical techniques; however, the best outcomes seem to occur with the use of intramedullary nailing (11), vascularised fibular transplant and external fixation with the Ilizarov technique (12, 13, 14, 15, 16, 17). On the other hand, positive results are never higher than 70%, and the number of patients undergoing total or segmental amputation continues to be quite high (18).

Several prognostic factors have been considered to assign patients to different preoperative risk groups such as the age of onset, the involvement of the fibula, the degree of deformity and shortening, ankle motility and co-morbidities (19). All patient treatment should be carried out up until the time of skeletal maturity, as such pathology is unlikely to develop afterwards.

There have been numerous studies on stem cell osteogenesis evaluation in healthy patients. However, few studies deal with the use of stem cells in patients with CPT (20, 21). The rationale for the use of autologous mesenchymal stem cells derives from the results obtained by Leskelä and Granchi, who observed different osteogenetic potentials in stem cells taken from the tibia of patients affected by pseudoarthrosis compared to stem cells taken from the iliac crest (22, 23). Indeed, cells taken from the iliac crest have significantly higher osteogenic potential than those taken from the pseudoarthrosis site.

The purpose of this paper is to evaluate the effectiveness of *in-situ* injections of Bone Marrow Aspirate Concentrate (BMAC) as an adjuvant therapy for congenital pseudoarthrosis of the tibia in patients treated with external fixation and that of radiographic healing over time compared to external fixation treatment alone.

MATERIALS AND METHODS

We performed a retrospective review of clinical and radiographic records of patients affected by CPT and treated in the Paediatric Orthopaedics and Traumatology Department of the Gaetano Pini Orthopaedic Institute with *in-situ* injections of bone marrow aspirate concentrate (BMAC) on the pseudoarthrosis site, in addition to pseudoarthrosis site excision and application of circular external fixator frame in compression (Group A). The time needed to reach the radiological consolidation of the resection site was recorded

Table I. Radiographic Union Score for Tibial fractures (RUST).

Radiographic Union Score for Tibial fractures (RUST)				
Cortex	Fracture line, no callus (score 1)	Fracture line, visible callus (score 2)	No fracture line, bridging callus (score 3)	Total score (min=4;max 12)
Anterior				
Posterior				
Lateral				
Medial				

and compared to that needed for patients treated with only pseudoarthrosis site excision and application of circular external fixator frame in compression (Group B)

We evaluated radiologic healing time, in both groups, by examining results with the RUST scale (radiographic union score for tibial shaft fracture); (Tab. I) A RUST score above 10 signified complete healing, namely, complete healing of at least 2 cortical bone surfaces and presence of callus on the 2 remaining cortical bone surfaces, or complete healing of 3 cortical bone surfaces with no trace of callus on the 4th. We calculated in months the time between healing (RUST >10) and the positioning of the circular external fixator.

We evaluated the results through the non-parametric U-Mann-Whitney Test, with a two-tailed hypothesis and significance level of $p < 0.05$. Group A consisted of 8 patients with an average age of 20.3 months at diagnosis (ranging from 5 months to 8 years); 3 females and 5 males unilaterally affected by pseudoarthrosis of the tibia (5 left and 3 right). Group B consisted of 10 patients with an average age of 22.1 months at diagnosis (ranging from 5 months to 7 years): 4 females and 6 males unilaterally affected by congenital pseudoarthrosis of the tibia (4 left and 6 right).

We performed the diagnosis according to the radiographic criteria of the Boyd Classification (Fig. 3). In Group A, there were 2 class-1 patients, 2 class-2 patients, 1 class-3 patient, 2 class-4 patients and 1 class-5 patient. In Group B, there were 1 class-1 patients, 4 class-2 patients, 2 class-3 patient, 2



Fig. 4. Lateral and AP X-rays shows intramedullary nailing of the tibia in a patient with CPT that was 15 months old; Note the anterior bowing of the tibia in the lateral projection.

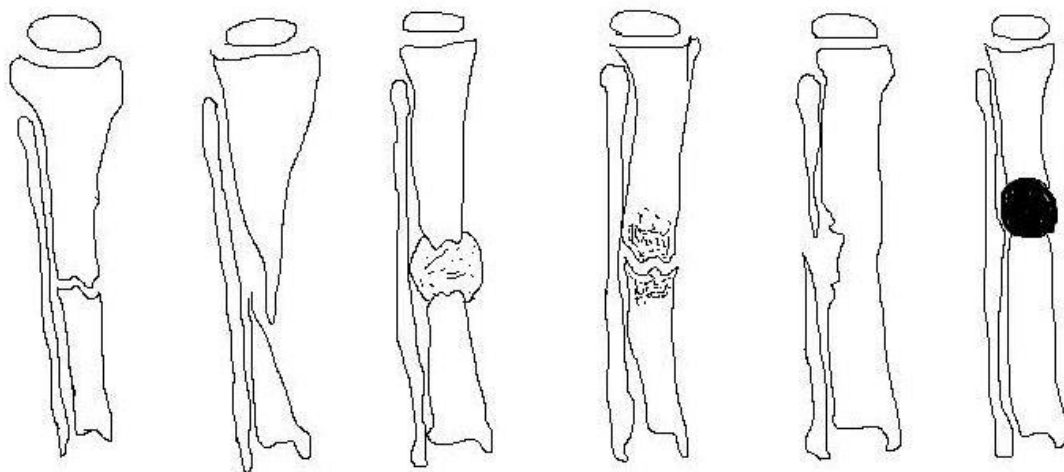


Fig. 3. Boyd classification: **a)** class1: anterior bowing associated with congenital malformations **b)** class 2: anterior curvature associated with hourglass deformities of the extremities that become sclerotic and rounded while the medullary canal is obliterated **c)** class 3: the pseudoarthrosis is found between the upper 2/3 and the lower third and originates from a cyst **d)** class 4: sclerotic and non-sclerotic areas are found within the bone **e)** class 5: CPT associated with fibula dysplasia **f)** class 6: CPT associated with interosseous fibroma or schwannoma.

class-4 patients and 1 class-5 patient.

The average shortening of the affected limb at the time of surgery was 7.44 cm (ranging from 2 to 15 cm). In Group A, the average shortening was 7.63 cm (ranging from 3 to 14 cm). In Group B, the average shortening was 7.3 cm (ranging from 2 to 15 cm).

The average procurvature deformity was 30° for Group A (ranging from 22° to 40°). The average procurvature deformity was 31.4° for Group B (ranging from 22° to 40°). The average age of the patients was 7.13 for Group A (ranging from 6 to 9 years), and 7.7 for Group B (ranging from 6 to 10 years).

All patients surgically treated with external fixation and included in the study were older than 5 and they presented pathological fractures. Patients younger than 5 years who at diagnosis presented fractures with congenital pseudoarthrosis or significant deformities of the affected limb received the intramedullary nailing treatment (Fig. 4-5). The rationale for this therapy is not bone healing, which is not readily achievable without removal of the pseudoarthrosis focus but repositioning the affected limb along the correct anatomical



Fig. 5. Lateral and AP X-rays shows intramedullary nailing of the tibia in a patient with CPT that was 15 months old; Note the anterior bowing of the tibia in the lateral projection.

axis. All patients underwent clinical and radiological evaluation after 1 week, 1 month and monthly until the external fixator was removed and then every 3 months until 2 years from the index procedure.

Surgical technique

The surgical procedure consisted in all cases in the resection of the pseudoarthrosis site until healthy margins were achieved by distal fibular osteotomy and application of the circular external fixator according to Ilizarov's principles. In Group A patients, the first surgical step was the aspiration of 50 to 60 ml of bone marrow from the anterior iliac wing with a Jamshidi needle linked to a syringe which was pre-filled with 0.5 ml of heparin in saline solution.

The bone marrow was then filtered with a specific kit (IOR-G1, Novagenit, Italy) and concentrated in a cell separator at 3200 rpm for 12 minutes, obtaining 8-10 ml of bone marrow rich in nucleated stem cells. The bone marrow aspirate concentrates thus obtained was subsequently injected at the level of the pseudoarthrosis resection site after the circular external fixator frame was applied and the periosteum was accurately sutured.

RESULTS

The radiographic evolution of healing was assessed in the 8 patients treated with external fixation and mesenchymal stem cells and in the 10 patients treated only with external fixation (Fig. 6a-b-c-d-e) (Fig. 7 a, b, c, d, e) We evaluated the results according to the RUST score system (radiographic union score for tibial shaft fractures).

The average healing time was 6.37 ± 1.19 months for GROUP A and 8.1 ± 1.79 months for Group B. The p-value was 0.0455 ($p < 0.05$). The variance was 1.41 months for Group A and 3.21 months for Group B. The Z-Score was 1.99918. Therefore, there is a statistically relevant improvement of healing time in patients affected by congenital pseudoarthrosis of the tibia treated with external fixation and bone marrow aspirate concentrate compared to patients affected by the same pathology treated only with external fixation.

In parallel to these findings, we observed that during the 2-year follow-up of Group A only, 1 out

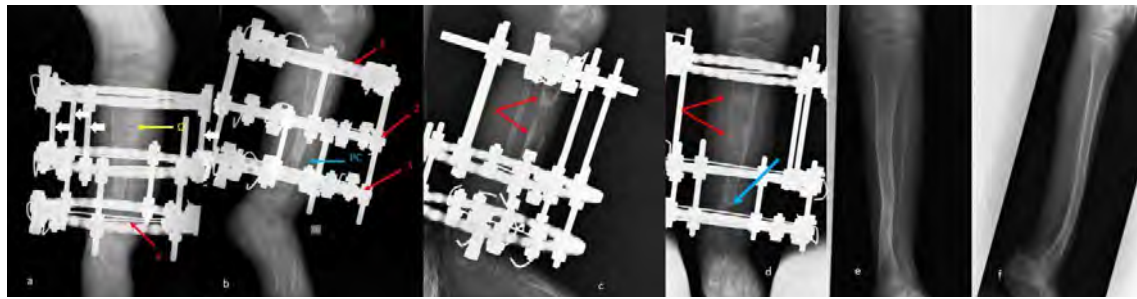


Fig. 6. X-rays of GROUP A patient (7 yrs): **a, b**) Application of the circular frame: note the site of osteotomy (O, yellow arrow), the site of Pseudoarthrosis (PC, azure arrow) the K wire (k), the 3 ring (proximal, distal and intermediate) and bars (white arrow) **c, d**) Evidence of initial bone healing (at PC site, azure arrow) and lengthening of the tibia (red arrow) , **e, f**) Xrays after treatment shows complete healing of the PC site despite the presence of anterior bowing of the tibia.

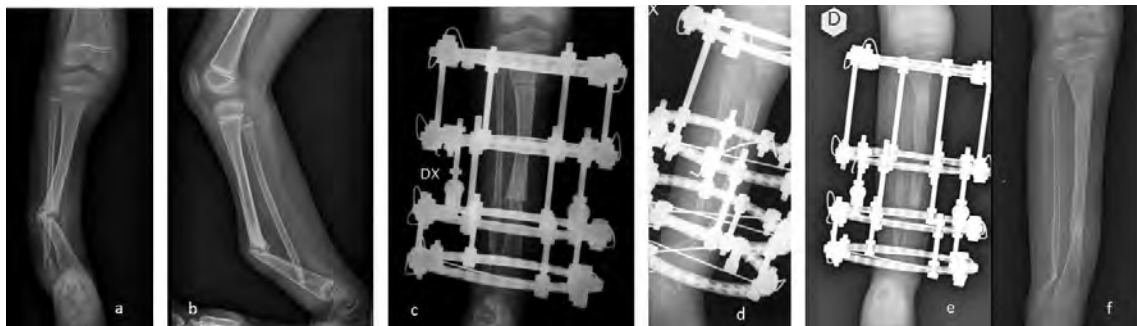


Fig. 7. **a, b**) X-rays showing CPT at the diagnosis in a patient of the B GROUP **c**) Post-operative X-rays: application of a circular frame after the removal of Pseudoarthrosis focus and osteotomy of the proximal tibia **d, e, f**) X-rays show bone healing after 6 months, 1 year and after circular frame removal.

of the 8 patients treated had a refracture compared to 4 out of 10 patients in Group B. There were no reports of significant complications related to the bone marrow aspiration procedure. Only 2 patients reported superficial skin infection treated with antibiotics for 10 days. The patients reported neither vascular nor nervous damage.

DISCUSSION

Congenital pseudoarthrosis of the tibia (CPT), characterised by the onset of structural anomalies or fractures predisposing paediatric patients to deformities, is a great challenge for paediatric orthopaedics. There are several theories about the aetiology of the disease that describe the crucial role of periosteum in bone vascularisation. Macroscopically,

the cortical bone surface and the periosteum appear thickened; medullary reactive fibrosis deprives the cancellous bone of its typical trabecular structure. Microscopically, at the basis of the reactive fibrosis, it was possible to note a diffused thickening of the vascular wall of the periosteal capillaries responsible for reduced blood supply and tissue hypoxia (5).

Some authors consider the close correlation with neurofibromatosis type 1 as a genetic theory that is the root cause of the pathology (6). Wu et al. claim (25) an increase of osteoclastic activity in patients affected by NF1 and confirm the hypothesis of the genetic role of the NF1 gene that works synergically with the mutation of the PeriCre gene to reduce the number and activity of the osteoblasts. In 10% of the cases, CPT can be associated with fibrous dysplasia, also known as Campanacci syndrome (26). Other

authors (27) believe that the cause is a hamartoma generated by a cellular component, which does not differ from the pathological tissue and is divided in bone, cartilaginous and adipose tissues. Despite the lack of fibrocartilage and endochondral ossification, the presence of fusiform cells in the pseudoarthrosis focus indicates an alteration of the microenvironment that determines a non-maturation of the multipotent cells.

The fracture of the affected bone characterises the clinical history, the diagnostic process and the therapeutic pathway of the disease. Medial and posterior deviations of the anatomical axis of the tibia, with significant alteration of the weight-bearing axis of the lower limb, leads to a greater compressive force on the convex side. In this first phase, the patient is still asymptomatic or shows mild degrees of deviation. The condition can remain stationary, but the thinning of the cortical bone on the convex side and the increase of the compressive forces predispose patients to bone microfractures. In the initial phases before the fracture, clinical manifestations are characterised by local or knee pain due to alterations of normal gait kinetics. Following a trauma, often low intensity, fractures determine local pain, functional impotence, oedemas or ecchymoses and vascular and/or nervous deficiencies (28).

The pseudoarthrosis focus, after the fracture event can evolve in several ways based upon age and bone growth (29). In young patients, the traction exerted by the elongation of the fibula and the absence of mechanical stimuli exerted by weight causes a bone gap increase. During the reabsorption stage, the bone appears as slightly deviated, with a mirror image in the two fragments. In patients older than 4-5 years, the linear growth rate of the limbs is reduced. The two sections of the tibia are subject to continuous mechanical stimuli with the apposition of new bone. However, bone apposition failure caused by the disease leads to bone hypertrophy, cortical sclerotisation and medullary canal obliteration. Reduced blood supply in the marrow area causes fibrosis with thickening of the periosteum and further reduction of the vascularisation of the pseudoarthrosis focus. Consequently, the CPT prognosis is influenced by the age of manifestation,

presence of fractures, degree of limb deviation and/or shortening influence.

Comparing two X-rays of the lower limbs in anterior-posterior and lateral view projection is the diagnosis gold standard (30). The CT scan confirms radiographic results by showing osteolytic lesions containing solid tissue. Mahnken et al. report that MR is reliable to measure the extension of the pseudoarthrosis focus by assessing the thickening and hyperintensity periosteum in T1 or STIR sequences (2).

Researchers have created many classifications to describe the great clinical/aetiological and treatment variability of the disease. Andersen came up with the first classification in 1973 (7). In 1982, Boyd modified Andersen's classification in 6 forms (8). In turn, Crawford changed the previous classification (9). The most recent classification, rarely used, was described by El-Rosary-Paley, based on the clinical parameters of the patient upon diagnosis. (10)

The use of surgery for congenital pseudoarthrosis of the tibia is still widely debated in literature, as so for the clinical status, age and clinical manifestation of the disease. An EPOS study (31) reports a better degree of bone healing and a lower degree of recurrence in patients who underwent the first operation after 3 years of age, acknowledging that conservative treatment is an excellent waiting strategy. Surgery in patients who are excessively skeletally immature can cause growth delays, dysmetria and axial deviations associated with a severe disease.

The treatment of congenital pseudoarthrosis of the tibia has been widely debated in literature to identify the best therapeutic strategy with fewer complications and lower recurrence. Non-operative treatment consists of the use of plasters and braces, which are ineffective in treating the disease following a fracture. Many authors implemented electrostimulation (32) or pulsed electromagnetic fields. Presently, literature describes their beneficial effects in adult populations affected by post-traumatic pseudoarthrosis.

The intramedullary fixation, the fibular vascularised graft and the external allograft fixation are surgical methods that received considerable

attention. There is a correlation between age at the time of surgery and a patient's prognosis; Boero (15) and Ghanem (33) describe a difference of more than 50% of patients treated before and after 5 years of age. According to many authors, the range between 3-6 years of age is the best period for surgery.

When using intramedullary nailing, one should consider the positioning, permanence of the implant and growth rate. Removal difficulties upon bone healing from pseudoarthrosis can lead to higher limb length discrepancy, instability and nail breakage (34). An EPOS study reported a good outcome in 45% of trans-calcaneal approaches and 50% in trans-tibial approaches (31). Expandable intramedullary nails that allow adequate bone growth are becoming increasingly common (35).

The use of vascularised fibular grafts allows for bloc removal of the pseudoarthrosis focus, with a biological stimulus to bone healing and the implantation of new healthy tissue. Association with external or internal techniques does not allow to identify the intrinsic capacity of the graft in determining healing (11).

The Ilizarov external fixator has higher success percentages in the literature compared with other methods (13, 36, 37). The therapy allows patients to bear weight earlier, as well as to control dysmetria and potential axial deviations and can be associated with pulsed electromagnetic fields (38, 39). However, it has limited use due to management difficulties, high rates of infection and implant-induced discomfort (37).

Masquelet et al. (40) proposed an innovative, two-step technique, by creating a biological chamber in the pseudoarthrosis focus, previously removed in 2-3 months because of tissue stimulation.

The latest research focused on the use of stem cells in CPT (41) can differentiate into connective progenitor cells and create new muscle, bone, cartilage and adipose tissue. Leskela (22) and Granchi (33) found different development potentials in the osteogenic line and stem cells taken from the tibia of patients affected by CPT, even though these are still lower than those from the iliac crest. From these findings, we can surmise that two main mechanisms act on the pseudoarthrosis focus. One is determined by anatomical alterations of the bone

and the periosteum that cause the formation of the pseudoarthrosis focus. The other is mediated by a functional defect of the osteoprogenitor cells located in the focus, that does not provide enough stimulation for bone repair. The use of stem cell therapy in association with the complete removal of the pseudoarthrosis focus finds its rationality in this pathogenetic model.

Tikkanen et al. (21) have analysed the bone tissue of amputated tibiae previously treated with Mesenchymal stromal cells. They found that MSC transplantation normalised bone remodelling, promoted bone resorption and improved its overall structure. They found no signs of aberrant bone formation or malignant transformation. They even showed bone healing *in vivo* in the treatment of 2 cases refractory to the surgical procedure alone. They demonstrate that the transplanted cells actively participate in and guide the tissue repair process in a trophic manner with paracrine secretion of growth factors during the acute reaction, inflammation, proliferation and remodelling phases.

According to their findings, the MSC injection can also improve the bone growth rate in the pseudoarthrosis site when compared with patients only surgically treated. We also hypothesize that the lower refracture rate in the case group was due to the better bone tissue quality and structure, according to what Tikkanen claimed. The number of osteoclasts in the cortical bone was twice as high compared with the monitored situation before MSC transfer and the mineral content of the bone improved after transplantation.

In more recent studies, there is an increased use of BMPs (42-43). RhBMP-2 has been shown to induce bone formation and resorption in non-human primate models. Likewise, BMP therapy is used to induce osteogenic formation in combination with traditional fixation methods to reduce the time prior to initial union. According to Das et al. (44), their results showed, that patients achieved primary fracture healing after surgery, but, on follow-up, and in comparison, to autologous bone grafting, BMP was not a better option.

However, there are no long-term studies concerning the use of stem cells in association with

different fixation methods that might prove their methodological superiority in terms of clinical and radiographic outcomes. In conclusion, injection of MSC in the pseudoarthrosis site after focus removal in combination with circular external fixation achieves faster bone healing compared with external fixation alone, and the lower percentage of refracture may be associated with the better quality and structure of the new bone. However, it would be desirable to have a longer follow-up to determine if the results of the BMC as adjuvant therapy would hold up over time.

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Tips and tricks for writing a scientific manuscript

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An original scientific manuscript is the target for any researchers whose aim is to show the innovative results arising from the original intuitions that drove all their experiments. Time and patience are essential to decide how to present the data, how to conceive the tables and figures representing the main outcomes of the research, and how to read and mention the necessary references. Few basic rules may help in this difficult task. The first basic rule is: “do not follow the sequence of the paper”. On the opposite, i) start writing the “Materials and Methods (or Patients and Methods when dealing with a clinical study)”, ii) then write the “Results” section, iii) then, write the “Discussion” paragraph, in which the principal investigator explains the results and the innovations proposed, iv) then, write the “Introduction”, which should be clear and concise. The last element to be written should be the “Abstract”, which is the “interface” between the authors and the readers. The second basic rule is that any of the central chapters of the manuscript, i.e. “Materials and Methods” (MM), “Results” (R) and “Discussion” (D), should follow a methodical and sequential description of the topics in a “corresponding sequence of paragraphs”. In other words, in the R and the D chapter sequence of the paragraphs should be linked to the sequence of the concepts described and discussed in the paragraphs of the MM chapter. Thus, a sequential description of concepts will be easily followed by the writers, facilitating both the authors in the organization of the data and the reader in finding a reasonable “answer” to all the aspects of the study mentioned in the MM chapter. In this article, these two rules are extensively described and several tips and tricks for each chapter are suggested to ease the composition of a scientific paper. Indeed, it may be possible to solve the complex problem of “writing a scientific paper” by means of separating it in main sections (chapters) and subsections (paragraphs) and dealing with them one by one. Naturally, this takes time and passion, but, as affirmed by Steve Jobs, “the only way to do great work is to love what you do”.

A famous quote from Paolo Comoglio, Biology Professor at the University of Turin, was “science is 10% inspiration and 90% of perspiration”. And this is nothing but the truth in the field of orthopaedic research. Indeed, from a single brilliant inspiring idea, it follows a long period of striving to correctly conceive an experiment either *in vitro* or *in vivo* in human clinical trials. The completion of a research

project may already represent a long road full of obstacles, from culture chamber contamination to animal sudden death, to serious adverse events in clinical trials. Nonetheless, it comes a time when the bulk of the information is sufficient to conclude our experimental work and, if happy, the data is enough to demonstrate a specific result, then this is the time to starting to writing a manuscript that may best

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represent all our previous efforts. This moment may be exciting, but it is also a time of perspiration.

An original scientific manuscript is undoubtedly the target of any researcher because it is meant to show to the scientific community the innovative results arising from the original intuitions that drove all the experiments. Indeed, the outcomes can be compared to an “identity card” resulting from a long path of research, efforts, and discussion.

Writing a scientific manuscript takes time. Time and patience are essential to decide how to present the data and how to read the necessary references. Moreover, tables and figures should schematically represent the main outcomes of our research. Over the years, we developed a possible scheme to be followed, to write a draft of the paper and it could represent a potential “philosophy”, which may facilitate the writing. The first basic rule is: “do not follow the sequence of the paper” (11). Indeed, an easy way to conceive a manuscript is:

- i) start writing the “Materials and Methods (or Patients and Methods when dealing with a clinical study)”.
- ii) subsequently, proceed with the “Results” section;
- iii) then, write the “Discussion” unit, where the principal investigator (P.I.) must explain and justify the results and the innovations proposed; moreover, the author needs to compare the new data with the most recent scientific publications;
- iv) then, write the “Introduction”, which should be clear and concise;
- v) Finally, focus on the “Abstract”, which is the most delicate section of the paper. Indeed, the abstract should clearly explain the central focus of the research project. Thus, it could be considered the most important “interface” between the author and the public and it must be written at the very end of the work when all the aspects of the paper have been clarified.

Figures and tables may be created at any time, choosing the best images and the clearer graphs to visually show the concepts and the acquisitions and clues of the study.

But how can we practically start to write the very first section of the manuscript, i.e. “Materials and Methods”?

This question introduces the second basic rule:

any of the central chapters of the manuscript, i.e. “Materials and Methods” (MM), “Results” (R) and “Discussion” (D), should follow a methodical and sequential description of the topics as a “corresponding sequence of paragraphs”. In other words, in each chapter, the sequence of the paragraphs in R and D should be linked to the sequence of the concepts that have been described and discussed in the previous MM chapters MM of the manuscript. This sequential description will facilitate the authors in the organization of the data and, at the same time, the reader will find a reasonable answer to all the aspects of the study. In an example, if the first paragraph of the MM will describe the “criteria of choosing the study population”, in the first paragraph in the R section the reader will find all the information about the population and in a corresponding paragraph in the D section, the authors will discuss the choice of the specific population involved in the study and any peculiar aspect linked to that population. This may be resumed in the sequence (see Fig. 1):

A (MM), A' (R), A'' (D)

A1 (MM), A1' (R), A1'' (D)

A2 (MM), A2' (R), A2'' (D)

in which each “A” represents a point or an aspect of the study presented in the MM that will be linked to a specific result in the R section and then discussed, in light of the present literature, in the D chapter. As an example, in an *in vitro* study of a certain source of stem cells for a specific tissue repair (9), the sequence may be:

MM

A=the source of cells/explants used for the experiments; A1=the phenotypic characterization of the cells; A2 = how the cells have been cultured; A3= the differentiation process of the putative cells toward a specific cell line (scaffold used, differentiation medium);

R

A'=results about the source of cells used (number/gram of cells obtained); A1' = characterization of the cells (surfaces markers expression, telomere, etc.); A2'= shape of the cells in primary culture and the scaffolds; A3'= the description of the cells and the matrix observed at the end of the differentiation process, with

any possible quantification of the results (i.e. immunofluorescence semi-quantitative analysis by a program as Image-J)

D

A'' = discussion about the advantages of this specific cell source compared to other cell types and the method of isolation; A1'' = explanation and discussion about the cell characterization; A2'' = description about cell shape and elucidation of the scaffold's choice; A3'' = why our results may signify a possible differentiation toward a specific cell line, what are the limits intrinsic in our method of differentiation etc...

The above-mentioned example shows what it may be considered a "sequential correspondence" in paragraphs between the different chapters of the paper. A different structural sequence can be found in manuscripts dealing with different types of studies as the preclinical animal and the clinical phase-I research works. The preclinical animal studies need to be presented with an extensive description of animal source in MM, and, in the R section, the complication observed during the follow-up and the health conditions of the animals during the time of the study. On the other hand, a clinical study will need a very precise description of the procedure proposed to the patients and, in the results, the tolerability, safety, and feasibility of this procedure in the case group, compared to the control group.

However, another important issue is needed while visualizing the general "schematic drawing" of a scientific paper. This may be considered a "third rule" that is: to have a "null hypothesis" that you try to reject in the design of the study. The null hypothesis is the one that is obtained when the study fails to demonstrate any improvement. In other words, the "null hypothesis" represents the failure of the study to improve a certain experimental setting. In an example: a failure to obtain a specific commitment of a cell line toward a differentiation pathway, or the inconclusive result of a certain drug or surgical procedure in improving animal or patient health and performance when compared to a control group.

For the concept of the rejection of the null hypothesis see, as an example, the beginning of the discussion in Bonasia et al 2016 (2).

The null hypothesis may be declared at any point during the Introduction, preferably at the end of this section. This offers good help for the beginning of the D section. Indeed, the very first paragraph of the D section should be focused on a "brief recapitulation" of the concept and new acquisitions of the study (6). This allows for bringing the reader directly to the center of the research subject and this effect may be easily obtained starting with quotes as "The most important finding of the present study was that the null hypothesis was rejected and the use of...". In this way, rejecting the null hypothesis will intrinsically summarize a clear statement of the results of the study. Moreover, in the same paragraph, the writer can proceed with summarizing the most important details of the project and its achievements.

Considering these three simple and quick basic rules, a schematic sequence of the entire scientific paper may be hypothesized as shown in figure 1. Furthermore, peculiar details regarding every single chapter may be considered.

MATERIALS AND METHODS

Being the first section to be addressed during the manuscript composition, it represents the descriptive part of the entire research project. Indeed, it corresponds to a long time during which the researchers performed different experiments or procedures. The questions to be answered in this section are not about the rationale of the project. Any personal evaluation must be skipped and moved to the D section of the manuscript. Essentially, MM should describe in detail the experimental planning, all the materials and techniques used. Moreover, MM should be concise and should provide enough elements to allow for replicating the experiments (11).

The MM section may start with a brief sentence concerning the ethical approval of the study, either with the number of approvals, if available, or with a statement referring to the institution where the study has taken place. Then, the sequence of the paragraph (A, A1, A2) may follow the schematic structure: i) study setting, ii) source of cell/participants, iii) design of the study (time and setting for cell culture/animal housing, patient follow up), iv) culture condition/treatments or interventions, v) methods for analyzing the endpoints and the outcomes

(i.e. immunofluorescence *in vitro*, MRI *in vivo*, tools to evaluate outcomes).

The last part of MM is dedicated to a brief paragraph analyzing the statistical power of the study and the statistical tools used to analyze the project data. The statistical significance must be declared, i.e. assessing that “ $p < 0.05$ was considered significant”. If any peculiar tool was used to elaborate the data, a brief description is needed. In an example, if the freeware program “Image-J” was used to obtain a semi-quantitative representation of the intensity of a certain signal (as immunofluorescence), at this point of the chapter it may be favorable to insert a description about how this freeware works and how the non-numeric values of the light intensity are extrapolated into numeric values from the rough images.

Any help from a biostatistician may be useful at this moment to ensure the manuscript a correct statistical power (adequate cohort of cases and controls) and correct randomization that must be accurately described.

RESULTS

Following the rule of the correspondence, the

author will “aseptically” present all the results related to the previously mentioned sections, declaring the p -value and presenting the mean values with the correct Standard Deviation (or Median values with the standard error, depending on the statistical setting). Thus, the R section may follow the general schema of “A”, A1’, A2’. In this section, no personal evaluation is allowed. Figures may report the same values declared in the R section, but they are fundamental for the reader to better visualize and comprehend the concepts of the study. If the numbers available are copious, figures may also be used to shorten the results section thus leaving in the main text only the most relevant numbers and values of the study.

DISCUSSION

At this point in the manuscript, the author must be prepared to discuss all the data comparing them with the existing scientific literature. It is a unique occasion to “make the research project alive” outlining all the positive and innovative aspects of the study design and the results obtained and

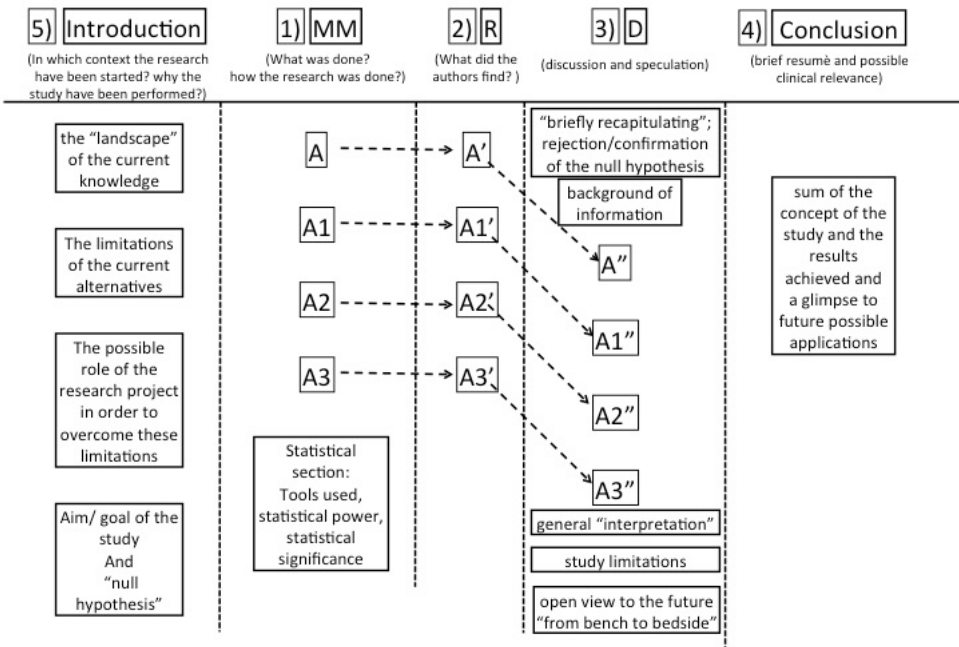


Fig. 1.

justifying any single new acquisition considering the current knowledge. The author should speculate a possible personal explanation to the main findings of the study.

As previously mentioned, the author should start the section by “briefly recapitulating” the concept of the work and the main innovative aspects of the research. This may be done, as mentioned, together with the rejection of the null hypothesis [i.e. the beginning of the discussion in Bonasia et al 2016 (2)]. It is important to mention in this short paragraph the principal findings of the study to “grab” the attention of any possible reader; thus, this person will potentially read the entire chapter with interest (i.e. the beginning of the discussion in Bonasia et al. 2014 (1) for clinical work, or in Marmotti et al. 2013 (8) for a preclinical work).

Then, an overview of the present knowledge related to the topics of the research may follow, as a necessary and more detailed extension of the introduction. This should be a general paragraph where the author could mention the alternatives to the treatment/operation/drugs that are present in literature and the most important papers inherent to that specific subject [see as an example the first part of the discussion in Bonasia et al 2014 (1) or Marmotti et al 2012 (9)]; Being still a general knowledge subsection, the writer should not mention his study, but he should give a “landscape” of the present situation in which the study took place. This section may represent a necessary background of information that the reader has to recall (or even learn for the first time!) to be able to fully understand the concepts and the principles of the research presented by the writer.

Then, the author has to become more specific and, in light of the present literature inherent to the research project, he has to discuss “point by point” all the previously mentioned section in MM and R [see, as an example, the discussion in Marmotti et al. 2013 (8)]. In other words, he should be able:

- i) to present all the results achieved in the order in which they have been reported in the R section (following the schematic sequence of A', A1', A2'...);
- ii) to “build” for each section a discussion paragraph

(A'', A1'', A2''...) where the findings are compared to the results of previous studies published in literature; this implies that the new innovative (and even sometimes conflicting) aspects of the work are examined and for each aspect, the writer should give a comment to justify/explain/sustain the positive value of his finding compared to what other Authors have previously found.

This section is important because it gives the real value of the study and the writers and coworkers should carefully plan it with extensive knowledge of the present literature. The innovative aspects of the study may be ascertained essentially from that part of the manuscript. Moreover, this “point by point” discussion of the work could also help the author in the introduction of the next paragraph that should contain a general “interpretation” of the main essential concept of the study.

When an innovative result is achieved or when the research has offered an “intuition” of a possible innovative role of a cell population/ a procedure /a drug used during a preclinical or clinical work, the writer could report his interpretation of the theory that derives from his research, thus offering to the reader any possible inherent clinical relevance or potential future applications and further studies around his intuition. See, for example, the central part of the discussion in the article of Marmotti et al. 2013 (7).

To complete the discussion, the author should add two final subsections. The first is a brief paragraph on the study limitations. This part should include any possible criticism about the statistical power, the potential small numbers of the different categories of the studies (specimens/samples/patients) and any potential conflicting results that have not been dealt with during the previous sections (i.e. a surgical procedure performed by different surgeons, the use of a “historical” control group in a case-control study or in an *in-vitro* study). A mention of the nature of the work itself may be considered a “polite” limitation. As an example, an “*in-vitro*” study should be considered a preliminary experiment and the inherent limitation of the “*in-vitro*” setting compared to those of clinical work may suggest careful consideration of the results achieved. The same comment may

also be added when dealing with preclinical animal works, mentioning the different repair potential of small animals compared to humans or the differences between humans and animals regarding certain biological constituents (i.e. the famous and debated bioactive substance named platelet-rich plasma or “PRP”).

The second and final paragraph is an “open view of the future” that the authors may offer to the readers. This part should contain a “take-home message” dealing with future hopes and potential uses of the research. Thus, the authors can conceive any possible future studies and clinical applications of their research (see as an example the final part of the discussion in Marmotti et al. 2013 (7)).

A separate section named “conclusion” at the end of the manuscript may be required by some journals. This section is an easy task for the writer because he should just summarize in one or two sentences the concept of the study and the sum of the results attained, without any personal comment. Clinical implications and any future possible applications and studies may also be concisely mentioned. This section should not be seen as a duplication of the manuscript contents but as a brief specification of the work done. Readers who do not have enough time to read all the paper may spontaneously skip all the intermediate sections and they might deal immediately with this final part of the manuscript. Therefore, a brief and complete synopsis may be useful to present all the work in a few words and to provoke interest in any potential occasional reader.

INTRODUCTION

Having written the entire main sections of the paper, the writers now will easily deal with the introduction. The introduction should start with:

- i) a brief paragraph describing the “landscape” of the current knowledge about the setting of the study (i.e. the use of a certain cell population, the current use of a certain procedure or drug to improve the development of a certain disease or the evolution of a specific degenerative disease);
- ii) a second brief section describing the present limitations of the current use of a specific cell

source or the current treatments available at large scale for a specific disease;

- iii) a third brief paragraph presenting the possible role of his research to “overcome the present limitations”.

This sequence can focus the reader’s attention on the clinical problem, and it may offer the reader a quick view of the setting in which the study is allocated. In other words, the writer has to answer the question “why has the study been performed?”. See as an example the Introduction of Bonasia et al 2016 (2).

The last section of the Introduction is dedicated to present the aim or goal of the study and the “null hypothesis”. This part is the “concretization” of the struggle of the researchers in trying to positively modify a certain biological or clinical situation (i.e. cell differentiation, the progress of a specific disease, *in vivo* repair process). It should be clearly described and declared, and it may be followed by a brief sentence regarding the possible consequence of obtaining positive findings and results from the experiments that will be presented in the next session of the paper.

Then the null hypothesis may be stated as the hypothetical situation in which the results of the study will nullify the aim and the hopes of the researchers because no difference would have been observed between “case and controls” at the end of the experiments. It is the “saddest” ending that the research may have, and it represents the potential failure of the study to improve a certain experimental setting.

In literature, there are rare but very interesting scientific papers in which the authors will recognize a confirmation of the null hypothesis. In light of this eventuality, the authors will address all the D section of the paper justifying their null hypothesis and offering a clear description of what should not be done in a certain *in vitro* of a preclinical or clinical setting. This specific “negative” setting may be dealt with by same sequence as the one previously described and the innovations offered to the reader will be symbolized by the concept of “not performing” a certain procedure/treatment/ surgical procedure.

ABSTRACT

The abstract should be ideally the last part to be written or revised by the authors before submitting their work to a specific journal. It should represent the “identity card” of their research and often it is the interface that allows the reader to choose, or not, to read the entire manuscript.

Having written the entire paper, it should be easy to compose the abstract as a sequence of brief sentences summarizing the different sections of the manuscript.

Indeed, the writer may start with a simple phrase inherent the background of the study and the aim of the study, that is what exactly has been tested by the researchers or, in other words, what has inspired the writers and co-workers in starting all the research path and what they hoped to obtain the end of their work. Then, a phrase shortly describing the MM and R section should follow. A third phrase should give a brief clue about the meaning of the results achieved and a possible preclinical or clinical relevance of the work. See, as an example, how the abstracts of the KSSTA journal or the America Journal of Sports Medicine are structured. The writer may easily follow the sequence “Background” – “Purpose” – “Study Design” (*in vitro*, preclinical, phase I clinical, level of evidence) – “Methods” – “Results” – “Conclusions”.

It is of paramount importance to limit the abstract at a certain number of words, depending on the journal’s specific rules. And, most important, the abstract should be, in a certain way, attractive for any readers to “grab” their attention and to motivate the readers to fully “immerse” in the whole manuscript.

FINAL REMARKS

At that point, figures and tables should be properly revised. Good advice is to try to conceive any figure and table as if they could be read as a standalone part of the manuscript (6). This last act should be done with attention to include, in all the figures, a properly detailed legend depicting extensively all the abbreviations used in the corresponding figure or table. The statistical significance ($p < 0.05$ or less) should be always mentioned in the figures or in the legends when data and numbers are presented

in tables or histograms. As a personal advice, the author should try to use the easiest form of the histogram for data presentation, to facilitate the reader to comprehend the data distribution “at a glance”. Colors should be carefully used to outline the differences between the study groups.

The author should pay attention to specific images as, for example, the pictures of immunofluorescence that may result in “all black” images if colors and brightness are not properly adjusted. The same attention must be used when showing histological samples that need a “referring scale” that allows for a better comprehension of the dimension in the microscopic scale. Sometimes, the legend of the figure may also contain brief comments of the “general meaning and concepts” of the results presented by the images, so allowing for a “shift” of sentences from the discussion to the legends of the manuscript figures if the discussion may seem too long at the final revision of the paper.

A quick look at the references must be done before submission, to ensure that every citation has been transferred with all the information needed.

Last but not least, all the co-workers may ask themselves: “is the title properly attractive for all our work?”. The title may be considered as the “symbol” of the research work and it is the first interface between the Authors and the future readers. Indeed, the manuscript will be catalogued in any search engine, as Pubmed, by the title and the keywords the authors will decide to choose for “capturing” the main topic of the research. Thus, any writer should realize that, in a long list of “pertinent” articles around a specific topic, his manuscript will appear along with many other articles.

To have more possibilities for “eye catching” the readers, the title should be as short and provocative as possible. It should contain some words related to the topics of the research as well as some hints about the results reached, generally in a straight literary style and in a clear sentence. It is uncommon to use the form of an interrogation for a title of an original scientific manuscript: that “questioning style” is more often adopted for review or meta-analysis. As an example, when a reader looks for titles of original scientific papers on the common debated topic of the

intra-articular PRP injection to prevent osteoarthritis, he will find a bunch of possibilities ranging from a straight phrase as “Hyaluronic Acid Versus Platelet-Rich Plasma: A Prospective, Double-Blind Randomized Controlled Trial Comparing Clinical Outcomes and Effects on Intra-articular Biology for the Treatment of Knee Osteoarthritis”(4) to the more informative sentence as “Platelet-Rich Plasma Intra-articular Knee Injections Show No Superiority Versus Viscosupplementation: A Randomized Controlled Trial” (5). On the other hand, when looking for review about that topic, the reader can often find the use of an interrogative form as in the title “Does Intra-articular Platelet-Rich Plasma Injection Provide Clinically Superior Outcomes Compared With Other Therapies in the Treatment of Knee Osteoarthritis? A Systematic Review of Overlapping Meta-analyses” (3) or in the title “Does platelet-rich plasma have a role in the treatment of osteoarthritis?” (10).

In any case, any occasional reader will be caught by the more attractive and provocative title. A good practice for the writer is to empathize with the reader and to ask himself if he would have read an abstract (and subsequently an article) with the title he has chosen. In such a “roleplaying” situation, the writer will be able to “feel”, naturally and consequently, any variations needed in the title (and even in the abstract) to create the very final version of the paper to be submitted to the selected journal.

Thus, at the end, it is possible to solve a complex problem as “writing a scientific paper” by means of separating it in sections and subsections and dealing with them one by one. Naturally, this takes time and “perspiration”. However, a nice complete manuscript may be achieved using some of the clues and advice aforementioned that may be able to make the workflow easier and faster and to allow for keeping in mind a general structure of the paper while dealing with the single sections. And the rest is up to our imagination, for the love of our research and a bit of courage and bravery in starting such a hard task. Indeed, as Steve Jobs said in 2005 (12), “the only way to do great work is to love what you do”. So “Stay Hungry, Stay Foolish”, and above all good luck!

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