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ARTHROSCOPY IN OSTEOCHONDRAL PATHOLOGY OF THE ELBOW: INDICATIONS, TREATMENT AND COMPLICATIONS

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The arthroscopic technique has revolutionized orthopaedic surgery in the last forty years, due to the improvement in surgical technique and innovations in technologies. Actually, knee and shoulder arthroscopy are commonly used to treat the most frequent pathologies with mini-invasive approaches demonstrate recovery of function and outcomes. Not the same thing can be said for other joints such as ankle, elbow and hip, where the narrowness of the space makes the technique more challenging. In this study, a brief review of the literature and the history of elbow arthroscopy are described. Indications, surgical technique, risks and complication, tip and tricks, advices and notes to avoid complications are reported. Elbow arthroscopic surgery is a difficult technique that requires a long learning curve, but in an experienced surgeon's hands, it is a safe and successful methodology when applied with correct indications and cautions.

Elbow arthroscopy has been more recently introduced in clinical practice than knee or shoulder arthroscopies and this technique is promising and innovative (1). The first attempts date back to Burman, who published an anatomic study, which appeared in 1931. The experience proved rather unsuccessful, due to the narrow space of the joint and the proximity of neurovascular structures. Not surprisingly, in 1932, Michael Burman (2, 3), a forerunner of arthroscopy, concluded that the elbow was not accessible arthroscopically. This technique was discontinued for almost half a century. However, since the early '80s, thanks to the improvements of anatomical knowledge and the evolution of surgical instruments and techniques, there has been a progressive diffusion of the arthroscopy, allowing surgeons to perform reliable and safe procedures in the treatment of numerous joint pathologies (4).

Improvements in anatomical knowledge, surgical instruments and training of surgeons have also allowed this technique to evolve over time, to standardize surgical steps and to ensure that today it is considered a safe surgical and common procedure when in reliable hands. Indications have been extended to many other diseases, so that the number of annual procedures is increasing continuously (4-6).

On the other hand, due to the elbow narrowness, anatomical difficulties and to the proximity of neurovascular structures, it is still a very demanding technique (4, 7-9). To date, elbow arthroscopy indications include chondral lesions, primary and secondary degenerative arthropathy, synovial membrane pathology, post-traumatic stiffness, septic arthritis, especially for diagnostic purposes and capsule-ligamentous instability.

Contraindications are mainly represented by scars and adhesions of previous surgical procedures or trauma that change the normal topographical anatomy and severe arthritic degeneration that compromise joint biomechanics.

Indications

Main indications are: "loose bodies" removal, osteoarthritis, post-traumatic stiffness, synovitis,

Key words: elbow, arthroscopy, surgical technique

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septic arthritis, osteochondritis dissecans, lateral epicondylitis in which conservative treatments have failed and when there are symptoms that alter normal activities of social or working life, such as limitation of joint motility and/or pain (4, 6, 8, 10).

The elbow's range of movement (ROM) varies from -21°/12° of extension up to 122°/164° of flexion. A minor ROM of 30°-130° or a ROM of less than 100° are considered a clear indication for surgical treatment (6, 7, 11, 12). From a meta-analysis of over 30 articles and 798 patients, it is clear that the arthroscopic arthrolysis technique is indicated in less severe cases, in compliance with the rule for which the treatment must be the least invasive and the least dangerous possible (11).

Intra-articular loose bodies

Among the different pathologies of the elbow, the presence of intra-articular loose bodies represents the most frequent indication (13, 14). The presence of loose bodies may be secondary to articular cartilage traumas, acute or repeated, impingement between trochlea and olecranon, synovial chondromatosis, osteochondritis dissecans or Panner disease and osteoarthritis.

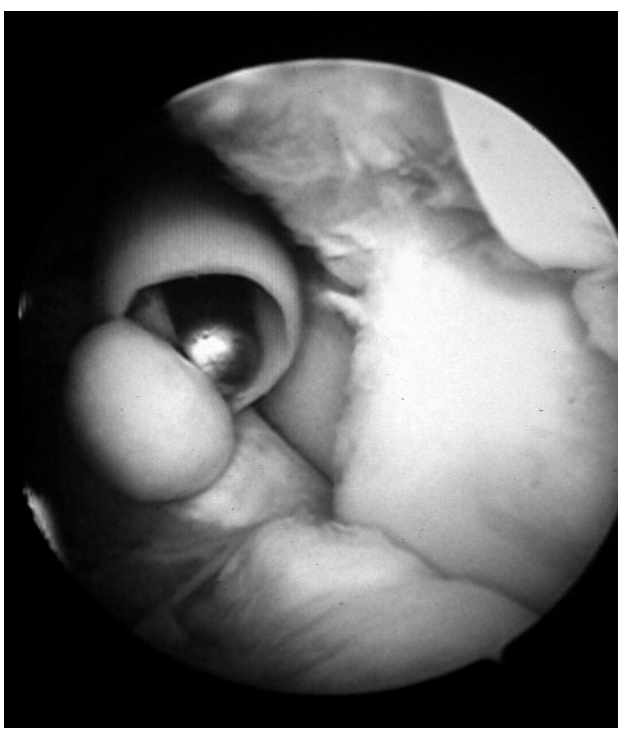

Fig. 1. *Arthroscopic view of the elbow: removing "loose bodies".*

Free intra-articular loose bodies are often multiples and are located at different points of the elbow. The patient complains of repeated articular blocks, frequently accompanied by pain and, infrequently, by signs of ulnar nerve compression. In cases secondary to severe osteoarthritis, the appearance of pain at the average degrees of flexion is observed, with stable contraction of the elbow. Radiographic examination is not always the golden standard exam for this pathology, due to the frequent presence of not-calcified and cartilaginous loose bodies (25-30%). Therefore, it is particularly advisable to perform a second-level examination, such as computed tomography (TC), Magnetic resonance imaging (MRI), and ARTRO-MRI, in order to better define the number and location of the free bodies.

The surgical technique involves a complete examination of the joint; often, the so-called loose bodies are not evident, but they are in continuity with the synovial membrane. Once identified and released, they should be extracted with appropriate instruments. In the case of very voluminous fragments (> 2cm), these will be reduced in size with manual or motorized tools; to avoid the risk of loss into the soft tissues, it is advisable to extract them through an arthroscopic cannula (Fig. 1). In case of osteoarthritis and anterior or posterior osteophytes, the only removal of loose bodies does not lead to the disappearance of symptoms, but it is necessary to associate the removal of the osteophytes with a motorized cutter or osteotome. Results, in cases of non-severe osteoarthritis, are excellent (15, 16). While, in presence of severe osteoarthritis, the removal of loose bodies does not improve the patient's condition and, therefore, the elbow arthroscopy should be contraindicated.

Osteochondritis dissecans of the elbow

Osteochondritis dissecans of the elbow (17) is a lesion of the articular surface of the lateral humeral condyle, characterized by the detachment of a fragment of cartilage and subchondral bone (18). From an etiopathogenetic viewpoint, it is agreed that an important role in the genesis of this disease is performed by repeated microtraumas. The pathology is observed more frequently in two categories of sportsmen: pitchers and gymnasts (19). In the first case, forces in compression exerted on the radio-

humeral joint during the launching phases could determine the onset of the disease; while, in the second case, the mechanical stress is associated with the weak vascular component of the epiphysis, which is modest during the childhood (20). Currently, the most accredited hypothesis is that the repeated microtraumas determine a fatigue fracture of the subchondral bone, with subsequent bone resorption, detachment and fissuring of the fragment that has become avascular and formation of loose bodies.

The infantile form of osteochondritis, known as Panner disease, was firstly described in 1929. It appears in children between 4 and 10 years of age and at its onset there seems to be a vascular lesion similar to that observed in the Perthes disease (21). The treatment of these young patients consists, in absence of intra-articular loose bodies, in an anti-valgus immobilization for analgesic purpose; in cases of advanced osteochondritis with osteochondral detachment and fissuring, the removal of free bodies by arthroscopic pathway is indicated. The long-term results are still good in both cases (22).

The osteochondritis dissecans symptomatology is characterized by pain on the lateral margin of the elbow, swelling and restriction of the elbow range of movement. The X-ray of the elbow highlights the characteristic radiolucency of a portion of the humeral condyle and, in advanced cases, the presence of free osteochondral fragments in the joint. In doubtful cases, the X-ray test tangent to the lesion, the CT scan and the MRI may provide useful information (23).

The osteochondritis dissecans treatment depends on clinical symptomatology; the removal of loose bodies is indicated in the presence of articular blocks with excursion deficits, possibly associated with chondroplasty with motorized instruments to promote the formation of a fibrocartilaginous substitute tissue. Other surgical procedures, such as the fixation of the fragments, the radial capitellum osteotomy and bone grafts, do not guarantee better results than the removal of loose bodies alone. Short-term results of the arthroscopic treatment are good and show a more rapid and complete functional recovery compared to the open surgery (24, 25).

Posterior elbow impingement

Another cause of elbow pain, frequent in pitchers and baseball players, is the posterior impingement with formation of postero-medial osteophytes of the olecranon and trochlear chondromalacia (26) (Fig. 2).

Valgus stress and hyperextension to which the elbow is subject during the launch phase are cause of this pathology. These patients typically experience pain at forced extension and valgus stress, often accompanied by an extension deficit.

Arthroscopic treatment, in these cases, has the dual advantage, over arthrotomy, to reduce morbidity and ensure better visualization of the trochlea chondromalacia and allows posterior osteophyte removal, joint debridement and trochlear chondroplasty (Fig. 3); However, especially in professional athletes, this procedure is not conclusive because of the frequent recurrence of osteophytes (27, 28).

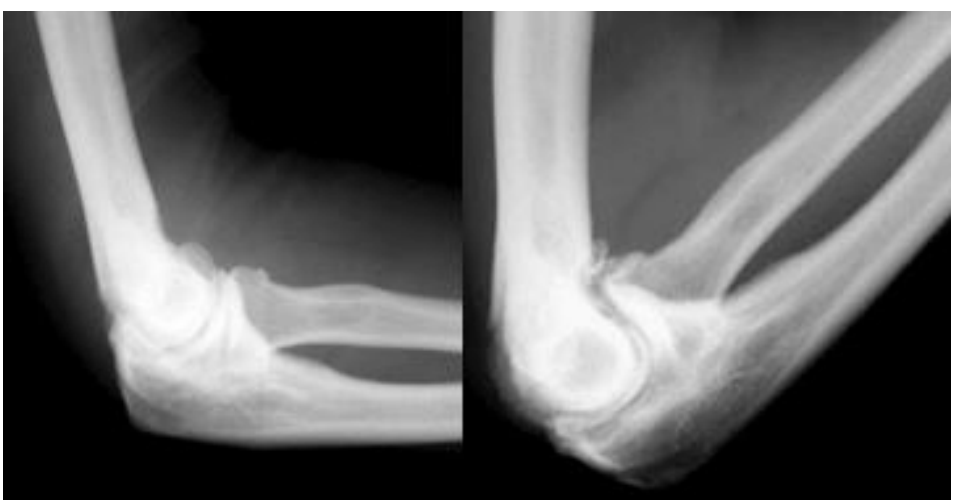

Fig. 2. *Elbow X-ray: post-traumatic osteoarthritis.*

Surgical technique

The surgical technique is now codified and standardized, as described extensively in literature. There are variants related to the surgeon's preference. The patient position can be supine, lateral or prone. The most advantageous one is the prone position with the upper limb abduct to 90 degrees, elbow flexed to 90 degrees and free forearm without suspension traction system (Fig. 4).

Anaesthesia can be general or loco-regional. The advantages of general anaesthesia are linked to the fact that neurological functioning can be verified immediately in the postoperative time. On the other hand, the advantages of loco-regional anaesthesia are related to the lower pharmacological load and lower systemic risks. Normally, the surgical procedure is performed with a tourniquet at the root of the limb. Before surgery, the main anatomical landmarks can be identified and marked with a dermographic pen. On the basis of these, we proceed to surgical accesses (arthroscopic portals). Portals can be multiple, but routinely two: anteromedial and anterolateral.

Preventively, the joint cavity is insufflated with 15-20 cc of saline solution in order to relax the joint capsule and stave off the neurovascular structures. This elbow joint injection is normally performed on the "soft spot" (direct side access) commonly used for infiltrations but also by one of the planned portals. Normally, but it depends on the surgeon's preference, the first portal to be realised is the anterolateral one with the "Out-In" technique. This is expected at about 2 cm proximal and 1 cm before the lateral humeral condyle.

Through the antero-lateral portal, a cannulated trocar equipped with a removable core is introduced into the elbow joint; then, the joint is extended with the liquid, through a dedicated arthroscopic pump connected to the guide and, finally, the camera at 30° or 70° is introduced. Only at this point, it is possible to realize the second portal: the antero-medial one with the "In-out" technique, under direct visual control from the inside. Therefore, numerous other accesses are possible. Once portals have been realised, it is possible to use different motorised or not instruments with the protection of dedicated plastic cannulas, generally of 5 mm, such as electro frequency vaporizer, cutters and shavers, pliers, basket, scalpels, scissors, etc. At the end of the procedure, a drainage can be inserted and the arthroscopic portals are sutured (6, 7, 8).

Arthroscopic portals and neurological structures

Numerous studies have examined the relationships between arthroscopic portals and nerve structures. The radial nerve is about 5-10 mm from arthroscopic portals, but for anatomic variability, it can also be at 2-3 mm (12, 29, 30, 31, 32, 33).

Fig. 3. *Arthroscopic view of the elbow: cartilage damaged with osteophytosis and joint calcifications.*

The distension of the capsule with the saline solution allows to remove nervous structures from the surgical field. In presence of a typical capsular retraction associated with post-traumatic stiffness, the capsular distension decreases by 38%, decreasing the protective effect of the distension (29, 34). In fact, in case of post-traumatic stiffness, the joint capsule is thickened and the joint space is reduced due to a greater fibrosis (8).

Post-operative treatment

The post-operative treatment is basically the same for all the pathologies described. The immediate active mobilization of the elbow is essential. In cases of joint excursion deficit, continuous passive mobilization is indicated.

The main advantage of the arthroscopic elbow surgery compared to the open one is a more complete visualization of the joint surfaces, thanks to the use of different portals, avoiding large surgical scars.

In addition, arthroscopy minimizes the risks of infection and rigidity, and accelerates the post-operative recovery.

Complications

Arthroscopic elbow surgery complications occur in less than 10% of cases. These are usually minor, such as iatrogenic damage of the articular cartilage, tools breaking, complications derived from the use of tourniquet and persistent drainage from arthroscopic portals. Neurological complications represent a feared and very serious occurrence, in particular those affecting the radial nerve that is very close to the anterolateral portal.

Neurological complications

The occurrence of neurological damage is widely documented in the literature and is underestimated. Even using safe and validated techniques, the risk of neurological damage cannot be eliminated (32, 35, 36, 37, 38). The incidence of this kind of complications varies from 0 to 14% (5, 8, 29, 37). In general, the treatment of post-traumatic stiffness with the elbow arthroscopy technique has a lower incidence of complications than open techniques (5% *vs* 23-78%) (11). Neurological injuries are generally transient and heal spontaneously within the first 6 months (5, 6, 7, 10, 29, 37).

The main causes of neurological injury are: compression by the tourniquet, incorrect skin incision, transposition of the ulnar nerve, failure of the ulnar nerve neurolysis, presence of post-traumatic adhesions, altered anatomy following fractures, direct lesion (section), local anaesthetics, use of retractors, thermic damage (vaporizer), stretching, compression. Neurological injuries in elbow arthroscopy are more frequent in cases of rheumatoid arthritis and capsular release (37, 12).

According to a recent publication, nerve injuries attributable directly to the arthroscopic procedure are less than 21%. In other cases (79%), causes are: compression by the tourniquet (42%), incorrect skin

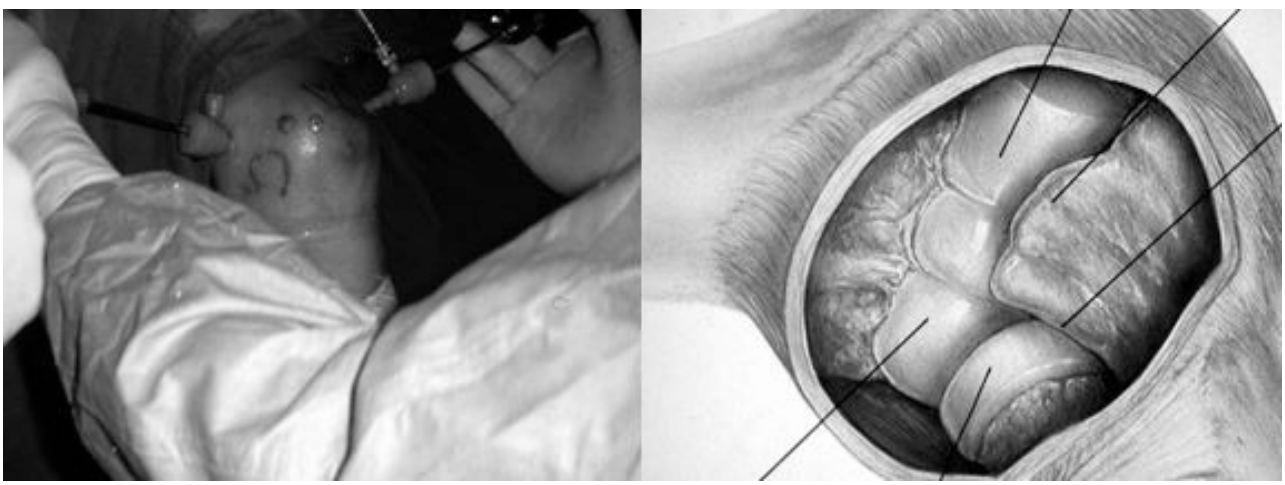

Fig. 4. *Arthroscopic portals: identifying preoperatively anatomical landmarks and marking them with a dermographic pen is essential to avoid neurovascular injuries. View of the medial and lateral arthroscopic portals in prone position.*

incision (29%) and ulnar nerve transposition (10).

Technical advices for the prevention of neurological complications

The literature provides a series of tips for the prevention of nerve injuries, which do not consist of the guidelines, but they simply are recommendations related to the experience of various authors. Among these, we report:

Identify preoperatively anatomical landmarks, neurovascular structures and portals and mark them with a dermographic pen (8).

Inject, before surgery, 15-20 cc of saline solution through the "soft spot" to allow the neurovascular structures to move away (6).

Avoid access with sharp instruments, do not use access below the radius-ulnar joint line, and avoid using an aspirator associated with the "shaver" near nerves (10).

Avoid excessive intra-articular pressure; it is better to isolate the ulnar nerve in cases of severe ROM limitation (6).

In some cases, it is possible to identify arthroscopically and/or visually nerve structures and protect them with retractors (10). The use of retractors can however constitute a hazard and must be done with caution (6). The surgeon's experience and training are certainly useful but it is not the only variable that influences the risk of nerve injury associated with the procedure (9).

In conclusion, the arthroscopic release, especially in case of rigid elbow, is a procedure that is not without risks even in expert hands (10).

DISCUSSION

Although indications are limited, elbow arthroscopy is a reproducible and safe surgical technique, if performed by experienced surgeons. Osteochondral lesions can be effectively treated with this technique, limiting the morbidity and the fearsome complications associated with the open surgery. However, compared to the arthroscopic technique of other districts, in the elbow more attention is required to the topographic anatomy for potential iatrogenic complications during the realization of the portals.

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COMPARATIVE EVALUATION OF MENISCAL PATHOLOGY: MRI *VS* ARTHROSCOPY

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The meniscal pathology of the knee is one of the clinical realities the orthopedic surgeon must daily confront with. The diagnosis is generally both clinical and instrumental; among the different diagnostic imaging techniques, Magnetic Resonance Imaging (MRI) appears to be the most accurate method regarding sensitivity and specificity for the study of meniscal fibrocartilages and articular cartilage. In an attempt to clarify the roles of MRI and diagnostic knee arthroscopy, we performed a retrospective comparative study of the two methods to assess their sensitivity and specificity in the diagnosis of meniscal pathology. We evaluated 105 consecutive patients with a clinical diagnosis of intra-articular knee pathology who were subjected to MRI examination and subsequently to surgical arthroscopy, recording on a graphic card the surgical and radiographic findings expressed by a blinded expert radiologist. Comparison of MRI and arthroscopy data showed, for the internal meniscus, values of 98.5% sensitivity, 94.7% specificity and 93.8% "K" index for MRI compared to arthroscopy, and of 90%, 98.6% and 90.5% for the external meniscus. These results allow us to state that the diagnostic capacity of MRI appears to be very high and therefore crucial in the planning of the correct surgical treatment of individual patients, thanks to its ability to highlight even small changes affecting intra-articular structures.

The increased incidence of traumatic and degenerative lesions of meniscal fibrocartilages, associated with the greater diffusion of sports practice among young people and the tendency to gain weight among older patients, explains the high number of surgical indications for knee meniscal disease (1-3). The diagnosis is generally clinical and instrumental, with percentages of specificity and sensitivity close to 100% (4). In the preoperative planning, some authors underline the need for an MR assessment before performing a knee arthroscopy, while others show that an accurate clinical examination yields equal, if not superior, diagnostic abilities compared to MRI (5-7). In an attempt to clarify the roles of MRI and diagnostic knee arthroscopy, we performed a retrospective comparative study of the two methods to assess their sensitivity and specificity in the diagnosis of meniscal pathology.

MATERIALS AND METHODS

From February to August 2018, surgical knee arthroscopy in 105 consecutive patients was performed, all diagnosed with intra-articular knee pathology. All patients had previously undergone an MR examination of the injured knee, following the onset of painful symptomatology and after clinical indication. The mean age of the patients was 40.3 years (range 16-75) with a male to female ratio of 2:1. All patients at the time of the admission were submitted to an objective examination, including meniscal tests according to McMurray et al, the grinding test

Key words: meniscal tear, knee, MRI, arthroscopy

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and the pressure test on the affected joint space line. All arthroscopic procedures were performed by an experienced orthopedic surgeon (V.C.).

Before proceeding to the treatment of the lesion found, video recordings of the different joint compartments were performed. The status of meniscal fibrocartilages was verified by careful palpation with a particular instrument (the probe) and by exploring the posteromedial and posterolateral recesses. At the end of the intervention, the presence of any dimorphisms or lesion of the menisci or their integrity was reported on a specific evaluation form. This form consists of an anamnestic part referred to the patient and two separate parts for the graphic recording of the surgical and radiographic findings. Specifically, the two menisci were represented by schematic drawings according to an axial and sagittal plane that allowed an easy and complete graphic interpretation of the possible lesions found and a quick comparison between the two methods. The classification of the lesions was made according to the location and the lesion plane, dividing the meniscus into the three classic portions (anterior horn, body, posterior horn), and recognizing three different cleavage planes (radial, horizontal and longitudinal). Subsequently, all the MRI images were evaluated by an expert radiologist (A.B.), blinded to the arthroscopic findings.

We excluded all patients subjected to arthroscopy after more than 6 months from the MRI examination, as we believe that the evolution of the meniscal lesions could affect the goodness of the MR *vs* arthroscopy comparison. At the end of the study, we re-evaluated all cases comparing the surgical and MRI reports and calculating the rate of true positives, true negatives, false positives, false negatives and thus sensitivity and diagnostic specificity, with the corresponding 95% concordance intervals, positive and negative predictive value, and "K" correlation index. For a further study of the diagnostic capabilities of MRI, we also divided our sample into age groups, creating, in in this way, three groups (16-30, 31-50 and 51-70 years).

RESULTS

The results of our study showed that the total prevalence of lesion was 80.6%, with greater involvement of the internal meniscus (52.4%) compared to the external one (14.3%). In 19% of cases, both menisci were affected. Patients presenting at arthroscopy with the integrity of meniscal fibrocartilages (14.3%), underwent surgical treatment due to intraarticular problems of different nature (chondropathy, patellar malalignment, LCA lesion, Baker pseudocyst, etc.). Among older patients in particular, we found the simultaneous presence of meniscal and cartilaginous lesions. The most frequently encountered meniscal lesion in the internal meniscus was the complex lesion (26%), followed by the flap lesion (24%), the longitudinal (17%) the radial (9%) and bucket handle tear (7.5%); rarely did we find a double bucket handle tear (2.5%) or the presence of parameniscal cysts (2.5%).

The percentage of meniscocapsular separation was 10% (Fig. 1), while we did not find horizontal lesions or a discoid dysplasia in any case. In 22% of cases, the arthroscopic examination showed the presence of a meniscal fibrotic degeneration; this finding was almost constant among patients belonging to the highest age group or in those with chronic ACL ("knee abusers").

We observed a strong association between ACL and meniscal lesions (83.7% of cases). In particular, the internal meniscus was involved in 72.2% while the external meniscus in only 16.6% of cases; in 11.1% of cases both menisci were involved; in only 7 cases (16.2%) there was an isolated functional ACL insufficiency, demonstrating the important role of the menisci in stabilizing the knee joint. As we have already pointed out, the external meniscus showed different incidence and modalities of injuries compared to the medial meniscus. The most frequent lesion was the longitudinal one (19%), followed by the complex (12.5%), flap (9.3%), radial (6%) and bucket handle (3%). The incidence of cystic degenerative lesions with the formation of parameniscal masses occurred in 3% of cases, similarly to the medial meniscus. A meniscocapsular separation was found only in 3.1% of cases, while we observed a high incidence of discoid meniscal dysplasia (19%) (Fig. 2), only half of these latter being symptomatic. Degeneration of the external meniscus was present in 31% of cases.

Analyzing lesion localization, we found that in most cases tears occur at the level of the posterior horn in both menisci; localizations to the body of the meniscus are rare and ones to the anterior horn even rarer, both for the internal and external meniscus. The MRI sensitivity values in the diagnosis of the meniscal lesions were 98.5% for the internal meniscus and 90%

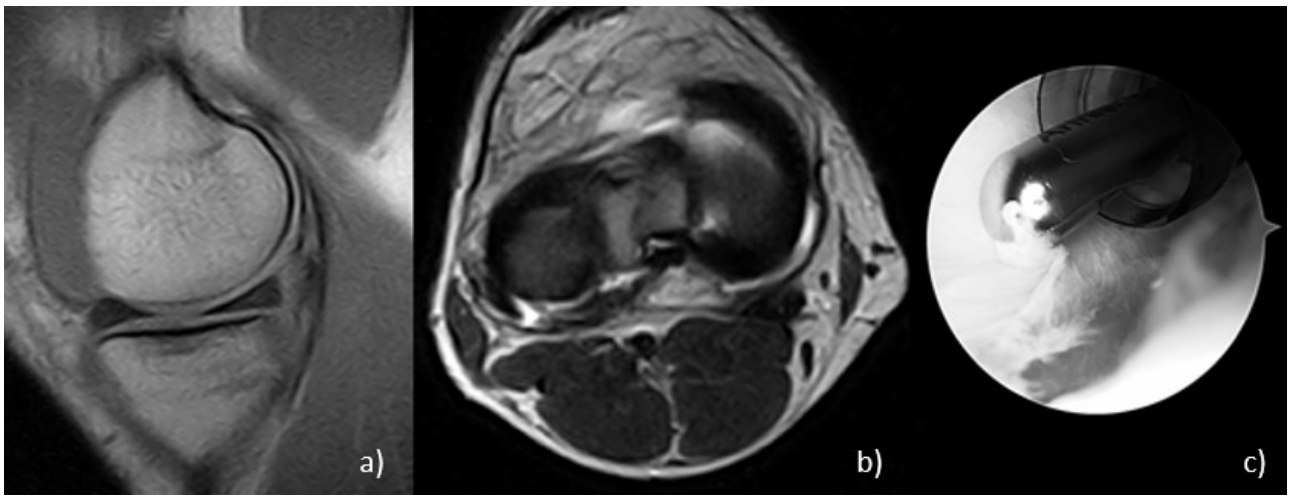

Fig 1. *Sagittal PD (**a**) and axial T2 (**b**) weighted MRI images showing meniscocapsular separation of the posterior horn of the medial meniscus. Arthroscopic findings (**c**).*

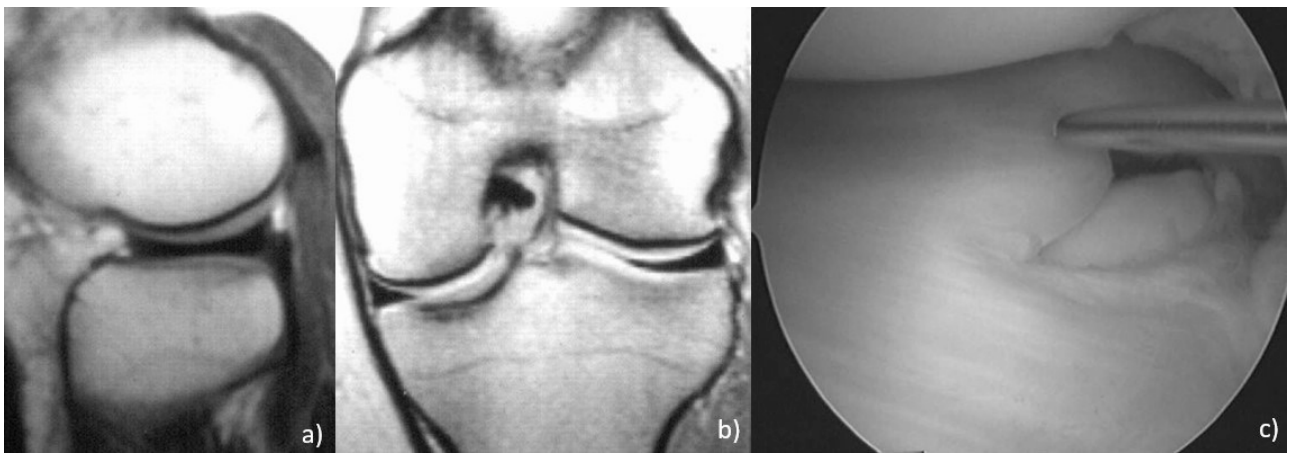

Fig 2. *Sagittal (**a**) and coronal (**b**) images showing discoid dysplasia of the external meniscus, confirmed at arthroscopy (**c**).*

for the external meniscus with 95% confidence intervals calculated between 95% and 100% and between 79% and 100% respectively.

In regards to specificity, values were 94.7% for the internal and 98.6% for the external meniscus, with concordance intervals calculated at 95% respectively between 87% and 100% and between 96% and 100%. The correlation "K" indices between the two methods were 93.8% for the internal meniscus and 90.5% for the external meniscus. However, when describing the type of lesion, MRI showed different sensitivity and specificity values; notably, the sensitivity and specificity values for the internal meniscus were respectively 71.4% and 94.9% for meniscocapsular separation, 57.1% and 100% for the bucket handle tears, 0% and of 100% for the radial injury, 68.42% and 96.51% for the complex lesion, and 60% and of 93.6% for the longitudinal lesion.

The results for the external meniscus were as follows: sensitivity and specificity respectively 60% and 100% for the discoid-type dysplasia, 0% and 100% for the bucket-handle tears, 40% and 100% for complex lesions, and 50% and 97% for longitudinal lesions (Fig. 3). The total amount of false negatives and false positives for site and type of meniscal lesion at the MRI evaluation was 15 cases, 10 for the internal meniscus and 5 for the external meniscus.

By classifying these patients by age group, we observed a higher frequency of error among younger patients; 9 cases between 16-30 years of age (average

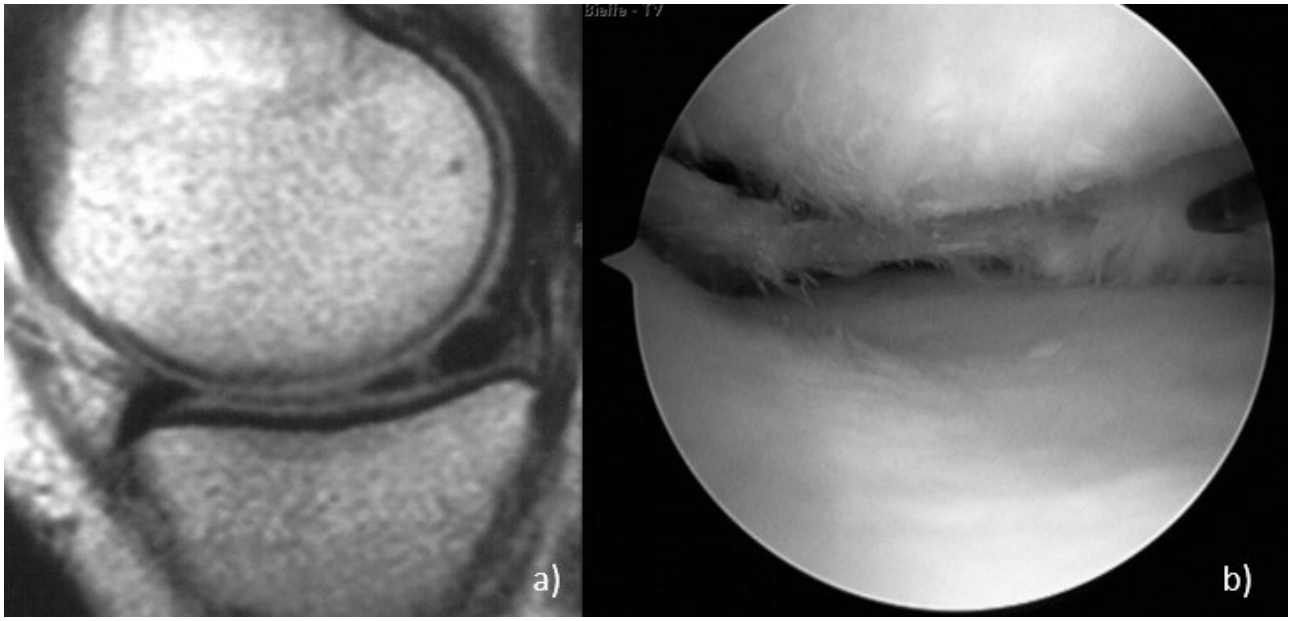

Fig 3. *Sagittal (**a**) MRI findings of longitudinal degenerative lesion of the posterior horn of the medial meniscus, and corresponding arthroscopic findings in (**b**).*

age 20.4), 4 cases between 31-50 years of age (average age 33.2) and 2 cases between 51-70 years of age (mean age 62.5). The most frequently misdiagnosed MRI lesion was the meniscocapsular separation of the body-posterior horn and the radial lesion in both menisci.

DISCUSSION

In general, and in agreement with many authors in recent studies, our results showed high sensitivity and specificity (8) of the MRI in the diagnosis of internal meniscus lesions. We have also found that these values are directly related to the type of meniscal lesion being very high for complex lesions, bucket handle tears, longitudinal tears and for meniscocapsular separation, but being extremely insensitive in the detection of radial type lesions (5, 9, 10). The latter data still generates controversy today; some authors, with whom we feel in agreement, argue that at the base of this phenomenon there is the characteristic pattern of meniscal lesion, challenging to highlight in the three standard scanning planes (11). However, very recent studies state that by integrating all scan planes, mainly the axial, every type of meniscal injuis, including radial injury, can be diagnosed with the same accuracy (4, 8, 12, 13).

The analysis of the results obtained from the radiographic and arthroscopic evaluation of the external meniscus allows us to state that the diagnostic capacity of MRI, unlike what is reported by several authors in the literature is very high, with values lower than those for the medial meniscus (14). Also for the external meniscus, as well as for the internal meniscus, the highest percentages of error occurred in the diagnosis of radial lesions with sensitivity values equal to 0%; the same value was found for bucket handle lesions. The phenomenon, in our opinion, is to be correlated with the sample size we studied with only 2 cases of radial lesions and 3 cases of bucket handle lesions that had a negative influence on the results of the statistical survey.

Sample analysis by age groups showed a higher incidence of MRI diagnostic errors in young patients; this phenomenon, particularly evident for the menisci, is likely to be related to the etiopathogenesis of the same lesion. In fact, at the base of these meniscal tears in young sporting patients, there is almost always a high energy trauma that determines at the same time involvement of all the articular structures with the formation of perilesional edema, which appears to be hyperintense like meniscal lesions.

Although arthroscopy represents the "gold-

standard" for the diagnosis and treatment of meniscal pathology, MRI has proved to be important in the choice of the correct operative treatment of individual patients, thanks to its ability to highlight even small signal intensity changes (7, 15-18). This was very evident in cases of femoral and patellar chondromalacia, in cases of clinically silent Baker pseudocysts and in cases of osteochondritis dissecans that probably without the specific information of the method would have gone unnoticed by arthroscopy.

The use of this diagnostic method also allows us to evaluate the quality of the meniscal parenchyma, useful information for therapeutic purposes but difficult to assess even through careful arthroscopic examination.

Given those reason, and also because even minimally invasive arthroscopy presents the traditional and specific risks of surgical trauma, the clinical indication to arthroscopy should always be based on a thorough anamnestic and objective examination, with the integration of the information obtained from the MRI (19).

Therefore, we believe that, although arthroscopy represents the gold standard for the diagnosis of meniscal lesions, MRI, thanks to the high sensitivity and specificity demonstrated in the present study, represents a valid aid to the orthopedic surgeon for the solution of clinical-diagnostic problems. Preoperative imaging instrumental evaluation may provide the possibility to choose the best treatment option (meniscectomy *vs* meniscal suture), giving the opportunity to know the quality of the meniscal tissue that is going to be treated.

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ARTHROSCOPIC ANATOMIC REPAIR OF BANKART LESION IN RUGBY PLAYERS

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Recent studies have reported equivalent outcomes of arthroscopic and open shoulder stabilization. However, surgical strategy for shoulder instability is a challenging and controversial problem for surgeons that have to treat collision sport athletes. In fact, only few studies support the arthroscopic surgery for this group of patients. The aim of this study is to evaluate the outcome of arthroscopic stabilization in a homogenous population of professional young athletes practicing in high-level collision sport. We treated 22 consecutive professional rugby players, with a mean age of 23.6 years, affected by traumatic anterior shoulder instability. All patients underwent arthroscopic Bankart repair with bone suture-anchors. Exclusion criteria were: failed previous shoulder surgery, atraumatic, multidirectional or posterior instability, bone defects greater than 20% of the anterior-inferior glenoid, engaging Hill-Sachs, rotator cuff tears, capsular-ligament avulsion on the humeral side (HAGL). Patients were evaluated according to Constant score, Rowe score and Visual Analogue Scale (VAS) for discomfort and handicap. The mean follow-up was 40.7 months (range, 6 to 87 months). All patients except one were able to return at the same previous sports level at 5 to 6 months postoperatively. Re-dislocation occurred in 3 players for high impact trauma during competition or training. Our results confirm that, also in the collision sport patients, anatomic arthroscopic Bankart repair is a good option for the treatment of traumatic anterior instability without associated lesions.

Players of contact or collision sports may develop shoulder instability as a result of acute or repetitive trauma during training and matches.

Instability in a collision athlete is a challenging problem related to the return to sport and risk of recurrence. There is no consensus in the literature regarding the treatment modality: few reports support the arthroscopic treatment of this group of patients (1-3).

In previous studies, initial experience with arthroscopic glenohumeral stabilization resulted in failure rates that were significantly higher than the traditional open procedures. However, many studies show similar results with arthroscopic shoulder techniques as compared with the 'anatomic' and 'non-anatomic' open repairs (4-7).

We evaluated the results of arthroscopic shoulder stabilization in a homogenous population of young male professional athletes of a collision sport (rugby), having the same competitive potential.

MATERIALS AND METHODS

We retrospectively evaluated, thirty-one elite

Key words: traumatic shoulder instability, collision sport, arthroscopy, Bankart repair

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professional rugby players (31 shoulders) underwent arthroscopic shoulder stabilization for anterior shoulder instability. Out of these, 22 were included in our study and 9 were excluded according to exclusion criteria of: failed previous shoulder surgery, atraumatic and multidirectional instability, glenoid defects greater than 20% of the glenoid circumference, engaging Hill-Sachs, tears of rotator cuff or capsule at the humeral insertion (HAGL).

All players were male with a mean age of 23.6 years (range 17 to 35). Of these 22 patients 4 were < than 20 years old. The dominant arm was involved in 10 patients. Anterior instability was defined as a subluxation or dislocation in an anterior or anterior-inferior direction. 15 patients had a documented anterior shoulder dislocation that required formal reduction, and 7 patients had a history of episodes of subluxation with "dead arm" symptoms. Eight players had their first dislocation during game, while others sustained their first dislocation during training. Six shoulders dislocated once, 8 shoulders dislocated 2-4 times, one shoulder dislocated 6 times.

All patients were initially treated conservatively with a personalized physiokinetic therapy (PKT) without improvement.

We assessed patients by physical examination and under anesthesia in the theatre prior to their operation evaluating range of motion and the humeral translation. The patients were also assessed with an imaging protocol of Anterior-Posterior X-Rays, Stryker view, West Point axillary view and MRI arthrogram.

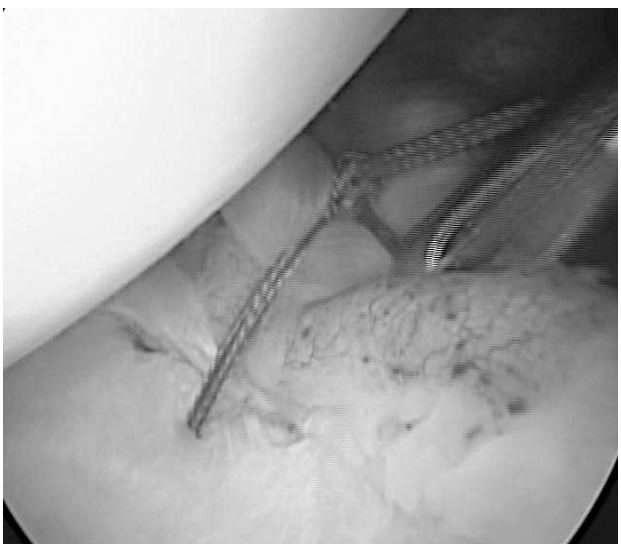

Fig 1. *Arthroscopic view of the inferior glenohumeral ligament repair/retention with double-loaded anchor.*

Finally, all patients underwent arthroscopic treatment of the capsulolabral detachment with suture-anchors technique by the two senior authors (C.A.; C.V.). All patients underwent interscalene block, and placed in lateral decubitus position with the arm in abduction of 45° and flexion of 15°.

Diagnostic arthroscopic examination was performed through the standard posterior and anterior-superior portals in order to identify every associated lesions. Intraoperative findings were recorded in a computerised database.

An additional mid-glenoid working portal was placed in the rotator interval just above the superior margin of the subscapularis tendon. After placing the scope into the anterior-superior portal, the Bankart lesion margins were abraded after the anterior-inferior capsulolabral ligamentous complex was released to allow adequate vertical shift. The suture anchors preloaded with braided non absorbable sutures, were inserted into the glenoid rim at the chondral margin. Depending on the lesion size, two or three anchors were used for the capsulolabral re-attachment (Fig. 1).

Postoperatively an abduction pillow sling was used for the first 4 weeks. During this period, the patients were instructed to perform active motions of elbow and wrist. Mobilization, proprioceptive neuromuscular facilitation arcs and stretching program commenced in the fifth week. All athletes followed a supervised rehabilitation program.

Patients were assessed preoperatively and postoperatively with the Rowe score, the Constant score and visual analogue scale (VAS) for discomfort and handicap. Paired-samples T-test was performed to assess the significance of changes between the preoperative and postoperative shoulder scores (significance was set to $p<0.05$).

RESULTS

During surgery, no engaging Hill-Sachs lesion was found in any patient. The types of capsulolabral lesions included a "classic" Bankart lesion in 14 shoulders, a bony Bankart lesion (<20%) in 4 shoulders, and an ALPSA lesion in 4 shoulders. In 5 and 3 shoulders, the anterior capsulolabral lesion was associated with type II and type III lesions respectively. No patient had a rotator cuff tear.

The mean follow-up was of 40.7 months (range, 6 to 87 months). Physical examination in follow-up was performed by the same independent observer. None of the 22 athletes had clinical signs of anterior instability. In all cases, postoperative apprehension and relocation tests were negative. In 21 shoulders, there was no pain at the time of the final follow up; one patient, the oldest in our series, had moderate pain for the first 6 months after surgery.

At the final follow-up, all patients had full range of movement. Neither intraoperative complications nor any postoperative infections were observed. Bar one, all patients were able to return to sports at the same previous level at 5 to 6 months postoperatively. Re-dislocation occurred in 3 players (13.6%); 2 players (19 and 17 years old respectively) following violent trauma during the match at 11 and 17 months after surgery, 1 player (21 years old) after violent trauma during training 14 months postoperatively.

In the VAS scale for discomfort and handicap, Rowe and Constant scores revealed significant improvement after surgery ($p<0.05$) (Fig. 2), and patient satisfaction was excellent in all patients. At final follow up, the preoperative mean Rowe score increased from 42.5 points (range, 15 to 65) to 90.5 points (range, 75 to 100) and the mean Constant score increased from 65.5 points (range, 43 to 77) to 96.0 points (range, 86 to 100).

DISCUSSION

Many of the lesions of the musculoskeletal system that we find in the game of rugby are similar to those that we can find in other contact sports and the incidence of injuries typically increase as the playing level is increased (8).

Training injuries are significantly more severe than injuries sustained during competition. The incidence and severity of injuries is related to training activity and playing position: forwards sustain more severe shoulder injuries. The proportion of recurrent training injuries is similar to that reported for match injuries (9-11). During a collision sport like rugby, forces applied to the shoulder can either be indirect with the player falling onto his outstretched hand and forearm or directly through a point of impact on the shoulder

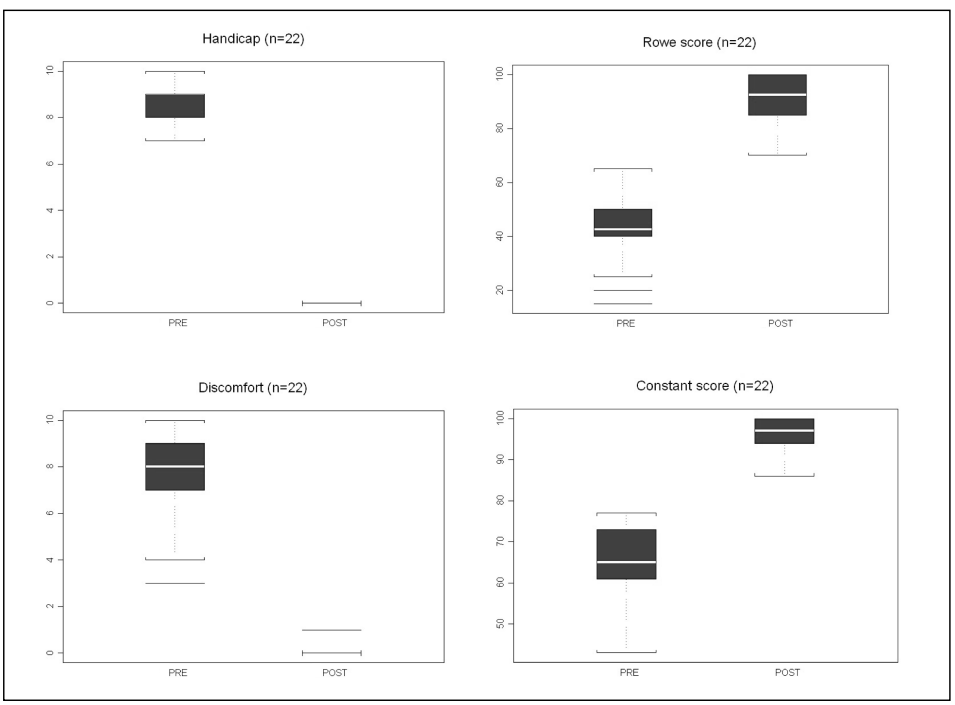

Fig 2. *Each graph shows the distribution of pre-operative and post-operative values of respective scores. All clinical outcomes are improved after arthroscopic anatomic repair ($p<0.05$).*

(12, 13). Most common shoulder injuries include contusion, acromioclavicular injuries, glenohumeral dislocations, clavicle fractures, rotator cuff tears and muscle sprains, axillary nerve injuries and traumatic myositis ossificans (14).

After a traumatic shoulder dislocation, it is important to restore the delicate balance between the stability and the complete articular excursion existing in the shoulder.

Since the first description of the pathological lesions in shoulder instability a century ago (15, 16), much has been understood about the biomechanical basis of the shoulder joint stability and the consequent treatment methods.

For many years, the Bankart's lesion has been considered the fundamental lesion of anterior shoulder instability. Nowadays however, we know that the Bankart's lesion alone is not enough to cause a dislocation (17), but it is only one of the most common lesions in this pathology. Other lesions, such as an excessive capsular extension, an engaging Hill-Sachs and a glenoid bony defect greater than 25-30% of the total surface, can cause instability if they are not recognized and repaired (18, 19).

Arthroscopic Bankart repair has variable results in literature (20-23). For this reason, the open Bankart procedure had been recognized as the gold standard for many years (24). Burkhart and Debeer's study contributed to clarify the controversial debate about the superiority of the open technique (25). This study illustrated that, in most of the cases, shoulder instability is caused by the association of several lesions, including soft and bone tissues, and surgeons must appreciate each lesion and use the best surgical solution for each case.

Many authors have reported good outcomes of arthroscopic Bankart repair for instability in athletes. O'Neill observed postoperative subluxation in 12% of collision athletes through a transglenoid arthroscopic technique (26). Bacilla et al. reported an instability recurrence rate of 7% in 40 high-risk patients after arthroscopic repair with non-absorbable sutures and anchors. They found that 29 of 32 patients involved in athletic activities returned to their respective sports at the same or higher level (27). Gartsman et al. reported similar results: 49 patients with good or excellent results in a population of 53 patients (28). Ide et al. showed no difference in recurrence rate between contact athletes and noncontact athletes (29). Mazzocca et al. found recurrent dislocation in 11% of athletes younger than 20 years involved in collision and contact sports who had undergone arthroscopic Bankart repair (30). Treating 160 rugby players arthroscopically, Larrain et al. obtained good or excellent results in 94.9% of cases in the acute instability group and 91.8% in the recurrent instability group (31).

However, several authors reported a higher risk of recurrence of instability in collision athletes. Interestingly high recurrence rate in collision athletes have also been reported with open procedure (32). Torrance et al. reported that young athletes (particularly those aged <16 years old) have a higher risk of recurrence (33).

Kropf et al. commented that the shoulder instability in athletes participating in collision sport is a challenge but this issue alone does not represent a contraindication to arthroscopic shoulder stabilization (34).

Published results of arthroscopic stabilization surgery for anterior shoulder instability in collision athletes are variable and often difficult to interpret and compare because of the heterogeneity of examined samples and the different surgical techniques.

Conversely, in our study the same exclusive inclusion criteria, surgical technique and post-operative protocol were considered: in the presence of this homogenous pattern, we demonstrated a good control of joint stability, obtaining a significant improvement in clinical outcomes with excellent ability to return to the same previous sport level. We also had low rate of recurrence (13.6% of the total). In line with literature, this risk was higher for the youngest athletes of our population (50% of players aged less than 20 years) but, even in these cases, arthroscopic Bankart repair can be considered safe as first step treatment, because it does not compromise joint anatomy and permits a following more invasive Latarjet procedure (35).

This study had several weaknesses related to the retrospective design: the small number of cases, the absence of a control group and the short mean time of follow up; however, we will continue to investigate

these patients to update the clinical outcomes.

In conclusion, our study shows good or excellent results with arthroscopic treatment for anterior shoulder instability in a collision sport like rugby.

The higher rate of failure in collision athletes should be attributed more to kind of sport and comorbidities than to surgical technique. Rugby players remain at risk of potential recurrence because of its intrinsic characteristics (31).

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THE COMBINED USE OF PLATELET RICH PLASMA AND HYALURONIC ACID: PROSPECTIVE RESULTS FOR THE TREATMENT OF KNEE OSTEOARTHRITIS

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Osteoarthritis represents an important social economic burden with a high incidence worldwide. Conservative management of knee OA consists in several therapeutic options: pharmacologic therapy such as analgesics, non-steroid and steroid anti-inflammatory drugs, physical therapy, and injective therapy with hyaluronic acid (HA) and platelet-rich plasma injections (PRP). The aim of our study is to evaluate the effect of combined autologous PRP and HHA (Hybrid Hyaluronic Acid) viscosupplementation on clinical outcomes of patients with knee OA, by assessing the subjects before and after injective treatment. The study was conducted on 60 patients with an age between 40 and 70 years old affected by unilateral symptomatic knee osteoarthritis (stage II and III of Kellgren-Lawrence scale) nonresponsive to pharmacologic and rehab treatment. We divided the patients in two groups, and we treated the group A with injection of HHA and group B with HHA+PRP. Each patient received 3 injections at an interval of 1 week for 3 consecutive weeks. The patients were evaluated by the Knee Injury and Osteroartrhitis Outcome Score (KOOS) and Visual Analog Scale (VAS) at 3, 6 and 12 months after treatment. Statistical comparison between groups showed a significantly better result for the group B concerning the KOOS value, at 3 months and at 6 months. This difference, although clinically relevant, lost the statistical significance at 12 months. The VAS trend differently showed a significant difference at 3 and 12 months, while at 6 months the superiority of group B did not achieve statistical significance. Few studies investigated the effects of HA+PRP combined treatment for knee OA. Numerous studies demonstrated the efficacy of HA injection therapy in knee OA for a clinical point of view, reducing the pain and improving the quality of life. PRP preparations also improved functional outcome scores compared to hyaluronic acid and placebo in patients affected by knee OA. Based on our results we can conclude that the combined PRP and HHA treatment is not only a safe and efficacious procedure which can provide functional benefit but is also significantly better than HHA injective therapy alone, as demonstrated by the comparison within our cohort.

Osteoarthritis (OA) is an important social economic burden with a high incidence worldwide. In the U.S., it is estimated that 240 people per 100,000 are affected by this condition per year (1). Its prevalence increases with age, especially in women (2). Being the most common chronic degenerative joint disease in the elderly, OA is a multifactorial disease characterized by the imbalance of synthesis and degradation by chondrocytes, resulting in alterations in the composition of the cartilage matrix (3), degeneration and thinning of cartilage and bone contact, which eventually lead to symptoms of stiffness, pain and

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limitation in movement (4). It is also strictly associated with changes in the synovial fluid. Indeed, cartilage, subchondral bone, and synovium interact with each other playing key roles in the pathogenesis of OA (5). Conservative management of knee OA consists in several therapeutic options: pharmacologic therapy such as analgesics, non-steroid and steroid anti-inflammatory drugs, physical therapy, and injective therapy with hyaluronic acid (HA) and platelet-rich plasma (PRP) (6, 7).

Hyaluronic acid is a large glycosaminoglycan that is naturally found in the synovial fluid and plays an important physiological role in synovial joints (8). Viscosupplementation with HA provides joint lubrication and shock absorbing function because it replaces the physiological glycosaminoglycan produced by the joint. The aim of viscosupplementation therapy is to reduce pain and restore the viscoelastic properties of the synovial fluid (9). Normally, in adults, HA concentration ranges from 2.5 to 4.0 mg/ml (10), but in OA it is reduced by 33-50%. It is currently used in clinical practice to reduce pain and improve function (10).

The Hybrid Hyaluronic Acid (Sinovial HL, IBSA) (11) is composed by a combined blend of high and low molecular weight chains (12). Hybrid HA has been proved to be superior in stimulating extracellular matrix production and increasing the GAG content in vitro. Moreover, it has been demonstrated that HA displays systematically higher viscosity after mixing with PRP, increasing the regeneration of cartilage and reducing the levels of inflammatory cytokines (12). However, few studies have proved the clinical efficacy of HL mixed to PRP. PRP is defined as autologous blood with platelet concentrations above the physiological baseline. The rationale of injection therapy of PRP is to improve the reparability of endogenous cells and to accelerate the repair process by direct and indirect mechanism (13).

The efficacy of combined used of PRP and HA, was demonstrated through *in vitro* and *in vivo* studies. Anitua et al. (14) evaluated the potential effect of pure PRP to induce tendon cells and synovial fibroblasts migration and examined whether the combination of PRP with HA improves their motility *in vitro*. Moreover, they proved that PRP improves the biological properties of HA *in vitro* (15). Chen et al. demonstrated that HA and PRP could rescue pro-inflammatory cytokines-induced degeneration through chondrogenic signaling recovery. Moreover, they showed that intra-articular injection of HA+PRP can attenuate cartilage degeneration in an animal model.

Therefore, this study provides evidences that HA+PRP combination could be recognized as an intra-articularly injectable, regenerative and anti-inflammatory treatment for OA. Dallari et al. (16) compared the efficacy of autologous PRP, HA and a combination for Hip OA and demonstrated a significant clinical improvement in patients treated by PRP and no significant improvement in pain in the group treated by PRP+HA. Yu et al. (17) suggested that pharmacokinetic interaction of PRP and HA can have beneficial effects on body pain, and alleviate arthralgia, cartilage destruction and bone damage. The aim of our study is to evaluate the effect of combined autologous PRP and HHA viscosupplementation on clinical outcomes of patients with knee OA, by assessing the subjects before and after injective treatment. Comparing one group treated with HHA alone and another treated with a combination of both PRP and HHA, our null hypothesis is that both groups can achieve similar results, independently form the adjuvant effect of PRP.

MATERIALS AND METHODS

Patient population

This study was performed at the Department of Orthopedic and Trauma Surgery and the Immunohematology Transfusion Medicine Unit of Campus Bio-Medico University Hospital of Rome, Italy. The Local Ethics Committee approved the study and all participants provided written informed consent prior to enrollment.

The study was conducted on patients with an age between 40 and 70 years old affected by symptomatic knee osteoarthritis (stage II and III according to Kellgren-Lawrence scale) nonresponsive to pharmacologic treatment, rehabilitation or physical therapy. No previous injective treatment was administered to the patients to be included in the investigation. Inclusion and exclusion criteria are summarized in Tables I and II.

Study design

Since September 2015, patients were randomly assigned by a computer derived random charts into 2 groups: group A received 3 injections of HHA and group B received 3 injection of HHA combined to PRP at interval of 1 week for 3 consecutive weeks. Randomization ensured that the baseline characteristics of the 3 groups were comparable with respect to age, sex, weight, height, body mass index (BMI), and pre-injection KOOS. 30 participants in group A were given 3 injections of HHA at an interval of 1 week for 3 consecutive weeks, 30 participants in group B received 3 injections of PRP+HHA at an interval of 1 week for 3 consecutive weeks.

Type of treatment

In our study, two type of injective treatment were

Table I. *Inclusion criteria.*

INCLUSION CRITERIA	
Symptoms duration of more than 3 months	
Radiographic signs of knee degeneration evaluated by Radiographs (RX) of the lower limbs under loading of the affected knee in the Rosenberg X-ray projection (a posteroanterior weight-bearing in 45° of flex- ion projection) and a lateral (full-extension) projection (Kellgren-Lawrence scale II and III).	
KELLGREN-LAWRENCE SCALE[28]	
GRADE	**DESCRIPTION**
0: Normal	
1: Questionable	Doubtful narrowing of joint space and possible osteophytic lipping
2: Mild	Definite osteophytes and possible narrowing of joint space
3: Moderate	Moderate multiple osteophytes, definite narrowing of joint space, some sclerosis, and possible deformity of bone ends
4: Severe	Large osteophytes, marked narrowing of joint space, severe sclerosis, and definite deformity of bone ends

Table II. *Exclusion criteria.*

EXCLUSION CRITERIA
Age< 45 years old or >70
Kellgren-Lawrance score >3
Other pathologies such as : diabetes mellitus type II, rheumatoid arthritis, cardiovascular disease, coagulopathies, immunodepression
Varus morphotype > 20° or valgus >20°
Patients in therapy by anticoagulants or antiaggregant drugs 10 days before injection
FANS or steroid drugs used during the 5 days before the sample and the infiltration
Patients with Hemoglobin (Hb) value < 12g/dl and/or platelets <150.000/mmc
Patients infected
Neurologic o psychiatric diseases

evaluated. The first one consisted of HHA (Sinovial High-Low, Sinovial HL, 3.2%, 64mg/2ml, IBSA), composed of 32 mg of high-molecular weight (1100-1400 kDa) hyaluronan and 32 mg of low-molecular weight (80-100 kDa) hyaluronan. It consists of a saline tamponed by hyaluronic acid sodium salt with viscoelastic proprieties. Other components of the product are: sodium chloride, sodium phosphate and water. The second treatment involved a double injection of HHA and autologous PRP, subsequently injected into the knee. For the preparation of autologous PRP, we used a standardized technique, previously described (18). All co-interventions during the follow-up period were discouraged, but the prescription of pain medication if necessary, was allowed.

Injection technique

The injection technique used for both groups was the superolateral approach, ensuring intra-articular penetration of the drug. After the injection, the patients were monitored for 10 min to ensure there were no adverse reactions.

Outcome measures

The patients were evaluated with the Knee Injury and Osteroartrhitis Outcome Score (KOOS) and Visual Analog Scale (VAS) (19). VAS is a measurement instrument for pain, considering a visual line of 10cm, where the patients must indicate the level of pain. When responding to a VAS item, respondents specify their level of agreement to a statement by indicating a position along a continuous line between two end-points. The primary efficacy criterion was change from baseline in joint pain, measured using KOOS. The KOOS parameters and VAS scale were measured before the first injection and at 3, 6 and 12 months after the completion of the treatment.

Statistical analysis

Numerical variables (KOOS and VAS scores) were reported as mean and standard deviation. The comparison at each point of follow-up between groups was carried out through an unpaired Student's *t*-Test. A post-hoc power analysis was carried out, basing on the KOOS value at last follow-up. The results of the power analysis showed that our cohort was enough to grant a beta power of 0.80 with an alpha value of 0.05.

RESULTS

Sixty-five patients out of all patients treated at our institution for grade II-III OA met inclusion criteria for the present investigation. Of these, 62 signed informed consent and were included in the study; however, two of them were lost to follow-up and were

Table III. *Results (Group A: HHA; Group B: HHA+PRP).*

Group (follow-up)	VAS	P value VAS	KOOS	P value KOOS
A (baseline)	6.2 ± 1.3	0.134	44.4 ± 4.1	0.071
B (baseline)	6.8 ± 1.7		42.7 ± 2.5	
A (3m)	1.5 ± 0.9	0.002	66.4 ± 6.8	0.0019
B (3m)	0.6 ± 0.99		70.9 ± 4.2	
A (6m)	1.4 ± 1	0.062	72.3 ± 4.9	0.0093
B (6m)	0.9 ± 1.2		75.5 ± 4.9	
A (12m)	1.8 ± 1	<0.0001	68.7 ± 9.7	0.1003
B (12m)	0.6 ± 1		71.8 ± 2.3	

then excluded from the study. Therefore, sixty patients were included and randomized into two groups of 30 patients each.

The patients presented left knee OA in 32 cases and right knee OA in 45 cases (17 patients had bilateral OA). At baseline KOOS and VAS of the involved knee averaged respectively 42±2.6 and 6.8±1.7 in group B (combined treatment), and 48.5±1.3 and 6.2±1.3 in group A (HHA alone). Considering the baseline values, the groups were considered comparable, as the p value for KOOS comparison at baseline was 0.071, while for VAS was 0.13. At the follow-up steps, the KOOS and VAS value increased form baseline in both groups. However, statistical comparison between groups showed a significantly better result for the group B in KOOS value, at 3 months ($p=0.0019$) and at 6 months ($p=0.009$). This difference, although clinically relevant, lost the statistical significance at 12 months ($p=0.1$). The VAS trend was different, showing a significant difference at 3 and 12 months (respectively $p=0.002$ and $p<0.001$), while at 6 months the superiority of group B did not achieve statistical significance ($p=0.062$). In Table III, the results are shown in full with numerical data.

DISCUSSION

A wide spectrum of non-conservative and conservative treatments (pharmacological and non-pharmacological) for knee OA is available. Non-pharmacological modalities including dietary supplements and physical exercises.

From a pharmacological point of view, many drugs are used in knee OA such as paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), or opioid analgesic. Also, slow-acting supplements, including glucosamine, chondroitin sulfate, and diacerein can be used. Otherwise, the most common pharmacological treatment used in knee OA is the injective therapy. Corticosteroids, viscosupplementation with HA, blood derivates (PRP), a combination of PRP and HA are commonly advocated.

Hyaluronic acid is, as an integral component of synovial fluid, often used in clinical practice for treating knee OA. Numerous studies demonstrated the efficacy of HA injection therapy in knee OA. A meta-analysis by Dan Xing et al. (20) showed that HA is an effective intervention in treating knee OA without increased risk of adverse events. Clinical improvement after HA intraarticular injection was demonstrated also by Bhandari et al. (8) that shown a consistent and statistically significant improvement in pain, function and stiffness up to 26 weeks in patients treated by HA compared with groups treated by placebo or controls. Therefore, although a general consensus on the efficacy of HA does not exist, several evidence support the use of this treatment in knee OA (21). PRP is obtained by a centrifugation process which separates solid and liquid components of blood. The rationale of injection therapy of PRP is to improve the reparability of endogenous cells and accelerate the repair process by direct and indirect mechanism (13), because PRP contains a large pool of growth factors implicated in the regulation of articular cartilage, replacing and repairing the damaged tissues.

Campbell et al. (22) reported in a meta-analysis that PRP is a possible solution to lead a symptomatic relief if compared to placebo and HA treatment. The use of PRP indeed, led to significant improvements in patient outcomes at 6 months after injection, and these improvements were seen starting at 2 months and were maintained for up to 12 months. It has been demonstrated by many studies that PRP therapy has more advantages compared to HA injection therapy. Riboh et al (23) demonstrated that PRP preparations improved functional outcome scores compared to hyaluronic acid and placebo in patients affected by knee OA. Moreover, some studies (24), demonstrate that PRP injection might promote not only the replacing of cartilage with an increase rate of chondrocyte proliferation, but also the restore of synovial and meniscal tissue.

Additionally, other bioactive molecules released by platelets, such as fibrin, act as a scaffold and chemo-attractant for further migration of stem and other cells to the damaged tissue that trigger a healing response (25). We investigated the combined approach with HHA and PRP for the treatment of knee OA. We have previously demonstrated the *in vitro* superiority of PRP+HA compared to PRP alone proving the synergistic proprieties of PRP and HA when combined. Indeed, Russo et al. (12) showed that chondrocyte

cell viability and proliferation rate increased in cultures treated with a combination of PRP and HA (with a concentration higher than 1%). Moreover, the anabolic properties of OA chondrocytes, measured as GAG synthesis, were significantly increased when HA was used in combination with PRP.

This stimulation effect was attributed to the presence of the low molecular weight fraction. These factors are able to stimulate cartilage matrix synthesis and to reduce the effects of catabolic cytokines such as tumor necrosis factor alpha (TNF-a) and interleukin-1 (IL-1β) (25) HA has molecular characteristic that promotes the combination with PRP and the slow and gradually activation of the platelets in the articulation. Moreover, the viscoelastic proprieties of the HA, allow the lubrification of the joint and work with "cellular carrier" for the platelets.

It has been demonstrated that HA displays systematically higher viscosity after mixing with PRP (12); increase the proliferation of chondrocytes, has an anti-inflammatory effect, decreasing biomarkers of inflammation, reduces the cartilage degeneration, reducing the COMP-2 levels (26). In our study we demonstrated that HHA+PRP for the treatment of knee OA may be a valid alternative treatment in patients affected by knee OA. Indeed, even though the KOOS and VAS values were increased from baseline in both groups, the PRP+HHA group showed significantly better KOOS values at 3 and 6 months and VAS values at 3 and 12 months. Few studies were published about the combination of PRP and HA for the treatment of OA. Dallari et al. (16) studied this association for the treatment of Hip Osteoarthritis. A total of 111 patients were divided in 3 groups and received 3 weekly injections of either PRP, PRP+HA or HA. They concluded that intra-articular PRP injections gives a significant clinical improvement in patients with hip OA without relevant side effects for up to 12 months as compared with the other treatments. While the group treated with PRP+HA did not have a significant improvement in pain symptoms. On the other hand, Yu et al. (17) showed that PRP+HA treatment significantly improved arthralgia, reduced humoral and cellular immune responses compared with PRP or HA treatment alone. These results are obtained studying a total of 360 patients with knee OA divided into four different treatment groups: double-blind treatment with PRP, double-blind treatment with HA, combined therapy of PRP and HA and placebo group.

Another study by Lana et al. (27) conducted on 105 patients with mild to moderate knee OA, divided into 3 group (PRP, HA and PRP+HA) reported that the combination of HA and PRP lead to better outcomes than HA alone up to 1 year and PRP alone up to 3 months. They demonstrated a significant decrease in pain and functional limitation when compared to the group treated by HA alone at 1-year post treatment; and significantly increased physical function at 1 and 3 months when compared to PRP alone. Therefore, the results presented in this investigation are in accordance with those already presented in the literature. Limitations of present study are represented by unblinded study protocol and of absence of placebo group. Furthermore, considering the inclusion and exclusion criteria, the patient population was extremely selected, and this may affect the results.

Based on our results we can conclude that the combined PRP and HHA treatment is not only a safe and efficacious procedure which can provide functional benefit but is also significantly better than HHA injective therapy alone, as demonstrated by the comparison within our cohort. However, further evaluations of clinical outcomes in randomized controlled trials including placebo group are still necessary.

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SPORT ACTIVITY AS RISK FACTOR FOR EARLY KNEE OSTEOARTHRITIS

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There is wide discussion about the association between sport activity and musculoskeletal disorders, as sports-related joint loading increases the risk of osteoarthritis (OA). The present article reviews the current available literature on the connections between participation in several sports and athletic activities and prevalence of knee OA, especially focusing on early knee OA. The study was based on an electronic search through web databases including Medline, Cochrane and Google Scholar. Articles were retrieved and evaluated, and case series, retrospective studies, case-control studies, prospective cohort studies and randomized controlled trials were considered for inclusion. The main data were extracted and summarized in tables and text. Athletic individuals do show an increased prevalence of knee OA, especially for professional athletes when compared to general population or non-professional athletes. Furthermore, several features related to sport activity were associated to increased risk of early knee OA, such as knee ligamentous injury, concussion, high-impact sports and different team roles. Methodology and results of the included studies are barely comparable, thus preventing the authors to carry out an accurate and systematic comparison of the results of the included studies. Only low level evidence studies are available, and better designed studies, with radiological and functional evaluation of the knee based on internationally validated measures, should be planned. Also, follow-up of patients during and after their life-period of sport involvement should be considered.

The practice of sport offers numerous health benefits: fit people live longer, as engaging in regular physical activity can help prevent health issues (1-5). Regular exercise markedly reduces the risk of obesity and cardiovascular disease, stimulates endorphin production and generally boosts our immune system, improving our mental health and wellbeing, leading also to lower level of stress and overall a better quality of life (1-5).

There is wide discussion about the association between sports injuries and musculoskeletal disorders, as sports-related joint loading increases the risk of osteoarthritis (OA) (6), the most common form of degenerative arthritis (7). Despite the recent advances in research and development of new promising therapies, no treatment can efficiently and safely cure OA, and we can only try and plan interventions to prevent its development (8). Maintenance of the normal structure of the cartilage and its characteristics largely depend on its mechanical loading (9), which could explain why the best preserved cartilage is found in areas of high load bearing and contact (9).

Not all cartilage stresses positively affect the development or preservation processes though: the implication of high-intensity exercise or increasing

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physical activity levels especially in older age groups, has been acknowledged and associated with the initiation of catabolic changes in cartilage which eventually lead to OA (10, 11). Actually, even before the presentation of the structural changes of the cartilage that define – by clinical, radiographic or arthroscopic evidence – early osteoarthritis, it could be highlighted a state of pre-OA, in which biological degenerative processes, triggered by the above mentioned risky behaviors, begin to impair the cartilage in a non-clinically relevant fashion (12). From this perspective, some kind of sport activity may induce a premature transition from pre-OA to full-blown OA.

As a result, mechanical demands exceeding articular cartilage tolerance play a massive role in joint degeneration. In fact, the occurrence of early OA following an intense period of physical activity has been frequently observed; in particular, athletes who practice sports which include rapid acceleration with instant deceleration or continuous training with high impact on joints, or who compete at elite level for long periods of time, show higher likelihood of developing OA. On the other hand, a sedentary lifestyle has been equally linked with increased levels of catabolic events that contribute to cartilage weakening, favoring the onset of OA.

There seems to be an undeniable association between some sports and an increased risk of OA: sports with major risk are those involving repetitive, high intensity impact forces through the affected joints. In particular, two different mechanisms seem to be involved in the development of OA in sport: the first one is the repetitive joint overload; in relation to this, various factors – among which sport practice equipment, body weight, limb alignment, muscle imbalances, quality of the technical gesture – can shorten the progression to OA or, instead, be modified to save the joint (13). The second one is the frequent occurrence of trauma to the joint (13); sport-related knee injuries involving ligaments, menisci and cartilage are associated with an accelerated progression of knee OA which may lead to rapid joint failure (14). Therefore, there is a recognized need to restore the articular structures to protect the knee (13).

Early knee OA can be defined as mild to moderate knee pain during walking and activities and radiographic evidence of Kellgren-Lawrence grade I or II OA.

The present article reviews the current available literature in order to understand: 1): whether a correlation exists between sport participation and the development of early knee osteoarthritis; 2): the clinical and radiological features by which early knee OA is defined in the literature; 3): the influence of the different sport activities and level of activity (leisure, semi-professional and professional) on the development of early knee OA.

MATERIALS AND METHODS

Eligibility criteria

Peer-reviewed articles in English, French, Italian, and Spanish were eligible for inclusion. All the studies included regarded the relationship between osteoarthritis of the knee and sport participation. The studies had to report knee OA prevalence (with detailed description of radiographic and clinical criteria to define OA) in a population of adult athletes or retired athletes. Furthermore, the studies included had to stratify the cohort for type of activity. The types of studies included were randomized clinical trials (RCT), case series (CS), prospective cohort studies (PCS), while case reports, reviews of the literature and meta-analyses were excluded. Studies on animals, *in vitro* or biomechanical studies and cadaver experimentations were also excluded.

Information sources and search

An electronic search of online databases including Pubmed - Medline and the Cochrane Central Registry of Controlled Trials was performed. The search was carried out by 2 authors. The period during which the search was carried out went from March to August 2018, but no interval of study publication period was set to consider them eligible. The search strings used were: ("sports"(MeSH Terms) OR "sports"(All Fields) OR "sport"(All Fields)) AND ("osteoarthritis, knee"(MeSH Terms) OR ("osteoarthritis"(All Fields) AND "knee"(All Fields)) OR "knee osteoarthritis"(All Fields) OR ("knee"(All Fields) AND "osteoarthritis"(All Fields))); ("sports"(MeSH Terms) OR "sports"(All Fields) OR "sport"(All Fields)) AND ("osteoarthritis"(MeSH Terms) OR "osteoarthritis"(All Fields)).

Study selection

The studies eligible for inclusion were retrieved in full-text. After removal of non-relevant studies, a manual search was also performed through the bibliography of each included article, to identify potentially missed eligible publications. Duplicates were removed. Clinical studies eligible for inclusion were categorized by study type, in accordance with the Oxford Centre for Evidence-Based Medicine.

Data collection process

All the studies included were analysed by two reviewers, and the following data were extracted and summarized in tables: study type and level of evidence, type of sport involved, prevalence and grade of knee OA. Furthermore, the main aim and main results of the studies included were reported into tables.

RESULTS

Included studies

From the search performed, 18 studies met the inclusion criteria and were included in the review process. All of these studies were observational, of these, 9 were Case-Control Studies (CCS), and 2 were retrospective cohort studies (RS). The main level of evidence was III, according to the Oxford classification. Details of included studies are summarized in Table I.

Observational strategies

To assess the prevalence and grade of knee OA, magnetic resonance imaging (MRI) was used in one study (15), and radiography (Rx) and MRI in another one (16). Radiographic and clinical evaluation were used in combination in the majority of the studies (17-25), and functional evaluation associated to Rx in two articles (26, 27). Only 3 studies evaluated knee OA grade throughout the Kellgren-Lawrence classification (15, 16, 27). Concerning the groups for comparison of prevalence, in one study professional athletes were compared to non-professional (16) and in 2 other studies with general population (18, 28). Furthermore, to evaluate the association between knee OA and previous injury, a comparison of OA development in injured and non-injured athletes was carried out in three studies (29-31). Five studies reported exclusively about knee OA (16, 19, 30, 24, 27), while the others reported outcomes of OA of the knee and other joints.

Type of sports evaluated

Football was the most commonly evaluated sport (25, 26, 29, 30), with 3 studies evaluating former players and 1 evaluating active athletes. Secondly, active runners were evaluated in 4 studies (20-22, 24) and former runners in another one (19). Moreover, former soccer players were evaluated in three investigations (16,18, 28). Athletes participating in other sports were active or retired in: ballet, volleyball, martial arts, track and field, basketball, ski, table tennis, handball, ice hockey, canoeing, bicycle racing, and swimming. A total of 7.783 athletes were included in the studies evaluated.

Main outcomes and OA prevalence

The knee is the commonest site for development of OA in former athletes (17, 32). MRI studies assessed the presence of knee articular cartilage thinning and irregularity, especially over the medial femoral condyle (MFC), and subchondral marrow changes in the lateral femoral condyle (LFC). OA was present in 50% of the cohort of professional ballet dancers, with 5 patients showing grade I and 2 patients showing grade II (15). Arliani et al. showed that functional scores impairment was associated to the degree of MRI degeneration.

Comparing a group of former professional athletes with non-professional athletic controls, the SF-36 activity subscale was significantly lower in the former, as were VAS for pain and KOOS subscales for symptoms and quality of life related to the knee. Furthermore, the prevalence of OA was higher for professional athletes both in the dominant (66.6% *vs* 46.7%) and non-dominant (66.6% *vs* 43.3%) knee (16).

Functional evaluation (27), showed impaired Western Ontario and McMaster Osteoarthritis Index (WOMAC) in athletes, with higher prevalence of knee symptoms than in controls (68.2% *vs* 27.3%). A similar comparison (29) showed that former football players had increased prevalence, compared to the general population (43.4% *vs* 19.5%) at a mean

Table I. *Details of included studies.*

Study and year	Type of study (LOE)	Joints evaluated	N.er of patients	Sport	Main aim	Main results	Knee OA prevalence assessment	Knee OA grade
Angioi et al. 2014	-	Hip, knee, spine, ankle, foot	15	Ballet	To evaluate the prevalence of OA, through MRI evaluation	In the knee: thinning and irregularity of articular cartilage over MFC, bone marrow changes in LFC.	50%	I (5 patients) II (2 patients)
Arliani et al. 2014	CCS (III)	Knee	27 (30 control group)	Former professional soccer players	Compare the prevalence of OA in former professional athletes and non-professional-athletes. Evaluation through Rx and MRI	SF-36 was lower in the group of players, than in control group, furthermore, KOOS and VAS evaluation showed significant differences in pain, symptoms and quality of life	66.6%	Kellgren Lawrence classification OA in dominant limb : 0 (3 patients) I (6 patients) II (7 patients) III (8 patients) IV (3 patients)
Golightly et al. 2009	-	Knee, Arm, Ankle	2538	Retired National Football League Players	To describe the prevalence and determinants of arthritis and osteoarthritis in retired professional football players	In the knee: increased prevalence of knee OA in players who had sustained a knee injury	43.4%	
Iosifidis et al. 2014	CCS (III)	Hip, Knee, Ankle	218 (181 group control)	Former elite male athletes (soccer, volleyball, martial arts, track and field and basketball players, and skiers)	To investigate the prevalence of clinical and radiographic OA of lower limb joints, compared to general population	In the knee, radiographic changes were significantly more common in former athletes than controls	20.34% Radiographic OA 8.71% Clinical OA	
Lynall et al. 2017	CCS (III)	Knee	2696	Retired National Football League Players	To examine the association of concussion and lower limb injuries with OA prevalence	In the knee: concussion increases the risk of OA		
Morrey et al. 2012	CS (III)	Hip, Knee	709	Former Male Elite Athletes	To correlate intense exercise program with OA, need for arthroplasty, and knee injuries	In the knee: knee injury increases the risk of OA	19.4%	
Rajabi et al. 2012		Knee	22 (22 control group)	Ex-elite table tennis players	To compare radiographic OA and functional evaluation of athletes and controls	In the Knee: altered lower limb alignment	78.3% radiographic knee OA	Kellgren Lawrence classification 0 (5 patients) 1 (5 patients) 2 (6 patiets) 3 (5 patients) 4 (1 patients)
Tveit et al. 2012	CCS (III)	Hip, Knee	709	Former elite male athletes (soccer, handball, and ice hockey players and canoeists, runners, weight lifters, gymnasts, swimmers, biathletes, cyclists)	To determine whether OA and arthroplasty in the hip and knee are more common in former elite male athletes than in the general population.	In the Knee: impact sports increases the risk of OA	19.4%	
McDermott and Freyne 1983	-	Knee	20	Middle and long distance runners	Clinical and radiological study of the knee joints in middle and long distance runners	In the Knee: Degenerative changes were significantly associated with the presence of genu varum and history of severe injury	30%	
Moretz et al. 1984	CCS (III)		23	High school Football players	Clinical and radiological study of the knee in high school Football players		No statistically significant increase in OA	
Lane et al.	CCS (III)	Hands,	41 (41	Long-distance	Clinical and		No	

1986		lateral lumbar spine, knees	control group)	runners	radiological correlation of running with osteoarthritis and osteoporosis.		difference in the incidence of OA between runners and nonrunners	
Lane et al. 1993	CCS (III)	Knees, hands, lumbar spine	35 (38 control group)	Runners	Clinical and radiological of 5-year longitudinal effects of running and aging on the development of OA		No difference in the incidence of OA	
Lane et al 1998	CCS (III)	Knee, Hip	28 (27 group control)	Runners	Clinical and radiological study to correlate running with hip OA, progression of radiographic knee OA, and changes in BMD after 9 year of follow-up in runners		No difference in the incidence of OA	
Kujala et al. 1995	-	Knee	117	Former top-level male athletes (long-distance runners, soccer players, weight lifters, shooters	To determine the relationship between different physical loading conditions and findings of knee OA	OA risk is increased in subjects with previous knee injuries, high BMI at 20 years, previous participation in heavy work, and in subjects participating in soccer	3% shooters 29% soccer players 31% weight lifters 14% runners	
Deacon et al. 1997	RS (III)		50 (50 group control)	Retired elite footballers	To determine the functional and radiological status of knee joints compared with active population	In the Knee: history of intraarticular ligamentous and/or meniscal injury had a greater risk of functional osteoarthritis and radiological osteoarthritis than those with a history of collateral ligament injury or no injury	66% Total 34% Nil 30% Mild 11% Moderate 25% Severe	
Larsen et al.	RS (III)	Knee,	69	Former national players	Long-term outcome injuries in former national team elite football followed by clinical and stress radiographic examinations	In the Knee: lesions of the the knees increases the risk of OA	63%	
Turner et al. 2000	-	Lower Limb, Knee	284	Former professional players	To describe the long term impact of football on the health related quality of life (HRQL)	In the Knee: knee is the most common site of OA	28.8% Right Knee 21.8% Left Knee 50.6% Knee	
Drawer and Fuller 2001	-	Ankle, Knee, Hip	185	Former footballers players	To quantify the prevalence of osteoarthritis and the severity of pain in the lower limb joints of players retired from English professional soccer		Lower limb OA 32%; More respondents were diagnosed with knee OA than either ankle or hip OA	

***LOE**: Level Of Evidence **BMD**: Bone Mineral Density, **MRI**: Magnetic Resonance Imaging, **MFC**: Medial Femoral Condyle, **LFC**: Lateral Femoral Condyle.*

age of 55 years (in the knee, shoulder or ankle). Radiographic changes occurred more often in athletes than in controls in a radiographic evaluation (18) (20.3% *vs* 12.9%). The prevalence of OA also varied with type of sport involvement: Kujala et al. reported a 3% prevalence in shooters, 29% in soccer players, 31% in weight lifters and 14% in runners (19).

Factors associated to OA development

The role of play influenced also prevalence, which

was increased in linemen and lower for quarterbacks, wide receivers or others special roles in the team (29). Similarly, Iosifidis et al. (18), reported that sport activity significantly affects knee OA development, with increased risk for subjects involved in soccer and basketball (18, 19). In evaluation including several sports, it was reported that impact sports increased the risk of OA (28). Surprisingly, some studies of the 1990s showed that running did not increase the prevalence of OA, when a cohort of active runners was compared with non-runners, both in the short (20) and long term (21, 22). More recently, a meta-analysis evaluating data from 112.192 subjects investigated the association of recreational and competitive runners with hip and knee OA, evidencing a significantly higher prevalence of hip and knee OA (13.3% *vs* 3.5% *vs* 10.23%) in competitive runners, compared to recreational runners and controls (33). Recreational running is not associated with OA, but competitive runners show higher rates of joint degeneration (33).

A history of concussion during one's athletic career produced an increased risk of developing knee OA (30), as well as previous injuries of the knee (19, 24, 31). Deacon et al. (26) showed increased risk for those athletes who had sustained an injury to menisci or central pivot ligaments, compared to those with injury of collateral ligaments. Conversely, Larsen et al. reported that the injury of medial collateral ligament (MCL) was associated to increased OA rate (23). Biomechanical factors associated to developing OA included *genu varum (23,27)*, which was found in 73.3% of former elite table-tennis player, compared to 32% of non-athletic controls (27). Furthermore, incidence of cardiovascular disease, diabetes and obesity was increased in athletes reporting OA (29). Previous participation in heavy works requiring squatting and kneeling, is also likely to increase the risk of OA development (19).

DISCUSSION

The aim of the present systematic review of the literature was to understand and clarify the impact of sport activities on the development of knee osteoarthritis in active and retired athletes. Sport-involved individuals do show an increased prevalence of knee OA, especially for professional athletes when compared to general population or non-professional athletes. Furthermore, several factors related with sport were associated to increased risk, including knee ligamentous injury, concussion, and high-impact sports and team roles.

Participation in several sport activities has been associated with a higher incidence of OA affecting specific joints. For instance, knee or ankle injury/trauma as well as hallux rigidus condition have been identified as the most common risk factor in soccer players. Indeed, a recent review showed how, in former soccer players, the prevalence rates of hip and knee OA were significantly higher, compared to sex- and age- matched controls (34). Cyclists are more likely to experience knee related issues while fencing has been associated with a higher likelihood of osteoarthritis of the hip joint while riding has major incidence of gonarthrosis (35, 36).

The risk of developing OA is significantly reduced in some sports such as swimming and any other water activity, golf and non-agonistic cycling as well as yoga, Pilates, gentle exercise and short walking. Osteoarthritis is a multifactorial pathology, which involves all the joints of the human body, but is more likely to affect those joints that are subjected to increased loading. In fact, apart from genetic, epigenetic, immunologic and metabolic factors, mechanical stress of the cartilage is one of the major responsible for osteoarthritic degeneration. Thus, the joint of the lower limbs, which sustain one's body weight have an increased prevalence of OA, in the general population. In sport activities, a sum of loading forces must be added to body weight (37), especially in movements such as jumping (38), running, catching, and cutting. Therefore, these activities predispose to increased joint stress and development of OA (39).

In vitro studies on articular cartilage showed that mechanical stress on chondrocytes of the joint cartilage has different effects according to its frequency of application and magnitude. Highly repetitive stress on cartilage tissue increases glycosamminoglican production and chondrocytes proliferation (14). However, the magnitude of the joint loading forces is the main factor that influences cell viability and cartilage degeneration, since overcoming a

given threshold of magnitude conversely produces chondrocyte death (40). Therefore, in sports where repetitive microtrauma is imposed on the joint, no beneficial effect can be expected, since the magnitude of these high-frequency impacts is above the physiological threshold. In fact, walking, which loads the joint with minimal force in addition to weight, is beneficial for joint cartilage (41).

In a report of 2015, the prevalence of OA in general population was 14.2%, with a 10.5% of the sample reporting knee OA at an average age of 52.5 years (42). In all the studies included in the present review, the prevalence of knee OA in athletes was at least increased two-fold. The prevalence ranged between 19.4% and 78.3%, varying especially according to the activity practised. Comparison between athletes and the general population confirmed these data (29), and comparison between professional and non-professional athletes showed increased prevalence among professionals (16). Several intrinsic factors of sport activities are associated to the development of OA.

High-impact sports and activities of cutting, pivoting and changes of directions are associated to increased risk, especially in soccer and basketball (18,19). Conversely, in sports in which these actions are not required, such as running, the prevalence of OA was not different from that in general population, even in the very long term (22). Furthermore, experiencing a knee injury or a concussion during athletic career is also correlated to increased prevalence of OA after retirement (19, 30, 31). High-level sport participation, especially for those activities where the risk of trauma is high, is not advisable for people with other predisposition to developing OA (obesity, familiarity, rheumatic disease).

Conversely, activities where lower loading on the knee is provided, including walking and jogging, could be beneficial not only for the joint, but also for general health of the individual. Especially swimming, where gravity does not act on the joints, is advisable for those subjects who require intensive activity for metabolic problems and obesity risk. Regrettably, the level of evidence of the studies included in this review was low. The majority of the studies were observational studies in which self-reported questionnaires were collected from the cohort. However, a significant strength of the studies was the number of patients included, which, in some cases, overcame the threshold of two thousand. A few studies reported functional outcomes assessed though internationally validated scores (KOOS, WOMAC, SF-36).

There is an increased prevalence of knee OA in retired or active athletes. Factors influencing the increased risk of developing OA were the level of activity, the type of sport and the experience of knee trauma or concussion during sport activity. However, only low level of evidence studies are available, and better designed studies, with radiological and functional evaluation of the knee based on internationally validated measures, should be planned.

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VASCULAR ENDOTHELIAL GROWTH FACTOR EXPRESSION AS A BIOMARKER OF PROGNOSIS IN PATIENTS WITH CHONDROSARCOMA, EWING'S SARCOMA AND OSTEOSARCOMA. CURRENT CONCEPTS

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With the advent of the molecularly targeted therapies, identifying molecular therapeutic targets and molecolar marker is increasingly important, especially in neoplastic diseases. Several studies show VEGF is involved in neo-angiogenesis in many solid cancers, as breast, lung, renal, gastric carcinomas, through promoting endothelial cell growth and migration. Conversely the relationship between VEFG and tumours of the musculoskeletal system is yet unclear, in particular the role of VEGF has not yet been completely understood in these tumours. Chondrosarcoma, Ewing's Sarcoma and Osteosarcoma are the tumours of the musculoskeletal system in which the activity of VEGF has been closely studied. The present study aims to give an overview focused on the relationship between VEGF and these three cancers.

New insights into the pathogenetic and proliferative mechanisms of human cancers have led to the identification of several proteins acting as messenger molecules and modulators of tumour growth. Targeting these molecules has led to investigation of new pharmacologic agents that can be effectively used to control tumour growth (1). Examples of these proteins include vascular endothelial growth factor (VEGF).

There are many studies assessing the prognostic role of VEGF expression in several tumours. VEGF plays an important role in the tumour angiogenesis. It is a dimeric glycoprotein, composed of a family of proteins that includes VEGF-A, VEGF-B, VEGF-C, and VEGF-D. In vitro VEGF induces vascular endothelial cells proliferation, as well as migration and prevents apoptosis of these cells in vivo; VEGF expression by tumour cells is stimulated by hypoxia, paracrine cytokines and activated oncogenes and it provides a wide surface of permeable CD31-positive micro-vessels from which tumour cells can be sustained and enter the circulation (2, 3). VEGF expression in primary tumours and metastases shows a statistically significant correlation with poor prognosis in several pathologies such as breast, lung, renal, gastric, colon-rectal and oesophageal carcinomas (4, 5).

The present paper explores the role of VEGF as a prognostic marker in the tumours of the musculoskeletal system and to underline its importance as a target of the newest therapeutic strategies for the treatment of these pathologies.

Chondrosarcoma

Chondrosarcoma, Ewing's Sarcoma and Osteosarcoma are the only tumours of the musculoskeletal system in which the role of VEGF as prognostic marker is described; the major part of papers concerning this issue is about Chondrosarcoma (CH). It represents the second most common primary malignant bone tumour in adults. Chondrosarcoma is

Key words:osteosarcoma, chondrosarcoma, Ewing's sarcoma, vascular endothelial growth factor, prognosis, biomarker, narrative review

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a cartilaginous tumour characterized by the synthesis of pure hyaline cartilage and usually appears on scapula, ribs, sternum or pelvis.

Conventional CHS subgroup represents 80% of total cases and can be histologically subdivided in low-grade, intermediate- grade or high grade (6-7). Radiation and chemotherapy are not effective on CHS, complete surgical resection with wide margins remains the only available treatment (8). In this regard, a better understanding of molecular survival pathways involved in CH and its chemo- and radio-resistance mechanisms is necessary to develop efficient therapeutic strategies.

VEGF and Chondrosarcoma

Normal cartilaginous tissue is avascular, formed on chondrocytes and extracellular matrix, but in adults, the presence of vessels in this contest is usually associated with pathologic status, such as tumours. Vessel formation in cartilaginous tumours is induced by hypoxia, IL-1b and more importantly by vascular endothelial growth factor (VEGF) pathways: this step is fundamental for both neoplastic growth and migration. The prognostic evaluation and the efficacy of treatment modality largely depend on the acknowledgement of the biological asset in cartilaginous bone tumours. Kalinski and Roessner (9) have identified three vascular patterns in cartilaginous tumours according to the micro-vessel density within the tumour lobes and VEGF immunostaining. In their case series Cintra et al. (10) show a strong association between the vascular pattern, evaluated by CD34 staining and overexpression of CD34, and patient's prognosis, in particular poor prognosis and high vascular counts, even if enchondroma and conventional low-grade chondrosarcoma display a similar vascular pattern to normal cartilage. According to this, Shima et al. (11) show in their paper a strong VEGF immunoreactivity in grade III chondrosarcomas, but weak or absent expression in grade I tumors or benign enchondromas. Given the crucial role of VEGF as promoter of growth and migration of cartilaginous bone tumor and as prognostic marker, the challenge now is to identify, envelop and spread treatment strategies headed to the inhibition of VEGF pathway and the improvement of patient's prognosis and survival. CHS shows vascularization that grows with increasing histological grade.

Novel targeted therapy which represents a new relevant therapeutic approach will open new treatment options by targeting several pathways responsible for processes of proliferation and invasion. Survival pathways such as vascular endothelial growth factor (VEGF) have been shown to be involved in proliferation of chondrosarcoma cells and antiapoptotic proteins may play a relevant role. In contrast with chondrosarcoma, which occurs in the axial skeleton, chondroma has a specific predisposition to the appendicular skeleton and it is the most common benign tumour of the hand. This lesion has a limited potential for malignant transformation and there is still a real difficulty in differentiating chondromas from low-grade chondrosarcomas (12).

Using a xenograft CH model, Morioka et al. (13) showed that chemotherapy combined with antiangiogenic therapy allowed to induce tumor necrosis via the annihilation of tumor-associated microvasculature. Thus, as tumours depend on angiogenesis for survival and further growth, inhibiting this pathway may be a promising strategy for inducing growth arrest, in terms of therapeutic potential. Concerning VEGF, its expression is dependent on HIF-1α (hypoxia inducible factor-1α) that induces the transcription of several proangiogenic factors and the most important of which is the VEFG (14). Thus, there are several potential pharmacological inhibitors of HIF-1α that could be applied to CH management, as it contributes to chemoresistance and radio-resistance; for instance, sunitinib and pazopanib, a tyrosine kinase inhibitors, were reported to achieve relief and durable response in a patient with metastatic CH undergoing this multitargeted therapy (15).

Ricciardella et al. (12) investigated the expression of VEGF together with other growth factors and proliferation markers in 8 cases of hand chondroma and on the basis of their histologic results, a specific model of tumour progression based on the indicators of angiogenesis could be related to hand tumours, in which VEGF expression should be the first stadium of the tumour aggressiveness.

Ewing sarcoma

Ewing sarcoma family tumour (ESFT) is a common malignant tumour of children and adolescents. It frequently occurs in bone as well as soft tissue and is regarded as the second most common bone cancer in the paediatric population after osteosarcoma. It

is an aggressive tumour with metastases present at diagnosis in 20% to 25% of cases. Although modern treatment regimens including surgery, chemotherapy and radiotherapy have increased the survival rate to more than 50% in patients with localized disease; patients with metastatic disease still have poor survival (16).

VEGF and Ewing's sarcoma

The angiogenic growth factor VEGF has been identified in ESFT cell lines where it was shown to contribute to tumor vasculogenesis (17), and inhibition or blockade of VEGF resulted in suppression of Ewing sarcoma tumor growth (18).

These findings have led some investigators to advocate for the use of the anti-VEGF inhibitor bevacizumab in treating ESFT (19). Atif A. et al. (20) showed differential expression of VEGF in 57% of ESFT cases. Tumor cells with a VEGF staining score of 0 to less than 100 (negative to weak expression) were found to be associated with a good prognosis. Although these results were statistically significant, only for staining scores less than 100, there appears to be a trend association of VEGF expression with poor prognosis. This is not surprising, as VEGF expression has generally been associated with poor prognosis in other soft tissue sarcomas (21). Two previous studies have reported on the immunohistochemical expression of VEGF in ESFT with apparently contradictory results. Fuchs et al (22) in which they identified VEGF expression in 55% of tumor cases in association with worse prognosis. However, in another study, expression of VEGF-A, one of the main VEGF family members, was associated with better survival (23). These inconsistent results point toward the need for further studies involving larger series of patients. As these are uncommon tumors, collaborative studies that pool patients may be necessary to more fully understand the roles of these proteins in tumor behavior.

Osteosarcoma

Osteosarcoma is a malignant tumour of mesenchymal origin and primarily occurs in children, adolescents, and young adults. This pleiomorphic tumour of the bone depends on new blood vessel development, also known as angiogenesis, for tumour growth and metastasis.

Although modern multimodality treatment has significantly improved tumour resectability and the long-term outcome of these patients, 25-35% of patients with initially non-metastatic disease subsequently develop metastasis and this remains the major cause of death. At the same time, axial skeletal osteosarcoma preliminarily responds poorly to chemotherapy and has been proven to have an even more dismal prognosis (24-25).

VEGF and Osteosarcoma

Recent studies have focused on the role of angiogenesis in osteosarcoma, albeit with controversial results (26, 27). Several groups have evaluated tumour micro-vessel density and outcome in osteosarcoma. Expression of VEGF has been suggested as a means of evaluating the prognostic importance of angiogenesis in osteosarcoma (28, 29). Angiogenesis is known to be a fundamental factor in the local growth of tumours and in progression with metastases and is most commonly assessed by measuring either the expression of vascular endothelial growth factor (VEGF) in cancer cells or tumour CD31- or CD34-positive micro-vessel density (MVD). Cancer cells respond to an early hypoxic stage by activating signalling pathways that induce cell proliferation, the production of angiogenic factors such as VEGF and new endothelial cell formation in order to provide a new vascular supply (30, 31).

VEGF expression in primary tumours and metastases shows a statistically significant correlation with poor prognosis in several pathologies such as breast, lung, renal, gastric, colon-rectal and oesophageal carcinomas. A correlation between the histological grade of malignancy and VEGF expression has recently been found also in chondrosarcoma (32, 33). Several studies have evaluated the potential role of angiogenesis and of VEGF in particular, also in osteosarcoma. However, the majority of these included heterogeneous series and produced conflicting results because VEGF expression in osteosarcoma was evaluated only before or only after neoadjuvant chemotherapy, in primary tumours and/or in metastases. Nevertheless, these studies demonstrated that VEGF has a predictive significance as a marker of poor prognosis and of the risk of metastasis and high VEGF expression is associated with poor overall survival (34, 35).

The osteosarcoma is a highly vascularized tumor and the angiogenesis is a very import process for its development and progression. The new vessels provide nourishment to the tumor tissues and promote the transport of tumor cells to the other body districts (metastasis). Therefore, as shown by Zhu XZ et al. (36) in their study, the inhibition of VEGF or its receptors could become the new target in the treatment of osteosarcoma in order to reduce its growth and development.

DISCUSSION

The findings from this review suggest that VEGF has a crucial role as biomarker predictive of prognosis in the tumours of the musculoskeletal system. Its overexpression strongly correlates to aggressiveness and malignity of these tumours, poor prognosis and poor survival of patients. Further studies should be performed to validate the biologic role of VEGF, understanding the biological asset of these tumours and the molecular mechanism involved in drug resistance phenomenon would help us in the elaboration of specific therapeutic strategies that could interfere with these specific refractory pathways such us VEGF.

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HIP MEGAPROSTHESIS IN ONCOLOGICAL SURGERY: OPEN QUESTIONS

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Prosthetic replacement with modular implants has become the most common reconstructive technique of bone loss of the lower limb after tumour resection. The use of the megaprosthesis in bone metastasis, silver-coated megaprosthesis and the use of Trevira tube are not uniform and represent an "open question" about the use of megaprosthesis. The following paper aims to review the current literature in this topic.

Prosthetic replacement with modular implants has become the most common reconstructive technique of bone loss of the lower limb after tumour resection (1-3).

In recent years, megaprosthesis has been used not only in the treatment of the primary bone tumours but also in patients with bone metastasis (4-6). Thanks to the progress of implant technology the number of complications is reduced, especially infections and dislocations. Nowadays, the antiseptic role of silver is well known (7), the addition of silver on prosthetic devices have demonstrated to reduces the post-operative infections. Fixation of the soft tissues in hip megaprosthesis in oncological surgery can be accomplished by suturing them onto the tumor prosthesis by means of attachment tubes, usually made from polyethylene terephthalate (PET), mostly known by its commercial name Trevira.

The use of the megaprosthesis in bone metastasis, silver-coated megaprosthesis and the use of Trevira tube are not uniform and represent an "open question" about the use of megaprosthesis.

The aim of the following review is to understand the current knowledge about this "open question" and its use routinely in the medical practice in hip megaprosthesis in oncological surgery.

Primary tumor vs metastasis

Traditional indications to prosthetic replacement are primary bone tumors, but this kind of surgery can be performed also in metastatic bone lesions, that can cause pathologic fractures (8) and intense pain in oncologic patients. Use of megaprosthesis implants in metastatic patients is not standardized but increasing evidence suggests that resection of a solitary metastasis is associated with a better prognosis in different tumors hystotypes (8, 9).

Potential advantages are: pain control, stable fixation and immediate weight-bearing (8). This affects positively quality of life of the patient and guarantees a local control of metastatic lesions (10, 11).

The surgeon's choice to use a megaproshtetic implant in patients with metastatic lesions must be guided by the patient performance status and general health conditions, that should be able to bear resection and prosthetic implant surgery. First implant itself is usually a complex procedure; prosthetic explant and re-implantation often represent a threat to patients'

Key words: megaprosthesis, hip, silver, metastasis, Trevira tube

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lives, with risk of other morbidity development and decline of patient's general health conditions (8).

Angelini et al. (8) identified several criteria for the implant of a hip megaprosthesis in metastatic patients:

1) patients' general condition;
2) extensive bone loss and bone destruction that precluded standard internal fixation or arthroplasty;
3) good prognosis regarding life expectancy. Additional indications included either:
4) painful lytic lesions unresponsive to radiation therapy;
5) avulsion of the lesser trochanter;
6) lytic lesions at least 2.5 cm in diameter causing pain with weight bearing;
7) lesions that have destroyed >50% the cortex. According to Kawaguchi, tumor resection must include tumour itself and a reactive zone of 2-3 centimetres are considered a safe margin (12).

In literature, several authors (4-6) compared the use of megaprosthesis in primary tumors and in secondary lesions. The authors showed that Musculoskeletal Tumor Society Scoring System (MTST) was higher in patients affected by primary tumors than in metastatic ones (80.2% vs 66.7%) (6). Yazawa et al (13) also compared MTST score between patients affected by primary tumour or metastatic lesions.

Usually hemiartrhoplasty is the most performed surgery in prosthetic replacement, rarely the surgeon recurs to total hip arthroplasty (THA), because the use of the endoprosthetis alone guarantees the joint stability, and the THA conversion is not necessary (14). Also, most patients with metastatic disease undergo postoperative radiotherapy to consolidate local therapy for pelvic disease control, which may further decrease the incidence of clinically relevant acetabular metastases (6).

Although megaprosthetic replacement is becoming a more frequently performed surgery, it often has complications. Several authors showed in their studies how prosthetic dislocation is the most frequent complication in the follow-up (1, 8, 11).

Dislocation rates ranged from 1.7% and 11.1% for hemiarthroplasty and 6.5% and 22% for THA (5, 6). Prosthesis dislocation can be reduced by using TREVIRA tube (2, 11, 15). Another complication observed is the periprosthetic fracture, the aseptic loosening of the implant (16) and wound dehiscence (8) that usually needs a re-intervention.

In literature, only one study compared directly the rate of complication between endoprosthetic implant in primary tumors versus metastasis. Sezgin et al (17) showed that complication rates in the primary bone tumor group were statistically and significantly higher than those of the metastatic tumor group. This result most likely depends on the longest follow-up in patients with primary bone tumors (17).

Trevira tube

The two most relevant points in obtaining an acceptable and functional reconstruction of resected segments are represented by the need to provide adequate mechanical resistance and stability to the skeletal "substitute" while providing anatomical and firm fixation of the marginal soft tissues (joint capsules, muscles, tendons, ligaments etc.) at the surgical site (15).

Published literature supports the clinical evidence that soft tissues suturing over a Trevira tube surrounding megaprosthesis represent a valid anchoring system of these structures after resection for bone malignant neoplasm and provide an acceptable functional outcome in most cases (15).

A recent study compared fibroblastic cell culture potential growth over circular disks simple titanium coated *vs* titanium surrounded by Trevira. The collected results showed how the simulated cell replication over Trevira is equivalent to pure titanium, and even if the difference was not statically significant, the absolute cell count in the first 48 h after their seeding was relatively higher for the Trevira experimental group if compared to controls. The morphological evaluation of cells over the Trevira tube confirmed a satisfactory intracellular appearance and a healthy metabolic state as proven by sign of swelling of the cytoskeleton, a sign of active cellular replication (15).

From a clinical point of view, the data presented could suggest that the use of a Trevira coated modular or custom-made megaprosthesis, could be indicated for early functional rehabilitation, given the relatively quicker and larger adhesion of soft tissues over the device which makes it particularly useful in young and active patients, willing to regain the best

musculoskeletal function as soon as possible, after such a devastating and invasive procedure (15).

Gosheger et al, in a population of 54 patients (33 proximal femur replacement, 5 total femur replacement and 16 proximal humerus replacement), used Trevira tube for reconstruction of the capsule and refixation of the muscles and to minimize the risk of dislocation (2). Dislocation was observed in only 2 patients who had proximal femur replacements. No dislocation was observed in patients with a total femur endoprosthesis or a proximal humerus endoprosthesis. There was no significant increase in the rate of infection. The histopathologic findings in 6 patients showed tissue ingrowth into the tube. In this kind of replacement, frequent complication (up to 37%) is postoperative dislocation of the hip (2). In this study instead using the Trevira tube for capsular reconstruction of the hip in proximal femur replacement, a dislocation occurred in 2 of 33 patients (6%) (2). In addition, the Trevira tube allows early mobilization of patients with a proximal or total femur replacement because of a good stability, in fact the Trevira tube allows reattachment of the abductor muscles.

Hardes et al used the Trevira tube in humerus and proximal femur replacement (18). Tendons and muscles were reattached with a non-resorbable wires (Ethibond). The macroscopic and microscopic study demonstrated that fibroblasts migrated into the tube mash. No cases of luxation have occurred when the tube was used in combination with a bipolar head.

In a study of Schmolders et al (19), 30 patients were treated by using a modular tumor endoprosthesis (MUTARS®) following intra-articular resection of the proximal humerus. Fifteen patients received treatment by using a Trevira tube. The study demonstrated that replacement of the proximal humerus by using a Trevira tube in combination with a modular tumor endoprosthesis is a safe and viable treatment option for both bone tumors and metastases. There was no statistically significant increased risk of infection by using Trevira tube even among immunosuppressed patients.

Silver-coated megaprostheses

The incidence of infection varies, depending on the location of the implant. Periprosthetic infections occur in up to 19% of cases in proximal femur replacements and up to 11% of cases in distal femur replacements (20).

Implants surface predispose to bacterial colonization, so systemic treatments have a significant role and many intra- and perioperative antibiotic prophylaxes have been proposed (21).

Biofilm formation protects the bacteria from the immune response of the host and antibiotics. One possible approach to minimize the risk of infection is to coat the surface of the prosthesis with an antimicrobial substance (22).

It has been shown that silver has a biocidal effect; therefore, it has been incorporated into the surfaces of numerous medical devices (7). Moreover, human toxicity is very low (20). Scoccianti et al. demonstrated that there was no clinical evidence of argyria, and no local or systemic side effects related to silver after implant of silver-coated megaprostheses after tumor, trauma or failed arthroplasty (23).

Silver-coated hip megaprostheses have been introduced in medical practice almost 25 years ago for the treatment of local periprosthetic infections and have been recently proposed as first implant in patients with an acceptable life expectancy.

The bactericidal mechanism of the released silver ions is the inactivation of bacterial enzymatic functions and the generation of intracellular reactive oxygen species (ROS). Because of 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. It remains unclear if silver coating could lead to other implant complications or to frequent soft tissue infections (21).

Donati et al. performed a retrospective study analyzing patients affected by primary or metastatic proximal femoral tumors, treated with wide margins resection and megaprostheses reconstruction with a minimum of 12-month follow-up (21). Thirty-eight patients were treated with silver-coated megaendoprostheses, whereas in 30 other cases uncoated titan modular tumor hip prostheses were implanted. The infection rate in silver-coated prosthesis was 7.9%. In the uncoated prosthesis

group, the infection rate was 16.7%. The difference between the two groups was not relevant for late (up to 6 months after surgery) infection rate. Similar rates of infections were found in subsequent studies, with no cases of silver toxicity (24).

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 (15). In a recent *in vitro* study, D'adamio et al demonstrated significantly higher antifungal effects of the silver-coated titanium group, against the different species and strains involved (25).

In the future, more studies will be necessary to analyze and compare the *in vivo* action of different silver-coating manufactures.

DISCUSSION

The use of megaprosthesis in patients with primary tumors and metastatic bone lesions is a viable and safe technique. Moreover, the use of Trevira Tube is a good option to achieve an early functional rehabilitation and a major prosthetic stability, both for primitive and metastatic diseases. There is no significant increased risk of infection correlated to the Trevira tube use. Silver-coated hip hemiarthroplasty is recommended as primary implants in all the primary or metastatic bone tumors involving the proximal femur in order to decrease the infection risk.

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POSTERIOR CRUCIATE LIGAMENT RECONSTRUCTION IN SKELETALLY IMMATURE ATHLETES

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Posterior cruciate ligament rupture is a rare knee ligamentous injury in skeletally immature patients with unfused growth plates. Despite being very uncommon, it still represents a significant challenge in terms of decision-making and treatment choice. The purpose of this case series was to report subject and objective outcomes (IKDC, TAS,LYSHOLM,KT2000) after PCL reconstruction in two teenage elite football players aged 15 and 16 respectively, who underwent surgical repair in July 2017 using for the femoral and tibial fixation of the PCL graft (hamstring tendons) respectively a curve cross-pin system and interferential screw. At fifteen months follow up, both athletes had returned to normal, pre-injury, competing levels with no leg discrepancy.

Lesions of the posterior cruciate ligament, especially in skeletally immature patients, are by far less common than anterior cruciate ligament equivalents (1-5). For this reason, and for the high risk of physical injury associated with surgical reconstruction, conservative treatments are used much more frequently than in ACL ruptures, leaving us with very poor literature, the majority of which being case reports. The best surgical treatment options are usually guided by the type of PCL lesion in each specific case, with avulsion injuries usually being managed with proximal or distal reattachment (6-14), and lesions with intra-substance tears or associated chronic instability treated with augmentation (15) and total PCL reconstruction (16-19).

Recently, there has been an increasing evidence that PCL deficiency is commonly associated with both meniscal and cartilage degeneration (20), making intervention in young patients even more crucial, thus rising a large interest in PCL reconstruction. The purpose of this study is to review our experience with two adolescent elite athletes who ruptured their PCL and were both treated operatively with success in 2017.

MATERIALS AND METHODS

Between April and July 2017, two patients with open physes were treated with PCL reconstruction. Both patients had an intra-substance tear of the PCL. None of them had cartilage or meniscus lesions. Follow-up was performed after 15 months for both patients. Patients were assessed pre- and post-operatively with the subjective and objective International Knee Documentation Commitee (IKDC) evalutation form, Tegner activity scale (TAS) and Lysholm score. Joint laxity was assessed with KT-2000 arthrometer.Panoramic AP standing radiographs of the lower limbs and lateral knee radiographs were also taken

Key words: posterior cruciate ligament, knee, athletes, reconstruction

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at follow-up to evaluate limb length discrepancies (LLD) and axial malalignment.

Surgical technique

Reconstruction was performed with the trans-tibial hamstring graft single tunnel PCL reconstruction technique. Physis-sparing drilling of the bone tunnel was performed only in the tibia using fluoroscopy. The tibial bone tunnel was drilled from the antero-medial part of the tibia to the posterior cortex ending distal to the physis, with a tunnel size of 8 mm. The femoral half tunnel was drilled inside out via the antero-lateral portal. The graft was then fixed on the femur with the pins and on the tibia with interferential screw. This is a modification of the technique described by Adriani (21) for PCL insufficiency in adult patients.

Postoperative care

The patients were placed in full extension with the use of a brace for 4 weeks. Recovery of the range of motion was started at the end of the 2nd post-operative week with active exercises, when the brace was unlocked to 0-90°. At the beginning of the second post-operative month, the brace was completely removed, and the patient started a progressive programme of muscular strengthening and recovery of the rom. Return to sports activity was allowed starting from the fifth post-operative month.

RESULTS

The mean age of the patient at the time of the surgery was 15.5 years (Table I). Pre-operative scores following the PCL injury were recorded in our physio-research clinic. Tegner activity scale (TAS) was 6 and Lysholm was 53+/-1, IKDC subjective score was 62+/-2, IKDC objective score was C. After 15 months, Tegner activity scale (TAS) was 8 and and Lysholm was 90+/-1. IKDC subjective score was 93+/-1, IKDC objective score was A (Table II). The side to side difference in manual maximum displacement test performed with KT2000 arthrometer showed a significant difference between the pre operative and the latest control (7.4+/-0.2 vs 2.1+/-0.3).All patients had a fully recovered ROM and none of them experienced complications or re-rupture (Table II). At the latest follow up both patients had returned to their sport activity with no leg discrepancy.

DISCUSSION

PCL injuries in skeletally immature patients are rare (6, 10, 22-25) and represent a significant surgical management issue. Ideally, ligament reconstruction results in a stable knee and therefore prevents future damage to the menisci and cartilages and further degeneration of the knee (20). On the other hand, conservative treatment prevents damage to the physes and subsequent growth disturbance (26). There are a few publications about the management of these injuries, mostly case reports, with controversial results. (15, 17, 18).

The best surgical treatment options are usually guided by the type of PCL lesion. Partial PCL lesion are treated conservatively with good outcome (26, 27). The majority of pediatric PCL injuries described were avulsion fractures involving an osteochondral fragment from either the distal femur (7, 9-11, 13), or proximal tibia (8, 14, 16) attached to an intact ligament, are usually managed with proximal or distal reattachment Lesions with intra-substance tears or associated with chronic instability have been treated with augmentation and total PCL reconstruction for some patients and conservatively in others. As reported by Scott and Murray, for intra-substance PCL injuries (28), good outcomes can be achieved with non-operative management in children. They strongly suggest that the decision to proceed with surgical intervention must be made after a prolonged period of targeted rehabilitation and when conservative measures have failed.

Based on our study, we strongly agree with this claim, and would like to highlight how the decision to intervene surgically was taken as there was severe instability in both patients and both of them had high demands in terms of returning to pre-morbid activity levels.

Furthermore, in a case report by Accadbled et al, an 11-year-old child underwent all inside PCL reconstruction and although no formal scores were kept of the child's recovery, the patient returned to pre-injury sports levels and remained completely

asymptomatic at two years (16). A similar case was reported in a 10 year old who underwent PCL reconstruction using a tibial inlay technique, reporting no physeal growth arrest and a return to pre-morbid sporting competitiveness (29). On the other hand, another recent study (30) reported that goodshort-term outcomes in a child with combined PCL and postero-lateral instability was obtained after non-surgical treatment.

In a further study, 11 patients treated conservatively after PCL ruptures were reported to have optimal outcomes with no residual knee laxity (19). Nonetheless, 8 of these 11 patients suffered from partial PCL lesions, and the authors concluded that the non-surgically treated group had by far a worse outcome compared to the surgically managed cohort.

Several techniques have been attempted in performing all epiphyseal surgery to avoid damaging the physis, yet studies surrounding PCL injuries in young patients have remained rare. Moreover, as surgical arthroscopic instrumentation, technical ability, and understanding of PCL mechanics and function have improved, outcomes of PCL reconstruction in adults have seen a gradual improvement. However, surgical management of acute PCL ruptures and PCL deficiency remains highly debatable, both considering how effectively knee instability and osteoarthritis may actually be prevented with surgical interventions (31) and also in terms of what represents the best technique.

Conflicting studies have emerged on a variety of technical considerations for PCL reconstruction in adults, such as single-bundle versus double bundle reconstruction (32, 33), transtibial versus tibial inlay approaches (23, 34) and allograft versus autograft (35, 36). On the other hand, since PCL injuries are by far less common in children, little research and few technical investigations have emerged in the paediatric field.

Table I. *The mean age of the patient at the time of the surgery.*

	Age	Follow up	Interval to surgery	Additional procedures	Complication
Child 1	15	16months	4months	None	None
Child 2	16	14 months	8months	None	None

Table II. *Activity scores.*

	IKDC	Tegner Activity score	Lysholm Fuctional score	A-P translation by Kt-2000
Child 1	Subjective score pre is operative is 64 Subjective score post operative is 94 Objective score pre operative is C Objective score post operative is A	Pre –operative 6 Post operative 8	Pre operative-52 Post operative 91	Pre operative 7.2mm Post operative 1.7
Child 2	Subjective score pre operative is 68 Subjective score post operative is 92 Objective score pre operative is C Objective score post operative is A	Pre –operative 6 Post operative 8	Pre operative 54 Post operative 89	Pre operative 7.6mm Post operative 2.4

In both of our cases, we decided to proceed with a relatively standard approach with regards to the femoral bone drilling, but we avoided placing any screws within the half bone tunnel, thus drastically reducing chances of any physeal damage.

Our method of a physeal sparing tibial tunnel combined with an anatomical femoral tunnel allowed to obtain good biomechanics of the knee with significant improvement in their IKDC, Lysholm and TAS scores and no leg discrepancy. Furthermore, as suggested by Falciglia (1), who evaluated ACL reconstruction techniques in Tanner stages 2 and 3 patients, partial transphyseal reconstruction can be performed, resulting in good mid and long term outcomes, without causing any growth disturbance. Extremely similar results were achieved by Kumar et al (37), who also agreed that good long-term results can be achieved with the use of a transphyseal technique in young children. Furthermore, as our patients were respectively Tanner stages 2 and 3, the risks of any growth disturbance is negligible.

Lastly, as mentioned by Brusalis and his colleagues, it is common for high-impact journals to unreliably define subjects' skeletal maturity, highlighting the need for standardized, pediatric-specific outcome measures to be applied in future studies. This would allow us to have more specific comparison with other studies, enabling us to produce more accurate data. Controversal is the choice of the graft for the reconstruction. Hudgens (38) reported no significant differences between allograft and autograft PCL reconstruction. Goddard (39) and Shah (40) showed excellent outcomes in the use of living parental allograft for ligament reconstruction. Use of allografts preserves the child's own hamstrings for future use. An important issue about cadaveric allografts is that they have been associated with higher failure rates (between 13% and 44%) in an adult population (41, 42), thus making them unsuitable for a paediatric population, where re-rupture rates are generally higher. The use of graft from a living donor may raise several ethical concerns regarding donor site morbidity and tissue rejection/reaction in the patient.

We would also like to clarify that the conclusions we have drawn from these two adolescent patients are limited by the shortage of cases we encountered. Furthermore, the great lack of literature on similar cases or experiences left us with little objective comparison for our results.

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SHOULDER PERIPROSTHETIC FRACTURE IN ELDERLY PATIENT: A MINIMALLY INVASIVE OSTEOSYNTHESIS AND "OFF-LABEL" TREATMENT WITH TERIPARATIDE. A CASE REPORT AND LITERATURE REVIEW

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A case of shoulder periprosthetic fracture in elderly patient. The patient underwent a minimally invasive osteosynthesis and "off-label" treatment with teriparatide. An 80-year-old woman patient following an accidental fall reported a transverse displaced diaphyseal fracture of the right humerus, distal to the stem of the inverse prosthesis. The patient suffering from severe osteoporosis and chronic ischaemic heart disease. The patient underwent fracture osteosynthesis surgery using a Hoffmann III mono-axial external fixator. Teriparatide administered at a dosage of 20 micrograms/day, for four months. At six months from the beginning of the hybrid treatment, a complete healing of the fracture was observed radiologically and clinically. It is possible to affirm that the use of teriparatide off-label has a positive and additive effect in promoting the healing of fractures.

The healing of the fracture is one of the most extraordinary processes of body repair, as it does not result in scar tissue, but in the *restitutio ad integrum* of the tissue. This process is the result of the coordination of immune and haematopoietic cells which represent the "players" of phases that occur from the fracture event to healing.

The healing of the fractured bone tissue is guaranteed by a process with well organized stages. Two distinct processes can be recognized: an anabolic phase, characterized by the formation of new tissue, and a catabolic phase characterized by a remodeling of the newly formed bone tissue in trabecular and cortical bone. Initially there is an extravasation of cells from the bloodstream (macrophages, granulocytes, lymphocytes, monocytes), able to release cytokines capable of recruiting other inflammatory cells and facilitating the migration of mesenchymal cells. This step is followed by the formation of a fibrous callus: growth factors stimulating the proliferation and differentiation of mesenchymal cells in condroblasts and fibroblasts, lead to the production of fibrocartilage in the fracture site.

The intense cellular anabolic activity leads to an increase in oxygen consumption with consequent hypoxia in the fibrous callus. Hypoxia is the main stimulus to the release of angiogenic factors such as VEGF; this determines the invasion of fibrous callus by vascular tokens resulting in a new blood supply and oxygen necessary for osteoblastic differentiation

Key words: teriparatide, fracture healing, minimally invasive, periprosthetic fracture

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of mesenchymal stem cells. The following processes are represented by the encondral mineralization (a process that traces the embryogenesis of the bone tissue), with intense osteoblastic activity supported by morphogenetic bone proteins (BMP). The mineralized matrix gradually replaces the soft-callus.

The last phase is bone remodeling: the osteoblasts release factors that promote osteoclast differentiation and control the reabsorption and the bone apposition processes (RANK-L); these events lead to the remodeling of the mineralized callus and the reorganization of the hard-callus into cortical and trabecular bone.

Bone repair depends on three essential factors: the activation of mesenchymal stem cells, the release of growth factors and the production of regulatory factors. This process is also influenced in a decisive way by three conditions: adequate blood flow, good contact between bone fragments and good stability of the fracture outbreak. At the end of the process, the higher the bone mineral density and the calcified tissue content, the better will be the biomechanical properties of the bone callus.

Several factors can alter this process, including ageing, osteoporosis, and comorbidity. The consequent alterations of the bone metabolism negatively affect the repair of the fracture. The possibility of modulating the anabolic and catabolic phenomena in the bone, both locally and systemically through the use of drugs, opens a new horizon on the strengthening of bone healing, in particular in those conditions in which a diminished resistance is revealed and therefore a lower mechanical competence of the bone tissue.

Nonunion

Nonunion is a fearful complication in the healing process of a fracture. Nonunion refers to the failure to consolidate a fracture after at least 6 months from the trauma and is characterized by the presence of fibrocartilaginous and non-bone tissue in the interfragmentary region. Delayed bone healing must be differentiated from the non-union, which is a failure to heal the fracture within 6 months of the initial trauma. The nonunion is classified according to the morphological and topographical appearance. First of all, it is necessary to distinguish between non-infected and infected nonunions.

According to the Weber and Cech classification, aseptic nonunions, depending on the vitality of the bone fragments, are divided into hypertrophic and atrophic.

The hypertrophic / hypervascular nonunions are further subdivided into:

Flared nonunion: largely hypertrophic and rich in callus. They usually follow an unstable fixation or a premature load.

Oligotrophic nonunion: non-hypertrophic and without bone callus. They generally follow a displacement of the fracture.

The atrophic / avascular nonunions are further divided into:

Dystrophic nonunion, characterized by the presence of an intermediate fragment with decreased blood supply.

Necrotic nonunion, characterized by the presence of one or more necrotic intermediate fragments.

Nonunion with loss of substance, characterized by the loss of diaphyseal bone fragments.

Atrophic nonunion, characterized by the absence of intermediate fragments; the ends of the fragments are osteoporotic and atrophic.

The parathyroid hormone and the teriparatide

Parathyroid hormone (PTH) is a 84 amino acid hormone secreted by the 4 parathyroid glands. PTH participates to the maintenance of normal levels of circulating calcium. In the intestine, PTH promotes the reabsorption of calcium through specific receptors. Also in the intestine the vitamin D system is active with both metabolites (cholecalciferol and 1,25 hydroxycholecalciferol) which intervene, albeit quantitatively, on intestinal absorption of calcium and phosphorus.

It is known that hydroxylation of the cholecalciferol in 1,25 hydroxycholecalciferol is partially dependent on the action of PTH, even if recently it has been shown a hydroxylation action of the cholecalciferol at the level of lymph node stations by cytokines in the immune system; at renal level the PTH has a powerful phosphatic effect and promotes the tubular reabsorption of calcium, for which the evaluation of

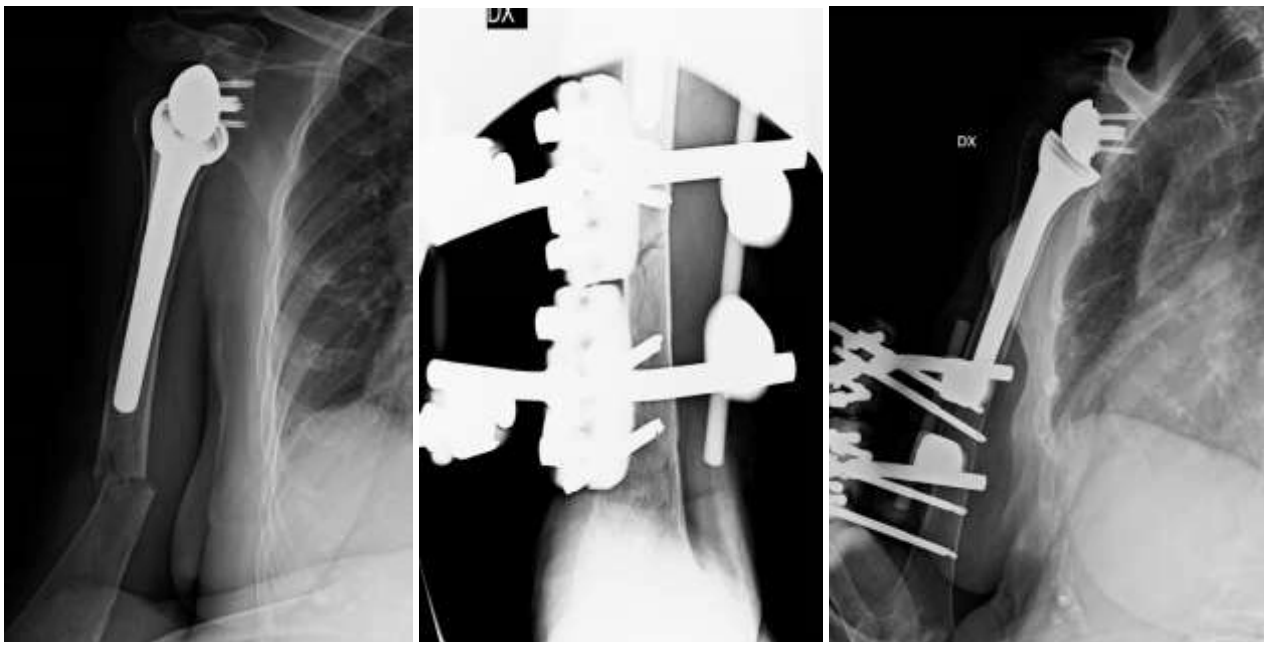

Fig 1. *Shoulder periprosthetic fracture; Osteosynthesis with Hoffmann III mono-axial external fixator; Osteosynthesis with Hoffmann III mono-axial external fixator.*

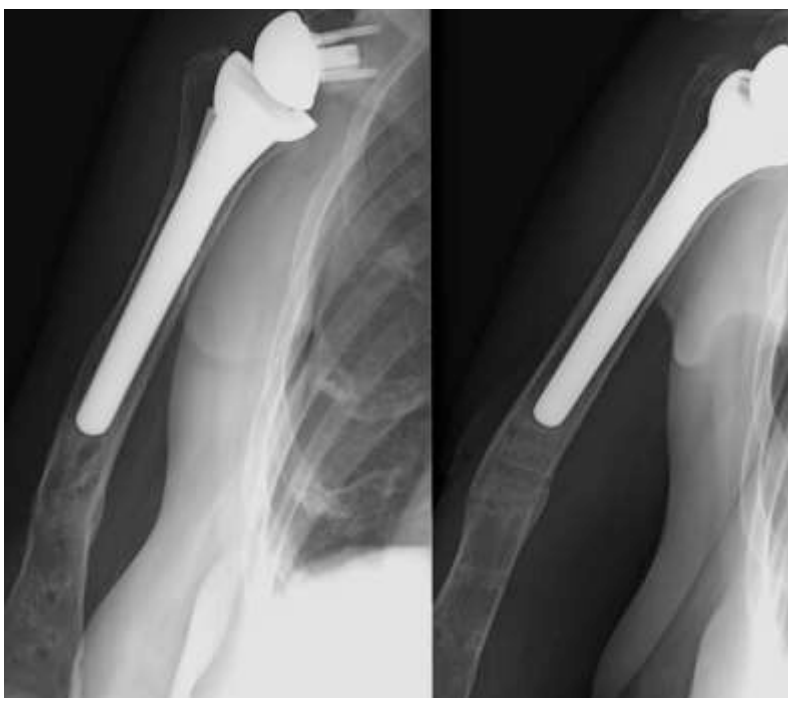

Fig 2. *Complete healing of the fracture after six months.*

the urinary quantity of calcium excreted within 24 hours (under conditions of hydrosaline equilibrium, i.e. in conditions of non-utilization of loop diuretics or of saline infusions) is a fundamental parameter for the recognition of an alteration of the calcium metabolism. At the bone level, PTH recognizes receptors on osteoblasts (but not on osteoclasts).

The uninterrupted activation of osteoblasts in the presence of continuously high levels of PTH, which are observed in the conditions of hyperparathyroidism - both primary and secondary - causes a secondary increase of the activation of osteoclasts in order to mobilize bone calcium to maintain normal values (secondary hyperparathyroidism) or high values (primary hyperparathyroidism) of calcium-ion.

The situation is different and PTH shows an anabolic action in the presence of discontinuous therapeutic doses of PTH 1-34 (that is, in the conditions of daily use of injections of PTH 1-34, teriparatide, for anabolic bone). In addition, studies on mice have documented that in the trabecular bone the intermittent use of parathyroid hormone inhibits the apoptosis of osteoblasts. It is possible that a similar mechanism of action may be is responsible for the effect of the hormone on bone formation, even if such result has not yet been proven in humans.

At the base of the molecular mechanism there would be the activation of antiapoptotic metabolic pathways, the inactivation of proapoptotic proteins and the increased expression of genes encouraging cell survival; moreover, some of the effects could be traced to the increased local production of factors such as the similar insulin growth factor 1 (IGF-1) and the fibroblastic growth factor 2 (FGF-2).

The teriparatide is the active fragment (1-34) of the endogenous human parathyroid hormone. Teriparatide, as a bone-forming agent, has been used to treat osteoporosis and has become a promising therapeutic agent for improving fracture fracture healing. The primary physiological mechanism of teriparatide involves the activation of osteoblasts: intermittently administered teriparatide may shift bone resorption of osteoclasts to activation of osteoblasts. Teriparatide plays an important role in the coupling of osteolysis and osteogenesis and is an essential regulator in remodeling. Teriparatide has been shown to improve bone microarchitecture, increase bone mineral density and reduce the risk of vertebral and non-vertebral fractures.

Scientific studies suggest at least two mechanisms through which teriparatide promotes bone formation: 1) stimulation of endochondral ossification, perhaps slowing the differentiation of hypertrophic chondrocytes and therefore maintaining a pool of proliferative chondrocytes 2) stimulation of mesenchymal cell differentiation in osteoblasts. Teriparatide has been used as an off-label therapy to speed up fracture repair and treat non-union.

The scientific literature

Teriparatide was licensed for treatment of post-menopausal osteoporosis by the US Food and Drug Administration in 2002. In the recent years, the efficacy of teriparatide in promoting fracture healing has been reported in numerous animal models and clinical studies.

In the literature, it is possible to consult a series of clinical and case report studies, which highlight the results obtained by the "off-label" administration of Teriparatide in order to encourage the healing of post-traumatic bone fractures, in particularly in cases in which was observed a framework of non-union.

In 2016, Aspenberg published on the journal of bone and joint surgery, a prospectic double blinded randomized controlled study on the effect of teriparatide therapy on the pertrochanteric hip fracture (ao/ota 31-a1 or 31-a2), about 224 patients. In conclusion, it was shown that teriparatide was associated with less pain and a shorter time to healing of the fracture.

In 2014, Hisakazu Tachiiri reported two cases, of delayed union that were effectively treated with teriparatide. In the first case, a 72-year-old woman underwent osteotomy for the treatment of hallux valgus. Bone union was still not observed 4 months after surgery. Therefore, weekly teriparatide (56.5 mg) injections were administered, resulting in the initiation of bone union within 4 weeks and complete bone union 4 months after the first teriparatide injection. In the second case, a 72-year-old woman underwent open reduction and internal fixation of an olecranon fracture. Bone union was delayed 4 months

after surgery; therefore, weekly teriparatide (56.5 mg) injections were started. In conclusion it was shown that teriparatide administration was effective for bone healing and useful for delayed union.

In 2017, Li Xiaofeng reported a case of a 44-year-old suffered closed fractures of the right tibia and left femur, he underwent retrograde intramedullary nailing. Radiographs obtained 11 months postoperatively revealed a persistent fracture gap and no evidence of bone bridging at the fracture site. Therefore, to diagnosis of nonunion was made. The patient refused to undergo another operation; instead, off-label use of teriparatide was accepted (20 micrograms / day). After 4 months of treatment, the radiographs showed a decrease of the fracture gap and bone bridging between the fracture fragments.

In 2014, Coppola reported a case of four patients received Teriparatide for management of non-unions after open fixation of traumatic fractures of the lower limb. Teriparatide administration resulted in adequate bone callus over the site of nonunion in all the patients, and clinical and radiographic evidence of sound union.

In 2012, Lee YK reported a case of three patients, who had a nonunion of the femur even after the initial surgical intervention that was medicated with teriparatide. Teriparatide was administered for 3-9 months after a diagnosis of nonunion. A successful union was obtained in all three patients without further surgical intervention, and no adverse events related to the use of teriparatide were observed.

The important role of teriparatide was confirmed in a study by Ren et al, who showed a lack of endogenous PTH (1-84) restrained fracture healing, whereas, if exogenous recombinant human form of parathyroid Hormone (1-34) was combined with endogenous PTH (1-84), endochondral bone formation, and callus remodeling, and mechanical bone strength were improved to promote fracture healing.

Our case

We report the case of an 80-year-old woman suffering from severe osteoporosis and chronic ischaemic heart disease, who underwent reverse prosthesis surgery of the right shoulder in October 2017, due to eccentric shoulder arthrithis. In March 2018, the patient following an accidental fall in the home environment, reported a transverse displaced diaphyseal fracture of the right humerus, distal to the stem of the inverse prosthesis. The patient then underwent fracture osteosynthesis surgery using a Hoffmann III mono-axial external fixator, with two fiches implanted under the prosthetic stem and two fiches at the humeral condyle. Simultaneously administered, for the duration of four months, Teraparatide at a dosage of 20 micrograms / day, vitamin D at a dosage of 25,000 U.I. every 15 days and calcium at the dosage of 2500 mg / day (Fig. 1)

After two months from the application of the external fixator, this was removed and the arm was protected with a Sarmiento type orthosis.

At six months from the beginning of the hybrid treatment, a complete healing of the fracture was observed radiologically and clinically the patient was able to mobilize the upper limb without feeling pain (Fig. 2).

DISCUSSION

The transverse diaphyseal fractures in the osteoporotic patient are at high risk of nonunion. In the case described above, a treatment possibility consisted of performing an invasive surgery with posterior access and osteosynthesis with plates and screws. this type of treatment could cause a great loss of blood during and after the surgery in an elderly cardiopathic patient. This choice was also discouraged by the anesthetist who was treating the patient. However, conservative treatment is not indicated as these types of fracture are highly unstable. Therefore, the most appropriate decision consisted a minimally invasive osteosynthesis with external fixation and "off-label" treatment with Teriparatide.

In conclusion, on the strength of available data, it is possible to affirm that the use of teriparatide off-label has a positive and additive effect when combined with surgical treatment in promoting the healing of fractures.

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MODULAR DUAL MOBILITY CUPS WITH MULTIHOLE METAL BACK IN TOTAL HIP ARTHROPLASTY REVISION: A SYSTEMATIC REVIEW

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Dislocation after hip revision is a frequent complication; amongst the strategies to prevent dislocation dual mobility (DM) implants are gaining popularity. We want to evaluate the reliability of non cemented DM cups with multihole metal back and chrome-cobalt liner called Modular Dual Mobility (MDM). We performed a systematic review and selected 5 studies with a total of 285 hips who underwent revision surgery with MDM implants. The mean survivorship rate of the 5 studies was 92.46% (range 90–96%). 267 prosthesis (93.6%) were still implanted at the last follow-up; the mean weighted follow up was 38.7% (range 24-48). We found 13 mechanical complications in 285 hips (4.5%). Five of them were treated conservatively; the other 8 were treated with re-revision. Nine of these complications were dislocation and recurrent instability; 2 of them were associated to metallosis and adverse local tissue reaction. There was 1 patient that had episodes of subluxation; 2 cases of impingement and 1 case of metallosis. Zero intraprosthetic dislocations (IPD) occurred in 285 hips. A 93.6% survivorship is a good result for MDM implants, considering that most of patients had important bone loss and went through multiple revisions. The rate of dislocation is very low compared to the mean rate of dislocation in revision hip surgery. In our review, fretting is a rare complication but it can lead to ALTR and metallosis. For this reason, MDM implants have to be used in selected cases at high risk of dislocation. In conclusion MDM is a great option for decreasing dislocation rate in hip revision, but a longer follow-up and a greater number of cases is needed to assess its reliability.

Total hip arthroplasty (THA) is constantly on the rise within orthopaedic surgery and, as a result, so are THA revisions (1). Dislocation and recurrent instability is the most frequent reason for revision and is the first reason for failure in a revised THA (2). A lot of strategies are used to prevent instability during primary and revision THA. First of all it is mandatory to achieve a correct positioning of the implant, in particular cup inclination and combined anti version (3-4). The use of large femoral heads is another important cause of reduction of dislocation in the last few decades (5). The Dual Mobility (DM) implants in primary THA are a relatively old solution for decreasing instability rate (6). These implants are constituted by a monoblock metal back cup with no possibility of stabilization with additional screws. In the last decade Modular DM (MDM) implants were introduced. They are constituted by a multihole metal back and a chrome-cobalt (Cr-Co) insert. These new implants allow for the reduction of the risk of dislocation after revision THA and at the same time achieve a good primary stability of the cup through the positioning of additional screws.

MDM implants are at risk of mechanical failure in two ways. Firstly by intraprosthetic dislocation, a well known complication of DM implants (7). Nowadays with the last generation of polyethylene, this complication seems to be reduced. Secondly, by

Key words: THA, total hip artrhoplasty mobility cups, dual mobility, MDM implants

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metallosis and adverse local tissue reaction (ALTR) due to the fretting between metal back and Cr-Co insert (8). This problem is still debated in literature.

Since 2010, a relatively high number of MDM THA were implanted. With this review of the literature, we want to clarify the rate of success of MDM THAs and their complications.

MATERIALS AND METHODS

A comprehensive research of PubMed electronic was performed from January 2009 to January 2019.

We researched the articles using the following outline: dual mobility [title] AND hip [title] AND revision [title] AND arthroplasty [title]. We found 172 articles. Two authors screened the abstracts of all articles using the following exclusion criteria: articles written in non English language; studies focusing only on primary THA and studies with hip revision with DM implant monoblock and/or cemented. We found 23 eligibile abstracts (Fig. 1). We analyzed the full manuscripts and included only studies or case series/case reports with revision DM implants with multihole metalback. In this way, we excluded 17 papers fort the reason that they all used monoblock DM. We evaluated the 6 remaining papers searching for the overall survivorship of MDM implants and for mechanical failures or complications excluding infection and loosening, as these events are not related to the MDM implant.

RESULTS

We evaluated the survivorship in 5 studies. One of the 6 papers was excluded because it did not differentiate the survivorship between primary and revision MDM THA. Therefore, we included 285 hips. In 11 cases an Integra cup®, Groupe Lépine, Genay, France was implanted. In the other 274 hips a Modular Dual Mobility (MDM) (Stryker, Mahwah, NJ) was implanted. The mean survivorship rate of the 5 studies was 92.46% (range 90-96%). Two-

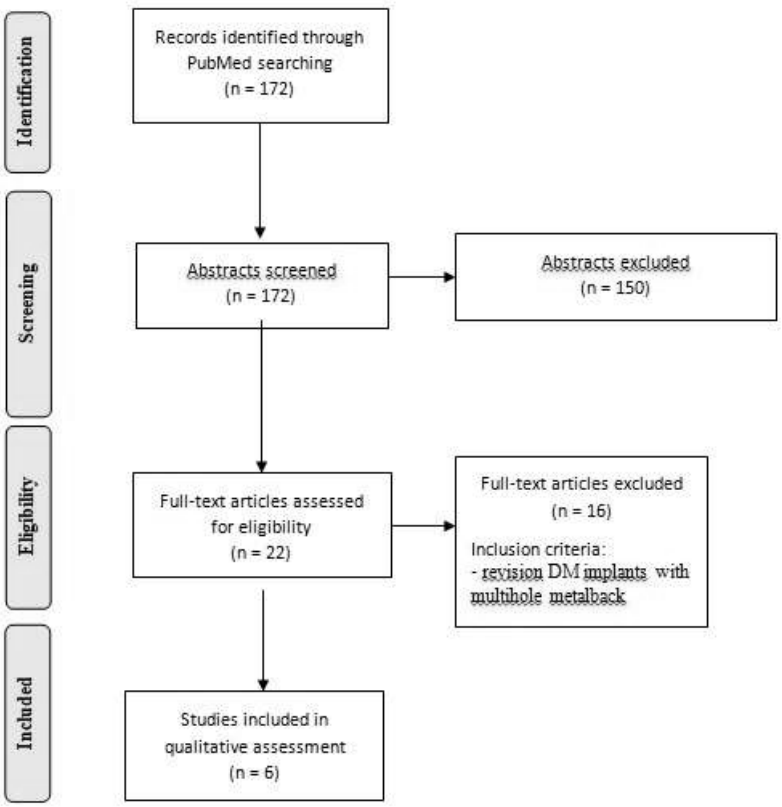

Fig 1. .*Research results.*

hundred-and-sixty-seven prosthesis (93.6%) were still implanted at the last follow-up; the mean weighted follow up was 38.7% (range 24-48). We found 13 mechanical complications in 285 hips (4.5%). Five of them were treated conservatively; the other 8 were treated with re-revision.

Prudhon and Sutter had respectively 1 and 2 cases of dislocation treated with closed reduction with no further episodes of dislocation (10, 11). Jauregui had 1 case of dislocation treated with re-revision (11). Five cases of recurrent dislocation were all treated with re-revision. Diamond et al. (12) described two of them. There were 2 cases of Metal on Metal THA with pseudotumor revised with MDM; at the time of the re-revision recurrence of the pseudotumor was diagnosed in both cases.

Sutter et al. described a case of metallosis; at the time of re-revision there was wear on the metal lining on the side close to the metal back. Harwin described one case of cup impingement that was treated with re-revision (13). One case of subluxation and one of femoral neck impingement were described, both treated conservatively. Lange was excluded because he described 40 implants without differentiating between primary and revision (14); we still included this data: an overall survivorship of 90% and 2 cases of recurrent dislocations treated with re-revision. All data are reported in Table I.

This article does not differentiate between primary and revision THA; we included it in the table, but we decided to not evaluate the rate of survivorship and complications.

DISCUSSION

DM implants are a well-known option for decreasing dislocation rate. They have been implanted for treatment of primary osteoarthritis since 1975 and their reliability is fully demonstrated in the literature (15). In the last decade few studies showed good outcomes using DM implants in revision THA (16). Most of them implanted monoblock DM that do not allow stabilization of the cup with screws or if they do, only from the hook of the cup (17). These monoblock cups are not adequate in hips with bone loss defect; in fact, few authors described implantation of cemented DM cup in the presence of medium or severe acetabular bone loss (18-19). Nowadays always more frequently young people with acetabular bone loss go through a cup revision; for these patients, cemented cups are not the ideal treatment. For this reason MDM's were manufactured.

Table I. *Survivorship of implant*

Paper	N° of revision with MDM (implant name)	Surivorship of the implant	Mean Follow-up	Mechanical Complications
Prudhon et al. 2014	11 (Integra DM cup, Lepine)	(90%) 1 infection	24	1 dislocation (closed reduction)
Jauregui et al. 2015	60 (MDM Striker)	(96%) 1 aseptic loosening	30	1 dislocation (revised)
Sutter et al. 2017	69 (MDM Striker)	(91%) 6 failures	38	2 dislocations (closed reduction). 1 recurrent dislocation (revised) 1 metallosis probably of the metal liner (revised)
Lange et al. 2017*	Less than 40(MDM Striker)	(90% considering also DM non modular)	36	2 recurrent dislocation (revised)
Harwin et al. 2017	85(MDM Striker)	95,3 % 4 failures	48	1 recurrent dislocation (revised) 1 cup impingement (revised)
Diamond et al. 2018	60(MDM Striker)	90% 6 failures	38	3 recurrent dislocation (revised); 2 of them had recurrent pseudotumor at time of revision oft he MDM. 1 subluxation (conservative treatment) 1 femoral neck impingemetn (conservative treatment)

**This article does not differentiate between primary and revision THA; we included it in the table, but we decided to not evaluate the rate of survivorship and complications.*

Our results demonstrate a mean survivorship of 93.6% at a weigthed mean follow up of 38.7% (range 24-48). This is a good result for MDM implants, considering that most of our patients had important bone loss and went through multiple revisions. A 4.5% of mechanical complications related to the MDM cup is a very good result; rate of dislocation after revision with non DM cup reaches 39% in literature (20). Zero intraprosthetic dislocations (IPD) occurred in 240 hips; this is an interesting result because IPD was the most worryingly complication in DM implants (7). Three cases (1%) of metallosis with adverse local tissue reaction (ALTR) were reported; 2 of which already had a pseudotumor due to a Metal on Metal THA.

Reports in the literature have evaluated fretting and corrosion damage between the acetabular shell and modular metal inserts in these modular systems with contrasting results (21-23).

In our review fretting is a rare complication but it can lead to ALTR and metallosis. For this reason MDM implants have to be used in selected cases at high risk of dislocation.

In conclusion, MDM is a great option for decreasing dislocation rate in hip revision, but a longer follow-up and a greater number of cases is needed to assess its reliability.

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CHARACTERIZATION OF HUMAN COSTAL CARTILAGE: IS IT AN ADAPT TISSUE AS GRAFT FOR ARTICULAR CARTILAGE REPAIR?

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Several techniques and different biological or artificial tissues have been proposed as graft to restore articular defects. However, among the numerous and heterogeneous procedures proposed over time, the current literature findings are not conclusive. The aim of the current study is to evaluate if human costal cartilage can be suitable as graft for restoring articular cartilage defects. Knee articular cartilage and costal cartilage samples were obtained respectively from patients that underwent anterior cruciate ligament reconstruction (samples from notch plasty) or knee joint replacement and ear reconstruction or rhinoplasty through rib graft. The samples were stained with hematoxylin eosin, safranine-O, Gomori paraldehyde-fuchsin and Von Kossa for light microscopy. Immunohistochemistry was performed using anti-collagen I, II, IV and anti-SOX9 antibodies. Furthermore, samples were analyzed by transmission electron microcopy (TEM). In both cartilage, the cells are arranged in quite similar layers and the matrix show the same hyaline appearance: presence of type II collagen and solphated glycosaminoglycans, and absence of type I collagen and SOX-9. The bigger difference between the two hyaline tissues is the presence of perichondrium that surrounds all the specimens of costal cartilage. It consists of two separate layers where the inner one seems to get thinner with aging. The results show that rib cartilage seems to be an adapt tissue as graft for articular cartilage repair from a histological point of view. However, to date its therapeutic potential remains to be clearly defined by animal and clinical studies.

Three different types of cartilage have been described in humans: fibrous, elastic and hyaline cartilage. These tissues differ each other from site, biochemical composition, structure and function.

The fibrous cartilage was found in the pubic symphysis, intervertebral discs, menisci and temporal mandibular joint. It was also described in ligaments and tendons in physiological and pathological condition (1, 2). Moreover, it is characteristic of scar tissue in articular cartilage lesions differing in structure, composition and functional properties from the healthy articular hyaline cartilage (3, 4). It contains both type I and II collagen. The elastic cartilage was found in the outer ear, Eustachian tube and epiglottis and its extracellular matrix is characterized by type II collagen and great amount of elastic fibers.

Hyaline cartilage is the most widespread cartilage type. Indeed, it covers the articular surfaces of synovial joints and forms the cartilaginous bars of costal cartilage; meanwhile, it characterizes the growth plate. Its extracellular matrix is constituted

Key words: costal graft, cartilage repair, hyaline cartilage, costal cartilage

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of type II collagen without type I collagen or elastic fibers.

Articular cartilage is a thin layer of hyaline cartilage micro-structured in a specialized fashion. This confers unique viscoelastic properties on the tissue supporting high cyclic compression load during joint movement.

Costal cartilage constitutes the anterior arch of the ribs in direct continuation with the bone rib posteriorly and with the costo-sternal joint anteriorly in the fixed ribs. It is surrounded by a vascularized thin layer of perichondrium which could have a role in growth and repair chondrogenesis (5).

In the last years, several techniques and different biological or artificial tissues have been proposed as graft to restore articular defects (6, 7). However, among the numerous and heterogeneous procedures proposed over time to treat cartilage defects, the current literature findings are not conclusive. Each technique presents limitation and no consensus regarding which method is superior has been obtained (6).

Considering its hyaline nature, the costal cartilage might constitute a suitable tissue as graft in articular cartilage defects. Indeed, it has been used in repairing cartilage lesions in the upper limb with promising results (8). Only three studies in rabbits have been found regarding the repairing of articular defects of the knee by costal grafts (9-11). Dajiang Du et al. sliced rib cartilage into 3- to 5- mm fragments and then harvested cartilage grafts in the rabbit knee lesions in one-step technique (9). Mori et al. prepared osteochondral grafts by mounting cancellous bone onto costal cartilage for 1 month and then used the pre-constructed osteochondral graft to repair the osteochondral defect in two steps technique (10). Lastly, Szeparowicz et al. used costal cartilage of the rabbit as source of autologous chondrocytes for transplantation (11). However, there are no studies in recent literature about the characterization of human costal cartilage from a histological, immuno-histochemical and ultrastructural point of view. This is probably due to the absence of relevant pathologies affecting this tissue.

In the present study, a detailed biological characterization of human costal cartilage was performed in order to evaluate if this tissue can be suitable as graft for restoring articular cartilage defects.

MATERIALS AND METHODS

Patients and tissues

Patients were treated at the University Hospital "Ospedali Riuniti" of Ancona (Italy). Before the beginning of any study-related activities, each patient signed informed consent. The study was approved by our institutional review board.

Knee articular cartilage was obtained from 8 subjects with and age of 18, 24, 33, 40, 65, 69, 75 and 77 years, respectively (mean: 50.13), that underwent anterior cruciate ligament reconstruction (samples from notch plasty) or knee joint replacement (samples from unaffected compartment).

Costal cartilage samples were obtained from 8 patients with an age of 16, 20, 28, 30, 37, 40, 45 and 50 years, respectively (mean: 33.25), that underwent ear reconstruction or rhinoplasty through rib graft. A subcostal incision about 5 cm was made near the sternum, along the seventh rib. Separation of the overlying muscles was carried out to expose the rib, a sub perichondrial dissection of the seventh costal cartilage with delivery of the distal part of the rib was done and the required tissue was harvested.

During surgery, waste fragments of articular cartilage, perichondrium and costal cartilage that were not of any medical use, were collected and immediately transferred to Laboratory of the Clinical Orthopaedics, Università Politecnica delle Marche (Italy) for histological analysis.

Histochemistry

For light microscopy, specimens were fixed in neutral formalin for 48 h, paraffin embedded and then cut into longitudinal sections (thickness 3 to 5 μm) and stained with hematoxylin eosin, safranine-O, Gomori paraldehyde-fuchsin and Von Kossa.

Immunohistochemistry

Tissue section from all samples were dewaxed and rehydrated in a graded ethanol series. Endogenous

peroxidase activity was blocked by immersion in distilled water containing 3% hydrogen peroxide for 10 min to avoid unspecific staining. The following antibodies and dilution were used for the labelling: 5 μg/mL monoclonal anti type I collagen (Immunological Sciences, Roma, Italy), 10 μg/mL monoclonal anti type II (Oncogene Research Products, La Jolla, California USA), 1:500 polyclonal anti type IV collagen (Abcam, Cambridge, England), 1:1500 polyclonal anti SOX-9 (Abcam, Cambridge, England). Slides were incubated 1 hour at room temperature, then washed in TBS. EnVision + Dual Link System-HRP (Dako, Agilent, Santa Clara, CA, USA) was used to highlight the antigen-antibody binding, following the manufacturer's recommendations. Sections were observed with a Leica microscope (Cambridge Ltd, England). For the negative control, the primary antibody was replaced with non-immune serum.

Transmission Electron Microscopy (TEM)

Small samples of cartilage were fixed with 2.5% Glutaraldheyde in 0.1M Cacodylate buffer (pH 7.2), for 1 h at room temperature and subsequently overnight at 4°C. Washing samples were then post-fixed in 1% osmium tetroxide for 1 h and dehydrated using acetone series and finally embedded in epoxy resin. Ultrathin sections (50 nm thick) were obtained and stained with Lead Citrate. Images were taken at 80 K Volts in a Philips CM10 electron microscope.

RESULTS

Articular cartilage

Articular cartilage samples showed the classical features of hyaline cartilage characterized by the presence of chondrocytes, glycosaminoglycan, type II collagen, and the absence of type I collagen and SOX-9, consisted with previous histological analyses (12). In particular, three zones of articular cartilage were recognized: the superficial, middle and deep zone. In the superficial zone, chondrocytes were typically flattened and aligned parallel to the articular surface; in the middle and deep zones, instead, chondrocytes were typically arranged in columnar orientation, parallel to the collagen fibers and perpendicular to the joint line (13). No substantial age-related differenced was revealed in the samples.

Rib perichondrium

Hyaline cartilage of human rib was surrounded by perichondrium, a thin layer of dense connective tissue. It was characterized by an eosinophilic layer with few, scattered, flattened fibroblast-like cells. Two layers of perichondrium were recognized: an outer fibrous layer and an inner cellular layer. The former consisted of collagen fibers and fibroblast-like cells; the latter was made up of small elliptical cells lying parallel to the surface. Fibers from both layers heavy stained for type I and type IV collagen whereas no positivity was found for type II collagen (Fig. 1). We observed that inner layer was most represented in samples from young patients, meanwhile, it seemed to get thinner with aging. Blood vessels were identified by type IV collagen staining in both layers. Perichondrium showed no positivity for SOX-9 in all specimens.

Costal cartilage

Numerous chondrocytes inside lacunae and a homogeneous extracellular matrix were observed by haematoxylin-eosin staining (Fig. 2A-C). Considering the chondrocytes orientation and their phenotype, three layers were identified. In the outer layer, we observed numerous, flattened small chondrocytes, arranged on 2-5 rows aligned parallel to the rib perichondrium. Immediately deep to the outer layer, we observed a middle and deep zone characterized respectively by spherical chondrocytes with a sparse distribution in extracellular matrix and hypertrophic chondrocytes arranged in columnar orientation, parallel to the collagen fibers and perpendicular to the perichondrium. An evident metachromasia of the cartilaginous matrix was observed by Safranin-O staining (Fig. 2C). This particular histological organization of the costal cartilage was very similar to the articular one.

Extracellular matrix showed strong positivity for type II collagen whereas no positivity was found for type I collagen (Fig. 1). Blood vessels, lymphatics, and nerves were not found in the extracellular matrix.

Type IV collagen was found in the pericellular matrix surrounding chondrocytes in all the samples; no positive stain was found in the interterritorial matrix. Type IV collagen staining was evident in all

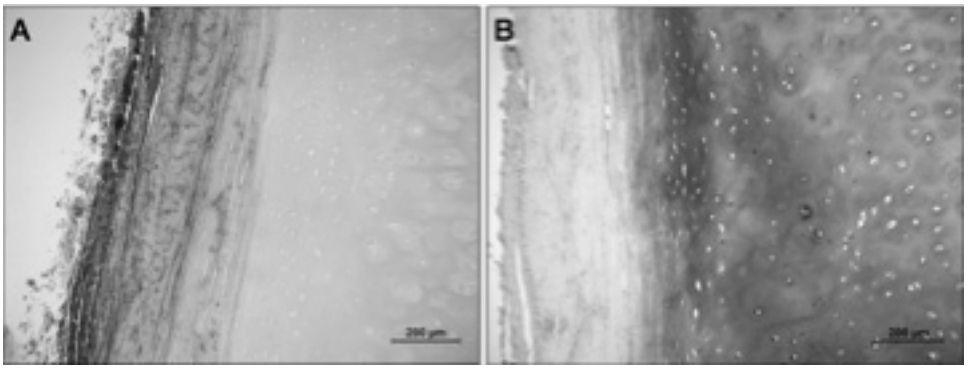

Fig. 1. Human rib cartilage and perichondrium from patient of 50-year-old. ***A***: Rib perichondrium heavy stained for type I collagen; no positivity was found in rib cartilage (original magnification x10); ***B***: Rib cartilage heavy stained for type II collagen; no positivity was found in perichondrium (original magnification x10).

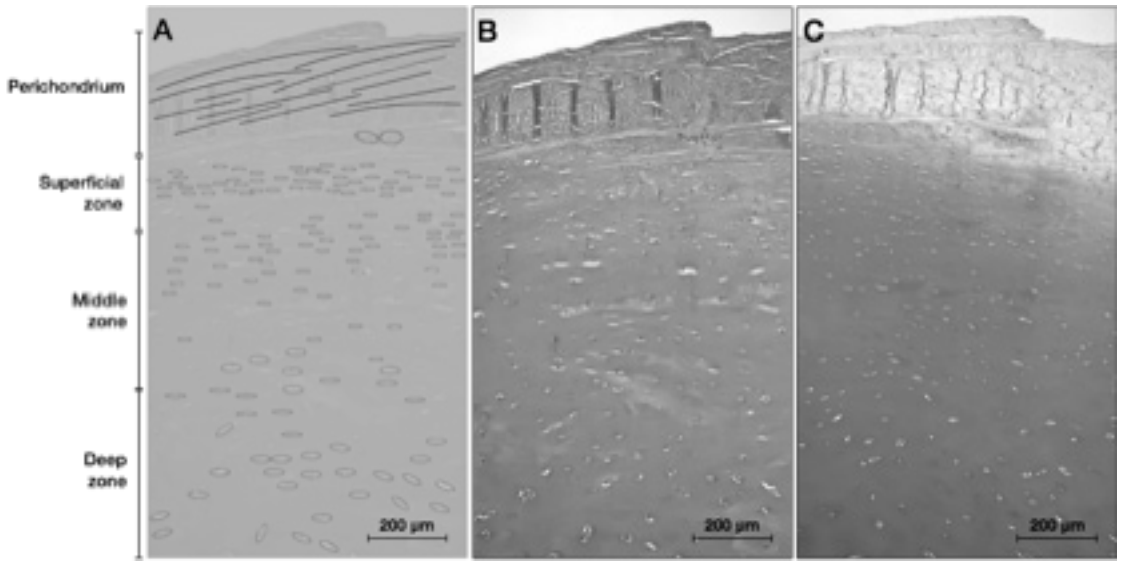

Fig. 2. Human rib cartilage and perichondrium from patient of 16-year-old. ***A***: Schematic representation of perichondrium and costal cartilage; ***B***: Chondrocytes inside lacunae and homogeneous extracellular matrix are clearly observable (haematoxylin and eosin, original magnification x10); ***C***: Metachromatic staining is evident in matrix of the rib cartilage but not in the perichondrium (safranin-O, original magnification x10).

the layers of costal cartilage in younger subject, while it disappeared in the deep layer of aged subjects, where a strong positivity for Von Kossa and an acidophilic pattern in Gomori paraldehyde-fuchsin staining were observed (Fig. 3).

By immunohistological examination with anti-SOX 9 antibodies, we observed a strong positivity in the nucleus of superficial chondrocytes, meanwhile we noted a progressive decrease of the staining moving to the deeper layers of the specimens (Fig. 4). SOX 9 staining resulted negative in the samples from aged subjects with more than 30 years old (4 subjects)

Transmission Electron Microscopy (TEM)

At TEM analysis, abundant rough endoplasmic reticulum, lipid droplets, and cytoskeleton fibrils were observed both in articular and costal chondrocytes (Fig. 5).

The costal matrix consisted of a dense network of fibrils embedded in proteoglycan gel. In the outer layer, the collagen fibrils ran in parallel to the surface.

Toward the inner cartilage, the collagen fibrils were randomly arranged (Fig. 6), but successively they were characterized by a homogeneous course, perpendicular to the perichondrium.

DISCUSSION

Costal cartilage represents the major site of hyaline cartilage in humans. However, to the best of our knowledge, studies regarding a detailed description of human costal cartilage have not been found. In the present study human costal cartilage was characterized by histological, histochemical, immuno-histochemical and ultrastructural analysis in subjects of various age. These observations were compared to the better known articular cartilage, in

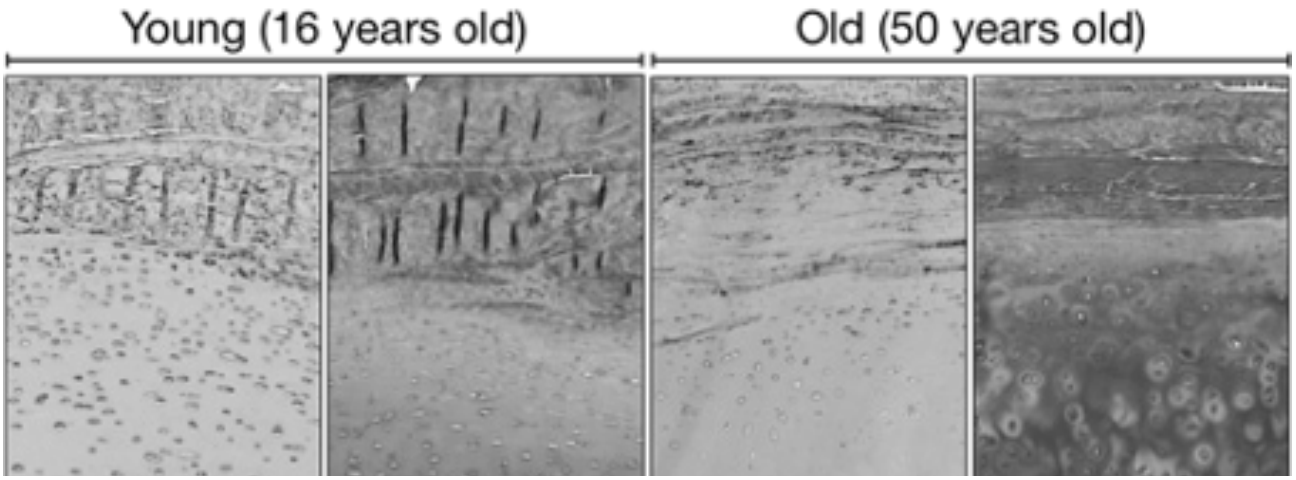

Fig. 3. Human costal cartilage with perichondrium. ***A*** and ***B***: Sample from from patient of 16-year-old; ***C*** and ***D***: Sample from from patient of 69-year-old; ***A***. Perichondrium stained for type IV collagen. It is worth of note the strong positivity around chondrocytes (original magnification x5); ***B***: The absence of orange color demonstrates the absence of acidophilic pattern (Gomori paraldehyde-fuchsin, original magnification x5); ***C***: The superficial chondrocytes show positivity for type IV collagen (original magnification x5); ***D***: The three zones of costal cartilage are well recognized. It is worth noting the strong positivity of orange color in the deeper layers of cartilage, where no positivity for type IV collagen is found (Gomori paraldehyde-fuchsin, original magnification x5).

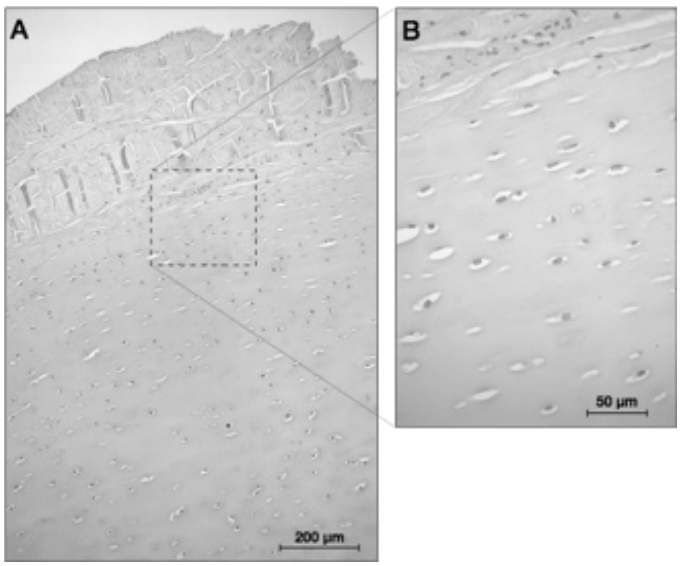

Fig. 4. *Human rib cartilage and perichondrium from patient of 16-year-old.* ***A****: Immuno-histochemical analysis of formalin-fixed, paraffin embedded costal cartilage tissue, staining for anti SOX9 antibodies (original magnification, x10);* ***B****: Chondrocytes positivity at SOX9 antibodies (original magnification, x40).*

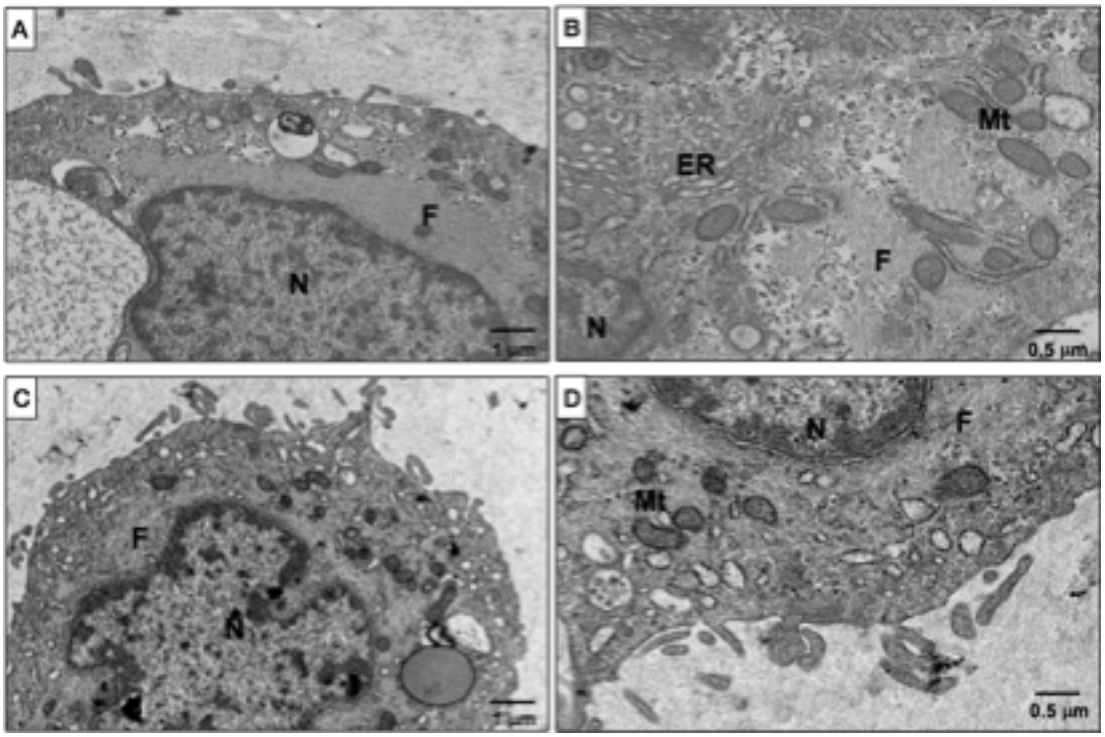

Fig. 5. TEM analysis. ***A*** and ***B***: Chondrocyte from articular cartilage; ***C*** and ***D***: chondrocyte from rib cartilage. Both chondrocytes show a cytoplasm containing abundant rough endoplasmic reticulum, mitochondria and lipid droplets, ***F***=fibers of cytoskeleton; ***Mt***=mitochondria; ***N***=Nuclei; ***ER***=endoplasmic reticulum.

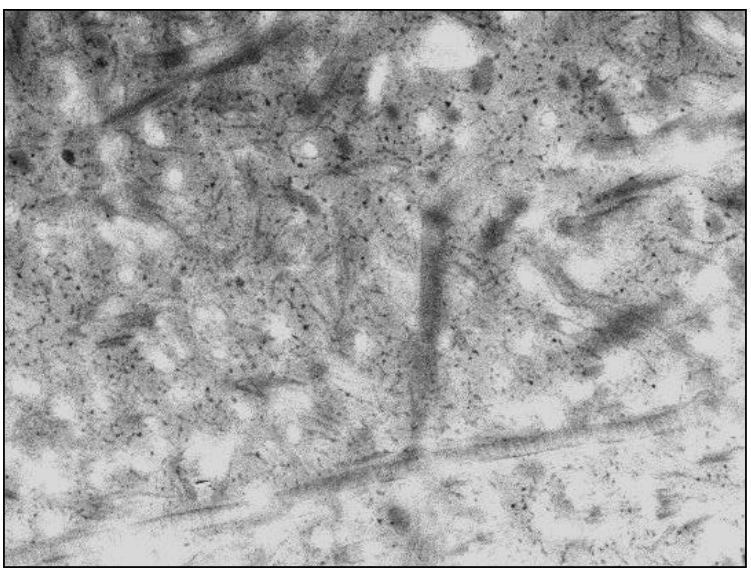

Fig. 6. TEM analysis. Extracellular matrix of rib cartilage is constituted of a dense network of collagen fibrils embedded in a proteoglycan gel. In the middle zone of rib cartilage, the collagen fibrils are randomly arranged.

order to evaluate if costal cartilage from a histological point of view can be suitable as graft in articular cartilage defects (12).

About the structure of the costal cartilage compared with the articular one, it is interesting to note that the two tissues have a very similar histological structure. In both cartilage the cells are arranged in quite similar layers and the matrix show the same hyaline appearance: presence of type II collagen and solphated glycosaminoglycans, and absence of type I collagen and SOX-9.

It has been recognized that the middle and deep zone of articular cartilage are responsible for providing the greatest resistance to compressive forces, whereas the thin superficial zone protects deeper layers from shear stresses (14). Considering the orientation of the chondrocytes, the biochemical composition of the matrix and the disposition of the collagen fibers in costal cartilage, we are allowed to postulate that a chondral graft harvested from costal cartilage could be able to support the biomechanical loading imposed by a joint.

The deeper layer of the chondral rib, similarly to articular cartilage, shows a calcified appearance that becomes more pronounced in aged subjects. Therefore, this zone could represent a side adapt for osteochondral integration.

The bigger difference between the two hyaline tissues is the presence of perichondrium that surrounds all the specimens of costal cartilage. It consists of two separate layers where the inner one seems to get thinner with aging. The chondrogenic capacity of the perichondrium was first demonstrated by Skoog et al. in 1972 and it was assigned to the inner layer (15). Even though we did not analyze its biological capacity, we suppose that the thinning of the inner layer of the perichondrium after the achievement of skeleton maturity, could correspond to a progressive reduction of its chondrogenic potential (16).

In our research, we stained all specimens with anti-SOX 9 antibodies. SOX 9 is a transcription factor that acts during chondrocyte differentiation. Indeed, it has been well established that mesenchymal stem cells that undergo chondrogenic differentiation express SOX-9 that it is suppressed in hypertrophic

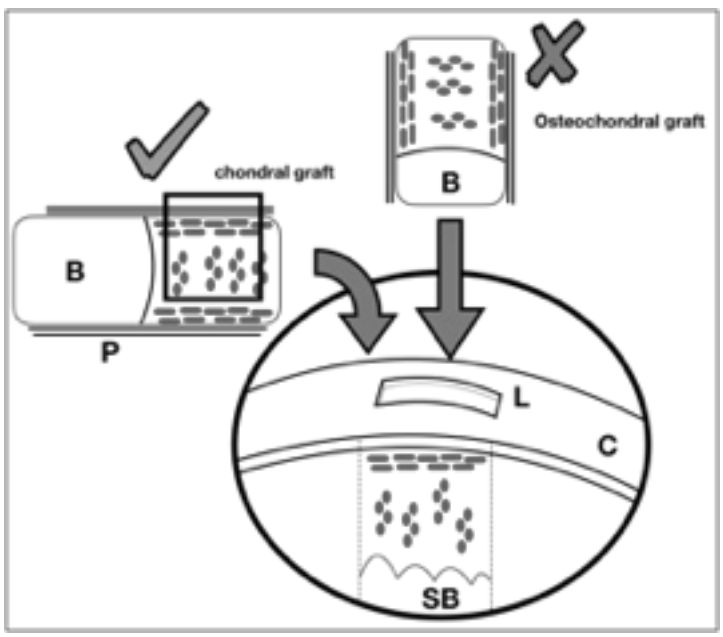

Fig. 7. Schematic representation of chondral and osteochondral graft from the rib. ***B***: bone; ***P***: periosteum-perichondrium; ***L***: lesion; ***C***: articular cartilage; ***SB***: subchondral bone. See the text in discussion.

and mature cartilage (17). For these reasons, we expected to find several cells stained with anti-SOX 9 antibody specially in the inner layer of perichondrium. However, all specimens showed no positivity for SOX 9 in both inner and outer layers. In contrast, our results showed a strong positivity for SOX 9 in the superficial zone of the rib, especially in samples from younger patients.

Ohlsén in 1976 showed that free perichondral grafts harvested from rabbit's ears and transplanted to several recipient tissues, produced new cartilage only when the perichondrium was grafted in the presence of clotted blood (18). In accordance with these evidences, the results of the present study support the hypothesis that the chondroprogenitor cells do not lie in the inner layer of perichondrium: only few cells have been observed in our specimens and they stained negatively for SOX 9. Chondroprogenitor cells could derive from the peripheral blood through vessels located in both layers of perichondrium and subsequently they could growth and differentiate under stimuli released from the perichondrium (19).

In repairing articular defects, some authors used rib osteo-chondral graft, with the bone-side of the graft in contact with subchondral bone in order to obtain bone integration (20). However, in this way chondrocytes and fibers would be located in a perpendicular direction respect to the compressive forces within the joint (Fig. 7, red cross). Thus, on the basis of the histological appearance, in our opinion rib cartilage should be harvested and inserted in a articular cartilage lesion as shown in Fig. 7 (green tick), in order to reproduce better the microarchitecture of the articular cartilage.

About the clinical relevance of this study, the results show that rib cartilage seems to be an adapt tissue as graft for articular cartilage repair. The main elements supporting the use of rib cartilage as articular graft are: i) articular and rib cartilage show a very similar structure and composition; ii) the perichondrium in the rib graft could promote the chondrogenesis process and facilitate the fixation of the graft to the surrounding healthy cartilage; iii) a right orientation of the costal graft could conferee biomechanical properties similar to the healthy articular cartilage and facilitate the integration between calcified cartilage of the deep zone of the graft and the subchondral bone of the articular lesions.

Further animal and clinical studies can define the therapeutical capacity of the costal cartilage as graft in the treatment of articular cartilage defects.

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MODULAR IMPLANT DESIGN AFFECTS METAL ION RELEASE FOLLOWING METAL-ON-METAL HIP ARTHROPLASTY: A RETROSPECTIVE STUDY ON 75 CASES

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Metal-on-Metal (MoM) total hip arthroplasty (THA) has been associated to wear and metal-ions release, controversially related to a variety of clinical complications. Little is known about the relevant design-dependent parameters involved in this process. The present study investigated the correlation between metal ion release in blood and revision rate as a function of: (i) specific MoM implant modular design parameters, (i.e. acetabular cup and femoral head diameters, taper adapter material and size, femoral neck material and modularity and stem size); (ii) MoM bilaterality. Co and Cr ions concentration levels in blood of 75 patients were retrospectively-evaluated with a mean follow-up of 4.8 years (range: 1.8-6.3). Patients were divided in a unilateral and a bilateral group. Statistical analysis was performed to find any significant difference related to acetabular cup diameter, femoral head diameter, taper adapter material/size, neck material/size and stem size. The bilateral MoM group had 4-times higher metal ion levels in blood than the unilateral one (p=0.017 only Cr), related to a higher revision rate (30% *vs* 20%): differences were 10-times higher particularly with a 48 mm femoral head diameter (p=0.012) and a Ti-alloy neck (p=0.041). Within the monolateral group using a shorter taper adapter and a shorter neutrally-oriented neck demonstrated higher ion levels (p=0.038 only Cr and p=0.008 only Co, respectively). The aforementioned design-features and MoM bilaterality are important risk-factors for metal-ion release in modular MoM THA.

Total hip arthroplasty (THA) faced an innovation in the last two decades mainly related to the exploitation of modularity, potentially adapting to any peculiarity in patients' anatomy, and the introduction of new metal-on-metal (MoM) bearing surfaces, aimed at minimizing wear debris formation compared to conventional metal-on-polyethylene (MoP) couplings (1, 2).

Recent clinical experience highlighted new potential issues related to the release of metallic ions and the formation of corrosion products leading to many complications. Adverse Local Tissue Reaction (ALTR), osteolysis and pseudotumour formation have often been reported as a consequence of metal-ion release in presence of large (diameter ≥36mm) MoM THA for a variety of implant designs (3-8). However, it must be recognized that no clear cause-effect relation has ever been quantitatively demonstrated (5). Moreover, some authors put under discussion the utility of metal ion levels detection alone as a reliable predictor of periarticular tissue reaction even in symptomatic patients (9, 10). Clinical

Key words: modular hip prosthesis, metal-on-metal, metal ion release, cobalt, chromium, revision, metallosis

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evidence pushed several national and international bodies to draw precautionary recommendations on the management and monitoring of metal ions levels in THA, particularly when MoM surface-bearings are used (caution range 2-7 μg/l, critical threshold 20 μg/l for Co) (11, 12).

Despite controversial results not always leading to painful symptoms may suggest the involvement of specific biological factors (13, 14) other never-investigated design-dependent parameters (i.e. implant size and materials) are expected to play a significant role.

The aim of the present retrospective comparative study is, therefore, to investigate the correlation between metal ions release in blood and (i) specific MoM implant modular design parameters, (i.e. acetabular cup and femoral head diameters, taper adapter material and size, femoral neck material and modularity and stem size), and (ii) MoM bilaterality.

MATERIALS AND METHODS

Patient cohort

Seventy-five subjects (51 males, 24 females), implanted with at least one primary MoM THA between March 2008 and December 2011, have been retrospectively analyzed. All patients provided written signature on informed consent. Indication for surgery was justified by one of the following reasons: coxarthrosis, rheumatoid arthritis or avascular necrosis. Patients were divided in two groups. The first one received a unilateral MoM THA (monolateral group). The second one underwent a staged-bilateral MoM THA (bilateral group). All surgeries were performed via a posterolateral approach, the piriformis and conjoined tendons and the posterior capsule were repaired in separate layers using a transosseous technique. All patients involved in the study signed the informed consent for the treatment of their data.

Implants

All patients were implanted with at least one THA composed by a Harmony modular cementless femoral hip stem (Symbios Orthopédie SA, Yverdon-Les-Bains, Switzerland), a modular neck in Ti6Al4V or CoCrMo alloys coupled to a MaxiMoM taper adapter in CoCrMo or Ti6Al4V alloys, respectively, and a MaxiMoM femoral head-cup system (Symbios Orthopédie SA, Yverdon-Les-Bains, Switzerland) with a large diameter MoM CoCrMo couple bearing.

The femoral stems ranged between 9 and 16 in size. The neck length was classified according to the manufacturer as short and long. The taper adapters were classified according to the manufacturer depending on their size small (S), medium (M), large (L) and extra-large (XL). The femoral head and the monoblock cup diameters ranged in between 40 and 56 mm and 48 to 64 mm, respectively.

Metal ion level-measurements

Patients were retrospectively assessed for postoperative cobalt and chromium ions level in venous blood. All patients with a MoM implant underwent blood metal ion determination as part of a monitoring program at our institution. Recorded analyses were extracted directly from IRCCS Galeazzi Orthopaedic Institute database.

Co and Cr ions concentration levels were expressed in μg/l. Data were organized for each of the two groups and within each group as a function of the design feature of interest, namely: acetabular cup diameter, femoral head diameter, taper adapter material and size, neck material and size, stem size.

Clinical evaluation and Imaging

Patients routinely received a radiograph (X-ray) to confirm a correct implant positioning and osseointegration. Each patient was periodically followed by an attending physician that performed a physical evaluation of any symptoms (e.g. pain, functional impairment). Further metal-ion analysis in blood and/or diagnostic imaging analysis were requested in some cases. Extra-routine radiographic analysis was further requested to check for suspected images of osteolytic areas around the implant or loosening. According to international consensus (11,12), specific symptomatic patients underwent extra-routine nuclear Magnetic Resonance Imaging (MRI), using a Metal Artifact Reduction Sequence (MARS) protocol, to look for the presence of cystic/solid soft tissue masses.

In specific cases, the attending physician decided for a revision surgery upon careful evaluation of all acquired information.

Statistical analysis

Statistical analyses were carried out with IBM SPSS

Statistics 24.0 (SPSS Inc., Chicago, Illinois). Preliminary multilinear regressions were undertaken to evaluate the relationship of Co and Cr ions levels to time and other specific design-features. A logarithm was necessary to transform the asymmetric metal ion distributions to approximately normal distributions (16, 17), as confirmed by Shapiro-Wilk normality test. Student's *t*-test was used to compare unilateral and bilateral MoM patients' groups and subgroups for metal levels assuming a significance level of 95% ($p<0.05$). Metal ion levels were presented as box-plot whenever possible (number of samples ≥3), specific values were reported otherwise.

To keep consistency, only patients with complete metal ion levels data are discussed herein against X-rays and MRI imaging analysis. The revision rate was reported in terms of absolute (over the whole population) and relative (for each patients' group) frequency. No attempt was made to quantitatively correlate metal ion levels with positive MRIs, X-rays nor symptoms.

RESULTS

Patient cohort

Sixty-five patients (86.7%) received a unilateral MoM THA (monolateral group) with a male-female ratio of 42:23 (demographic data are summarized in Table I). Two patients within the monolateral group had a non-MoM THA with a monolithic femoral component on the contralateral side.

Ten patients (13.3%) received a staged-bilateral MoM THA (bilateral group) with a male-female ratio of 9:1. Only one patient had a Profemur Z femoral stem with modular neck, both in Ti6Al4V alloy, a CoCrMo taper adapter, a CoCrMo femoral head coupled to a Procotyl acetabular (all components by Wright Medical Technology, Inc., Arlington, TN).

Metal ion level-measurements

Complete data were collected for 45 patients (60% of all patients) (Table II): 38 in unilateral group (male:female ratio of 27:11), 7 in bilateral group (6:1). Nineteen patients (25.3%) presented incomplete or not-available data, while the remaining 11 (14.7%) were lost at follow-up.

The metal ion level analysis was repeated over time for 15 patients; the average value was considered in the subsequent analysis since no correlation was observed over time.

The linear regression analysis demonstrates a very weak correlation between metal ions concentrations and acetabular cup diameter, femoral head diameter and stem size for each patients' group.

In general, the bilateral MoM group (Co: 44.9±42.7μg/l; Cr: 23.0±21.4μg/l) exhibited 4-fold

Table I. *General demographic information for each patients' group and the overall population.*

	Monolateral group	Bilateral MoM group	All patients
Patients' population (#)	**65 (42:23)**	**10 (9:1)**	**75 (51:24)**
Age at first surgery (years) mean ± standard dev. (min - max)	58.2 ± 11.1 (22.2 - 75.7)	56.2 ± 9.7 (38.6 - 72.7)	57.9 ± 10.9 (22.0 - 75.7)
Age at second surgery (years)	-	0.8 ± 0.8 (0.0 - 2.6)	-
Lost patients at follow-up (#)	**11**	**0**	**11**
(%)	16.9%	-	14.7%
Patients with incomplete or not available data (#)	**16**	**3**	**19**
(%)	24.6%	30.0%	25.3%
Number of patients with complete ions level data (male:female)	**38 (27:11)**	**7 (6:1)**	**45 (33:12)**
(% of total population) (male : female)	58.5% (64.3 : 47.8)	70.0% (66.7 : 100)	60.0% (64.7 : 50.0)
Follow-up time (years)	4.0 ± 0.4 (3.1 - 6.4)	4.1 ± 0.5 (2.7 - 6.0)	4.0 ± 0.4 (2.7 - 6.4)
Patients with extra-routine RX analysis (#)	**29**	**8**	**37**
(% of total population)	44.6%	80.0%	49.3%
Positive extra-routine RX analysis (#)	**9**	**5**	**14**
(% of total population)	13.8%	50.0%	18.7%
Patients with extra-routine MRI (conventional / MARS) analysis (#)	**23 (7 / 16)**	**7 (3 / 4)**	**30 (10 / 20)**
(% of total population)	35.4% (10.8 / 24.6)	70% (30 / 40)	40% (13.3 / 26.7)
Patients with positive extra-routine MRI (conventional / MARS) analysis (#)	**18 (6 / 12)**	**5 (2 / 3)**	**23 (8 / 15)**
(% of total population)	27.7% (9.2 / 18.5)	50% (20 / 30)	30.7% (10.7 / 20.0)
Number of revised patients (#) (male:female)	**13 (7:6)**	**3 (2:1)**	**16 (9:7)**
(%) (male : female)	20.0% (16.7 : 6.1)	30.0% (22.2 : 100)	21.3% (17.7 : 29.2)
Age at revision (years) (male:female)	3.4 ± 1.1 (1.7 - 4.8)	5.0 ± 2.1 (2.8 - 7.0)	3.7 ± 1.4 (1.7 - 7.0)

higher metal ion levels in blood than the unilateral one (Co: 10.0±7.5µg/l; Cr: 4.5±3.6µg/l), however they resulted significant only for Cr (p=0.017) (Table II, Fig. 1).

In regards to intergroup comparison, we found significantly higher Cr levels in bilateral group than in unilateral one with a 48mm head diameter (respectively, 43.2±32.8µg/l *vs* 2.3±0.8 µg/l, p=0.012; Fig. 1), as well as with a Ti6Al4V neck material (respectively, 42.6±33.1µg/l *vs* 3.5±2.2µg/l, p=0.041; Fig. 3). Despite the trend is similar, no statistical difference was met for Co.

In unilateral intragroup comparison, we found significantly higher Cr and Co levels, respectively, with a short (S) taper adapter size than a medium (M) (respectively, 9.9±7.1µg/l *vs* 2.4±1.2µg/l, p=0.038)

Table II. *Demographic information for patients with complete metal-ions level data.*

	Monolateral group	Bilateral MoM group	All patients
Patients with complete Co-level data (#)	**38 (27:11)**	**7 (6:1)**	**45 (33:12)**
(% of total population)	58.5% (64.3 : 47.8)	70% (66.7 : 100)	60% (64.7 : 50)
Follow-up time (years)	4.0 ± 0.4 (3.1 - 6.4)	4.1 ± 0.5 (2.7 - 6.0)	4.0 ± 0.4 (2.7 - 6.4)
Co ion level (µg/l)	10.0 ± 7.5 (0.3 - 80.1)	44.9 ± 42.7 (2.5 - 234.8)	15.2 ± 18.0 (0.3 - 234.8)
Cr ion level (µg/l)	4.5 ± 3.6 (0.1 - 40.8)	23.0 ± 21.4 (1.7 - 119.0) *	7.4 ± 9.2 (0.1- 119.0)
Patients with Co < 2 µg/l (#)	**9**	**0**	**9**
(% of patients with complete ion level data)	23.7%	- %	20%
Patients with Co in the range 2-7 µg/l (#)	**12**	**4**	**16**
(% of patients with complete ion level data)	31.6%	57.1%	35.6%
Patients with Co in the range 7-20 µg/l (#)	**16**	**1**	**17**
(% of patients with complete ion level data)	42.1%	14.3%	37.8%
Patients with Co >20 µg/l (#)	**3**	**2**	**5**
(% of patients with complete ion level data)	7.9%	28.6%	11.1%
Patients with extra-routine RX analysis (#)	**17**	**6**	**23**
(% of patients with complete ion level data)	44.7%	85.7%	51.1%
Patients with positive extra-routine RX analysis (#)	**5**	**2**	**7**
(% of patients with complete ion level data)	13.1%	28.6%	15.6%
Patients with extra-routine MRI (conventional / MARS) analysis (#)	**17 (5 / 12)**	**5 (2 / 3)**	**22 (7 / 15)**
(% of patients with complete ion level data)	44.7% (13.1 / 31.6)	71.4% (28.6 / 42.9)	48.9% (15.6 / 33.3)
Patients with positive extra-routine MRI (conventional / MARS) analysis (#)	**12 (4 / 8)**	**4 (1 / 3)**	**16 (5 / 11)**
(% of patients with complete ion level data)	31.6% (10.5 / 21.1)	57.1% (14.3 / 42.9)	35.6% (11.1 / 24.4)
Number of revised patients (#)	**5 (3:2)**	**2 (1:1)**	**7 (4:3)**
(% of patients with complete ion level data) (male : female)	13.2% (11.1 : 18.2)	28.6% (16.7 : 100)	15.6% (12.1 : 25.0)
(% of total population) (male : female)	7.8% (7.1 : 8.7)	20% (10.0 : 10.0)	9.3% (7.8 : 12.5)
Follow-up time (years)	3.5 ± 0.2 (3.1- 4.2)	3.9 ± 0.8 (3.3 - 4.5)	3.6 ± 0.3 (3.1 - 4.5)
Co ion level (µg/l)	18.2 ± 10.4 (3.8 - 54.7)	155 ± 148 (49 - 260)	54.3 ± 45.2 (3.8 - 260)
Cr ion level (µg/l)	12.2 ± 8.3 (1.3 - 40.8)	69.6 ± 69.9 (20.1 - 119)	30.0 ± 23.0 (1.3 - 119.0)

**: Significant difference compared to the monolateral group (p<0.05).*

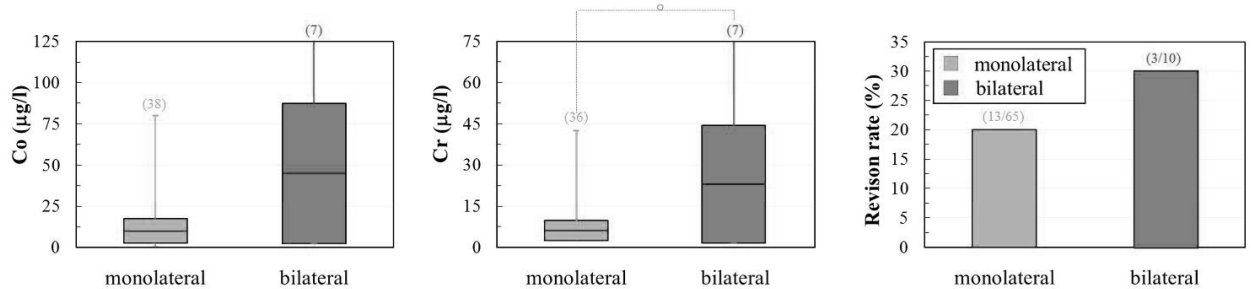

Fig. 1. *Box-plot of metal ions concentration levels and revision rate (calculated over the whole patients' population) for monolateral and bilateral MoM groups.*

(Fig. 2) and with a shorter neutrally-oriented neck size instead of a longer one (23.5±15.8 µg/l *vs* 3.5±1.6 µg/l, p=0.008) (Fig. 3).

No further significant differences were detected within each group nor among them considering cup diameter, taper adapter material (Fig. 2), nor stem size (Fig. 4) within the monolateral group.

Clinical evaluation and Imaging

In 37/75 patients (49% of total population) a further radiographic analysis was requested (Table I). Clear osteolytic areas and implant mobilization were positively assessed in 13 of them (17% of all patients): incidence was 2-fold higher in the bilateral group compared to the monolateral one (respectively, 4/10 *vs* 9/65).

Thirty patients (40% of total population) underwent an MRI, eventually according to an enhanced MARS protocol (Table I), confirming the presence of cystic/solid soft tissue masses in 23 cases (31% of all patients): again, the incidence was 2-times higher for the bilateral group compared to the monolateral (respectively, 5/10 *vs* 18/65).

When considering only patients with complete metal-ions level data, the relative incidence of positive RXs and MRIs confirmed to be about 2-times higher for the bilateral MoM group than the monolateral (Table II).

Revision

Sixteen patients (21% of total population) underwent revision surgery at an average postoperative time of 3.5±1.1 years (Tables I, II). In all revised cases, a ceramic head (Biolox Delta) was coupled to highly-cross-linked-polyethylene (XLPE) upon revision. Revision surgery due to sepsis was performed in 2 patients following a two-stage procedure with an antibiotic-loaded spacer.

The absolute revision rate was higher for the bilateral group (30%), but the sample size was different (13/65 *vs* 3/10, respectively). All revised patients reported symptoms (i.e. pain, functional

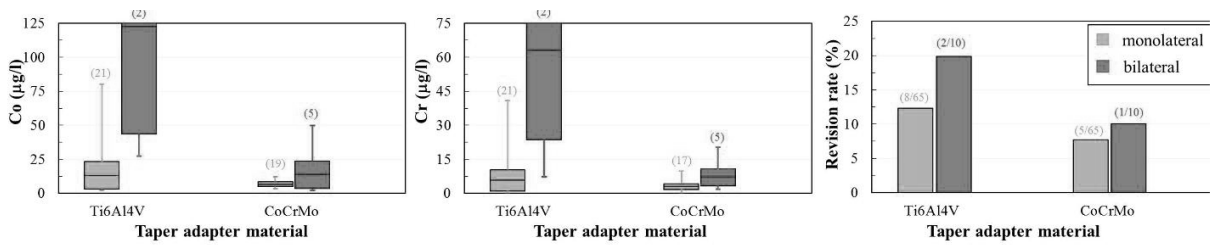

Fig. 2. *Box-plot of metal ions concentration levels and revision rate (calculated over the whole patients' population) as a function of taper adapter material. Statistically significant differences are indicated (*: p<0.05).*

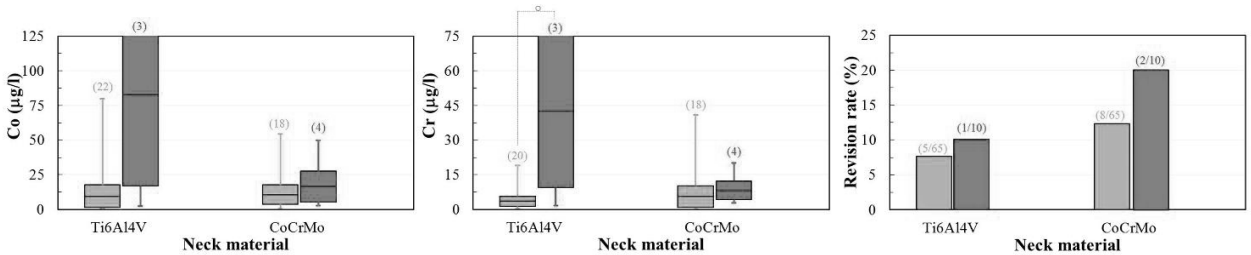

Fig. 3. *Box-plot of metal ions concentration levels and revision rate (calculated over the whole patients' population) as a function of femoral neck material. Statistically significant differences are indicated (* or °: p<0.05).*

impairment), sometimes confirmed through X-rays or MRI imaging analysis (Supplementary Material 1, 2).

Considering only patients with complete metal-ions level data (Table II), the relative frequency of revision was slightly lower (16%), but similar for both groups (bilateral: 2/7 *vs* monolateral: 5/38).

In general, all revised patients (Co: 54.3±45.2 µg/l; Cr: 30.0±23.0 µg/l) demonstrated significantly higher (Co: p=0.014, Cr: p=0.011) metal ion levels in blood than those unrevised (Co: 15.2±18.0 µg/l; Cr: 7.4±9.2 µg/l) (Table II). It is important to notice that such a result was not confirmed by a statistical difference between revised and unrevised patients within the monolateral group (Co: p=0.104, Cr: p=0.060).

Among the 7 revised patients with complete metal-ion level data (Supplementary Material 2), 5 had a positive MRI: 2 patients overcame the threshold of 20 µg/l for Co, while 2 were beyond the caution range for Co (2-7 µg/l). Despite the 2 remaining patients were in the caution range, both of them were revised due to implant loosening, but in one case a prosthetic joint infection (PJI) was the leading cause.

DISCUSSION

In the present study, we considered a large-head MoM THA design (femoral head diameters: 40-56 mm), based on modular parts differing in size and material, which has never been considered in the previous literature. Even considering only the unilateral group (the only one with enough samples), we noticed a slight trend toward higher average metal ion levels and higher absolute number of revisions with lower femoral head diameters (Fig. 1). Eight cases of revision at 44 mm, 3 at 40 mm and only 2 at 48 mm. As femoral head diameter and acetabular cup size are roughly proportional, the same trend could also be discussed for the latter parameter. Neglecting isolated peak values, the highest average metal ions concentrations were met at 44 mm for each of the two groups, without any significant difference compared to other diameters. A large systematic review reported highest metal ion concentrations after treatment with stemmed large-head MoM-implants and hip resurfacing arthroplasty (5), particularly in female gender (15). Beaulé and colleagues demonstrated that large-head MoM THA had significantly-higher Co level at 6 months, not confirmed for Cr, compared to hip-resurfacing system (16).

A pattern similar to the one we reported, with trend for ions concentration decreasing as bearing diameter increased, has been already showed for large-diameters THA (>55 mm) and hip resurfacing systems (17). Conversely, significantly higher Co levels for larger-head diameters (≥50 mm) compared to relatively-smaller head (range: 42-48 mm) in modular THA were also reported (8). The

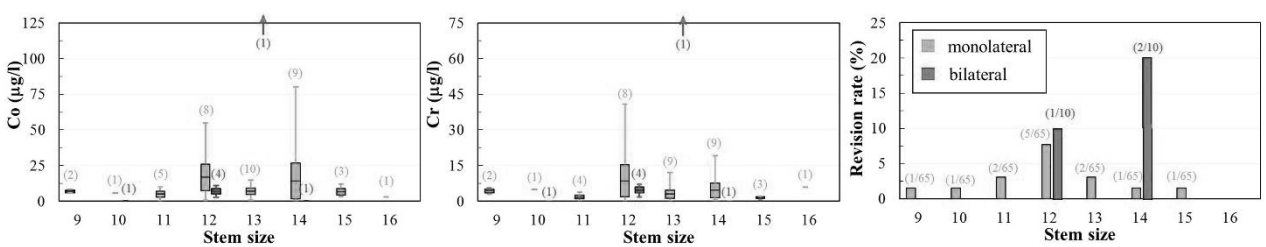

Fig. 4. *Box-plot of metal ions concentration levels and revision rate (calculated over the whole patients' population) as a function of stem size.*

explanation for higher metal ion release in smaller diameters should be searched in the reduced arcs of cover and the predisposition to edge wear of these components. On the other hand the open design of larger femoral heads (≥50 mm) with a larger contact surface for metal corrosion can account for higher metal ion levels compared to the closed head designs (≤48 mm).

Although the debate is still open, international, consensus-based statements on ion levels in blood have been defined: the threshold value for clinical concern is expected to be within the range of 2-7 µg/l, whereas excessive elevation (Co approximately 20g/L or above) of metal ions should prompt discussion with the patient about revision surgery because of potential osteolysis, tissue necrosis, and long-term health effects (11,12). Moreover, the current recommendation is to support metal ion level evaluation with specific imaging techniques (e.g. ultrasound, MARS-MRI, CT Scan,) and a systematic follow-up on patients implanted with a MoM bearing.

Beside femoral head diameters, other design-parameters needs further discussion against metal ion release. In fact, modular MoM THA designs often have several interfaces undergoing micromotions and susceptible of wear debris formation. Vendittoli demonstrated that the addition of a taper adapter with modular junctions and an open femoral head design causes more Co release than bearing surface wear in modular large-head MoM THA (8). Moreover, little is known on the consequences of using modular femoral necks and taper adapter with a variety of sizes and/or materials. To the best of our knowledge, these aspects

Supplementary Material 1. Diagnostic information for revised patients with incomplete/not available metal-ions level data and diagnostic imaging information (n.a.: not available; x: positive; o: negative; -: not done).

Patient	Co level (µg/l)	Cr level (µg/l)	RX	RMI	Symptoms (pain, functional impairment)	Suggested Diagnosis
M-20	100	n.a.	o	x	x	Metallosis
M-19	10.3	1.3	o	x	x	Metallosis
M-21	x	x	x	x	x	Metallosis
M-3	x	x	x	o	x	Cup mobilization
M-26	n.a.	n.a.	x	x	n.a.	Metallosis
M-23	n.a.	n.a.	x	x	x	Metallosis
M-25	n.a.	n.a.	x	-	x	Sepsis (Stapph.Epiderm.)
M-24	n.a.	n.a.	x	-	x	Cup mobilization
M-22	o	o	o	-	x	Stem mobilization

Supplementary Material 2: Diagnostic information for revised patients with complete metal-ions level data and diagnostic imaging information (x: positive; o: negative; -: not done).

Patient	Co level (µg/l)	Cr level (µg/l)	RX	RMI	Symptoms (pain, functional impairment)	Suggested Diagnosis
B-8	234.8	119.0	o	x	x	Metallosis
M-16	54.7	40.8	-	x	x	Metallosis
B-5	49.9	20.1	x	-	x	Stem mobilization
M-18	14.7	12.0	o	x	x	Stem mobilization
M-36	12.2	1.8	-	x	x	Periarticular cysts
M-17	5.8	5.1	x	x	x	Stem mobilization
M-12	3.8	1.3	x	-	x	Sepsis, stem/cup loosening

received very little attention in the literature.

As for implant modularity, the data collected for the unilateral group demonstrated significantly higher Cr levels using a shorter taper adapter size, while we noticed only a trend towards increased metal ion release with a Ti6Al4V taper adapter: in both cases this result is associated to a higher revision rate (Fig. 2). Despite only Co levels are significantly higher using a smaller neck instead of a long one (Fig. 3), we noticed a trend towards a slightly higher revision rate (7/65 *vs* 6/65, respectively); even though the average ion levels are similar, a femoral neck in CoCr is however related to a higher number of revision compared to Ti6Al4V (Fig. 3). These results may suggest that the modularity of neck-taper adapter system play an important role. In particular, increasing the bending stiffness of the neck-taper system (i.e. shorter/stiffer CoCr neck + shorter adapter size), may promote wear on the taper adapter, which would work as a damper interposed in-between the neck and the head taper joint. This mechanism may be promoted especially with a softer Ti6Al4V taper adapter with a reduced thickness (i.e. small size). To the best of our knowledge, only one recent radiographic study seemed to confirm our results towards an increased risk of complication (i.e. pseudotumour formation) in the long-term when a titanium taper adapter is used (18).

Regarding MoM bilaterality, we found that, in general, having a bilateral MoM THA led to higher Co and Cr values compared to the unilateral group, but they were significant only for Cr. Interestingly, Witzleb reported the same results for a THA with a smaller (28 mm) diameter until 1 year, but thereafter they did not notice any difference (19). Pelt found slightly higher cobalt levels in well-functioning MOM THA, not in chromium (20), while other study did not notice any difference (21). However, the difference we observed in metal-ions level found a confirmation in the absolute revision rate, which was higher for the bilateral group (3/10 or 30%) compared to the monolateral one (13/65 or 20%). Other studies including a variety of modular MoM THA designs reported variable revision rates: Bernthal found a 17% (or 12/70) for ultra-large-diameter femoral heads paired with a monoblock acetabular cup (22), while Mauer-Ertl reported a 27% (or 12/44) for large-head articular surface replacement systems (44-58mm) (23); Langton obtained a 6% (or 5/87) (24) and a 49% (or 42/87) (17) for large-head diameters THA (39-57mm and >55mm, respectively), whilst Koziara reported a 22% (or 21/66) (25).

The current retrospective study presents some intrinsic limitations. Information about the preoperative ion-concentration levels is missing. Data were not acquired at regular follow-up times, nor were they homogeneously distributed across the two groups. The limited sample size made, sometimes, impossible to perform any quantitative statistical analysis. This aspect was more critical for the bilateral MoM group, where different implant size and material were mixing up adding a confounding effect. Moreover, issues related to the ion level evaluation (9, 10), resulted in very highly-dispersed data, with rather high and isolated values.

The paper related modular design features of MoM THA to significant differences in Co and Cr levels in blood: neck length and taper adapter size were found to contribute in increasing metal-ion release.

Having a bilateral MoM THA may lead to higher absolute metal-ion levels in blood compared to a unilateral implant, however the revision rate is comparable.

Complete diagnostic imaging analysis and a rigorous clinical evaluation of patients, represent necessary information to integrate metal ion level measurements and to support physicians in decision-making process.

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CHEMICAL AND PHYSICAL INFLUENCES IN BONE AND CARTILAGE REGENERATION: A REVIEW OF LITERATURE

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Nowadays several studies demonstrate the influence of chemical and physical stimulation to bone and cartilage exist. The first studies date back to the 50s and for a long time, they did not have a strong impact on clinical practice. In recent times, however, the findings arising from these studies are increasingly used to address clinical problems such as osteoarthritis or non-unions. The aim of this article is to make a review of the literature of the state of the art about physical and chemical influences on bone and cartilage.

Updated data show that in the United States of America every year about 6 million fractures occur and that a percentage ranging from 5 to 10% of these fractures evolve in non-union (1). It is shown how the patient affected by non-union has a poor quality of life, even worse than dialysis or ischemic heart disease (2). Some non-unions are surgically treated, with varying success rates based on the type of non-union (atrophic *vs* hypertrophic) (3). Delayed bone healing increases the use of resources and increases the costs of health care for both patients and health care suppliers (4).

The aim of this report is to analyze and compare devices known as bone stimulators, which use several technologies that promote bone healing via applying energy fields.

The first use of electric current in the treatment of bone diseases involves electro-stimulation to induce or increase bone healing. Some reports confirm that Birch in 1827 experimentally used electric currents to heal a tibial non-union.

More recently, Fukada developed the theory of bone healing mediated by electric current that led to the application of piezoelectric fields in bone healing (5). Yasuda first described the concept of piezoelectric crystals and their action on bone when a mechanical force or stress is applied (6). The bone, similar to the piezoelectric crystals, tends to have an equal distribution of positive and negative electrical charges, symmetrically distributed, that create a neutral equilibrium until a mechanical or electrical stress is applied. These electrical charges are typically associated with the abundant calcium phosphate crystals and transmembrane potential present in the extracellular matrix and cells of this tissue.

Key words: bone, cartilage, chemical stimulation, physical stimulation

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When a mechanical stress is exerted on bone, the negative potentials tend to align on the compression side, whereas the positive potentials tend to align on the tension side. Due to the increased presence of negative potentials on the compression side of bone, further research has found that bone production is enhanced at the regions of negative polarity, and bone resorption is stimulated in the areas of positive polarity and tension (1, 7). Moreover, regions with an increased cellular activity tend to have negative potentials for example in the physis, and electronegative potentials promote cell proliferations in the fracture (8). In addition, the electric fields stimulate the expression of bone morphogenetic proteins, transforming growth factor-beta and insulin-line growth factor II in the extracellular matrix of bone and cartilage (9).

The positive effect of electromagnetic fields and electric current in bone regeneration has led to the development of new technologies to improve healing. Many of the efforts have focused on the long bone fractures (especially the tibia); but recently, studies have been also focusing on foot, ankle and wrist delayed unions, non-union and arthrodesis (10, 11, 12).

Bone stimulation techniques are mainly used for delayed unions and non-unions. Delayed union is defined as a delay in bone healing following a bone fracture, which shows no signs of healing within 6 months of the fracture event. Non-union is defined as a fracture that has not healed within 6 months.

These definitions do not take into consideration the physiological differences present in the healing process among different bones. According to Wiss and Stetson, the designation of a delayed union or non-union is currently assigned when the surgeon believes the fracture has little or no potential to heal (13). This definition, although realistic in clinical practice, does not consider the standardization of treatments but it allows the surgeon to decide on the subsequent therapies. However, it essential to remember that bone stimulation systems are only adjuvants to bone healing, and not the main actors of the process: modern methods of fixation, both internal and external, remain fundamental. Moreover, bone stimulation devices do not correct any deformities (varus/valgus or torsional) that may derive from the fracture.

Over the years, several devices have been developed that aim to stimulate bone-healing growth. The first and most important division is between devices that perform an electrical or an ultrasound stimulation. The subcategories include Direct Current (DC), Capacitive Coupling (CC), and Pulsed Electromagnetic Fields (PEMFs, inductive coupling).

Direct current

DC stimulating devices are created to convey a continuous electric current to the healing bone. This technique requires a surgical approach, where a cathode is placed closed to the affected area or in direct contact via a transducer. This device allows to concentrate the maximum amount of energy in the target area and to provide a constant electric current. The obvious disadvantage is that surgery, albeit minimal, is necessary to position the device, with possible complications: infections, wound dehiscence, bleeding, continuous medication and discomfort for the patient. To date, there is no randomized controlled trial that demonstrates the real effectiveness of this type of device, but clinical studies demonstrate efficacy up to 80% (14). These studies are mainly conducted on delayed unions and corrective osteotomies (15).

Capacitive coupling

The concept underlying the CC is similar: an energy source has more effect if it is concentrated in the area of interest. Unlike DC, the CC is non-invasive but it requires the application of skin electrodes close to the affected area. The DC needs an external transducer, a frequent battery change and can often lead to skin irritation. Several controlled studies have shown the efficacy of this type of treatment: the success rate varies from 60% to 77% (16); the best results have been obtained at the tibia level, probably due to thin layer of skin of this anatomical region (13, 17).

Pulsed electromagnetic fields

PEMF devices are non-invasive and do not require surgical procedure. They are based on the possibility of conveying this type of energy through soft tissues. This type of device produces a low-intensity electromagnetic field, which mimics the physiological conditions of bone healing. (18) The advantages of this type of stimulation reside in the non-invasiveness

and in the possibility of use even on cast devices.

The application time is crucial: the manufactures suggest 3 to 10 hours per day as the literature data demonstrate a strong reduction in the reliability for short stimulations (19). When applied correctly, PEMF has shown good results in the treatment of delayed unions and non-unions. Higher-level studies have included a randomized double-blind trial for 31 femoral intertrochanteric osteotomies (20), a multicenter double-blind trial in 45 tibial shaft non-unions (21), and several other small comparison studies focused primarily in long bone delayed or non-unions (11).

A 2011 meta-analysis attempted to summarize 4 randomized controlled trials, but due to the high heterogeneity of the studies, this was not possible (22). Beherns et al, assert that large, randomized, placebo-controlled trials are lacking, and much of the data reflect larger case series and comparative studies. Nevertheless, basic science and clinical evidence support the efficacy of bone growth stimulation as a fracture healing modality in the appropriate clinical situation (23). The most recent meta-analysis of RCTs on PEMF found that these devices might have significant benefits in healing time of acute fractures (11, 24).

Considering their results, Ehnert et al. suggest that a treatment with gradually increasing frequency might be of interest, as the lower frequency (16 Hz) could enhance bone formation, while the higher frequency (26 Hz) could enhance bone remodeling (25).

Kang et al. carried out a study where they evaluated the effectiveness of electromagnetic fields as pretreatment on mesenchymal stem cells to stimulate osteogenic differentiation. The results were encouraging, as they showed induced osteogenic marker expression via bone morphogenetic protein, transforming growth factor b, and Wnt signaling pathways based on microarray analyses (26).

Low intensity pulsed ultrasound

The function of Low Intensity Pulsed Ultrasound (LIPUS) is to transmit mechanical forces through soft tissues, to enhance micro-movements of the affected area; micro-movement generates a cast of second messengers that stimulate bone-healing process (27). The frequencies range between 1.5 and 3 hertz, with an application of about 20 min a day for up to 6 months. Despite its non-invasiveness, the treatment efficacy decreases in absence of contact between the hand-piece and the skin: this problem can be solved by using a plaster or bandages. LIPUS must be performed on a daily basis and this can decrease patient compliance. The first efficacy studies were conducted on animals (28), while the first studies on human beings were produced starting from the 50s of the last century (29). The results found in the literature are discordant, most of the studies demonstrate only a partial efficacy (30, 31, 32). The effect mostly described in literature is the decrease fracture healing time (30) that may be due to an enhancement in endochondral ossification as Katano suggests (33). In any case, stable fixation and a modest inter-fragmentation gap are crucial for a proper healing process as emphasized by Roussignol et al (34).

Physical influences on cartilage

Physical stimulations, such as pulsed electromagnetic fields, have been used for a long time in the context of bone regeneration and healing. Lately, several studies have been conducted also on osteochondral lesions.

Cheng et al. have shown that PEMFs cause an increase in DNA and collagen synthesis in chondroblasts (35). According to Iwasa, PEMFs stimulate chondrocyte proliferation, differentiation and extracellular matrix synthesis due to the release of anabolic morphogenic proteins such as BMPs and anti-inflammatory cytokines by adenosine receptors A2A and A3 in both in vitro and in vivo investigations. It is noteworthy that in clinical translational investigations a beneficial effect was observed on improving function in knee osteoarthritis (36).

Results show that BMC and PEMFs might have a separate effect on osteochondral regeneration, but it seems that they have a greater effect when used together. Biophysical stimulation is a non-invasive therapy, free from side effects and should be started soon after BMC transplantation to increase the quality of the regenerated tissue (37).

Hilz et al. have shown that seeded chondrocytes

on 3D scaffold express higher levels of chondrogenic markers when stimulated with electromagnetic fields (38).

Chemical influences on bone

Bone repair can also be influenced by chemical mediators. These chemical mediators can be conveyed *in situ* directly or by synthetic bone grafts enriched by these molecules. Therefore, these materials are both osteoconductive and osteoinductive (i.e. allogeneic or autologous bone graft).

The properties of a bone substitute, such as granule size, macroporosity, microporosity and shape, have been shown to influence the cellular inflammatory response. Ghanaati et al. analyzed the *in vivo* tissue reaction to three bone substitute materials (granules) with different chemical compositions (hydroxyapatite (HA), beta-tricalcium phosphate (TCP) and a mixture of both with a HA/TCP ratio of 60/40 wt%. Results showed that the chemical composition of bone substitutes significantly influenced the cellular response.

When compared to HA, TCP significantly attracted greater number of multinucleated giant cells within the implantation bed (39). Hydroxyapatite has always been considered a material with excellent osteoinductive capabilities, excellent biocompatibility and controlled biodegradability. This material is composed of a calcium and phosphate reticulum, with a hexagonal bipyramidal structure (40). The Ca/P ratio of calcium phosphate is a crucial factor that should be considered when selecting nano-to-micron particulate calcium phosphates for various orthopedic applications (41). Frasnelli et al. have shown that the replacement of carbon with strontium in the hydroxyapatite promotes cell growth without affecting the morphological characteristics of the cells (42).

In recent years, the attention of biologists and researchers focused on the use of mesenchymal stem cells (MSCs). A study by Castano-Izquierdo tried to define the ideal culture conditions to promote osteogenic differentiation of MSCs: the medium was enriched with a-MEM supplemented with 10% fetal bovine serum (FBS), ascorbic acid, b-glycerophosphate, and 10 nM dexamethasone. This study showed that chemical mediators present in the medium are essential for differentiation; moreover, culture time is also crucial: longer pre-culture periods lead to a progressive decrease in osteogenic potential (43).

Chemical influences on cartilage

To date very few studies deal with chemical influences on articular cartilage on humans: most of the researches are focused on animal models, mainly

Table I. *Summary table on chemical and physical influences on cartilage and bone.*

	Chemical influences	**Physical influences**
Bone	hydroxyapatite (HA), beta-tricalcium phosphate Ca/P ratio Strontium MSCs	*Direct current* *Capacitive coupling* *Pulsed electromagnetic fields* *Low intensity pulsed ultrasound*
Cartilage	Matrix metalloproteinases Transforming growth factor beta Calcium (Ca), Magnesium (Mg), Zinc (Zn), and Lead (Pb) MSCs	*Pulsed electromagnetic fields*

due to the difficulty in human samples' harvesting. Osteoarthritis (OA) is a degenerative condition caused by an alteration of multiple molecular signaling pathways that leads to a subsequent self-sustaining degradation of the articular cartilage.

Matrix metalloproteinases (MMPs), especially MMP-13, are key enzymes in the cleavage of type II collagen, which is a vital component for cartilage integrity. Transforming growth factor beta (TGFβ) can protect against pro-inflammatory cytokine-mediated MMP expression. With age, there is a change in the ratio of two TGFβ type I receptors (Alk1/Alk5), a shift that results in TGFβ losing its protective role in cartilage homeostasis. In this case, TGFβ promotes cartilage degradation, which correlates with the spontaneous development of OA in murine models. However, the mechanism underlying changes in TGFβ action with age has not been extensively studied (44).

In 2018 Kosik-Bogacka and colleagues demonstrated the correlation between calcium (Ca), magnesium (Mg), zinc (Zn), and lead (Pb) in degenerated cartilage obtained during hip replacement procedures. They found significantly higher concentrations of Ca, Mg, and Zn in men than in women. They also demonstrated a higher concentration of Pb in cartilage of patients over 65 years old. On the other hand, no relationship was found between Ca, Mg, Zn, and Pb levels and BMI (45).

Lately, the use of mesenchymal stem cells represents a valid treatment for osteoarthritis, due to their very well-known anti-inflammatory and regenerative properties (46). There are numerous preclinical studies that demonstrate the efficacy of MSCs in osteoarthritis (OA), but still few randomized controlled clinical trials. One of the few recent studies refers to the preliminary results on the application of autologous stem cells in the treatment of knee osteoarthritis (47). However, clinical evidences on the efficacy of MSCs in OA are still missing; thus, further clinical trials are required.

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FIBULA-PRO-TIBIA TRANSFER WITH EXTERNAL FIXATOR AFTER TIBIA FRACTURE WITH EXTENSIVE BONE DEFECT: A CASE REPORT

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A 27-year-old girl suffered a tibial fracture with an extensive bone defect due to a major trauma. At first, she was treated with a plate with the purpose to obtain a fibula-pro-tibia transfer, without any improvement. At one-year-follow up, a non-union due to mechanical hardware failure was shown by x-ray. Thus, a second surgery was performed: the ipsilateral fibula was tightly wedged between the preserved proximal and distal third of tibia with an external fixator. We report a follow up of 1 year after the reconstruction that allowed a good bone healing and a remodeling with also further ossification of the periosteal sheath of the fibula.

Case Report

In June 2009 a 27-year-old girl fell from a window and suffered an open fracture of her right tibia with an extensive bone loss (Gustilo type III) (1). She was treated first at another institute with internal fixation using the "fibula-pro-tibia" procedure (fusing the tibia and fibula together to create a one-bone leg). The proximal and distal part of the tibia were plated, and the screws were brought across to the fibula cortex (Fig. 1A).

At the 3- and 6-months follow-ups, X-Rays showed no evidence of bone healing and the patient's clinical conditions didn't improve. At the clinical inspection walking was not conceivable and pain did not permit joint mobilization, neither knee nor ankle. Besides, remodeling of the reconstructed tibia was not present at the radiological examination (Fig. 1A).

At 9 months follow-up the proximal screws appeared broken; however, no further treatments were applied (Fig. 1B).

The patient first presented to us in June 2010. She reported worsening in pain and a leg deformity was evident. X-rays showed hardware failure at the level of the distal fibula-tibia junction, due to non-union, and the consequent valgus deformity of the ankle (Fig. 2).

A surgical procedure became necessary: the skin and the soft tissues were compromised and the development of an atrophic non-union limited the therapeutic strategies. Moreover, a severe external popliteal sciatic nerve paresis and limitation of the

Key words: fracture, bone defect, external fixator, case report

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right ankle range of motion worsened the clinical conditions.

In July 2010 we opted for stabilization with an external fixator: the ipsilateral fibula was tightly wedged between the preserved proximal and distal third of tibia, as a local bone flap. Tibia was fixed to the fibula cortex with pins, to ensure stability and to restore the physiological load axis (Fig. 3A, B).

The patient was discharged from the hospital after 5 days from surgery, walking on crutches. A rehabilitation program was suggested, to increase muscle strength and to improve the neurological status.

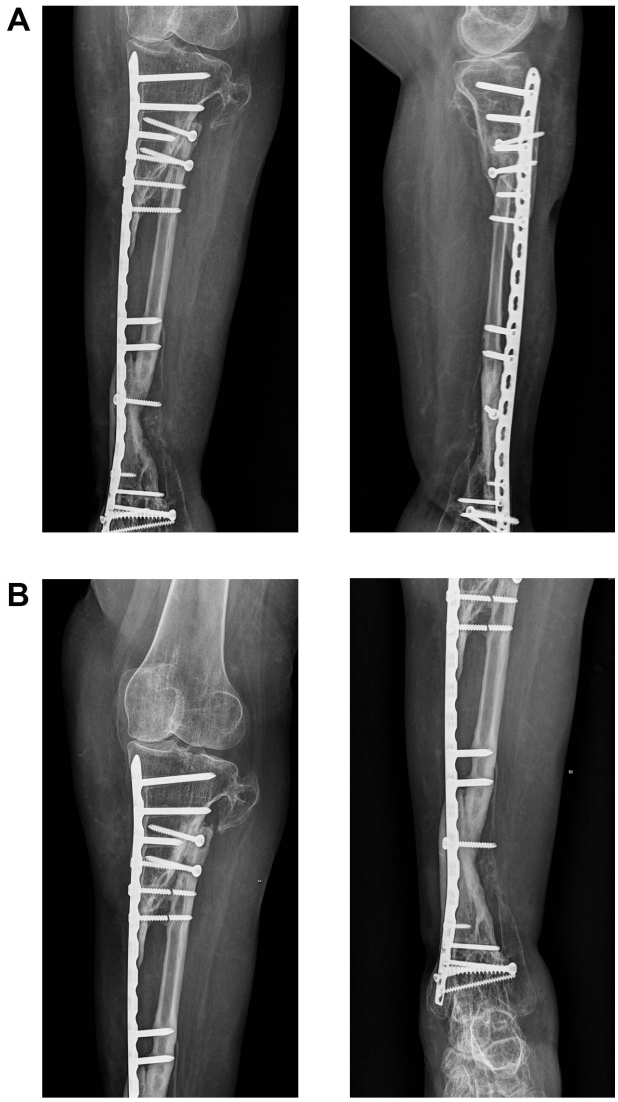

Fig. 1. ***A)****: The proximal and distal part of the tibia were plated;* ***B)****: proximal screws appeared broken at 9- month follow-up.*

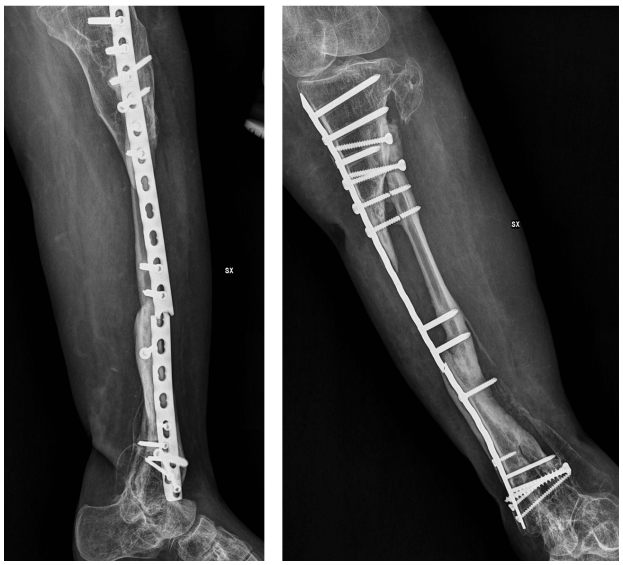

Fig. 2. *X-rays showed hardware failure at the level of the distal fibula-tibia junction, due to non-union, and the consequent valgus deformity of the ankle.*

At 1-year follow-up no evidence of bone healing was shown at X-rays (Fig. 3C); thus, the patient underwent another surgery five months later. We decided to increase the compaction thrust by using two olive wires: the first one was placed with an oblique direction, pushing the middle section of the fibula, to achieve medial translation of the fibula; the second one was placed with opposite direction, pushing the distal part of the tibia towards fibula, so as to obtain major stability of the frame and to decrease the distance between tibia and fibula (Fig. 3D).

In June 2011 radiological evidence of initial medial shift of the fibula towards the distal part of the tibia and early callus formation were found. A further surgery was necessary to ensure a complete medial translation: we replaced the former proximal oblique olive wire with a right direction one in order to enhance the medial shift (Fig. 3E, F).

In December 2011 X-rays showed a 12° valgus deformity of the distal part of the tibia (Fig. 4A) due to patient being overweight and to the relative instability of the external fixation frame. Bone healing process requires two conditions: the stability on the bony segment and their compression with a corrected axis load; therefore, we planned another surgery in January 2012 using an olive wire pushing the distal part of the

tibia, to obtain a reduction of the valgus displacement (Fig. 4B).

Six months after surgery, the compression force seemed inadequate, confirmed by radiological evidence of tibia and fibula diastasis. We opted for the use of a 3.5 mm cannulated screw to obtain better bone regeneration and compression, with the aim to reduce the dislocation, as shown in (Fig. 4C).

At the following yearly controls, encouraging bone healing signs with progressive fibula hypertrophy and improvement of the bone regeneration were assessed, especially in the proximal portion of the tibia, where formation of an exuberant callus was evident (Fig. 4D). In June 2015 bone regeneration was complete, and the fibula was totally integrated with the tibia.

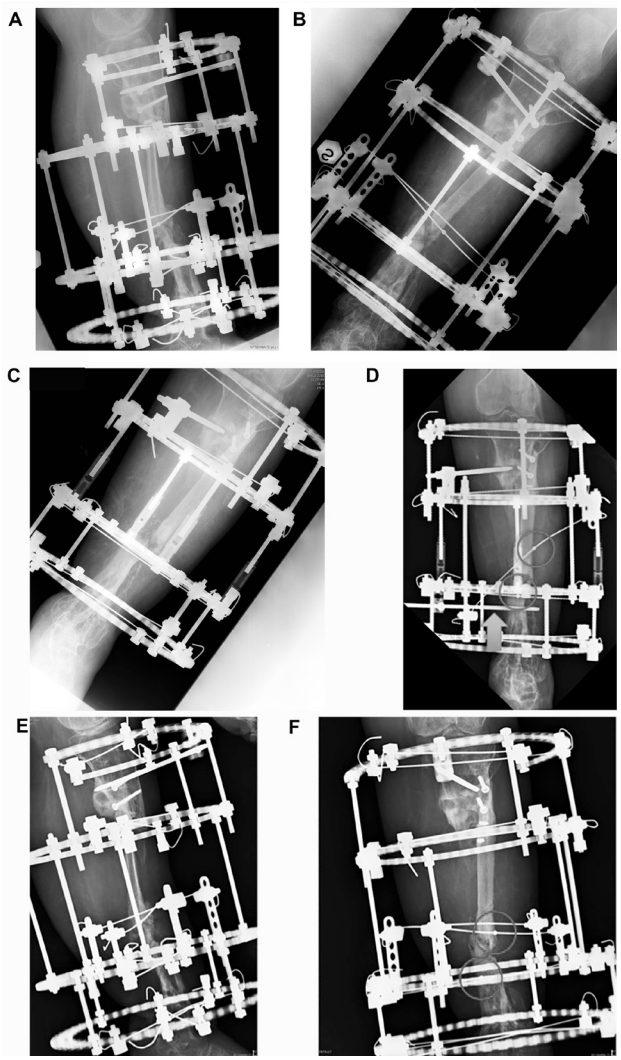

Fig. 3. ***A, B)****: Stabilization of bone graft by external fixator frame;* ***C)****: No evidence of bone healing at 1-year follow-up;* ***D)****: olive wires were used to increase the compaction;* ***E)****: Early callus formation;* ***F)****: change of olive wire direction.*

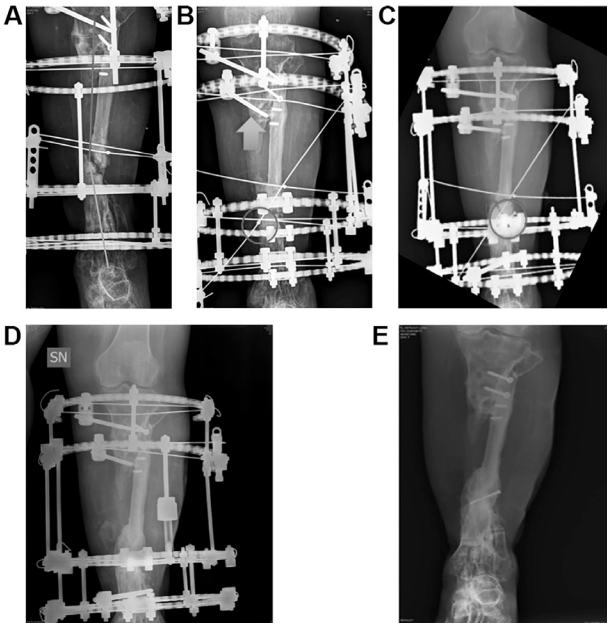

Fig. 4. **A**)*. The X-rays show a valgus deformity of the distal part of the tibia;* ***B)****. Reduction of the valgus displacement after the revision surgery with an olive wire pushing the distal part of the tibia;* ***C)****. A 3.5 mm cannulated screw was used with the aim to reduce the dislocation;* ***D)****. The last X-ray follow-up with the external fixator showing encouraging bone healing;* ***E)****: The x-ray control after the removal of external fixator; a satisfying result in terms of stability of the "new tibia" is evident and a complete load was allowed.*

In conclusion, after a 7-year treatment we obtained satisfying results in terms of stability of the "new tibia" and we removed the external fixator in January 2017, recommending a cast for the following two months, subsequently replaced by an orthosis Walker type that allowed complete load and the possibility to walk with a protected leg (Fig. 4E).

RESULTS

At one-year follow-up, a physical and psychological recovery was achieved. Patient was able to walk without crutches with less than 2 cm right lower limb hypometria, which was well compensated during the ambulation. Radiologically no evidence of valgus or varus deformity was present; however, a residual procurvatum of the tibia was shown in the lateral

view. An ankle arthrodesis was clinically assessed in association with deficit of the anterior tibialis, already present before our surgery. A complete knee ROM was otherwise found. During the 7-year treatment, no major complications had been reported, except for superficial pin site infections.

DISCUSSION

Tibial open fractures often result in a bone gap. In these cases, surgical repair may be difficult and unsuccessful, due to the entity of the defect, the soft tissue involvement and the vascular conditions, which may cause osteomyelitis.

Conventional bone grafting leads to optimal bone healing and satisfactory clinical result for defects shorter than 6 cm, if the area is well vascularized and not infected (2). In the case of major bone gaps, conventional techniques of bone grafting may increase the risk of non-union and infection; thus, advanced surgical procedures should be considered.

Flanagan JJ. et al. (1947) (3) proposed a hemidiaphisectomy of the affected bone; in this case, the removed cortex was used as a graft. During the years, some alternative limb-salvage techniques have been proposed by several authors. The surgical options that have shown the best clinical results are contralateral fibular grafting (4), the bone transport using the Ilizarov method (5), the Masquelet's Technique (6) and ipsilateral fibula-pro-tibia.

Ipsilateral fibular grafting was first proposed by Hanh in 1884. The surgical procedure was developed by Huntington (7) in 1905, who described the use of the whole segment of fibula to bridge a tibial defect with an internal fixation. Some authors modified the technique during the XX century, readapting it to the specific clinical cases (8-11).

In 1998 Catagni et al. (12) first, followed by Kim et al. (13), introduced ipsilateral fibular transfer with an external fixator using the traction by olive wires to accomplish gradual transport.

Although the potential advantages of this surgical procedure could be interesting, there are just few cases published in literature (12, 14, 15), probably due to the low incidence of the extreme clinical condition and the technical difficulties of the surgical technique.

The case we described had some additional issue: the neurological peripheral and the soft tissue conditions were seriously compromised; a previous treatment had been unsuccessful; moreover, a septic status limited the therapeutic possibilities. For all these reasons, the use of contralateral vascularized fibula was not preferable, to avoid possible complications to the unaffected limb. Besides the impaired vascularization of the receiving site would have possibly compromised the graft vitality.

The external fixator maintains the limb stability while achieving the transport of the ipsilateral fibula, which allows for early weight-bearing to increase fracture healing potential (16). The early load also leads to hypertrophy of the bone which is desirable in the fibula-pro-tibia transfer.

Amputation was maybe the only option and the simplest surgical solution to treat this patient, who appeared exhausted due to the failure of previous treatments. Despite the recent advances in leg prosthesis techniques (17), limb amputation is still considered disabling in our society and it is associated with anxiety related disorders and depression (18). Besides the cosmetic aspect needed to be considered in a 27-year-old woman. The cost difference between amputation and reconstruction has not been well assessed in literature; some studies underline that the surgical and medical expenses and the cost of rehabilitation after the surgical salvage procedures are higher than those for the amputation (13, 19). Williams, considering the need of prosthetic changes after a few years, reputed the long-term costs of amputation greater than the external fixator treatment, once limb salvage has been accomplished (20).

Amputation was the only therapeutic option in the past for open fractures with massive bone defects. Nowadays limb salvage surgery should be considered in these extreme situations as it could be a reasonable alternative. We think the fibula-pro-tibia transfer with the Ilizarov method may lead to a satisfying bone healing and compensatory hypertrophy of the fibula to create a one-bone leg. In our case, the 7-year treatment with the external fixator and the residual ankle arthrodesis represent the negative aspects of the procedure, but the patient well accepted these side-effects as this surgical technique allowed her to

maintain the lower limb and walk without pain. To date, the only limits of this surgical approach are the technical difficulties and the need of an experienced surgeon in the Ilizarov method.

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GENETICS IN ORTHOPAEDIC PRACTICE

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Abstract DNA holds genetic information in the nucleus of eukaryotic cells; and has three different functions: replication, storage of hereditary information, and regulation of cell division. Most studies described the association of single nucleotide polymorphism (SNP) to common orthopaedics diseases and the susceptibility to develop musculoskeletal injuries. Several mutations are associated with osteoporosis, musculoskeletal ailments and other musculoskeletal deformity and conditions. Several strategies, including gene therapy and tissue engineering with mesenchymal stem cells (MSC), have been proposed to enhance healing of musculoskeletal tissues. Furthermore, a recent technique has revolutionized gene editing: clustered regularly interspaced short palindromic repeat (CRISPR) technology is characterized by simplicity in target design, affordability, versatility, and high efficiency, but needs more studies to become the preferred platform for genome editing. Predictive genomics DNA profiling allows to understand which genetic advantage, if any, may be exploited, and why a given rehabilitation protocol can be more effective in some individual than others. In conclusion, a better understanding of the genetic influence on the function of the musculoskeletal system and healing of its ailments is needed to plan and develop patient specific management strategies.

Cell biology and genetics are rapidly evolving basic science fields currently being explored to provide a better understanding of the defects underpinning musculoskeletal diseases. Much research and development pertains to orthopaedics, and the study of genomics is the foundation to personalized medicine.

DNA is composed of two nucleotide chains forming a double helix, each consisting of a deoxyribose sugar–phosphate (phosphodiester bonds) backbone with bases bonded with complementary bases on the opposite chain. Eukaryotic cells host many DNA types mostly located in the nucleus (Table I). DNA has three cellular functions: replication (the two DNA strands separate, and each serves as a template for building a new complementary strand), hereditary information (every base pair and nucleotide sequence is necessary for build and maintain the organism), and regulation of cell division (through the expression of mRNA) (Fig. 1).

Nucleotides are the structural units of RNA and DNA. The current human genome sequence contains 2.85 billion nucleotides interrupted by only 341 gaps. It covers 99% of the euchromatic genome, and is accurate to an error rate of one per 100 000 bases (1).

Key Words: crisp, DNA, genetics, muscles, rehabilitation, tendon

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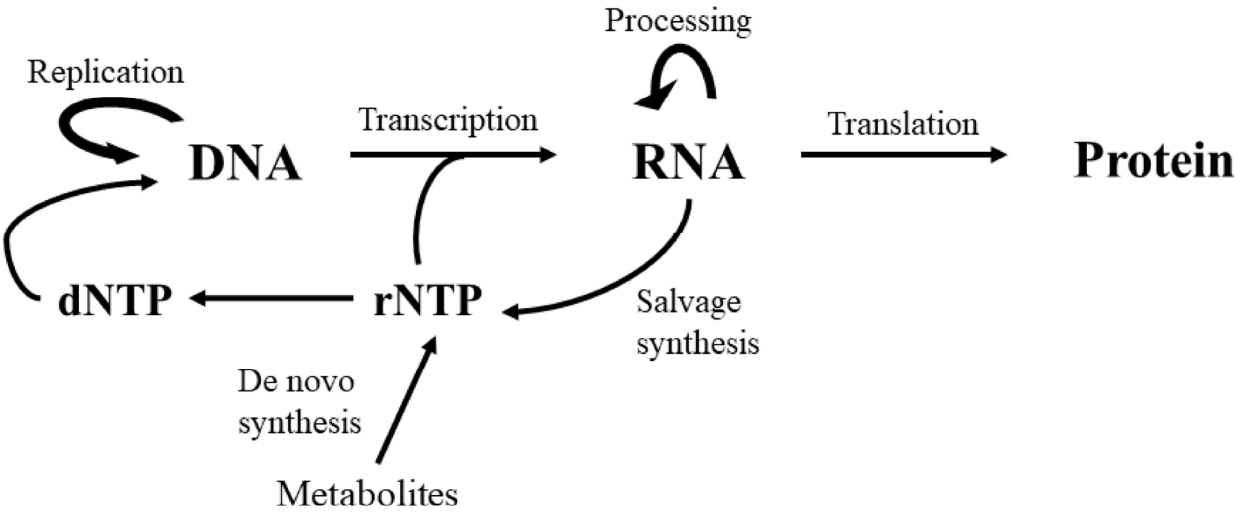

Fig. 1. *Central dogma of molecular biology: from DNA replication to protein synthesis.* ***dNTP****: deoxyribose nucleoside triphosphate,* ***rNTP****: ribonucleoside nucleoside triphosphate.*

Table I. *Rapid overview and description of DNA and RNA types.*

Type of DNA and RNA	***Abbreviation***	***Description***
Nuclear DNA	nDNA	In the nucleus, it has three cellular functions: replication, hereditary information, and regulation of cell division.
Mitochondrial DNA	mtDNA	A double stranded circular molecule located in mitochondria and derived from the bacterial genomes. It is inherited from the mother.
Transfer RNA	tRNA	A small chain of about 80 nucleotides, it transfers specific amino acid molecules to a growing polypeptide chain.
Ribosomal RNA	rRNA	Synthesized in the nucleolus, it is combined with protein to form a nucleoprotein called ribosomes which are formed by two subunits (large and small subunit). There are 4 different types (28S rRNA, 18S rRNA, 5.8S rRNA and 5S rRNA).
Messenger RNA	mRNA	It carries information from the nucleus to the ribosome and the coding sequence determines the amino acid sequence in the protein.
Micro RNA	miRNA	A small non-coding RNA molecule whose function is gene regulation, being complementary to a part of one or more messenger RNAs.
Short interfering RNA	siRNA	A class of double-stranded RNA molecules. They interfere with the expression of specific genes by complementary nucleotide sequences degrading mRNA after transcription.

The 46 human chromosomes, consisting of both DNA and RNA, are located in the nucleus of every cell: 44 autosomes, determining somatic characteristics, and two allosomes, responsible for sexual characteristics (1).

The Human Genome Project, started in 1990, produced a complete sequence in 2003: there are only 20 000–25 000 protein-coding genes, contrary to the expectation of as high as 2 000 000 (1).

Genomics of orthopaedic conditions

At the beginning of this millennium, orthogenomics was born (2-5). The importance of genomics in future orthopaedic practice was mentioned, but implementation has been slow. Strategies were suggested to identify the genetic bases of diseases, such as those with a significant genetic component (osteoarthritis), with underdeveloped surgical or medical treatments (disk degeneration), and those affecting large population (infection) (2-4) (Table II).

A recent review described the application of SNPs analysis in sports trauma, and discussed dosage effects between polymorphic collagen genes and Achilles tendinopathy or Ehlers-Danlos syndrome (6, 7). Most of the existing studies are published in non-orthopaedic journals. For example, information regarding bone-related cancers focuses on pathologic identification and chemotherapeutic management rather than on surgical management (5).

Paediatric osteosarcomas and Ewing sarcomas

Table II. *Overview of major musculoskeletal-related disorders and their inheritance patterns.*

Inheritance pattern	***Name***	***Associated gene***
Autosomal dominant	Achondroplasia	FGF receptor 3
	Spondyloepiphyseal dysplasia (congenita form)	COL2A1
	Multiple epiphyseal dysplasia	*COMP*, *COL9A1*, *COL9A2*, *COL9A3*, or *MATN3*
	Metaphyseal chondrodysplasia (Schmid and Jansen types)	COL10A1 and *PTH1R*
	Kniest's dysplasia	COL2A1
	Marfan syndrome	*FBN1*
	Ehlers–Danlos syndrome	*COL5A1, COL5A2 or TNXB*
	Osteogenesis imperfect (types I and IV)	*COL1A1* and *COL1A2*
	Osteochondromatosis	*EXT1 and EXT2*
	Polydactyly	*GLI3* gene, *GLI2*
Autosomal recessive	Metaphyseal chondrodysplasia (McKusick type)	*RMRP*
	Diastrophic dysplasia	*SLC26A2*
	Laron's dysplasia	*GHR*
	Hurler syndrome	*IDUA*
	Osteogenesis imperfecta (types II and III)	COL1A2
	Hypophosphatasia	*ALPL*
	Hereditary vitamin D-dependent rickets	*CYP27B1*, *VDR*
	Homocystinuria	*CBS*, *MTHFR*, *MTR*, *MTRR*, and *MMADHC*
X-linked	Spondyloepiphyseal dysplasia (tarda form)	Linked to X p22.12–p22.31
	Hunter syndrome	*IDS*
	Duchenne muscular dystrophy	DMD in Xp21.2-p21.1

express platelet derived growth factor (PDGF) ligand and receptor and/or KIT kinase. Drugs designed to target PDGF or KIT kinase (eg, imatinib mesylate) demonstrated effectiveness only against gastrointestinal stromal tumors and chronic myeloid lymphomas. However, one phase II trial did not support this treatment in pediatric orthopaedic tumors, but it is possible than, in the future, PDGF or KIT will allow investigation into application of orthopaedic oncology related drugs (8).

Genotype may predict the risk for osteosarcoma, Paget disease and chondrosarcoma and the prognosis following diagnosis (9-11). More mutations (e.g. p53 gene) occur exclusively in high-grade but not low-grade disease, and some patients progress from low to high grade, suggesting evolution simultaneously with progression. Additionally, SNPs in genes associated with osteosarcoma linked multiple biological processes with this cancer type (12).

Genetic contributions to the etiology and progression of common orthopaedic conditions are well studied in comparison with treatments and outcomes. Several mutations are associated with osteoporosis such as OPG genes, vitamin D receptor genes (VDR), LRP5 and others (13, 14). These genes are implicated in the inhibitions of osteoclast production and Wnt signalling, decreasing bone mineral density (BMD) and osteoporosis.

SNPs near OPG and Lrp5 increase the risk for osteoporotic fracture independent of decreased BMD. In particular, the prevalence of OPG related risk alleles in approximately 8,500 white women was 10-fold higher than the prevalence of glucocorticoid use (13). This suggests that genomic profiles are more relevant.

A recent study (15) confirms the importance of 12 loci as risk factors for bone fracture (2p16.2 (*SPTBN1*), 7q21.3 (*SHFM1*), 10q21.1 (*MBL2*/*DKK1*), 11q13.2 (*LRP5*), and 18p11.21 (*FAM210A*), *SOST*, *CPED1*/*WNT16*, *FUPB3*, *DCDC5*, *RPS6KA5*, *STARD3NL*, and *CTNNB1*. Furthermore, in the same study, using a scale GWAS meta-analysis identified other 4 new genetic determinants of fracture, all of which also influence bone mineral density [6q22.33 (*RSPO3*), 6q25.1 (*ESR1*), 7p12.1 (*GRB10*/*COBL*), and 21q22.2 (*ETS2*)] (15). Moreover, genetic predisposition to lower levels of vitamin D and estimated calcium intake from dairy sources were not associated with fracture risk (15).

Polymorphisms in the "disintegrin and metalloproteinase domain with thrombospondin motifs" 18 (ADAMTS18) gene encoding for antiangiogenic properties and transforming growth factor-β receptor type 3 (TGFBR3) genes, which regulates TGF-β signaling and extracellular matrix assembly, have been associated with BMD alterations, which have a heritability greater than 70% (16). Associations between cortical BMD and SNPs near the OPG, RANK, and RANKL genes have been discovered in both adolescents and elderly (16, 17).

Developmental dysplasia of the hip (DDH) and primary protrusio acetabuli (PPA) encompass the spectrum of acetabular development from a shallow acetabulum in DDH to a deep acetabulum in PPA. Both have an indeterminate aetiology and result in early onset osteoarthritis of the hip (18). A genetic hormone-related aetiology has been proposed (19-21). The association of developmental DDH and PPA with VDR polymorphisms Taq I and Fok I and oestrogen receptor (OR) polymorphisms Pvu II and Xba I suggest a possible correlation between gene polymorphisms and susceptibility and severity of DDH (22). Indeed, the Taq I VDR polymorphisms may be associated with abnormal acetabular morphology while the Xba I OR XX genotype with an increased risk of developing DDH; no associations were found with PPA.

The contribution of genetics to osteoarthritis (OA) has been estimated at 65% for the knee, 60% for the hip, and 39% for the hand (23). Association studies have detected two loci: growth differentiation factor-5 (GDF5), associated with bone and cartilage development, and component of oligomeric Golgi complex-5 (COG5) (11, 24).

There are 56 SNPs from 50 genes or gene loci, which have been associated with OA or OA subtypes (25). These genes affect Wnt-associated bone mass, bone changes in response to compression, cartilage turnover, chondrogenic processes mediated by TGF-β1, and the development of type II cartilage (25-28).

However, the effect size of these loci is very small, and more factors are necessary to produce clinical OA. Some OA SNPs are risk factors in both sexes or in select ethnic populations (25). For example, calmodulin-1 (CALM1) and asporin (ASPN) SNPs, identified in Japanese but not white and Greek patients with OA

(26, 29-31); or frizzled-related protein-2 (FRZB2) and collagen type II alpha-1 (COL2A1) were associated with OA in females and males, respectively; cartilage oligomeric matrix protein (COMP) demonstrated differential effects in both sex (26-32).

The origin of chronic pain, whose presence defines symptomatic OA, is not clear: indeed, the presence of radiographic abnormalities is not always associated with pain (33). The prevalence of radiographic knee degenerative joint disease was 19% and 28% among adults aged >45 years in the Framingham study and in the Johnston County OA Project, respectively, while the prevalence of symptomatic knee OA was 7% in the Framingham study and 17% in the Johnston County OA Project (34). Initially, pain in OA occurs episodically during movement and loading (35), while constant pain may occur later (35). Three relevant areas should be considered to explain OA pain: local processes in the joint, alterations of the nociceptive system, and general factors including comorbidities. Genetics is related to the second area, which is the most variable (36). There is an increase of mechano-sensitivity (37), a downregulation of substance P in neurons (38) and a genetic contribution with the association of 400 genetic markers in the genome of patients with OA (39). A genetic variant of catechol-O-methyltransferase (COMT) was associated with stronger hip OA pain (40), but not with knee OA pain (41). Another report described the association of a TRPV1 gene variant and a SNP in the PCSK6 gene with a lower risk of symptomatic knee OA (42, 43).

Annually, 1 million of total hip arthoplasties (THA) are implanted worldwide (44), and aseptic loosening (AL) has become more common (45), with high morbidity and mortality, especially in the elderly (46). AL results in progressive bone loss and periprosthetic osteolysis, accounting for 75.7% of all THA revisions (47). Pro-inflammatory mediators are implicated in aseptic osteolysis (48). SNPs in TNF-238 A allele and TNF-a promoter (49, 50), IL6-174G/597/572 (50-52), TGF-b1 (52), MBL (53, 54), GNAS1 (55, 56), OPG-163 (57, 58), RANK (50, 57, 59) and MMP-1 (51. 52, 60) predispose to aseptic loosening. The mechanisms of regulation and gene activation are still unclear. In the future, this knowledge would allow better planning and anticipating the need for early intervention (61).

Congenital idiopathic talipes equinovarus (CTEV) has a prevalence of 1 to 5 per 1000 live births (62, 63). Its etiology remains unknown, but it has both genetic and environmental components (62, 65), with extrinsic factors (e.g. congenital constriction bands, intrauterine poisoning), chromosomal abnormalities, and neuromuscular disorders. The role of inheritance in CTEV needs to be clarified (62, 66, 67).

Genomics in soft tissue injuries

The limit of each individual to perform a given type of exercise depends on the nature of the task, and is influenced by a variety of factors, including genetic make-up (68, 69). Recently, the relationship between polymorphisms and susceptibility to develop ligament and tendon injuries has been explored (68-70).

Collagen type I is the major constituent of tendons and ligaments. An alteration of COLIA1 genotype with the polymorphism Sp1 TT was associated with reduction of 85% the risk of cruciate ligament tears and shoulder dislocation (71, 72). No significant association was found between this SNP and Achilles tendinopathy compared with healthy Caucasian controls (73).

Type V collagen, quantitatively minor fibrillar collagen which heterotypic fibrils, regulates the size and configuration of type I collagen. Polymorphisms of the COL5A1 gene have been associated with Achilles and quadriceps tendon injuries and anterior cruciate ligament tears (74-76).

Tenascin-C (TNC) plays a critical role in transmitting mechanical tendon force, and it is expressed in the myotendinous and osteotendinous junctions (77-79), controlling cell-matrix interactions (80). The guanine-thymine (GT) dinucleotide repeat polymorphism was analyzed in association with Achilles tendon injuries (81), showing a significantly lower frequency of injuries between patients with 13 and 17 GT dinucleotide repeats, and control.

On the chromosome 9, between COL5A1 gene and TNC gene, lies the single gene determining the ABO blood group (82). Individuals with blood group O are more susceptible to tendon injuries (83, 84).

Genetics and rehabilitation

Genetics determines the response of individuals to their surroundings (85). Predictive genomics DNA profiling for athletic performance and injury rehabilitation allows to understand which genetic

advantages should be exploited. These findings could partially explain why an individual is able to excel in one sport discipline, and why rehabilitation protocol can be more effective in some individuals than others. Genetic factors play a critical role in determining high levels of sport performances and satisfactory rehabilitation results (86, 87). The physical performance phenotypes for which a genetic basis can be suspected include endurance capacity, muscle performance, and determinants of the behaviour of tendons and ligaments.

Endurance is the ability to perform high level aerobic exercise for prolonged periods. It is supported by enhanced mitochondrial function, as suggested by increased mitochondrial gene expression, and mitochondrial enzyme activity (88). The nuclear respiratory factor (NRF) 2 organizes the expression of nuclear and mitochondrial genes, explaining some of the inter-individual variance in endurance capacity (88).

Hemoglobin is a determinant of endurance performance, and SNPs in the hemoglobin gene could decrease the oxygen cost of running, explaining part of an individual variation in cardiorespiratory adaptation to endurance training (89). The Arg16Gly polymorphism in the b2-adrenergic receptor (ADRB2) gene may be associated with endurance performance status in white men (90).

Some other gene polymorphisms have been associated with sport performance and rehabilitation, although results are still preliminary or controversial. These include polymorphisms in the alpha2a-adrenoceptor gene (91), bradykinin beta 2 receptor, endothelial nitric oxide synthase 3 genes (92), vitamin D receptor gene (93), HIF-1 alpha (94).

Muscle performance is a direct consequence of the heterogeneity essential for its function, and is directed at optimizing the contractile responses (69). For example, the creatine kinase isoenzyme MM (CM-MM) is responsible of the rapid regeneration of ATP during muscle contraction, the actin-binding protein [alpha]-actinin-3 (ACTN3) a component of fast skeletal muscle fibres, and the myosin light chain kinase (MLCK) plays a critical role in the regulation of smooth muscle contraction (95), in particular, the R577X polymorphism (premature stop codon) associated with complete ACTN3 deficiency is more prevalent among elite endurance athletes (101, 102). The humans CK-MM gene sequence variation show a significant association with maximal oxygen uptake following 20 weeks of training (98), peak performance and less decline in force generation (99).

The ACE gene has 'I' (insertion) and 'D' (deletion) alleles (100, 101). Controversy exists about the association of the ACE gene variation and many heritable traits, including skill parameters and physical performance (102). For example, elite endurance athletes exhibit an increased frequency of the ACE I allele (103).

Other SNPs have been associated with muscle performance such as in the adenosine monophosphate deaminase 1 (AMPD1) gene or insulin-like growth factor 1 protein (IGF-1) gene (104). In particular, sedentary subjects with the TT genotype at the C34T AMPD1 gene showed diminished cardiorespiratory response to rehabilitation exercise (105-107).

To the best of our knowledge, no published study suggests to identify these polymorphisms to guide rehabilitation after musculoskeletal injuries. More evidence is needed to evaluate the benefits of genomic screening in patients to improve the outcomes of specific rehabilitation protocols.

Can we influence our genetics? Tissue engineering

In the last few decades, several strategies, including growth factors, gene therapy and tissue engineering with mesenchymal stem cells (MSC), have been proposed to enhance soft tissue healing (108).

Tissue engineering can be accomplished through the *in vivo* approach, which permits the self-regeneration of small tissue lesions, and the ex vivo, de novo approach, which produces functional tissue implantable in the body (109, 110). It is a multidisciplinary field founded on the use of healthy multipotent cells that are nonimmunogenic, the development of carrier scaffolds that provide short-term mechanical stability of the transplant, a template for spatial growth of the regenerate tissue and the delivery of growth factors that drive the process of cell differentiation and maturation (109, 110).

Growth factors (GFs), the signaling molecules involved in cell proliferation and differentiation, play an important role in regulation of tendon healing (111), determining intracellular changes and DNA synthesis or expression (87, 112-115). They can improve the strength of the repair by promoting the formation of more scar tissue modulating stiffness (111) and deliver

to the site of injury by direct application, for example, via local injection, or by using impregnated sutures or scaffolds. The main disadvantage of direct application is that GFs only remain at the site for a short duration.

Many other factors can be used, including cartilage-derived morphogenetic protein (CDMP) growth factor (116), PDGF (117), Interleukin-10 (118), VEGF (119), antibody to TGF-b1 (120) and IGF-1 (117, 121). Media consisting of PRP used for equine flexor digitorum superficialis tendon explants showed enhanced gene expression of collagen type I (COL1A1), collagen type III (COL3A1) and collagen oligomeric matrix protein (COMP), but no increase of catabolic molecules matrix metalloproteinase (MMP) 3 and 13 compared with other blood products tested (122). A double-blind, placebo-controlled trial demonstrated no benefit of intramuscular PRP injections compared with placebo injections (123).

MSCs can differentiate into a variety of specialized mesenchymal tissues (108). They can be applied directly to the site of injury or delivered on a suitable carrier matrix, which functions as a scaffold while tissue repair takes place (87, 112-115). Delivering MSC in organized collagen implants applied to large tendon defects can significantly improve the biomechanics, structure and probably the function of tendons after injury (124, 125). MSCs derived from synovium have a higher proliferation and differentiation potential than the other MSCs. Indeed, they can accelerate the early remodeling of tendon–bone healing producing more collagen fibers at 1 week and forming more oblique collagen fibers resembling Sharpey's fibers at 2 weeks (126). MSCs have been investigated in the management of tendinopathy, showing significantly improved tendon histological scores when injected in tendinopathic equine flexor digitorum superficialis (127). In rabbits, MSCs suspended in type I collagen gel and implanted into a surgically induced defect in the donor's patellar tendon demonstrated significant increases in maximum stress and strain energy density (128).

Gene therapy

Gene therapy delivers genetic material to cells using viral or non-viral vectors or direct gene transfer, resolving the problem of short time permanence of GFs in the site of injury (109, 110) (Table III). The use of vectors is associated with loss of transgene expression and adhesion formation secondary to inflammation (129). Gene transfer using vectors can be achieved *in vivo*, with direct application of the gene to the tissue, or *ex vivo* transfection, in which target cells are first removed and gene transfer is performed in the laboratory (129). *In vivo* transfection is less invasive, but with the risk of nonspecific infection of cells adjacent to the target site.

Adenovirus-based gene therapy is an efficient means of gene delivery to rabbit flexor tendons, but the transduction efficiency of transgenes was dose dependent (130). Rickert et al. (131) injected adenovirus particles into transected Achilles tendons of rats: *in vitro*, GDF-5 was secreted with a peak after 2 weeks, and *in vivo* after 4 weeks. The use of AAV vectors to transfer exogenous bFGF gene to proliferating tenocytes showed significantly increased levels of expression of type I and III collagen genes compared with those in the cells treated with sham vectors or in nontreatment controls (132).

The rate of transfection of a gene in rat patellar tendons using the HVJ liposome-mediated gene transfer method was significantly greater than controls (133), and, compared to adenoviral and AAV vectors it showed the most prominent healing response on injured flexor tendons of rabbit (134). Injecting directly into the injured patellar tendon of rats a HVJ-liposome suspension containing PDGF-B cDNA enhances the expression of PDGF in healing ligaments with angiogenesis promotion and collagen deposition in the wound (135). Gene therapy with BMPs may improve the healing ability of tissues. Achilles tendon transduced with BMP-14 exhibited less visible gapping, a greater number of neotenocytes and 70% greater tensile strength than controls at 2 weeks after repair (136). Majewski et al. (137) evaluated the effects of BMP-12 gene transfer on the healing of rat Achilles tendons using a genetically modified muscle flap, reporting acceleration and improvement of tendon healing.

A plasmid carrying the lacZ marker gene was injected into the Achilles tendons of rats and mice and into the patellar tendons of rabbits showing at 48 h transduced cells, a minority of the tendon cells (138). Kinetics study in rats showed a gradual decrease of β-gal-expressing cell number; at day 42, gene expression was no longer detected, without inflammatory reaction (138). Wang et al. (139) transferred, using a plasmid, the PDGF-B gene

Table III. *Overview on the main vectors used in gene therapy.* ***AAV****: adeno-associated virus,* ***HVJ****: hemagglutinating virus of Japan.*

Vector/Strategy	*Advantages*	*Disadvantages*
Adenovirus	Less tissue reaction than liposome-plasmid complexes. Most effective in the short term	Transient expression. Effect is dose dependent
AAV	Less tissue reaction than liposome-plasmid complexes, and, virtually, no response in the endotenon	Transient expression
HVJ-liposome plasmid complexes	More tissue reaction than other vectors	Compared to AAV and Adenovirus is the most effective technique[143]
Non-viral	Less pathogenic	Less efficient

to tenocytes obtained from explant cultures of rat intrasynovial tendons: RT-PCR showed significantly increased expression of type I collagen gene by tenocytes.

With the advent of clustered regulatory interspaced short palindromic repeat (CRISPR) technologies, AAV has shown promising therapeutic efficacy with good safety profile in animal and human clinical trials (140). It revolutionized gene-editing techniques because of its simplicity in target design, affordability, versatility, and high efficiency (141). CRISPR/Cas9-based RNA-guided DNA endonuclease has, rapidly, become the preferred platform of genome-editing for interrogating endogenous gene function *In vivo* (142, 143).

The CRISPR/Cas9 complex can be introduced into the cell in forms of DNA, messenger RNA, or protein (144). Because of the great potential of viral vectors, the major classes - lentiviruses (145), adenoviruses (146), retroviruses (147), AAVs (148), and baculoviruses (149) - have been employed to present CRISPR components into eukaryotic cells for genome editing. The AAV-CRISPR system has also been successfully used in mice to restore gene function in Duchenne muscular dystrophy (150-153) and other conditions. The AAV-CRISPR system holds enormous translational potential to develop therapeutic treatments for patients with severe and life-threatening genetic diseases by editing disease-causing or risk genes in the human body. The AAV-CRISPR system needs more tests *in vivo* to become a successful human gene therapy (140).

CONCLUSIONS

A better understanding of musculoskeletal system function and healing will allow specific management strategies to be developed. Many interesting techniques, discussed in this article, are at an early stage of development. Although these emerging technologies may develop into substantial clinical management options, their full impact needs to be evaluated critically in a scientific fashion.

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DECORIN AGE-RELATED VARIATIONS IN THE DISTRIBUTION OF PIG EXTRACELLULAR MATRIX MENISCUS

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Menisci act like shock absorbers and transmit load across the tibiofemoral joint by increasing congruency during movements or body weight load. This leads to decreasing the resultant stress on the articular cartilages. The meniscus has a dense extracellular matrix (ECM) composed of water, different types of collagens, and proteoglycans, such as decorin, aggrecan and biglycan. Decorin (DCN) regulates collagen fibrillogenesis acting on collagen fibrils diameter and fibrils orientation to achieve the proper assembly of its network. This work investigates the spatial disposition of this fundamental protein in pig meniscus' matrix by immunohistochemistry and western blot analysis. DCN shows an increasing trend, moving from neonatal to adult pig menisci. Adult meniscus, in porcine species, is the only one that could be considered fully mature and functional, and, even if an increasing trend is seen, no precise phenotypical switch points are seen in the age stages considered in this study.

The different shapes of the two ends of the knee joint, the convex femoral and the flattened tibial condyles, make essential the presence of the wedge-shaped menisci to allow the correct function of this joint (1, 2). Meniscus acts like a shock absorber and transmits load across the tibiofemoral joint by increasing congruency during movements or body weight load. This leads to a decrease in the resultant stress on the articular cartilages (1). Other functions of the meniscus are inherent to the distribution of nutrients within the articular space, stability, lubrication and proprioception to the knee joint (1). These functions are possible due to the peculiar structure that characterizes the meniscus: a triangular shape after transversal section. The apex directed towards the intercondylar notch is avascular in adulthood and for this reason it is called "white-white" zone. The external and wider border is vascularized throughout all its lifetime and it is called "red-red" zone (3). Between these two, there exists an intermediate, although not well outlined area with midway characteristics, called white-red zone. At each area corresponds a different cellular phenotype expression and a peculiar organization of the biochemical components.

The inner portion of the meniscus is characterized by round-shaped cells that resemble and act like the chondrocytes, the fibrochondrocytes (4, 5). On the other hand, the oval cells of the outer zone are classified and act as fibroblasts (5). A third cellular population characterized the most superficial zone of the meniscus and seems to have regenerative capacity and act as specific progenitor cells (6). Meniscus has a fibrocartilaginous nature and it is composed of an extracellular matrix (ECM) mainly composed of water (72%) and collagen (22%) (7). Collagen is the main fibrillar component of the meniscus and is

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primarily responsible for the tensile strength of the meniscus (8). Its distribution and amount depends on the meniscal area considered. The inner zone is composed of two different types of collagen (70% by dry weight): types II (60%) and I (40%) (9). On the contrary, the outer zone is characterized by type I collagen as the major constituent (80% of the total dry weight), in association with some variants (e.g., type II, III, IV, VI, and XVIII) that represent less than 1% of the total dry weight (1).

Collagen follows different patterns of distribution according to the considered zone. Two different configurations mainly represent these patterns: the circumferential and the transversal. An abundance of the circumferential disposition was seen in the femoral surface, while a radial disposition of the fibres characterises the tibial surface in the swine meniscus. These radially positioned "tie" fibres are woven between the circumferential fibres to provide structural integrity (1, 2, 10, 11-16) and allow the dissipation of the forces through the meniscal ligaments (17).

Other meniscal constituents include glycosaminoglycans (17%), adhesion glycoproteins (<1%) and elastin (<1%) (8, 18). The proportion of each component varies according to age or the presence of pathological condition (19). Meniscal glycosaminoglycans including aggrecan, decorin, biglycan and perlecan withstand compressive forces. Aggrecan is more abundant in the inner regions than the outer regions of canine, ovine and porcine menisci (20-22). Glycosaminoglycans are more abundant in the femoral portion than the tibial portion in the porcine meniscus (2). Decorin (DCN), so named for its ability to bind to and "decorate" collagen fibrils, has a core protein of approximately 38kDa; it is a small leucine-rich proteoglycan (SLRP) which binds 10 leucine-rich repeat sequences. It binds to and regulates collagen fibrillogenesis acting on collagen fibrils diameter and fibrils orientation to achieve the proper assembly of its network (23).

Absence of decorin in tendons, results in irregular collagen fibril morphology with fusion of adjacent fibrils (24). The complex composition and organization of meniscal extracellular matrix (ECM), necessary to provide the fundamental load-bearing and stress-dissipating properties of this tissue makes it challenging to create an engineered graft for its repair. A full understanding of the composition of the extracellular matrix of healthy meniscus is required to evaluate the degeneration that occurs in joint disease and the complex environment in which an engineered meniscal substitute would need to function (25). Furthermore, it must be considered that the extracellular matrix may influence cells triggering a different cellular response. For this reason, many tissue-engineering attempts have been made for tissue repair or regeneration by working on different ECM substrates.

Even if pig's meniscus is often used as a model for the human one (26-29), works regarding the different spatial distribution of DCN within its matrix are inexistent. This work aims to find out how DCN is distributed in the swine meniscus and how this distribution varies during growth.

MATERIALS AND METHODS

Study design

For the aim of this study, we obtained menisci from a local slaughterhouse, which breeds Landrace x Large White swine. Knees of adults (8 months old, weight 85-90 kg), young (1 month old, weight 10-12 kg), and neonates (stillbirths or dead in peripartum) were collected. The joints were dissected to isolate lateral and medial menisci. Capsular tissue and ligaments were gently removed; the menisci were stored in saline solution NaCl 0.9% and refrigerated. No animal was sacrificed for the purposes of this study; the research was approved by the Ethic Committee of the University of Milan (OPBA, 58/2016).

1.2 Micro anatomical analysis: Immunohistochemistry

Given the morphological similarities between medial and lateral menisci observed by a previous research (28, 29), only the lateral menisci were analysed (8 per group, n=24). Menisci were divided, through two radial-transversal cuts, into three different parts: anterior horn, body and posterior horn (fig. 1)..

Subsequently, each part was subdivided into an inner and an outer part through a longitudinal cut (Fig. 1). Samples were then fixed in 10% (v/v) phosphate-buffered formaldehyde (n=24), dehydrated in a graded 50% (v/v), 70% (v/v), 95% (v/v) and 100% (v/v) ethanol series, embedded in paraffin and cut into 4 µm-thick consecutive sections.

After rehydration, sections were washed in Phosphate Buffered Saline (PBS, pH 7.4) plus Triton for 5 min; moreover, block endogenous peroxidase using H_2O_2 for 8 minutes in a humidified chamber was applied and subsequently the slides were incubated with the first-step

primary antiserum, 1:500 decorin (abbit polyclonal, no. ABIN2783275; Antibodies-online, Aachen, Germany) for 24 h at 18-20°C in humid chamber, then washed in PBS, and subsequently treated with the rabbit EnVision system (Dakocytomation, Milan, Italy). The sections were then washed in PBS for 10 min and incubated with a 5 min 3.3' diaminobenzidine tetrahydrochloride (DAB)/ hydrogen peroxide, which results in a brown precipitate at the antigen site.

Counterstaining with Mayer hematoxylin for 1 min allowed a better visualizing of the morphological structure. The slides were then dehydrated and permanently mounted. Secondary antibody was EnVision Rabbit. The specificity tests for the antibodies were verified by incubating sections with: (i) PBS instead of the specific primary antibody; (ii) PBS instead of the secondary antibodies. The results of these controls were negative (i.e. staining was abolished). Photomicrographs were taken with an Olympus BX51 microscope (Olympus, Milan, Italy) equipped with a digital camera and final magnifications were calculated.

1.3 Protein extraction and Western blot analysis

For each experimental group (neonatal, young and adult), 8 specimens were processed (total n=24). The samples were pulverized for 2 min at 3000 oscillations/ min in a liquid nitrogen cooled dismembrator (Mikro-Dismembrator, Sartorius Stedim, Italy). They were then homogenized in a buffer containing 50 mM Tris-HCl, 150 mM NaCl, 0.1% SDS, 0.5% sodium deoxycholate, 1% NP40, pH 7.4, supplemented with protease inhibitor cocktail (Euroclone, Pero (MI) Italy) and centrifuged at 13000 g at 4°C for 10 min to discard cellular debris. Protein concentration in the extracts was determined using a BCA protein assay (Euroclone). After addition of 0.05% bromophenol blue, 10% glycerol and 2% b-mercaptoethanol, 50 ug of each sample was boiled and loaded onto 8% SDS-polyacrylamide gels.

After electrophoresis, polypeptides were electrophoretically transferred to nitrocellulose filters (Sigma-Aldrich, Milan, Italy); the membranes were incubated with 5% non-fat-milk for 1 h at room temperature to block the non-specific sites and then probed for 2 h at room temperature using anti-decorin (1:500; rabbit polyclonal, no. ABIN2783275; Antibodies-online, Aachen, Germany), anti-GAPDH (1:1000, clone GAPDH-71.1) and kept at room temperature for 2 h. The filters were then washed and incubated for 1 h always at room temperature, with HRP-labelled secondary antibodies (1:5000; Bio-Rad, Hercules, CA, USA).

For the last step of the procedure, the blots were developed using a chemiluminescent substrate (WESTAR Nova 2011, Cyanagen, Bologna, Italy) to detect and characterize the proteins C, as previously described. In order to compare target protein expression levels between neonatal, young and adult menisci, it was necessary to use a loading control to normalize the data measuring the levels of GAPDH (a marker for total protein in each sample) Immunoreactivity was detected by chemiluminescence autoradiography according to the manufacturer's instructions (Biorad, Milan, Italy), and the images were scanned. The optical intensities of the protein bands of interest were determined densitometrically using Scion Image software (Scion Corporation, Frederick, MA).

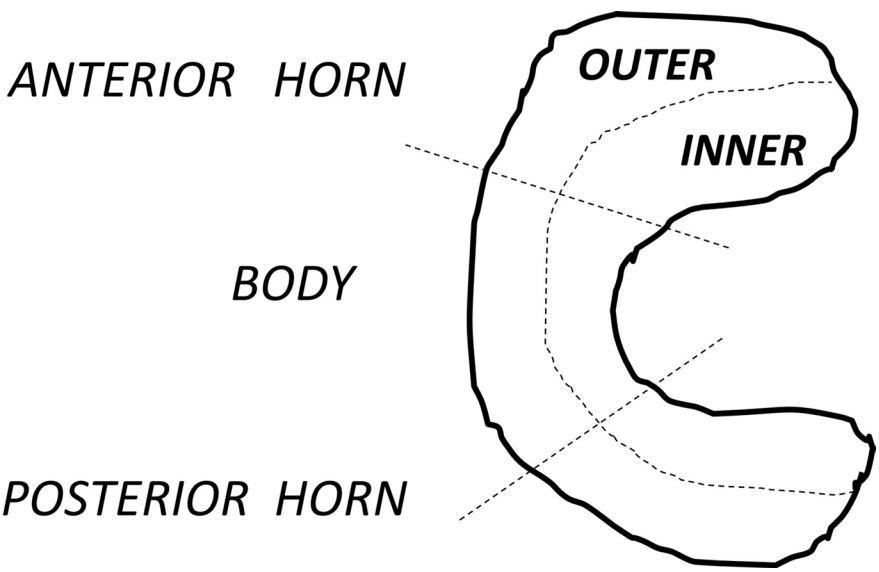

Fig. 1. *Schematic description of the cuts performed for the immunohistochemistry evaluation.*

RESULTS

Immunohistochemistry

Decorin shows a principally pericellular immunopositivity and increases with age (Fig. 2). It is present since the neonatal phase, even if with differences in the distribution: posterior horn (Fig. 2e, f) presents a higher immunopositivity compared to to the anterior horn (Fig. 2a, b) and body portions (Fig. 2c, d). Differences in the distribution of decorin is also seen between inner and outer regions of posterior horn (Fig. 2e, f), with an increased immunopositivity in the first (Fig. 2e) compared to to the latter (Fig. 2f). In young and adult meniscus, decorin shows a more homogeneous distribution among anterior horn, body and posterior horn (Fig. 2 a1-f1 and a2-f2). However, an increased immunopositivity is still present in the inner portion (Fig. 2 a1, c1, e1) of the young meniscus when compared to the outer one (Fig. 2 b1, d1, f1).

Adult samples show no differences between inner (Fig. 2 a2, c2, e2) and outer (Fig. 2 b2, d2, f2) portions with regard to the distribution of decorin. The pattern of distribution change between the two regions: in the inner part decorin shows a pericellular distribution (Fig. 2 a2, c2, e2, black arrows) while in the outer it is mainly linked to the presence of transversal fibers (Fig. 2 b2, d2, f2, white arrows).

2.2 Western blot analysis

Western blot in neonatal, young and adult animals, revealed the same trend of expression as immunohistochemistry, characterized by an increasing trend of the amount of this proteoglycan with age (Fig. 3B). In particular, adult menisci show the highest quantity of decorin when compared with both young and neonatal ones ($P<0,001$, for both comparisons; Fig. 3B).

DISCUSSION

In pig meniscus, decorin shows an age-related distribution. DCN is present since the earliest stage of development of this structure (in this case, at birth). Nevertheless, its distribution in neonatal specimens shows some peculiarity regarding the area of the meniscus that is taken into account: the inner portion of the posterior horn is the only one in which a satisfactory immunopositivity is observed at this time stage. This result agrees with a previous work of our research group (29) in which a precocious maturation of the posterior horn of the meniscus, due to the prevalent knee flexion that occurs in the swine model during gestation and the first weeks of life of the swine, is hypothesized.

The inner portion is richer of decorin even in the meniscus of young animals, as for all the other proteoglycans, as seen in previous observations in this meniscal portion of different species, like pigs (2, 22), canine (20), ovine (21) and human (18).

In the adult meniscus, the difference between inner and outer region distribution of decorin is not as demarcated as in the precocious age stages, and so the distribution of this proteoglycan results more homogeneous. Only the pattern of distribution seems to change: in the inner portion, the distribution is strictly linked to the cells presence, being mainly pericellular, while in the outer region the distribution of decorin principally follows the fibres trend. This peculiar pattern shows some affinity with what was observed, intriguingly in the juvenile (2-4 weeks), bovine meniscus by Vanderploeg and collaborators (25).

The precocious distribution, swine-adult-like, of this proteoglycan in the bovine model may be due to a different biomechanical stimulus given by the different weight of pigs and bovines at 1 month. This hypothesis, of a distribution linked to the weight, seems to be confirmed by the observation of Kavanagh et al. in 3 weeks and 8 months old rabbit's menisci: initially, decorin is present throughout the fibrocartilage, but by 8 months, its distribution is more in the periphery of the fibrocartilage (30).

DCN interacts with multiple collagens to create functional bridges between the pericellular matrix and the surrounding extracellular matrix and, in association with collagen type VI, is essential in cellular resistance to deformation (31).

In human beings, age-related changes in the composition and structure of collagens, proteoglycans, glycosaminoglycan chains and non-collagenous proteins have been reported: decorin and biglycan analysis showed that decorin is the dominant, endogenous, non-aggregating proteoglycan in the adult meniscus and cartilage (32, 33) but in immature articular cartilage biglycan

was present at much higher concentrations than decorin (34). In the present study biglycan was not considered but, given its mutually exclusively relation with decorin, as seen in rabbit and human, an influence of this proteoglycan on the behaviour of DCN that is seen in neonatal and young menisci, could not be excluded.

Naturally, further studies about this topic are essential to clarify the role of the different proteoglycans composing the meniscal matrix and their reciprocal relation.

Decorin shows an increasing in its amount trend, moving from neonatal to adult pig menisci. Adult meniscus, in porcine species, is the only one that could be considered fully mature and functional, and, even if an increasing trend is seen, no precise phenotypical switch points are seen in the age stages considered in this study.

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SURGERY WITHIN 48 HOURS IN HIP FRACTURES IN ELDERLY PATIENTS EXERTS A POSITIVE EFFECT ON POST-OPERATIVE HYPONATREMIA

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This study investigated the prevalence of hyponatremia during the hospital stay, in a cohort of elderly patients with hip fractures who underwent surgery within 48 h from admission. Records data were retrieved from the database of the San Giovanni di Dio e Ruggi d'Aragona Hospital of Salerno, Italy. All elderly patients (≥65 years old) with a documented hip fracture that underwent surgery within 48 h from admission, between 2016 and 2018, were included and divided in 4 subgroups according to their sex and type of fracture. Serum sodium concentration were monitored during the hospital stay and collected at admission, before surgery, after surgery and at discharge. The overall prevalence of hyponatremia was 23.99% (n=71/295), (24.3%, n=57/234 for female patients and 22.9%, n=14/61 for male patients). The percentage of hyponatremic patients with an intracapsular hip fracture was 27.17% (n=25/92), and 22.66% (n=46/203) in patients with an extracapsular hip fracture. The highest value of mean serum sodium concentration (139.2 mmol/L±4.4 SD) was found at the hospital discharge phase, and the lowest value (138.4 mmol/L±4.3 SD) was found during the pre-surgery phase. The lowest mean value of serum sodium was found before surgery, while the highest was after surgery. This could suggest that the early operative treatment and the accurate in-hospital monitoring are effective to treat or prevent this condition.

Hip fractures are one of the most serious and common fracture in the elderly, and are associated with high morbidity and mortality (from 14 % to 36 %) during the first year post-fracture (1-2).

Osteoporosis is the leading cause of hip fractures in such population (3). Among its several risk factors, osteoporosis has been associated with hyponatremia (4-6), which can either be considered as a risk factor for hip fractures (7, 8) or a consequence of the stress response to the trauma and subsequent surgery (9). Abnormalities in plasma sodium concentration are the most common electrolyte disturbance found in elderly (10), are associated with high morbidity and mortality (11), and have been extensively studied (12).

Hyponatraemia is defined as a serum sodium <135 mEq/l. In normal circumstances, the human body is able to maintain plasma sodium within the normal range (135-145 mEq/l) despite wide variations in fluid intake. (13) Hyponatremia is the most common disorder of body fluids and electrolyte balance encountered in clinical practice, with an incidence of 15-20% in hospital emergency admissions, and

Key words: hyponatremia, hip fracture, elderly, proximal femur fracture

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occurring in up to 20% of critical patients (14).

'Asymptomatic' chronic mild hyponatremia has previously been thought to be of no clinical relevance. However, recent evidence shows that, particularly in the elderly, it may contribute to impaired cognition (15), and increased risk of falls (16) and fractures (17). Recent studies suggest that the predisposition to hip fractures in patients with hyponatremia is correlated not only to a higher risk of falls, but also to associated osteoporosis (18).

Hyponatremia could contribute to produce fractures through two possible mechanisms: 1) impaired cognitive function with gait disturbances, inducing instability and falls (16), or 2) osteoporosis resulting from decreased bone mass or bone quality (19). In addition, inappropriate management of hyponatremia can lead to significant morbidity (20).

A rapid time from admission to surgery for hip fracture patients has been associated with higher rates of independent living and lower 30-day and 1-year mortality rates (21-24). Earlier surgery has also been shown to improve patient outcomes by reducing pain scores, lowering of the risk of bedsore formations and length of inpatient stay (21, 25, 26).

Surgical delays can result when one aims to avoid medical complications associated with hastened hip fracture surgery. However, delay is not justifiable in the presence of non-severe and isolated hyponatremia (27).

Compared to normonatremic patients, hyponatremic patients show a longer time from admission to surgery and an increased length of index hospital admission (28). Hyponatremic hip fracture patients not only spend more time in hospital than normonatremic patients, but are also generally readmitted earlier and more often to an inpatient setting (29).

The aim of this retrospective observational study was to determine the prevalence of hyponatremia in hip fracture patients who underwent surgery within 48 h from admission, and investigate its relationship with sex, age, type of fracture and delay before surgery.

MATERIALS AND METHODS

All records containing clinical and laboratory information about patients with a hip fracture admitted and operated from October 2016 to January 2018 were retrieved from the San Giovanni di Dio e Ruggi d'Aragona Hospital of Salerno database. Inclusion criteria were the occurrence of hip fractures (extra- and intra-capsular proximal femoral fractures), age ≥65 years, and time to surgery within 48 h.

A total of 295 patients were identified on the basis of the above criteria. They were divided in four groups according to sex and type of proximal femoral fracture: male with extra-capsular fracture, males with intra-capsular fracture, females with extra-capsular fracture and females with intra-capsular fracture.

After a visual check of the admission radiographs to confirm the diagnosis, the sodium serum concentrations were extracted starting on day of the admission to the day of discharge. All sodium concentration values were divided in four group: admission, before surgery, 48 h after surgery and discharge. Reporting the values "before surgery", the measurement used for statistical evaluation in case of multiple measurements was their mean. We calculated the "after 48 h surgery" measurement in the same way.

All data were collected by a qualified doctor (RA) and a medical student (AG). Statistical analysis was performed by an experienced researcher (NM) and a qualified doctor (FB) who had not been involved in data collection.

Serum sodium concentrations were determined by indirect potentiometry using the SYNCHRON© System (Beckman Instruments, Brea, CA, USA). The measuring equipment was calibrated with known standards each week, using the protocol suggested by the manufacturer.

For the purposes of this investigation, hyponatremia was defined as a serum sodium concentration <135 mmol/L (30) which occurred at least once during a patient's hospital stay from admission to discharge. The χ^2 test with the Yates correction was performed to compare prevalence across groups divided by sex, type of fracture. Regarding the statistical evaluation of each phase of length of stay (LOS), the *t*-Student test was used, and statistical significance was set at $p < 0.05$.

RESULTS

A total of 295 patients satisfied the inclusion criteria, with a mean age of 84 years±7.2 DS. There were more females (84 years±7.1 SD, *n*=234, 79.4%) than males (83 years±7.2 SD, *n*=61, 20.6%). Extracapsular hip fractures were equally prevalent in both male and female patients' group: 37/61 (60.6%) and 162/234

(61%) respectively. The remaining were intracapsular hip fractures, 22/61 (39.4%) and 65/234 (39%) in males and females respectively (Table I).

All patients were treated with nailing or hemi-arthroplasty within 48 h with a mean of 1.4 days±0.5 SD; the mean length of stay (LOS) was 10.7 days±6 SD, while the mean of the days in hospital after surgery was 9.3±6 SD.

The overall prevalence of hyponatremia was 23.99 % (n=71/295), (24.3%, n=57/234 for female patients and 22.9%, n=14/61 for male patients). The percentage of hyponatremic patients with an intracapsular hip fracture was 27.17% (n=25/92), while in patients with an extracapsular hip fracture it is 22.66% (n=46/203).

The highest value of mean serum sodium concentration (139.2 mmol/L±4.4 SD) was found at the hospital discharge phase, and the lowest value (138.4 mmol/L±4.3 SD) was during the pre-surgery phase.

The χ^2 test with the Yates correction showed a statistically significant difference between intracapsular fracture male group and the extracapsular female group ($p<0.01$). No significant difference was found between males and females, intracapsular and extracapsular fracture groups and female intracapsular and female extracapsular fracture groups.

Regarding the various phases of LOS, evaluation was performed using the t-Student test, and there were statistically significant differences between pre-surgery and post-surgery groups ($p<0.01$); no differences were found between admission and pre-surgery groups and post-surgery and discharge groups (Table II).

DISCUSSION

In the present cohort, the overall prevalence of hyponatremia was 23.99 % (n=71/295), (24.3%, n=57/234 for female patients and 22.9%, n=14/61 for male patients), slightly lower than the 26% reported by Cumming et al. (31) who studied the prevalence of hyponatremia in a population of elderly patients with all kind of fragility fractures. The incidence of hyponatremia in our sample is also higher than the one we found in our recent study (32).

The percentage of hyponatremic patients with an

Table I. *Cohort data.*

	Males	Females	ECPFF	ICPFF	Total
Number	*n* = 61 20.6%	*n* = 234 79.4%	N=203 22,6%	N=92 27,2%	N=295
Age	83±7.2	84±7.1	84±7.1	84±7.1	84±7.2
Days before surgery	1.5±0.6	1.43±0.58	1.5±0.5	1.4±0.6	1.5±0.6
Days after surgery	9.0±4.1	9.37±6.41	9.5±9.0	9.2±3.9	9.3±6.0
LOS	10.5±4.1	10.8±6.4	10.0±9.0	10.6±4.0	10.8±6.0

ECPFF: *extracapsular proximal femoral fracture;* **ICPFF:** *intracapsular proximal femoral fracture.*

Table II. *Mean serum sodium concentration[1] and prevalence of hyponatremia in each group.*

	Females intra	Females extra	Total Females	Males intra	Males extra	Total males	Total
Admission	138.60±3.54 7.25%	138.60±4.29 9.88%	138.60±4.08 9.13%	139.09±3.32 22.72%	137.17±4.17 2.70%	138.21±3.72 10.17%	138.57±3.83
Pre-operatory	138.40±3.85 7,25%	138.47±4.10 8.64%	138.45±4.02 8.26%	139.01±2.57 13.63%	137.16±4.09 2.70%	138.30±3.82 6.78%	138.44±4.31
Post-operatory	139.19±3.19 2.90%	139.29±3.49 4.94%	139.26±3.40 4.35%	139.80±2.56 9.09%	137.27±4.31 0%	138.85±3.52 3.39%	139.08±3.77
Discharge	138.41±3.78 4.35%	138.47±4.01 4.94%	139.26±3.95 4.78%	139.80±3.65 13.64%	137.16±4.76 0%	139,22±3.82 5.08%	139.13±4.46

[1]*: Expressed as mean ± SD.*

intracapsular hip fracture is 27.17% (n=25/92), higher than that reported in our previous study (9.4%) (32) and that reported by Cervellin et al. (22%) (33).

The structural changes in the aging kidney impact on glomerular filtration rate (GFR), renal blood flow (RPF) (34, 35), diluting and concentrating capacity (36-38), secretion of potassium (39), and ability to excrete an acid load. All these decline in the elderly as compared to young adults (40, 41). In normal conditions, elderly patients are able to maintain electrolyte balance (35). However, under stressful conditions, this ability to maintain homeostasis may be lost, making them more susceptible to hyponatremia, hypernatremia, volume depletion, volume overload, hyperkalemia, and metabolic acidosis (42).

Post-operative hyponatremia may result from a combination of non-osmotic stimuli for ADH release, such as subclinical volume depletion, pain, nausea, stress, edema, administration of hypotonic fluids (43) or excessive isotonic saline administration in the post-operative period (44).

ADH levels are universally elevated post-operatively when compared with pre-operative values (45). One of the most important factors resulting in hospital-acquired hyponatremia is the administration of hypotonic fluids to patients who have a compromised ability to maintain water balance (46-50). In adults, this will usually occur in the post-operative period (49).

The most important finding is that lowest mean value of serum sodium was found before surgery, while the highest was after surgery, in contrast to the finding of our previous study (32) where the highest mean value of serum sodium was before surgery and the lowest one after surgery.

This could suggests that the early operative treatment and the accurate in-hospital monitoring are effective to treat or prevent this condition. It is possible that this is consequent to the corrective effect of the administration of physiological solution during and after surgery on electrolytes balance. However, patients in our previous study received the same perioperative treatment, and therefore we hypothesize that is an effect of the early surgery.

Generally, post-operative hyponatremia occurs in <1% of patients, and symptoms from hyponatremia occur in 20% of these patients (43, 46, 51). Hyponatremia can lead to a wide spectrum of clinical symptoms, from moderate to severe or even life threatening, and is associated with increased mortality, morbidity and length of hospital stay in patients presenting with a range of conditions (52, 53). The symptoms associated with hyponatremia are various and related to severity and rapidity of the plasma sodium concentration decrease as well as the coexistence of neurological disease or other electrolyte abnormalities (54). Symptoms are more frequent if the reduction of plasma sodium concentration is rapid, while chronic hyponatremia (more than 72 hour duration) can be relatively asymptomatic, even when it is biochemically significant. (54) In acute hyponatremia, the main pathological consequence is the development of cerebral oedema, which leads to a raised intracranial pressure with the risk of cerebral herniation, hypoxia and even death (55). Chronic hyponatremia carries a lower risk of acute neurological symptoms because of the presence of chronic cerebral adaptive mechanisms (56).

The present study showed no significant differences in the LOS of hyponatremic and non-hyponatremic patients who received operative treatment within 48 h. Our previous study on the same type of patients, but who underwent operative treatment over 48 h, found that inpatient drop in serum sodium was independent predictors of longer LOS (28). This supports previous studies which investigated the advantages of early surgery in elderly patients with hip fractures in terms of reduced mortality, morbidity and length of hospital stay and costs (57, 58).

The lowest percentage of hyponatremic patients was found in males with an intracapsular fracture, and the highest one in the female patients with extracapsular fractures. An explanation to this result could be gender-related differences in sodium metabolism, release and responsiveness to vasopressin (AVP) and cellular Na+ homeostasis (59).

There is a gender-related difference in the antidiuretic responsiveness to endogenous AVP. This difference is dependent upon ovarian hormones. Gonadectomy had no effect on the antidiuretic potency of vasopressin in male rats, but gonadectomy decreased urine flow and increased urine osmolarity

in female rats (60). Intravenous infusion of hypertonic saline resulted in a greater increase in the urinary excretion of AVP in women than in men. This may suggest a greater osmotic sensitivity of AVP release in women than in men (61).

It is possible that central cholinergic and angiotensinergic mechanisms controlling AVP release are influenced differently by gender (62). These evidences corroborate the hypothesis that, in most of female patients, hyponatremia could be caused by the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and increased sensitivity to antidiuretic hormone.

This study presents several limitations. First, this work is a retrospective analysis of prospectively collected data. Second, the database used lacks data regarding comorbidities and drugs intake as hyponatremia can result from several comorbidities and drugs and it is not always easy to identify its actual cause. (48) A previous study reported that the majority of elderly patients, including those with fragility fractures, had hyponatremia of multifactorial etiology, and no significant differences were found in specific causes of hyponatremia between those developing fragility fractures and those who did not. (31)

Strengths of our study are the meticulous collection of the plasma sodium concentration for every patient in every specific moment of the LOS and the inclusion of only patients who underwent surgery within 48 h. To our knowledge, this is the first study that investigate the association of hyponatremia in specific patients with a proximal femur fracture treated within 48 h, and is the first that evaluated this association dividing LOS in admission, pre-surgery, post-surgery and discharge.

There was no statically significant difference in the prevalence of hyponatremia between the type of fracture and the type of surgery. The different type of surgery, hemiarthroplasty being more long-lasting and invasive than intramedullary nailing, seems not to influence serum sodium concentrations.

CONCLUSIONS

Serum sodium concentration improve after early surgery in patients with proximal femoral fracture. A systematic monitoring of electrolytes, in particular sodium, during hospital stay, from admission to discharge, is recommended to avoid potential complications from hyponatremia. Serum sodium levels should be regularly assessed and corrected when the value falls below the lower limit of the reference range. The management of hyponatremia needs to target the underlying etiology. The urgency of intervention is determined by the severity of symptoms and the potential for an adverse outcome.

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RESIDUAL MOBILITY AFTER REMOVAL OF INSTRUMENTATION IN PATIENT, WITH TYPE A2-A3 VERTEBRAL FRACTURES, TREATED WITH PERCUTANEOUS PEDICLE SCREW FIXATION

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Percutaneous techniques for treatment of thoraco-lumbar fractures type A2 and A3 are widely used. These techniques are considered temporary fixations and instrumentation must be removed with fracture healing. The aim of the study is to analyze clinical results, motility of treated segments and any loss of correction after the removal of instrumentation. We evaluated 36 patients who underwent surgery for removal of the instrumentation. Standard and dynamics x-ray before surgery and at 1 and 12 months after surgery were obtained. Radiographic evaluation was performed by comparing loss of correction after removal of the instrumentation, residual mobility of fractured vertebra, upper and lower level with values defined by Dvorak. For clinical assessment were used SF-12, Oswestry Disability Index (ODI) and Visual Analog Scale (VAS), administered before surgery and at 1 and 12 months after the removal. We analyzed a total of 108 levels in 36 patients. After removal of the instrumentation a normal range of motion was restored in the proximal and distal segment of the fracture, while at level of fractured segment we noticed a decrease in motility. Clinically, patients had a significant decrease in VAS and ODI at 1 month after removal. Our study shows that percutaneous fixation for treatment of thoraco-lumbar fractures type A2 and A3, allows to preserve motility of the treated segments after the removal of the instrumentation until 12 months. The removal of instrumentation is associated with good clinical results without of loss of correction in treated segment.

Mini-invasive surgery has become very popular in the last decades. Recently, percutaneous pedicle screw fixation has become one of the most used techniques in the treatment of type A vertebral fractures without neurological involvement which in the past years were treated with brace and bed rest with good results. However, residual kyphosis, pressure sores, prolonged recumbence, deep vein thrombosis are frequent complications related to with non-operative treatment (1-9). The advantages of percutaneous pedicle screw fixation are well known. Surgical treatment allows good restoration of the sagittal index (9, 10), early mobilization of the patients and rapid hospital discharge. Removal of the implant is advocated after the fracture healing to preserve mobility of the instrumented segment and to avoid a rupture of the implant due to the absence of arthrodesis, however identifying the right time of removal remains a topic of debate. Several authors described time related zygoapophiseal degenerative changes associated to hypo-mobility (11, 12, 13). In the last years some authors reported residual mobility after removal of the vertebral instrumentation (14). Moreover recent reports observed the presence of

Key words: thoracolumbar fracture, posterior implant, implant removal, percutaneous fixation, range of motion

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healthy intervertebral discs (IVDs) in non-fused segments once the instrumentation was removed (15). The aim of the study is to evaluate the residual mobility of the fixed vertebral segments, in patient with type A vertebral fractures treated by percutaneous pedicle screw fixation, after removal of the instrumentation, and its clinical impact on patients' quality of life.

MATERIALS AND METHODS

We retrospectively analyzed clinical and radiographic data of patients affected from Type A thoraco-lumbar fractures (Th6-L5) treated with percutaneous pedicle screw fixation (PPSF) between 2011 and 2017 in our institution. Only 68 patients had a good data set and were included in the study, 36 of which underwent surgical treatment for removal of the instrumentation. We included patients aged between 18- and 60-years-of-age with type A2 or A3 fracture at thoraco-lumbar spine, treated with PPSF. We excluded patients who reported others spinal fractures, patients with perioperative or post-operative complications, patients affected by osteoporosis, severe spondylosis, neoplasms and prior spine surgery.

Surgical procedure

All patients underwent PPSF by posterior approach using image intensifier guidance. All patients underwent general anesthesia. The procedure was performed using a conventional C-arm fluoroscopy. The entry point of the guide wire was careful located. Using a cannulated screw-driver, the cannulated polyaxial screws were inserted. After positioning all screws, 2 pre-shaped titanium rods were inserted and engaged. The instrumentation was removed after an average time of 302 days after treatment.

Radiographic evaluation

Standard and dynamic X-ray, before the removal and at 1 and 12 months after surgery, were obtained. Radiological evaluation was performed by three observers (two senior spinal surgeons and a senior radiologist) at 6 months after fixation removal, using dynamic radiography obtained in maximum flexion and extension. For the radiographic

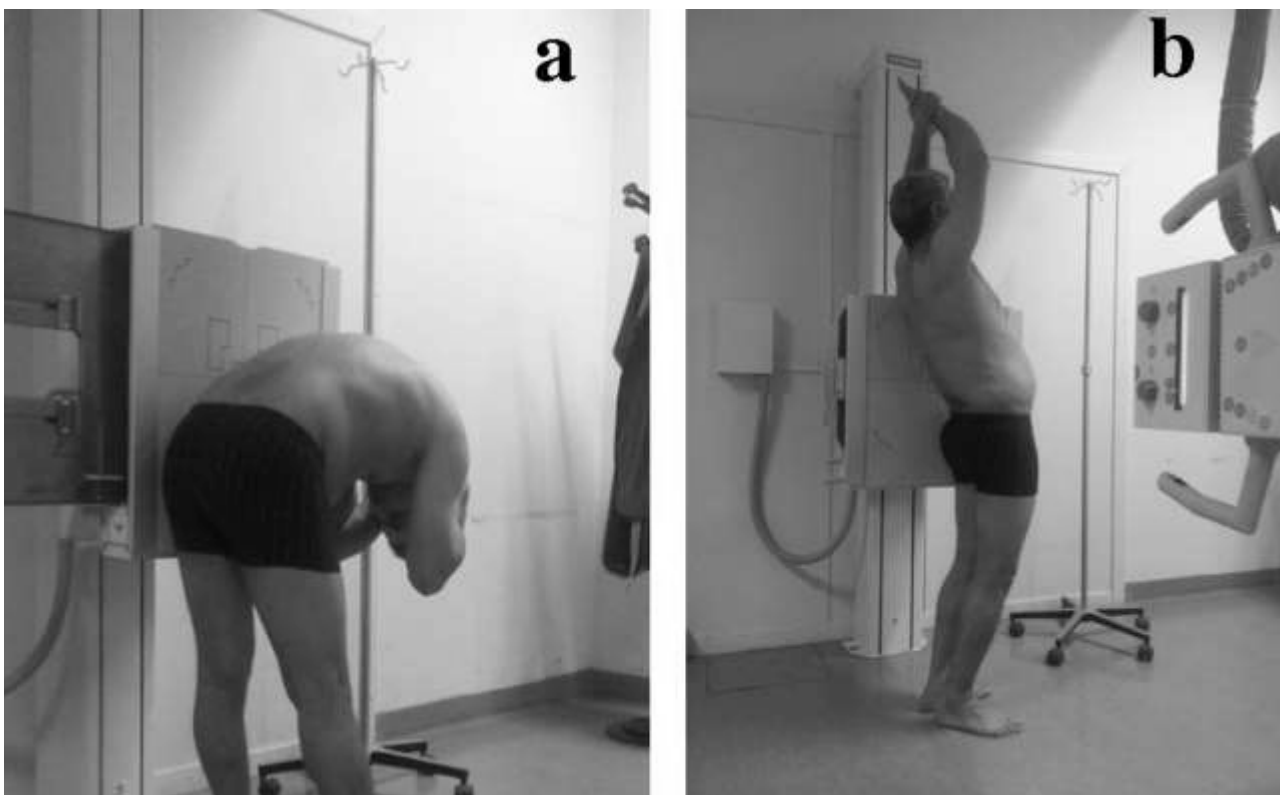

Fig 1. *A patient during a radiographical examination. The patient was asked to bend the upper body back and forward as much as possible.*

examination the patients stood in upright position and the hip joints were stabilized to avoid flexion-extension. The patients were asked to bend the upper body forward and back as much as possible. The examiner applied a flexing force in order to help the subject bend the upper body as much as possible (Fig. 1). In each patient, 3 levels were evaluated, divided into: fractured vertebra, upper and lower level, whereas spinal mobility was evaluated according to the technique described by Tanz (18), using X-ray in maximum flexion and extension (Fig. 2). The normal ROM established by Dvorak et al. (19) was used to compare our results. Mobility range of each segment was classified as "normal", "decreased" if mobility was below normal ROM and above the 20% of the average mobility for each segment and as "non-mobile" if the mobility was below 20% of the average mobility of each segment. In standing plain radiograph we also evaluated Segmental Kyphosis (SK) of the fractured level through measurement of Sagittal Index in accordance with Farcy et al. (10). All patients underwent a CT scan targeted at the vertebral segment affected by the fracture with sagittal and coronal reconstructions to evaluate the healing of the fracture after 6 months from surgery.

Clinical evaluation

Clinical and functional outcome were evaluated by Visual Analog Scale (VAS), Oswestry Disability Index (ODI) and Short Form General Health Status (SF-12) before the surgical treatment and at 1 and 12 months after the removal of the instrumentation. Statistical analyses were conducted using chi2 test and verified with Fisher's exact test for Oswestry Disability Index and SF-12. Student's *t*-test was used for Visual Analog Scale data, Sagittal Index and monosegmentary discal height. Significance was established for $p < 0.05$.

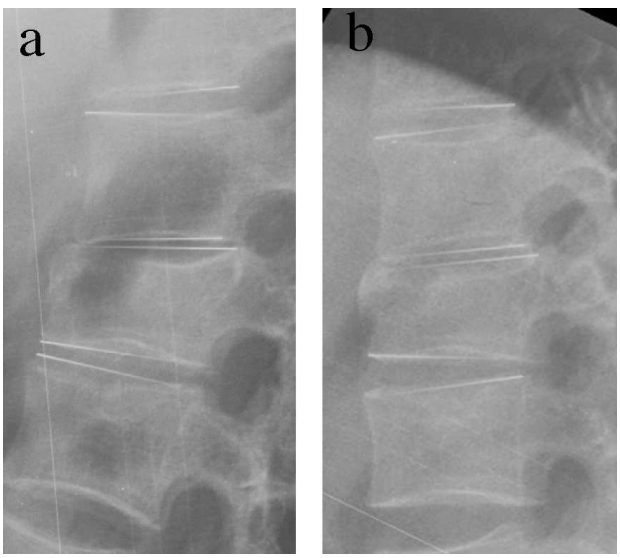

Fig 2. *Thoraco-lumbar X-ray, in maximum flexion and extension in a patient with L1 fracture after removal of instrumentation. It is possible observe a normal ROM in the upper and lower disc, but a ROM reduction in the fractured vertebra disc.*

RESULTS

We analyzed a total of 108 levels in 36 patients. 18 fractures were localized at L1 level, 5 at L2, 5 at L3, 4 at T12, 4 at T10. In 10 cases injury was provoked after falling from heights and in 26 cases with other various accidents. Twenty-nine of the patients included in the study were polytraumatized (Fig. 3). In 25 cases fractures were type A2 in accordance with AO spine classification and In 11 cases they were type A3. The mean age was 48 years (min 24-max 60), 23 M and 13 F, with a mean BMI of 26.4 (22.3-31.2) (Table I). According to the established criteria, all proximal levels (36) presented normal ROM. At the levels of the fracture we noticed 22 levels with decrease ROM, 6 levels were considered as non-mobile and 8 cases presented normal ROM. At the distal level in 32 cases we observed a normal ROM and only 4 cases presented a decreased ROM (Table II). Pre-operative Sagittal Index was 15.9°, after 1 month 16.3° ($P > 0.05$) and 17.1° ($p > 0.05$) after one year. The patients had an average preoperative "Oswestry Disability Index" of 24.3% (18-28%), of 17.5% (14-20 %,) after 1 month, and 11% (8-14%) after 1 year ($p = 0.02$). The mean preoperative VAS back was 4.13, 2.3($p = 0.02$) after 1 month, and 0.75 ($p = 0.002$) after 1 year of follow-up. The mean preoperative Short-Form 12 was equal to 44% (PCS) and 46.9% (MCS), to 45% (PCS) and 46.5% (MCS) ($p > 0.05$) after 1 month, to 52% (PCS) and 51.6% (MCS) after 1 year of follow-up.

DISCUSSION

Treatment of Type A2-A3 vertebral fracture is a debated issue. Surgical treatments allow to restore good

sagittal alignment and to avoid prolonged recumbence, deep vein thrombosis and other complications related to immobilization (3). Increased infection rates, post-operative pain, muscle denervation and high blood loss are related to a conventional approach (20-21). Percutaneous stabilization allows a significant reduction of the regional deformity derived from the lesion, with the restoration of a good sagittal alignment (30).

Minimally invasive surgery allows to reduce intra-operative blood loss, hospital stay and use of analgesic drugs (3). The removal of the instrumentation after fracture healing, given the lack of arthrodesis, is recommended to preserve the motility of the instrumented lumbar spine segments. Residual mobility can help IVDs to regenerate, since movement is essential for cartilage nutrition (15).

The early removal of the instrumentation prevents the occurrence of arthrosis of the zygapophyseal joints (ZJ), a possible consequence of prolonged fixation.

Table I. *Patients and fracture characteristics.*

Characteristics	Patient data
Age (yr)	48 *(range 24-60)
Sex (M:F)	23:13
BMI	26.4* (22,3-31.2)
Type of fracture	
A2	25
A3	11
Level of fracture	
T10	4
T11	0
T12	4
L1	18
L2	5
L3	5
*Values shown are mean	

Several authors described degenerative changes related to the zygapophyseal joint which lead to the hypomobility of the segment interested (19, 20, 22, 23).

In 1984 Kahnavotitz et al (24) studied the effect of internal fixation on the canine articular cartilage. They found irreversible histological changes at only 2 months post-operatively after instrumentation removal. Histological changes seemed to be related to the fixation time. Proietti et al. (13), analyzed modification of the ZJ adjacent to the fracture level after percutaneous pedicle screw fixation without fusion, using TC images. The authors described no degenerative changes at 4 months after fixation. Some differences were found at 8 months in the 21.42% of the cases and in the 76.92% at 12 months in the middle joints. The authors suggest instrumentation removal after the fracture healing between 6 and 12 months after fixation.

Significant degenerative process was related to the impingement between the tulip of the pedicular screw and the articular process of the vertebra at the entry point. As a consequence, much attention should be given to preserve articular anatomy during the surgical procedure. Gardner and Armstrong (25) performed a retrospective analysis on 20 patients treated with Harrington rods for spinal fractures. They highlighted no radiological evidence of arthrosis in 64% of cases and no evidence of damage at zygapophyseal joint.

Thirty patients with a thoracolumbar fracture treated using a Harrington rod were analyzed by Dekutoski (26). The rods were placed cephalad in three segments and caudal to the injured vertebra in two or three segments. A short arthrodesis was performed. The fixation was removed after at least twelve months. Muller et al (27) analyzed the range of motion after instrumentation removal in 20 patients treated with bi-segmental transpedicular instrumentation and mono-segmental fusion for thoracolumbar burst fracture. The fixation was removed at an average time of 16 months. They found normal motion of the temporarily stabilized segment in only 5 patients and reduction of motion in 6 patients. In 9 patients the authors described complete ankylosis. Other authors (28) described physiological motion of the temporarily fixed levels when the hardware was removed at six months. Dodd et al. (29) analyzed vertebral motion

Table II. *Range of movement of studied levels.*

	Normal ROM	Decreased ROM	Non-mobile
Upper Vertebrae	36	-	-
Fractured Vertebrae	8	22	6
Lower Vertebrae	32	4	-

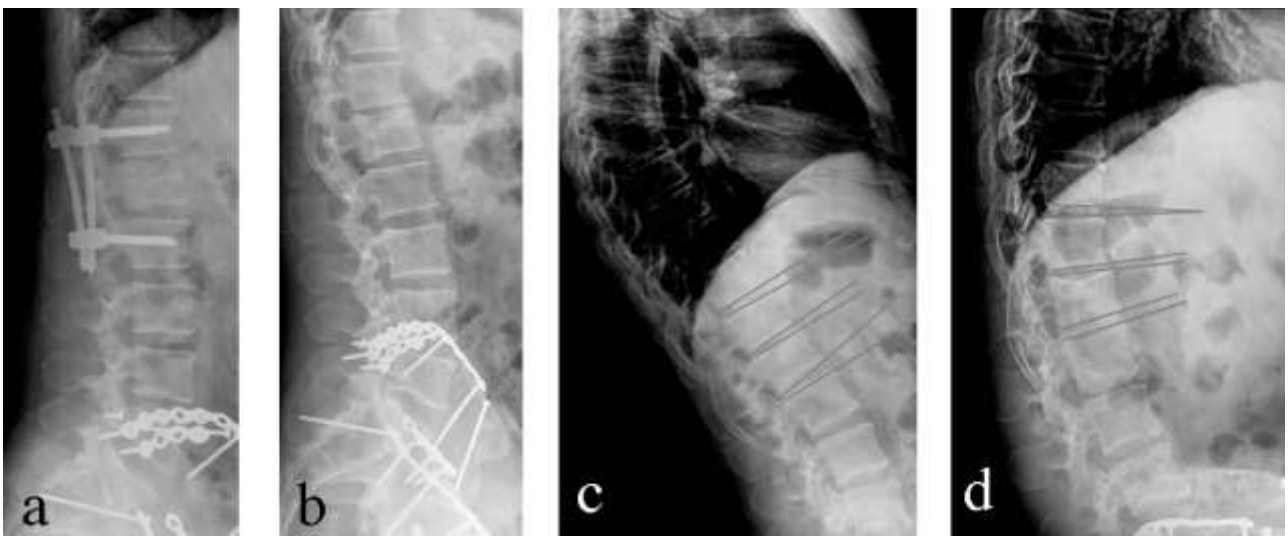

Fig. 3. *A 46-year-old male patient. Polytrauma with type A2 fracture of L1, fracture of the iliac wing and fracture of the anterior and posterior column of the left acetabulum.* ***a****): Postoperative X-ray of lumbosacral spine in lateral position;* ***b****): X-ray after instrumentation removal;* ***c, d****): X-Ray in maximum extension and maximum bending that highlight a normal ROM in all the segments examined.*

before and after Harrington rods removal in 5 patients affected by thoracolumbar fracture. The hardware was removed at 1 year in each patient. The authors affirmed that the temporarily fixed levels regained considerable movements once the rods were removed. In 1993 Lindsey et al (11) analyzed residual intersegmental spinal mobility of 57 patients after pedicle fixation of thoraco-lumbar fractures with open technique. Instrumentation was removed at 1 year after injury. At 2 years minimum follow-up of residual mobility was studied with dynamic X-ray. The results showed the maintenance of a residual mobility in the treated segment after instrumentation removal. Fractured level showed the maximum loss of movement probably due to the severe disc injury associated to the end plate disruption. In 2006 Yurac et al. (15) analyzed the mobility of non-fused segment, after hardware removal, on a cohort of 21 patients treated by indirect reduction and transpedicular instrumentation for thoracolumbar spine fractures. A long instrumentation and short arthrodesis were performed. In this study, the non-fused segments presented normal or decreased mobility in 83.2% of cases, when the removal of the hardware was performed before 10 months. When the hardware removal took place after 10 months, they showed 68.8% of mobility. In 2017 Smits et al (31) conducted a retrospective study on a cohort of 102 patient affected by thoracolumbar fractures

that underwent posterior implant removal after stabilization. The author found a minimal increase of segmental kyphosis after removal of implant which did not correspond with worsened clinical outcome.

If there are many different studies that analyze the removal of the implant and the consequent morphological and clinical results, only few analyzed residual mobility after instrumentation removal and only one study was found on this topic related to percutaneous fixation (32). In this study Kim et al sustained that the removal of implant after fracture consolidation preserves motion, but this study was conducted only on 16 patients, half of which had osteoporosis. The debate on the removal of the implant is still open in literature. From our results, results, it emerged that the non-fused spinal segment included in pedicle instrumentation maintain mobility in high percentage of cases, if instrumentation is removed before 10 months from fixation. Clinically, patients had a significant decrease in VAS and ODI at 1 month after removal. After removal of the instrumentation no significant loss of correction was observed.

In proximal and distal segment to the fracture a normal range of motion was restored, while at fracture segment level we noticed a decrease in motility, probably due to the fracture that affects the vertebral endplate promotes disc degeneration, regardless of the instrumentation. Among the limitations of the study we recognize the low number of patients and the presence of an inhomogeneous population.

Our study shows that percutaneous fixation for treatment of thoraco-lumbar fractures type A2 and A3 and the removal of implant within 12 months, allows to preserve motility of the treated segments. In our opinion percutaneous stabilization should be considered as a temporary stabilization and should be removed after the vertebral fracture has healed. The removal of the instrumentation in 12 months is associated with good clinical results without a significant loss of correction in treated segment.

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A THORACIC PAIN OF DIFFICULT DIAGNOSIS. UNUSUAL LOCALIZATION OF OSTEOID OSTEOMA

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Osteoid Osteoma (OO) is a benign tumor that can affect any age, but it occurs mostly in adolescents. Only few cases are reported in early infancy but very rare in advanced age. From our series of OO of the spine, we selected a rare case that combines many unusual features that makes diagnosis very difficult. A case of a painful thoracic syndrome in an old female patient due to an OO localized in the inferior edge of the left pedicle of T11 with engagement of the foramen was reported. The age of the patient, the absence of any typical clinical and diagnostic signs, such as nocturnal pain or side effects to NSAIDs administration, are unusual at presentation of OO. She presented instead, a type of pain to the chest that was stabbing, fulminating and radiating. The interest of the case is due to the association of a variety of clinical aspects that stimulate discussion as well as to the role of the modern investigative diagnostic process.

Osteoid osteoma (OO) is a benign bone tumor that manifests itself with painful symptoms that are difficult to diagnose when the lesion is less than 1 cm. Soon after the first historical description by Jaffe in 1935 (1), OO quickly became very well known among orthopedic surgeons as a typical cause of nocturnal musculo-skeletal pain. Classically the pain is deep, worsening at night and relieved by aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) (2). Unusual clinical presentation and localization in complex anatomic sites can make the diagnosis very difficult (3). Before a correct diagnosis is performed, many physicians could be involved in the diagnostic process and in the therapeutic decision. Despite the wide use of investigative technologies such as CT, scintigraphy and MRI, the tumor remains difficult to find with a consequent great diagnostic delay (4). Certainly, modern imaging technologies represent the most important tool to reach the diagnosis although they paradoxically could result confusing in the absence of a clinical suspicion, especially in cases with unusual presentation. In fact, the magnetic signal intensities of the tumor on T1 and T2 weighted MR images are often not specific, furthermore the visualization of the tumor is frequently hindered by an abundant edema of the surrounding bone marrow due to the prostaglandins released by the lesion. CT-scan is the most accurate exam to recognize the tumor, but it needs to be targeted on the lesion and carried out with very thin slices given the very small size of the nidus (5).

Many reports are published annually, focusing their attention on the various clinical and diagnostic aspects of OO, even though the common element remains the difficult diagnosis and as obvious consequence, the long history of an inexplicable pain.

From our series of OO of the spine, we selected a case that combines many unusual features that

Key words: pain, osteoid osteoma, MRI, CT, prostaglandins, thoracic spine, thoracic pain

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makes the diagnosis very difficult, and particularly stimulates discussion on some aspects of the clinical and diagnostic approach.

Case report

A 68-year-old female was referred to our spinal surgery department approximately six months after the onset of a painful syndrome because of suspected "atypical hemangioma". She was highly agitated and uncooperative, sweating, breathing superficially, with a hand on one side of the chest to sustain it. Neurologic examination was completely negative for motor and sensitive deficits. Medical history was characterized by a sudden onset several months before, with an acute pain of short duration in the dorsal tract of the spine that later became continuous, worsening at night, with more frequent short duration acute phases during the day. The patient described the pain coming from behind and penetrating into the dorsum with radiation to the chest and sudden interruption of breath. The pain was not related to the movements. The patient experienced also three major episodes of falls during walking because of a sudden onset of a violent, penetrat-

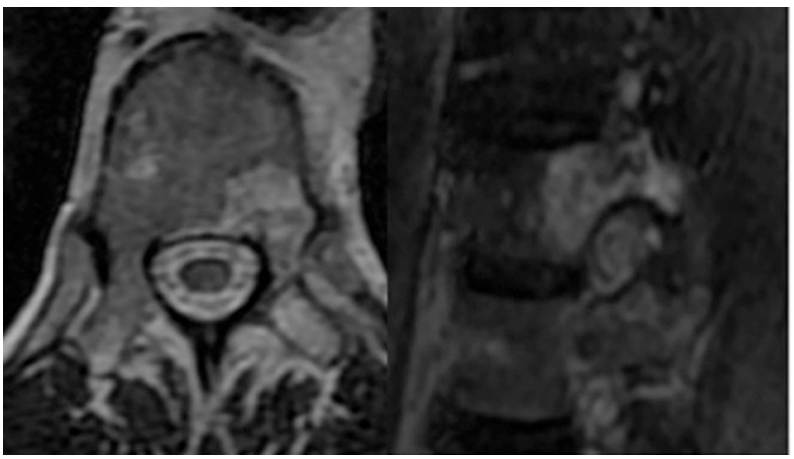

Fig 1. *T2-weighted MRI of the 11th thoracic vertebra.* ***Left pedicle****: transverse process and the posterior half of the vertebral body presents hyperintensity signal interpreted as atypical hemangioma. The nerve root inside the foramen appears increased in volume.*

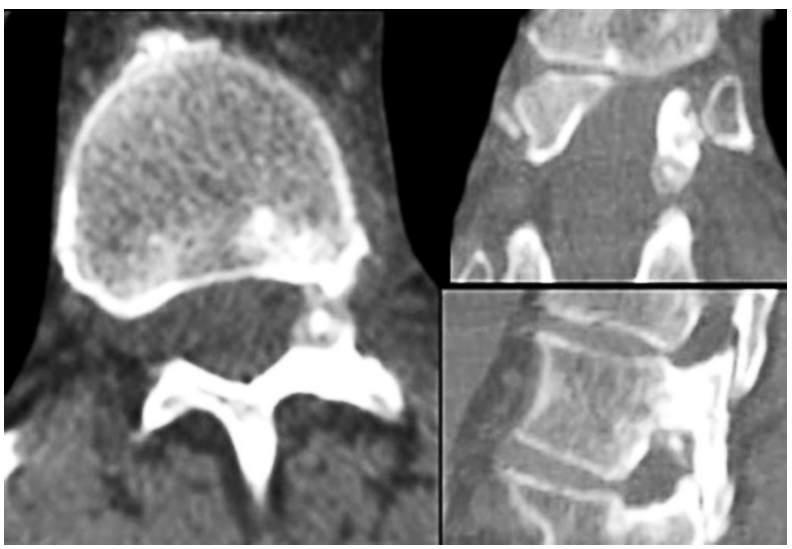

Fig 2. *Thin slices CT-scan. Axial, coronal and sagittal images passing through the foramen. A small, ossified core, surrounded by partially calcified tissue, is located at the inferior edge of the left pedicle of 11th thoracic vertebra, close to the nerve root. The bony trabeculae of the pedicle are thickened.*

ing pain with radiation to the legs. For the clinical characteristics, the pain was initially interpreted as a neuropathic pain due to a possible post-herpetic neuropathy. She began to suffer from insomnia, and she developed many behavior symptoms that were attributed as hysterical signs. The patient underwent full clinical and instrumental investigation with particular attention to cardiovascular and pulmonary functions without detection of any disease. She also underwent MRI at low magnetic field (0.3 Tesla) because of claustrophobia. MR examinations revealed a hypointense area on T1 and hyperintense area on T2 weighted images that involved the posterior pedicle, the transverse process and the posterior half of the left vertebral body (Fig. 1). No compression of neurologic structures was considerable except for an increase in size of the nerve root inside the foramen. The radiologists hypothesized an "atypical" hemangioma, and suggested a biopsy of the lesion. Due to the lack of consistency between the clinical picture and MRI findings, a CT scan with thin slices and a sequential angioscintigraphy were prescribed. The patient came back with a positive scintigraphy for local intense uptake of the Tc99mdp, highly suggestive of an OO and a CT scan with high resolution technology (very thin slices), which clearly demonstrated a small round shaped osteoblastic lesion located in the neural foramen, exactly on the inferior edge of the left pedicle of T11, showing the bony trabeculae thicker than normal (Fig. 2).

A small, ossified central core, surrounded by partially calcified tissue, occupied the foramen making contact with a nerve root and increasing in volume. The diagnosis of OO was highly suggestive so a surgical excision was indicated, given the close proximity of the tumor to the neural structures, to prevent possible neurologic damages, nevertheless an attempt to treat the lesion with radiofrequency was suggested. A percutaneous approach with radiofrequency was then carried out. With the patient lying in prone position, we put in place the electrode (Fig. 3) and RF is gradually administered with RF generator (RFG-3C Radionics, Burlington, MA, USA); reaching progressively the target temperature (9 min at 75° C). The patient was pain-free soon after the procedure without any complications. At 1-year follow-up, she was still pain-free.

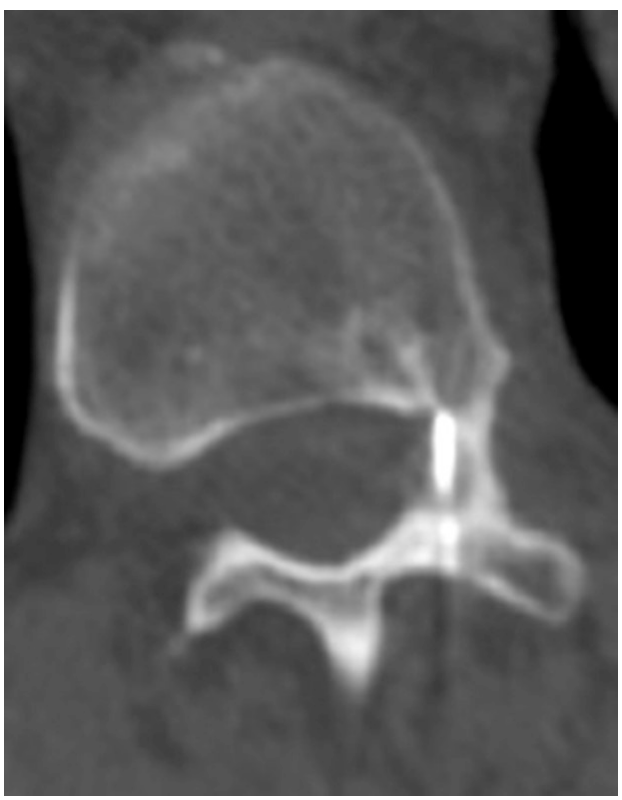

Fig 3. *Thin slices CT-scan. Axial image shows the final position of the electrode, with the active tip inside the nidus of the osteoid osteoma.*

DISCUSSION

The peculiarity of the case is the coincidence of several factors that, even if taken one by one, represent elements of originality. The first peculiarity certainly concerns the age of the patient. OO is a benign tumor that can affect any age but it occurs mostly in adolescent age. Only few cases are reported in early infancy but rare in advanced ages (4, 6). It means that OO is quite unlikely in the pathway of differential diagnosis in case of pain in elderly patients. In absence of typical clinical signs, such as nocturnal pain or evident sensitivity of the pain to NSAIDs administration, it is difficult to hypothesize the tumor as the source of a pain that, at the end of a long diagnostic process, represents really an unexpected surprise. The second peculiarity concerns the type of pain. Since its onset, the pain was reported as a stabbing, fulminating, radiating to the chest. Initially characterized by single episodes, which became even more frequent over time, until later on it

become almost continuous. Although a neuropathic pain was considered, the trigger point of the pain was unknown. Only after the recognition of the OO, it was possible to identify the exact pathogenesis of the pain. On CT imaging, the close anatomical proximity of the tumor to the nerve root in the foraminal canal was in fact evident. The nerve root also showed increased size in comparison with the contralateral. It has been proved that OO can release great amount of prostaglandins (PGE2 and PGI2), which are able to cause a series of secondary effects in the surrounding structures such as vasodilatation, edema, and reduction of the threshold for stimulation of pain receptors, thus inducing hyperalgesia (4, 7). It is likely that such intense, neurologic symptoms were caused by the direct effects of prostaglandins on the nerve root, rather than a direct compression of the nerve inside the foramen by a tumor with self-limited growth. Generally, in case of root compression by a more rapidly growing pathologic tissue, the pain is firstly deep and the symptoms are milder, while they quickly deteriorate due to sensitive and motor deficits by neurologic compression, and to bone osteolysis by infiltration of the tumor tissue (8). The third unusual feature concerns the diagnostic aspects. It is widely accepted that CT scan is the exam that better than any other is able to appreciate the exact morphology of an OO, but is quite limited by the high radiation exposure of the patient. Thus, due to this limitation, CT scan revealed essentially as a second step, an exam that must be clearly targeted on the suspected lesion. Currently, there is an increasing use of MRI as a diagnostic imaging exam of first choice, sometimes before standard X-ray examination and even self-prescribed by the patient given the very low invasiveness of the investigation. Therefore, MRI is frequently used improperly and not adequately supported by a clinical evaluation, which implies failure to reach the correct diagnosis. In our case, the patient was submitted to three MRIs without reaching the diagnosis.

Another peculiarity worth mentioning is that an image of a large area of hypointense signal on T1 and hyperintensity on T2 weighted MRI sequences that surrounds and hides the very small tumor lesion, is quite typical in OO. This feature is very frequent but often not specific due to the edema of the bone marrow mostly caused by vasodilatation due to PGs released by the tumor (9). In many cases, particularly in case of OO of the spine located in the vertebral body at the base of the pedicle, the area of hyperintensity involves a large part of the vertebral body and this might be falsely interpreted as an expression of a more aggressive disease or alternatively as an atypical hemangioma. Currently there has been a remarkable diffusion of low magnetic field devices, low cost with a low diagnostic definition used routinely for spine pathologies. Besides the cost, the main reason of the popularity of these machines is the reluctance to get into the closed tube of high-definition machine because of the claustrophobic feeling experienced by many patients. Low-quality images of open low-field magnetic MRI, in some cases, does not support adequately the clinical suspect obliging the physician to ask for a further exam with higher quality definition. In our case, the diagnosis of OO was impossible, also reviewing the images retrospectively, because of the low quality of imaging.

One consideration concern the use of term “atypical” hemangioma. A spinal hemangioma is a very common, asymptomatic, benign tumor-like lesion that generally does not need any treatment (5). The adjective “atypical” is frequently used by radiologists to refer to lesions that look different from the normal appearance of hemangioma in terms of signal intensity and morphology. Since the great abuse of this term in the daily practice can induce clinical confusion, it would be more useful to limit the term only in well-selected cases in which the suspicion is strong (10, 11).

The small size of the tumor, not exceeding 1.5 cm, and the localization in sites difficult to investigate with routine imaging examination, such as the spine, created the myth of OO as the most typical cause of a long lasting, hidden painful syndrome. In addition, the advent of modern techniques of imaging seem to not have disproved that it remains difficult to diagnose the tumor in the absence of a clinical assumption. Paradoxically, if not clinically supported, diagnostic imaging could result confusing, especially the most widely used MRI, because of the very low specificity of the exam (11). The sensitivity of MRI can obviously be improved by changing routine setting of the machine in case of a suspected or known lesion. Dynamic MRI significantly increased nidus conspicuity compared to a non-enhanced MRI.

In fact, the nidus contrast uptake starts in the arterial phase and is higher, compared to the surrounding bone marrow (12). However, despite the wide spread of new technologies of imaging, OO, located in difficult sites to investigate, remains a clinical challenge (13). MRI, especially low magnetic field, has a low definition so the effectiveness of the exam in diagnosing an OO remains controversial.

The best way to recognize morphologically OO is clearly the CT scan for its capacity to study the bone tissue, although the high radiation exposure suggests to limit the exam and to target it on well-defined suspected areas of the lesion. Given the very small size of the tumor, it is essential to carry out the examination with very thin slices. The availability of more sophisticated diagnostic image techniques currently allows recognizing the lesion compared to the past. What probably occurs today is the incorrect use that both physicians and patients make of the diagnostic exams. OO is a specific lesion of the bone that interests typically the orthopedics but in the first phases, and sometimes for long periods, even other physicians, such as family doctors, radiologists, neurologists and physical therapists are involved in the diagnosis and treatment of this painful syndrome. The use of RF is effective and safe for the treatment of spinal OO in well-selected patients. The use of this technique allows a reduction in operating time, blood loss, hospital stay and complications compared to traditional open surgery (14).

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O'NIL ANTEVERSA® MINI-PLATE FOR STABLE HIP FRACTURE: FIRST EXPERIENCE CONSIDERATIONS AND OUTCOMES

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Hip fractures are associated with a 20% one-year mortality and a 50% loss of function. Over 700,000 deaths are estimated to occur annually worldwide following hip fractures. Concern exist regarding which is the best implant for extracapsular fractures fixation. For a correct positioning of the cephalic screw, a new plate (O'Nil Anteversa® mini-plate, Intrauma, Torino, Italy) with a fixed 8°of anteversion in the axial plane was developed. A total of 22 patients with an intertrochanteric fracture underwent surgery with Anteversa® mini-plate between October 2016 and April 2017. Data collected included patients' age at surgery, gender, fracture type, operative side, surgeon, type of implant, TAD, CalTAD and TADCalTAD. All patients underwent clinical and radiographic evaluations according to the AO Surgery Reference classification. The mean TAD, CalTAD and TADcalTAD for the entire population of study were, respectively, 20.18±7.5 mm, 20.45±7.25 mm, and 40.62±14.44 mm. The mean TAD, CalTAD and TADcalTAD of those patients who experienced mobilisation of the cephalic screw were, respectively, 20.26±5.87 mm, 19.53±5.47 mm, and 39.8±11.16 mm. Three patients experienced mobilisation of the cephalic screw, and none of these had a TAD greater than 25 mm, a CalTAD greater of 25mm or a TADcalTAD greater than 50 mm. This type of device meets the essential requirements for a correct treatment of intertrochanteric fractures in elderly patients. However, the excessive need of attention in each step, and the consequent increased time of surgery, could be seen as a limitation for its use.

The incidence of extracapsular hip fractures continues to rise to epidemic proportions, and are one of the most frequent causes of hospitalization (1, 2). Many factors are implicated in this pathology: the rise of average life (3), lack of physical activity (4), malnourishment (e.g. decreased consumption of milk and proteins) (5), and abuse of alcohol and tobacco (6).

Over 700,000 deaths are estimated to occur annually worldwide following hip fractures (2, 6), the highest surgical mortality of any orthopaedic operation (7). The World Health Organization showed that hip fractures are associated with a 20% one-year

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mortality and a 50% loss of function (8). Italy has the lowest one-year mortality rate (mean 19.1%), but also the highest length of hospital stay (mean 23.3 days) when compared with other European countries (9).

Hip fractures are more common in females than males, with a ratio of 8:1, and with an age between 65 and 84 years; 90% of fractures is associated with osteoporosis. Since most patients are old, the surgical treatment should be rapid, allowing immediate loading in the post-operative period (10).

The best implant for extracapsular fractures fixation is debated. Following the AO Surgery Reference classification, intertrochanteric fractures classified as 31-A1 and 31-A2 are considered as stable fractures, and are conventionally treated using a sliding hip screw (SHS) rather than intramedullary (IM) nailing, with similar functional outcomes and advantageous cost-benefit ratio (11-13). Outcomes are favourable in intertrochanteric patterns (14, 15), but cut-out or mobilisations still occur despite improvements in the devices and surgical techniques.

There is an association between major complications, such as cut-out of the implant, and the tip-apex distance (TAD) (16), calcar referenced tip-apex distance (CalTAD) (17) and TADcalTAD (18) radiographic parameters.

The TAD obtained adding the distance from the tip of the hip screw to that of the apex of the femoral head on the anteroposterior (AP) and lateral views. Cut-off is set at a distance of 25 mm, since a distance of <25mm is associated with a significantly lower rate of cut out of the fixation device (19).

Kashigar et al (17) reported an association between CalTAD and cephalic screw mobilisation in elderly patients with hip fractures treated with nailing. The CalTAD can be calculated using the same above mentioned measurement technique of the TAD in the lateral view, while in the AP view the CalTAD measurement (in mm) is performed by moving a guideline to be tangent to the medial cortex of the femoral neck. The CalTAD cut off is set at 25 mm (18).

TADcalTAD is a recently introduced parameter, and it represented by the sum of TAD and CalTAD, with a cut-off at 50 mm (Fig. 1).

The most common mode of cephalic screw mobilization through the femoral head occurs when the fracture collapses in varus (20, 21): this tends to occur in elderly, osteoporotic patients, patients with unstable fractures, and after a poor reduction (22, 23). Other factors that lead to cephalic screw mobilisation are the implant angle and the position of the lag screw through the femoral head (21). In this context, the term "mobilisation" refers to an abnormal postoperative movement of the cephalic screw or nail with an increased TAD greater than 3 mm (18).

An angular stable plate (O'Nill Anteversa® mini-plate) with an 8° anteversion angle in the axial plane, that associates linear compression of the fracture with rotational stability, has been developed to optimize the positioning of the cephalic screw.

The purpose of this article is to describe our first experience with this kind of plate for treating intertrochanteric hip fractures.

MATERIALS AND METHODS

All patients admitted to the San Giovanni di Dio e Ruggi D'Aragona Hospital of Salerno (Italy) with a traumatic hip fracture treated with an Anteversa® mini-plate (O'Nil Intrauma, Torino, Italy), and with a minimum three-month follow-up, were included. Both AP and lateral plain radiographs were obtained, and fractures classified according to the AO Surgery Reference classification (16).

A total of 22 patients underwent surgery between October 2016 and April 2017, performed by the senior author (N.M.). The senior author is a fellowship trained Trauma and Orthopaedics consultant with a special interest in orthogeriatrics. He had performed more than 1200 procedures using a SHS device over a 20-year period for the operative management of extracapsular hip fractures.

All reductions of hip fractures were performed before the operation on a dedicated fracture table and evaluated using fluoroscopy. The quality of the reduction was classified as good, acceptable and poor according to the available scientific evidence (24).

The Anteversa® mini-plate provides for an anti-rotation screw, generally 10 mm shorter than the main cephalic screw. This anti-rotation screw was not used in seven patients because an oversight of evaluation by the performing surgeon. The position of the lag screw in the femoral head was recorded by dividing the femoral head into nine zones resulting from the combined permutations of the lag screw in AP and lateral views. The femoral head was then divided into thirds on both AP and lateral views to define the limits of the nine zones (Fig. 2).

All patients followed the same post-operative rehabilitation protocol until hospital discharge, at an average of 14 postoperative days. Patients were allowed

immediate weight bearing and mobilisation with suitable walking aids.

Data collected included patient's age at surgery, gender, fracture type, operative side, performing surgeon. The fracture type, type of implant, TAD, CalTAD and TADCalTAD were determined using preoperative and postoperative AP and lateral radiographs retrieved from the San Giovanni di Dio e Ruggi d'Aragona Hospital of Salerno (Italy) database.

All parameters were measured with the Picture Archiving and Communication System (PACS): a recent study showed that the PACS is suitable for measuring the tip-apex distance (25). Every measurement for each set of radiographs was repeated in a blind fashion after one month, comparing the two sets of measurements using the Cohen's Kappa test to calculate the intra-tester reliability. For the purposes of this article, we used the average between the first and the second measurement, and the sum of both.

All data were entered in Microsoft Excel software and the mean values of TAD, CalTAD and TADCalTAD were reported for the purposes of our study.

Surgical technique

The Anteversa® mini-plate device consists of a tube-plate with 2 holes of 5 mm diameter each for autolocking screws, which are angled and divergent, and a valgus angle of 130°.

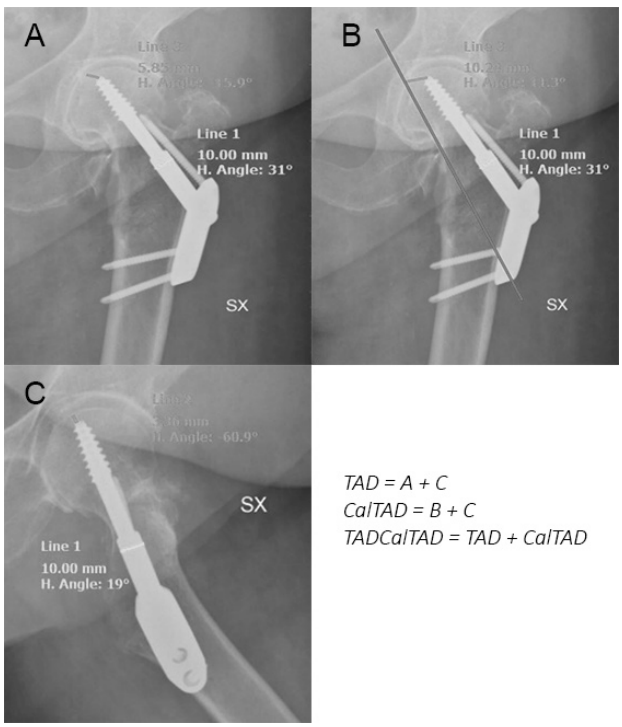

Fig. 1. *Schematic drawing of TAD measurement (**A, C**), CalTAD measurement (**B**) and TADcalTAD.*

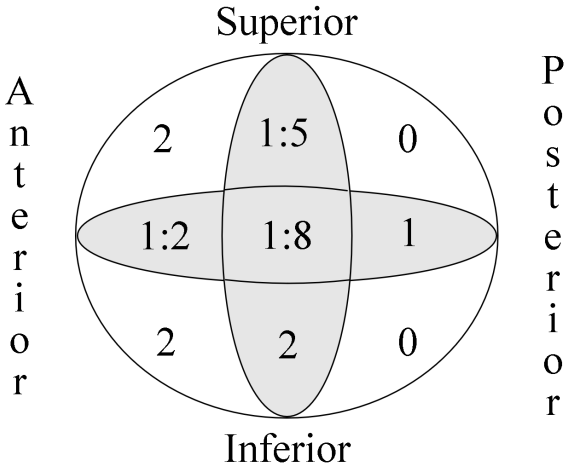

Fig. 2. *The distribution of lag screw positions in the femoral head and numbers of mobilisations for each position.*

The tubular portion presents 8° of anteversion. The cannulated cephalic screw has a diameter of 8 mm, and 11 mm in the threaded part. The anti-rotational nail for angular stability, which is located proximal to the cephalic screw, has a diameter of 5 mm. All components are made of AISI 316LVM-ISO 5832-1 steel that is compatible with magnetic resonance imaging (MRI).

The patient is placed supine on the operating table, then the fractured limb is pulled while the contralateral is abducted, extrarotated and flexed. Under fluoroscopic control, both in AP and lateral views, the reduction of the fracture is performed. This must be as more anatomical as possible; the reduction is classified as good, acceptable or poor according to the available scientific evidence (24). A subtrochanteric incision of 4.5 cm is performed, the vastus lateralis muscle is gently retracted, and a 130° plate guide is assembled onto the diaphysis. A wire guide is then inserted up to approximately 1 cm the subchondral tissue (Fig. 3). After a check for a correct positioning of the wire guide, the 130° guide is removed. The length of the cephalic screw should be then determined with the wire measure. If the guide wire is inserted up to the subchondral tissue, then 10 mm must be subtracted from the measured length in order to get an optimal TAD. The cephalic screw is then inserted, and the plate is placed sliding the cephalic screw and controlling the orientation of the femoral shaft, which is fixed with 2 angular stable screws. Finally, an anti-rotational screw is positioned above the cephalic screw. Routine AP and lateral radiographs are obtained.

The post-operative treatment consists of early partial weightbearing, as tolerated. As soon as the effect of the anaesthesia is over, patients are encouraged to perform simple exercises such as moving the toes, ankle, knee and

hip of the operated leg. A clinical and radiographic check is performed at 30 days. Other clinical and radiographic check-ups are performed 2, 6, and 12 months after surgery.

RESULTS

A total of 22 patient underwent internal fixation of an extracapsular hip fracture using an Anteversa® mini-plate. There were 4 males (18.2%), and 18 (81.8%) female patients, with a mean age of 84.7±8 years.

According to the AO Surgery Reference fracture classification, there were eight 31-A1 fractures (27.3%), eight 31-A2 fractures (27.3%), and six 31-B1 fractures (27.3%).

The quality of the reductions was classified as good in 19 patients (86%), and acceptable in 3 patients (14%). All patients had a minimum follow-up of 3 months, with a mean of 6 months and a maximum of 14 months.

The majority of the lag screws was placed in centre-centre and centre-superior positions (8 and 5, respectively). In the three patients in whom mobilisation occurred, the cephalic screw was implanted in a centre-anterior position, in a centre-centre position, and in a centre-superior position (Fig. 3). The small number of patients did not allow a meaningful analysis within the nine zones of the femoral head.

The mean TAD, CalTAD and TADcalTAD for the entire population of study were, respectively, 20.18±7.5 mm, 20.45±7.25 mm, and 40.62±14.44 mm. The mean TAD, CalTAD and TADcalTAD of those patients who experienced mobilisation of the cephalic screw were, respectively, 20.26±5.87 mm, 19.53±5.47 mm, and 39.8±11.16 mm. The mean TAD, calTAD and TADcalTAD of those patients who did not experienced mobilisation of the cephalic screw were, respectively, 20.17±7.86 mm, 20.59±7.6 mm, and 40.76±15.15.

Five patients (22.72%) had a TAD greater than 25 mm (mean 29.66±13 mm), with a CalTAD and a TADcalTAD greater than their cut-offs in, respectively, two and three patients.

Four patients (18.2%) had a CalTAD greater than 25 mm (mean 30.17±14 mm), with a TAD and a TADcalTAD greater than their cut-offs in, respectively, two and three patients.

Four patients (18.2%) had a TADCalTAD greater than 50 mm (mean 60.11±10.17 mm), with a TAD and a CalTAD greater than their cut off in, respectively, three and three patients. The Cohen's kappa test showed a good intra-tester reliability (0.9 and 0.85, respectively).

Seven patients (31.8%) were treated using an Anteversa® mini-plate without the anti-rotational screw (two patients with a 31-B1 fracture, two patients with a 31-A2 fracture, and three patients with a 31-A1 fracture). In only one patients was the TAD greater than 25 mm, while CalTAD and TADCalTAD were less than their respective cut-offs. These seven patients were the first treated with the Anteversa® mini-plate in our Institution.

DISCUSSION

In the USA, more than 90% of all proximal femoral

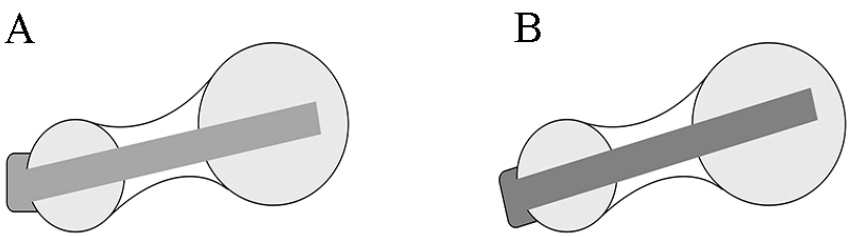

Fig. 3. *Correct positioning of Anteversa® mini-plate and cephalic screw (**A**) compared with the common SHS cephalic screw position (**B**).*

fractures occur in patients over 50 years, and the occurrence of hip fractures doubles for each decade over 50 years (26). Furthermore, intertrochanteric fractures are approximately the 50% of hip fractures, and the mortality rate in the acute phase is between 5% and 25% within the first year (26). Patients with a hip fracture are exceedingly fragile, and most of them will be unable to sustain a second operation or tolerate prolonged physical therapy.

Even after one operation, there is a 12-month mortality of 35% for men and 22% for women (27, 28). Sliding hip screw plate and cephalomedullary (CM) nail are the preferred treatment options for intertrochanteric fractures of the hip (29). However, CM nailing, compared with SHS, is associated with a shorter operating time, reduced intraoperative blood loss, and improved walking ability in unstable hip fractures (30-32).

The poor bone quality in the region surrounding the lag screw probably exacerbated the chances of mobilisation, and patients who have significantly multifragmented intertrochanteric fractures may be more prone to mobilisation (33). If revision surgery becomes necessary, a high mortality, or at the very least a high rate of in-hospital morbidity, and increasing costs are likely (34).

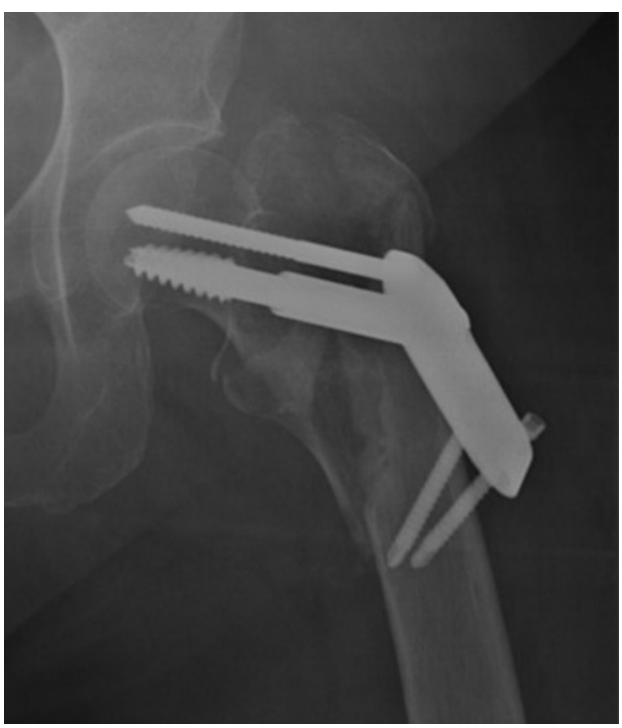

Fig. 4. *Radiographs of Anteversa® mini-plate with mobilisation of the cephalic screw for a 31-A1 fracture.*

The Anteversa® mini-plate was used, at the beginning, by the senior author (NM) as a SHS, with the only difference being the anteversion grade. In retrospect, it was not taken into account that SHS and Anteversa® mini-plate presented a different architecture, with the latter having a cilindrical shape, not an hexagonal one like the SHS.

Three patients (13.63%) experienced mobilisation of the cephalic screw, and none of these had a TAD greater than 25 mm, a CalTAD greater of 25mm or a TADcalTAD greater than 50 mm (Fig. 4). Among these three patients, two were treated with an Anteversa® mini-plate without the anti-rotational screw for 31-A2 and 31-B1 fractures; both had a good reduction, but experienced cephalic screw mobilisation before one month. One patient was treated with an Anteversa® mini-plate with the anti-rotational screw for 31-A1 facture; it had a good reduction but suffered mobilisation. These three patients were then operated again: the 31-A2 fracture with nailing, the 31-A1 fracture with DHS (Dynamic hip screw), and the 31-B1 fracture with a hemiarthroplasty.

We did not evaluate the bone mineral density (BMD) in our patients, but we point out that there is no agreement regarding values of BMD that may be used to indicate a higher risk of mobilisation in osteoporotic bone (35). Furthermore, the TAD is an independent predictor risk factor of cephalic screw mobilisation after internal fixation (24, 36), and the Singh Osteoporosis Index does not exhibit any significant relationship with the rate of cut out (17).

Unfortunately, the relatively small number of patients treated with the Anteversa® mini-plate in the present study makes more advanced analytical statistics impossible. To the best of our knowledge, there are no studies, in the currently available scientific literature, that report about the outcomes of the first surgical experience with the use of Anteversa® mini-plate.

Orthopedic surgeon may choose among several devices for the surgical treatment of hip fractures but not all devices are able to meet the technical requirements for an optimal fixation. Moreover, the scientific literature reports three major complications after internal fixation: varus collapse of the head/neck of the femur, excessive shortening of the femoral neck, and diaphyseal fracture distally to the internal fixation

devices, especially for the IM nail (37). The reason for these complications seems to lie in the design of the fixation devices, and in the wrong placement of the cephalic screw both in coronal and axial planes (21). To help the correct positioning of the cephalic screw, the Anteversa® mini-plate, which guarantees fixed 8° of anteversion, was introduced.

Surgery needs small-dimension accesses, thus allowing to save the site of the fracture and soft periosteal tissue. A recent study, despite small sample size limitations, showed that TAD and CalTAD do not seem to have a considerable influence on the clinical outcomes in patients treated with an Anteversa® mini-plate (38, 39). Therefore, we believe that the fracture fixation with Anteversa® mini-plate, performed following the appropriate surgical indications, offers the possibility to reach excellent results in terms of fracture reduction, with a low risk of cephalic screw cut-out.

The negative aspect of this kind of surgery is the need of particular attention for the technical execution of plating, since the non-insertion of the anti-rotation screw can be a risk factor for cut-out or fracture non-union: this can lead to delayed surgery time when compared to DHS or IM nail.

Given the small sample size, and considering that this was our first experience with Anteversa® mini-plate, this type of device meets the essential requirements for suitable treatment of intertrochanteric fractures in elderly patients. These requirements are represented by the screw plate that allows a good reduction of the fracture, and by the stability angle from the anti-rotation nail and the screw that guarantees a long-term stability.

The possibility of small incisions are another advantage of this plating procedure; however, the great need for attention to detail in each step, and the consequential increased surgery time, could be seen as a limitation for its use.

In conclusion, studies with a greater number of patients and longer follow-ups are needed to draw more definitive conclusions on the role of this implant in the management of intertrochanteric hip fractures.

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FUNCTIONAL OUTCOME AND MULTIDIMENSIONAL EVALUATION OF PATIENTS WITH MUTARS® RECONSTRUCTIONS POST LOWER LIMB TUMOR RESECTION AND REHABILITATION: PRELIMINARY RESULTS

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Modular prostheses are commonly used to reconstruct defects of the distal femur and proximal tibia after bone tumor resection. Improving patient's autonomy and giving them a better quality of life are the main goals. Post-surgical rehabilitation is very relevant after surgery. The aim of this paper is to study the short and mean time functional outcomes in patients treated with Mutars® reconstructions after proximal and distal lower limb tumor resection with a multidimensional analysis and a standardized stabilometric examination. Twenty-one patients (7 male and 14 women, mean age and standard deviation: 61.76±14.68) affected by primitive bone tumor (28.6%) or metastatic bone tumor (71.4%), treated with MUTARS® reconstructions after proximal (71%) , distal(23.8%) and both (4.8%) lower limb tumor resections, accepted to take part to the study. They were evaluated after one week (T0), one month (T1), three months (T2), six months (T3) and one year (T4) after surgery with standardized clinic evaluation and with multidimensional validated scales. Visual Analogic Scale (VAS during active movement), Short Physical Performance Battery (SPPB), Eastern Cooperative Oncology Group (ECOG), Karnofsky Performance Status (KPS), MusculoSkeletal Tumor Society rating (MSTS), Toronto Extremity Salvage Score scale (TESS). Patients underwent to an instrumental standardized stabilometric test after one month from surgery and in following evaluations to measure standing balance. Patients underwent to a rehabilitation program during three months after surgery. There was a significant improvement of hip flexion range of movement (p level: 0.008), and gait modalities (without aids) after three months from surgery (p level 0.02). There was a significant reduction in VAS after one month of surgery (p level 0.00). It was observed an increase of the SPPB value at T3 (p level 0.01), of MSTS and TESS at T2. Balance stabilometric evaluation did not showed significant increase at each timing also if Romberg perimeter decrease progressively. These preliminary results showed that, oncological patients, affected by bone tumors or metastasis, surgical treated with MUTARS® implant and admitted to the rehabilitation programs, can improve their gait modalities and functional daily life outcomes, until three months from surgery. A large sample will allow, necessary to define standardized rehabilitation protocols after oncological orthopedic surgery, in order to introduce guidelines that can be applied routinely.

Key words: modular prosthesis, bone tumor, outcome measures, balance, rehabilitation

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Modular endoprostheses are commonly used to reconstruct defects of the distal femur and proximal tibia after bone tumor resection. Rizzoli Orthopaedic Institute, in 2013, evaluated the incidence of bone tumor and estimated that in Italy primitive malignant bone tumours's onset was approximately 500 new cases/year, of which 20-25% osteosarcomas can affect all bone segments with a prevalence for long bones in almost 90% of cases (1). Every year in Italy, there are also 35.000 new cases of bone metastases, which are lung and liver cancers's secondary injury locations (2). The number of clinical cases is increasing for higher survival and chronic of cancer pathology. Oncological orthopedics deals with the treatment of the primary and secondary bone tumours and of the soft tissue connected to it. The MUTARS® system (Modular Universal Tumor And Revision System) was introduced in 1992 and has since been widely used in Europe, Australia, and various Asian countries to reconstruct defects after bone tumor resection (2). Post-surgical rehabilitation is very relevant after these surgical resection procedures.

Improving patient's autonomy and giving them a better quality of life are the main goals. The literature review shows an increasing attention to the analysis of the short and long-term functional outcomes following the implantation of modular prostheses but there are no validated guidelines. Currently, in literature, there are no studies regarding the analysis of the rehabilitation outcomes of these patients, with a multidimensional evaluation, with validated scale and instrumental stabilometric analysis of standing balance, due, probably, to the complexity of the oncological pathologies and treatments and for the decreased patient life expectancy. The aim of this paper is to study the short and mean time functional outcomes in patients treated with Mutars® reconstructions after proximal and distal lower limb tumor resection with a multidimensional analysis and a standardized stabilometric examination.

MATERIAL AND METHODS

Between February 2017 and December 2018, 21 patients with MUTARS® reconstructions after proximal or distal lower limb tumor resection were evaluated and selected at the Clinics of Orthopedics and Physical Medicine and Rehabilitation of the Gemelli Polyclinic Foundation, in Rome. (Table I). The inclusion criteria were patients with age ≥18 years, MMSE ≥24 that had signed an informed consent and privacy paper. The exclusion criteria were presence of cognitive, vascular and neurological disorders, Mutars® implants for non-oncological causes and patients treated previously with local arthrodesis surgery. Patients admitted to the study underwent a physical rehabilitation treatment after surgery, in different centers during 3 months after surgery. Patients were evaluated after one week (T0) post-surgery, with an anagrafic, anamnestic, oncological and surgical report and during outpatient visits at one month (T1), three months (T2), six months (T3) and one year (T4) after surgery with:

standardized clinic evaluation;

multidimensional and outcome validated scales;

instrumental standardized stabilometric test after one month from surgery.

The standardized clinical exam included:

the hip and the knee flexion range of movement (ROM) using a manual goniometer;

the quadriceps' muscle strength from 0 to 5 using the British Medical Research Council (BMRC) scale, scale (MRC) (3);

gait modalities: independent, with one crutch, two crutches, in a wheelchair or absent, because the patient was bedridden.

Self-sufficiency, physical activities and patient's life expectancy and prognosis were evaluated through validated scales:

active movement pain from 0 to 10 using the Visual Analogic Scale (VAS) (4);

Short Physical Performance Battery (SPPB) (5) scale that evaluates the balance, the walking time in 4 meters and the "sit to stand";

Eastern Cooperative Oncology Group (ECOG) scale (6) which assesses the ability to carry out the activities of daily life and the level of sedentariness deriving from the pathology. In T0 evaluations, the patient was asked to respond based on what he could do the week before admission; in evaluations in T0 the patient responded based on what he could do the week before admission;

Karnofsky Performance Status scale (KPS) (7) which assesses the daily activity, the personal care and the symptomatic condition that determine a possible and

proportionate health support. Also in this case the patients, after a week from the surgery, described their situation referring to the week before admission;

MusculoSkeletal Tumor Society rating scale (MSTS) (8) which evaluates pain, ROM, muscle strength, joint stability, joint deformity, acceptance of one's clinical condition and functionality. This assessment scale was also administred starting from T1.

Toronto Extremity Salvage Score scale (TESS) (9) in which 30 questions are asked about the difficulty in performing certain actions during everyday life.

Standing balance

The evaluation of static balance was assessed by a standardized stabilometry exam performed on a "Prokin PK 254 P" device produced by TecnoBody S.r.l. (Dalmine BG e Italy). This device consists of a static plate (47 cm of circumference) equipped internally with 4 piezoelectric sensors positioned at the extremity of the four cardinals points. The temporal resolution was 0.01 s, and the sampling frequency was 20 Hz. The patient was standing on the force plate, for 60 sec in position, with eyes open and close.

All data were analyzed by the ProKin 36 software in order to calculate Center of Pressure (CoP) sway on the X (anteriorposterior) and Y (medio-lateral) axes (mm), Center of Pressure (CoP) velocity on the X (anterior-posterior) (AP-vel) and Y(medio-lateral) (ML-Vel) axes (mm/s), Sway path (Perimeter, total length of CoP trajectory (mm) and the Area of the ellipse (mm2). Lower values of these measures suggest lower energy consumption in order to keep the trunk in a vertical position and therefore greater efficacy in maintaining the standing balance. We considered as primary measures the reduction of the length of adaptive

Table I. *Baseline characteristics of patients.*

Baseline characteristics of patients (Mean and Standard deviation)		
Age	61,76±14,68	
Sex (%)		
Men	33.3%	
Women	66,7%	
Body Mass Index		
Normal:	66,7%	
Underweight:	9,5%	
Overweight:	23,8%	
Tumor		
Primitive	28,6%	
Metastatic	71,4%	
Surgery		
Revision:	-	
Primitive:	100%	
Location		
Distal femur:	23,8%	
Proximal femur:	71,4%	
Both:	4,8%	
Resection Height	12,0471,4%±2,29	
Muscles disengaged		
max. gluteus, med. gluteus, v. lat.^	56,3%	
max. gluteus, med. gluteus, v. lat., tfl^	6,3%	
max. gluteus, med. gluteus: ^	12,5%	
max. gluteus, med. gluteus, tfl^	6,3%	
hip external rotator, v. lat ^	12,5%	
hip external rotator, ileopsoas ^	6,3%	
Number of Muscles	2,93±0,44	
Post surgery Infections %	13,3%	25%

^: *Muscles Disengaged: gluteus maximus, gluteus medius; v: lat :quadriceps vastus lateralis, external rotators of hip; tfl: tensor fasciae latae muscle, ileopsoas muscle.*

Table II. *Clinical evaluation of patients at each timing and significant values.*

Mean and standard deviation	T0 (n. 21 patients)	T1 (n. 12 patients)	T2 (n. 13 patients)	T3 (n. 6 patients)	T4 (n.3 patients)	p level
Deambulation (%): **2 crutches** **1 crutch** **Wheelchair** **No aids**	 **53,3%** **20%** **26,7%** **-**	 **16,7%** **75%** **8,3** **-**	 **-** **50%*** **-** **50%***	 **33,3%** **-** **-** **66,7%****	 **-** **66,7%** **-** **33,3%**	***0,02** ****0.09**
MRC° quadriceps strength	**2,0±0,47**	**3,25±0.86**	**3,84±0,37***	**3,83±0,75**	**4,33±0,57**	**0,08**
Hip ROM°° (n. 15 patients)	**21,6±11,6 (6pz)**	**43,0±22,2 (10pz)**	***73,5±14,7 (10 pz)**	**106,6±5,7 (3 pz)**	**105,00±7,0 7**	***0.008**
Knee ROM°° (n.5 patients)	**26,6±5,7 (5 pz)**	**30,0±0,00 (2PZ)**	**40,0±26,45 3 pz**	**61,6±49,0 3 pz**	**110±0.0**	

**:Wilcoxon's signed-rank test, p level≤0.05 was considered statistically significant; °MRC: Medical Research Council scale; °°ROM: range of movement.*

Table III. *Patients' outcome measures at each time and significant values.*

Mean and standard deviation	T0 (n. 21 patients)	T1 (n. 12 patients)	T2 (n. 13 patients)	T3 (n. 6 patients)	T4 (n. 3 patients)	P level
VAS°	6,2± 2,57	**3,66±2,67***	3,38±2,02	2,16±2,85	3,67±3,25	***0.00**
ECOG°°	1,4±1,34	2,76±1,25	2,31±1,43	1±0,89**	1,33±0,57	**0.08
SPPB°°°	0,5±0,70	8,0±4,22	10,07±2,36**	**10,33±1,96***	9,33±3,78	**0.09 ***0.01**
KPS^	83±15,12	70.35±31,95	70,62±36,41	90,0±10,95	83,33±5,77	
MSTS^^ %	-	*38,9±10,6	***52,27±13,31**	67,59± 19.35	65,6±15,1	***0.00**
TESS^^^	-	52,56±12,52	***66,73±16,52**	80,33±12,03	62,33±7,10	***0.03**

:Wilcoxon's signed-rank test, p level≤ 0.05 was considered to be statistically significant; **°VAS: visuoanalogic scale; **ECOG°°**: Eastern Cooperative Oncology Group; **SPPB°°°**: Short Physical Performance Battery; **KPS^**: Karnofsky performance status; **MSTS^^**: MusculoSkeletal Tumor Society rating scale; **TESS^^^**: Toronto Extremity Salvage Score.*

movements able to keep the body vertical, assessed by analysing perimeter and sway area values, as they represent parameters of global stability of the CoP.

Statistical analysis

Demographic and baseline clinical data of all patients were calculated as the mean values and frequency. The differences between pretreatment and post-treatment at all follow up measurements within patients were evaluated using Wilcoxon's signed-rank test. A P level of less than or equal to 0.05 was considered to be statistically significant.

RESULTS

Baseline characteristics of patients are described in Table I. Thirty-five patients have been identified; 5 of them refused to participate in the study and nine were excluded because they did not respond to

the criteria mentioned above. Twenty-one patients were included in the study, (7 men and 14 women). One patient died two weeks after surgery due to the progression of cancer disease. Their mean age was 61.76 ±14.68 years. Fifteen patients underwent surgery for metastatic lesions located in the proximal or distal femur (breast cancer in six patients, kidney cancer in three patients, myeloma, pancreas cancer, diffuse lymphoma and melanoma in one patients for each tumor). Six patients were affected by sarcoma. The MUTARS® implant was applied in 23.8% patients to the proximal part and in 71.4% to the distal part of the femur. In 4.8% of patients, the implant was applied at the proximal and the distal femur both. The most common complication after surgery was infection that occurred in 13.3% at T0, 25% at T1, 7.6% at T2, 33.3% patients at T3. All infections complications were managed clinically, without implant removal.

In Table II, we reported data of patients' clinical examinations at each timing. We observed a significant improvement of hip flexion ROM between T1 and T2 (p level: 0.008), after rehabilitation. There was an increase of the quadriceps muscle strength between T1 and T2, close to the significance (p level 0.08).

A significant improvement (p level 0.02) at T2 was observed in gait modalities, and a further improvement, close to the significance (p 0.09) between T2 and T3, with an increase of patients with good functional recovery; the percentage of patients walking without aids, in fact, increased from 50% (T2) to 66.7% at T3.

In Table III, we reported results of multidimensional outcome scales. There was a significant reduction in active movement pain at T1 (p level 0.00) after one month from the surgery, It was observed an increase close to the significance (p level: 0.09) at T2 and a significant increase (p level 0.01) at T3 of the SPPB values with better results in balance, walking time and "sit to stand" ability.

The ECOG score was nearly significant (p level 0.08) decreased between T2 and T3, with lower level of oncological disability. We observed a significant increase of the MSTS score at T2, (p level: 0.00) after three months post surgery. TESS score showed a T2 a significant increase (p level 0.03). No significant differences were observed in the values of the Karnofsky Performance Status at each timing.

Balance stabilometric evaluation did not showed significant increase at each timing also if Romberg perimeter decrease progressively at T2 and T3 but results were not significant (p level 0.08) (Table IV).

DISCUSSION

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Table IV: *Stabilometric evaluation of patients at each timing and significant values.*

Mean and standard deviation %	T0 (n. 21 patients)	T1 (n. 12 patients)	T2 (n. 13 patients)	T3 (n. 6 patients)	T4 (n. 3 patients)	p level
Romberg Perimeter	-	217,3±113,3	****193,00±22,63**	***161,50±52,10**	242,00±66,90	**0.08 *0.08
Romberg Area	-	434,6±373,5	404,00±578,41	383,67±148,31	463,00±312,06	
Perimeter oe^	-	298,0±130,67	337,60±87,28	270,83±79,35	175,33±3,21	
Perimeter ec^^	-	748,0±692,93	572,60±219,64	422,00±126,85	426,67±123,31	
Area oe^	-	125,33±60,28	277,80±254,15	101,33±81,46	97,00±94,62	
Area ec^^	-	667,66±791,26	442,20±252,71	220,67±75,30	328,33±306,97	

: Wilcoxon's signed-rank test, p level≤ 0.05 was considered statistically significant; **^oe: open eyes; **^^ec**: eyes closed.*

in bones tumors and, considering the extended life expectancy, also in metastatic patients, the number of primary joint hip and knee arthroplasties has increased (10). Modular arthroplasty with the MUTARS system, after tumor resection, allows an early ambulation and improves patients' quality of life after rehabilitation (11). There are no studies in literature that use a wide range of assessment scales and a standing balance evaluation in order to analyze outcomes after surgery and rehabilitation treatment of patients with bone tumor or metastasis.

The aim of our paper was to study functional results of treatment in patients with proximal or distal femur cancer (primitive or metastatic) with a multidimensional standardized evaluation and a stabilometric exam. Functional results were assessed as pain intensity in VAS score and performance in KPS and MSTS score. Furthermore, self-sufficiency and physical activities were examined through the SPPB scale and through the MSTS scale.

As literature suggests, the optimum results are verifiable in patients without actual pathological fracture, where tumor resection was performed with a wide margin of healthy tissues (12).

In this pilot study, no high sample has been achieved and only 3 patients were evaluated after 12 months from surgery. It was difficult to obtain long-term follow up due to numerous dropouts, caused by the underlying oncological disease progression and the general clinical conditions, as well as the high possibility of short-term death.

Several papers analyzed the medium and long-term complications of surgery in oncological patients with MUTARS prosthesis for bone tumor or metastasis (12, 13) but no authors studied their functional outcomes with a multidimensional evaluation and with a stabilometric exam, in order to analyze the role of the early rehabilitation and the effects on patients' autonomy after surgery. Therefore, it was also difficult to compare our results with those published in the literature.

Oncological pain after surgery and in follow up, does not allow articular movement and compromises autonomy. In literature, there are several significant data about pain measured by VAS score. After a joint replacement with modular prosthesis, we can steadily find a gradual reduction in pain, resulting in a functional recovery. All patients experienced improvement in autonomy, resulting from pain reduction (14, 15). Also in our study, a reduction of the VAS value was found, more significant after one month from surgery.

The improvement of ROM and muscle strength is progressive, like the self-sufficiency and psychophysical conditions evaluated by SPPB, MSTS and TESS score in the first 6 months after surgery. Despite ROM after MUTARS® implant is partially limited because of surgical reasons and structural needs of the prosthesis, we found a nearly significant hip flexion ROMs increase after 3 months from surgery and rehabilitation.

The most significant data was about the MSTS score that examined functional results, self-sufficiency and physical activities. We found an increase that is suggestive of better gait efficiency and physical performance. Our results are similar to literature data (14-16); patients showed a satisfactory functional recovery up to six months after surgery. According with literature we do not founded significant improvement in KPS score at each follow up. We observed a significant increase in SPPB values, after three month from surgery, according with TESS and ECOG scores. These data underline an increase in patient self-sufficiency over time.

In balance evaluation, we found a progressive decrease in the value of the Romberg Perimeter between T2 and T3 showing greater efficacy in maintaining the standing balance in time, during stabilometric test and according to patients' progressive acquisition of walking without aids and their functional recovery.

Therefore, there is strong evidence that oncological patients need to be included in early postsurgical rehabilitation treatment, in order to improve their outcome and quality of life.

In any case, our study has several limitations. In consideration of our number of samples, we can define our survey as a pilot study that provides a preliminary assessment to analyze data later in a higher sample.

A further difficulty was encountered in the attempt to evaluate the different subgroups (patients with proximal femur involvement, distal femur involvement and both), due to the lack of the sample

and the non-homogeneous representation of the same.

It is also necessary to specify that rehabilitation protocols applied were in different centers involved, as it was not possible to address all the participants at the same ward.

These preliminary results showed that, oncological patients, affected by bone tumors or metastasis, surgical treated with MUTARS® implant and admitted to the rehabilitation programs, can improve their gait modalities and functional daily life outcomes, until 3 months from surgery.

Despite our investigation was a pilot study, it was clear how a multidimensional evaluation is fundamental in oncological patients' follow up after surgery. It was useful to make a preliminary assessment of the impact of rehabilitation on these patients in the post-operative period. Using modular arthroplasty after tumor resection associated with functional rehabilitation is primary in order to improve the quality of life and the autonomy of the subjects examined. A large sample will necessarily allow to define standardized rehabilitation protocols after oncological orthopedic surgery, in order to introduce guidelines that can be applied routinely.

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EVALUATION OF QUALITY OF LIFE AND STATIC BALANCE IN POSTMENOPAUSAL OSTEOPOROSIS WOMEN AFTER TAI CHI CHUAN PRACTICE: AN OBSERVATIONAL RANDOMIZED CASE CONTROL STUDY

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Post-menopausal osteoporosis women are at increased risk for skeletal fractures with higher mortality and lower quality of life. Some studies have reported fall risk reduction in the elderly after Tai chi practice. Tai chi is a weight bearing mind-body exercise that has been reported to positively influence bone mineral density and improve postural control in different pathologies. The aim of this observational randomized case control study is to evaluate the effect of Tai chi on balance and quality of life in postmenopausal women with osteoporosis. A total of 98 postmenopausal osteoporosis women, aged 70.6±8.2 years (mean and standard deviation), (mean T-score of the hip and spine were-2.9± 0.92 and -2.8±1.08), have been recruited in outpatients University Physical Medicine and Rehabilitation Hospital between June 2016 and September 2018. They have been randomized to a Tai group (56 patients, mean age 71.61±7.97 years) practiced 6-month Tai chi program, two times week, plus standard care or to a Control Group (42 patients, mean age 69.71±8.61 years) practiced usual care. Patients with oncological, neurological, cognitive, vestibular and visual diseases were excluded. Patients were evaluated at baseline (T0), prior Tai chi and after 6 month (T1) with 36-Item Short Form Health Survey (SF-36), and a stabilometric-standardized exam performed for the evaluation, respectively, of the quality of life and the static balance. The groups were homogenous at baseline. T1 evaluation showed better results in Tai chi group, in SF36 Physical functioning (p level: 0.021), Physical health pain (p level: 0.020), Physical composite score (p level: 0.003) scores, compared with control group. There were not significant differences between groups in stabilometric analysis. Tai chi group showed significant better stabilometric values at T1 compared with T0 in mean anterior-posterior (p level: 0.001) and medio-lateral (p level: 0.019) velocity, in perimeter (p level 0.001) , and in the area of the ellipse (p level 0.006) in a within group analysis. Tai chi seemed to be effective in improving physical aspects of quality of life, in postmenopausal women with osteoporosis. Standing balance seems to increase after 6 months Tai chi program, in post-menopausal also if results were not significant. Further studies will be useful to measure effects of a Tai chi longer practice, as literature suggests, and a possible reduction of falling risk and fractures.

Key words: postmenopause, osteoporosis, Tai chi Chuan

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Osteoporosis is defined as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and in susceptibility to fracture risk. As the populations become older, the numbers of individuals who presented bone fragility and fracture risk increases (1). In 2010, it was estimated that 22 million women in the EU had osteoporosis using the diagnostic criterion of the WHO. At the age of 50, the lifetime risk of sustaining an osteoporotic fracture is close to 50% for women and more than 20% for men. In 2010, it was estimated that 21% of women from the European Union with an age between 50 and 84 years have osteoporosis (2, 3). Farmacological treatment reduce vertebral and nonvertebral fracture risk. Although a number of risk factors for falling are not modifiable, such as age, others are amenable to changes, like decreased visual acuity, medications that can diminish awareness and/or balance and home environment (4). Exercise programs focusing on gait, co-ordination and functional tasks, as well as muscle strengthening exercises other than just walking seem to improve clinical balance outcomes in older people (5, 6). Some studies have reported fall risk reduction in the elderly with Tai chi practice (7) with a lower fracture risk (8, 9). No studies have analyzed the effects of Tai chi on balance with stabilometric device. Furthermore, osteoporosis could be associated with decrease in physical function, social function, and well-being, which are all aspects of quality of life (QoL), when there is high risk of fracture (10, 11). In literature, no studies analyze quality of life in patients with osteoporosis prior the fractures. The aim of this observational randomized case control study is to evaluate the effect of Tai chi on balance and quality of life in postmenopausal women with osteoporosis in order to reduce risk of falling and prevent future fractures.

MATERIALS AND METHODS

An observational randomised controlled trial was carried out in outpatients at the University of Physical Medicine and Rehabilitation Hospital Foundation, A. Gemelli, between June 2016 and September 2018. The study included a total of 98 postmenopausal osteoporosis women, aged 70.6±8.2 years (mean and standard deviation) affected by osteoporosis evaluated by dual-energy X-ray absorptiometry (DEXA) measurement as a T-score lower than -2.5, according to the WHO Study Group definition. At the first visit, patients' mean T-score of the hip and spine were -2.9±0.92 and -2.8±1.08. Patients with oncological, neurological, cognitive, vestibular and visual diseases were excluded. The patients were randomized using a table of random numbers. The even numbers were allocated to the control group and the odd numbers to the study group. The study group (Tai Group: 56 patients, mean age 71.61±7.97 years) underwent a 6-month short form Tai chi program, two times weekly, for 45 min each session, plus standard care. Short-form Tai chi consisted of 12 forms that required whole-body movements to be performed in a continuous sequence demanding concentration (12).

A physiotherapist, who was qualified to teach Tai chi, conducted the training in 5-subject groups. The control group (42 patients, mean age 69.71±8.61 years) received a standardized counseling and practiced standard care as exercise programs focusing on gait, co-ordination and functional tasks, as well as muscle strengthening exercises other than just walking.

Patients were assessed before Tai chi practice (T0) and after 6 months (T1), with 36-Item Short Form Health Survey (SF-36) (13), a generic instrument with scores based on responses to individual questions that are summarized in eight domains, each of which measures a health concept: pain, physical functioning, general health perception, role limitation-physical aspect, role limitation-emotional aspect, energy/fatigue, social functioning and emotional health. These eight domains are scored from 0 to 100, with higher scores reflecting a better QoL.

The evaluation of static balance was assessed at T0 and T1 by a standardized stabilometry exam performed on a "Prokin PK 254 P" device produced by TecnoBody S.r.l. (Dalmine BG e Italy). This device consists of a static plate (47 cm of circumference) equipped internally with 4 piezoelectric sensors positioned at the extremity of the 4 cardinals points. The temporal resolution was 0.01 s, and the sampling frequency was 20 Hz. The patient was standing on the force plate, for 60 s in standardized position with eyes open and close. All data were analyzed by the ProKin 36 software in order to calculate Center

of Pressure (CoP) sway on the X (anteriorposterior) and Y (medio-lateral) axes (mm), Center of Pressure (CoP) velocity on the X (anterior-posterior) (AP-vel) and Y(medio-lateral) (ML-Vel) axes (mm/s), Sway path (Perimeter, total length of CoP trajectory (mm)) and the area of the ellipse (mm2). Lower values of these measures suggest lower energy consumption in order to keep the trunk in a vertical position and therefore greater efficacy in maintaining the standing balance.

Statistical analysis

Demographic and baseline clinical data of all patients were calculated as the mean values and frequency at the first visit. Student's unpaired *t*-test was performed to determine whether the two groups were similar at baseline and to determine differences at the end of treatment and follow-up between the two groups. Comparisons within and between groups were performed using the *t*-test, the *chi*-square test, and analysis of variance (ANOVA) models, as appropriate. A P value ≤0.05.

RESULTS

The total sample of patients, enrolled in this study was 98 women with postmenopausal osteoporosis, randomized in Tai group (42 patients, mean age 69.71±8.61 years, T-score of the hip and spine: - 2.97±0.81, -2.85±0.91) and Control group (56 patients, mean age 71.61±7.97 years, T-score of the hip and spine: -2.92±0.99, -2.96±1.27). Flow chart of the study population is in Fig. 1. At T1, in Tai group, 7 patients dropped out because they did not come to the control visit; in Control group 24 patients dropped out because did not come to follow up visit.

Analysis intra group for stabilometric and quality of life values of control group and in quality of life of Tai group do not show significant differences.

Tai group instead, shows significant differences within group through stabilometric analysis, with better values at T1 after 6 months of Tai chi practice, in Standard deviation anteroposterior OE (p level: 0.001) and mediolateral OE (p level 0.022); velocity anteroposterior (p level: 0.001) and mediolateral (p level: 0.019); Sway path OE (p level: 0.001) and Area of the Ellipse (mm2) OE (p level: 0.006) (Table V).

DISCUSSION

Osteoporosis is a common skeletal disorder characterized by decreased bone mass and increased susceptibility to fractures, which are associated with pain and decrease in physical function, social function, and well-being, which are all aspects of quality of life (QoL).

There is an increasing demand of nonpharmacologic therapy, such as physiotherapy and physical activity in patients with osteoporosis. Tai chi is often recommended to patients in addition to bisphosphonates administration increasing bone and muscle strength as well as coordination and

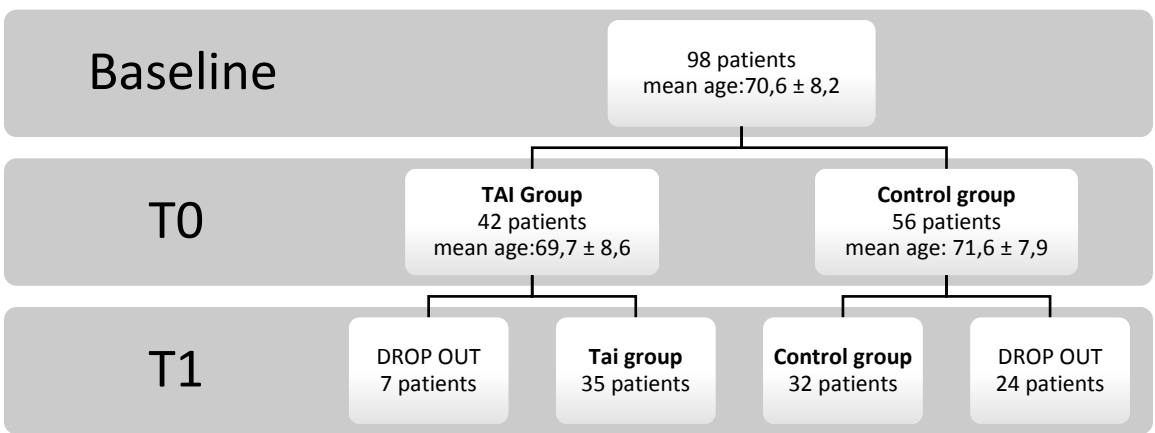

Fig. 1. *Flow chart of the study population.*

Table I. *Baseline stabilometric value of Tai group and Control group.*

T0 – stabilometric values (n.patients: 98) (mean ± standard deviation)	Gruppo Tai (42 patients)	Control group (56 patients)	P-Level
X CoP (mm) OE*	-2,33 ± 7,50	-1,90 ± 8,35	0,802
Y CoP (mm) OE	-19,70 ± 15,38	-16,08 ± 12,81	0,229
AP-Standard deviation OE	3,00 ± 1,09	3,24 ± 1,39	0,366
ML-Standard deviation OE	2,30 ± 1,07	2,80 ± 1,83	0,133
AP-Velocity(mm/s) OE	5,38 ± 1,37	6,20 ± 2,18	0,039
ML-Velocity (mm/s) OE	4,40 ± 1,68	5,63 ± 3,30	0,034
Sway path OE	179,70 ± 56,85	217,94 ± 102,90	0,038
Area of the Ellipse (mm2) OE	133,18 ± 93,40	190,35 ± 254,46	0,181
Romberg Perimeter CE ^/ OE	173,88 ± 55,52	165,29 ± 50,47	0,447
Romberg Area CE/ OE	241,43 ± 141,53	254,37 ± 186,55	0,718
X CoP (mm) CE	-1,28 ± 8,62	-1,57 ± 7,99	0,867
Y CoP (mm) CE	-18,18 ± 14,89	-16,55 ± 12,58	0,578
AP-Standard deviation CE	4,28 ± 1,18	5,08 ± 2,17	0,038
ML-Standard deviation CE	3,13 ± 1,26	4,18 ± 3,62	0,082
AP-Velocity(mm/s) CE	9,68 ± 4,56	10,49 ± 4,96	0,427
ML-Velocity (mm/s) CE	6,95 ± 3,00	8,82 ± 5,80	0,069
Sway path CE	316,95 ± 127,39	365,67 ± 191,41	0,171
Area of the Ellipse (mm2) CE	260,93 ± 156,56	460,98 ± 661,63	0,065

Table II. *Baseline stabilometric value of Tai group and Control group.*

T0 – SF36 values (n.patients: 98) (mean ± standard deviation)	Gruppo Tai (42 patients)	Control group (56 patients)	P-Level
Physical functioning	59,75 ± 13,24	56,53 ± 21,77	0,433
Role physical	53,13 ± 38,06	38,27 ± 41,49	0,085
Bodily pain	49,68 ± 21,98	43,67 ± 19,33	0,174
Gener Health	53,28 ± 18,46	46,55 ± 17,02	0,078
Vitality	55,75 ± 18,55	47,86 ± 17,17	0,040
Social functioning	66,15 ± 20,73	62,43 ± 23,32	0,434
Role emotional	49,18 ± 39,99	40,82 ± 45,80	0,367
Mental health	58,80 ± 15,35	52,08 ± 19,69	0,081
Physical Composite score	41,93 ± 7,43	37,92 ± 8,66	0,023
Mental Composite score	41,88 ± 9,41	40,37 ± 12,30	0,525
Physical Health Pain	56,48 ± 18,16	46,14 ± 22,75	0,022

*T0 values of SF36. The two groups do not show significant differences at baseline in balance scores. **: P <0.05 between-groups.*

balance (11, 14). Tai chi is thought to improve balance and reduce falls incidence by strengthening muscles of the knee and ankle, promoting even weight distribution and improving awareness of the body and movement (10). The evaluation of quality of life has been considered an important marker of the clinical evolution of patients with osteoporosis. Physical, emotional, and psychological incapacity, combined with the pain that results from hip, spine, or wrist fractures, can alter quality of life (11). The aim of this study is to evaluate the effect of Tai chi on balance and quality of life in postmenopausal

Table III. *Stabilometric value of Tai group and Control group and analysis between groups at T1.*

T1 – stabilometric values (mean ± standard deviation)	Gruppo Tai (35 patients)	Control group (32 patients)	P-Level
X CoP (mm) OE*	-1,60 ± 7,51	-0,75 ± 10,03	0,694
Y CoP (mm) OE	-16,40 ± 15,59	-18,75 ± 16,52	0,551
AP-Standard deviation OE	3,03 ± 1,01	3,38 ± 2,79	0,495
ML-Standard deviation OE	2,23 ± 0,77	3,00 ± 2,21	0,057
AP-Velocity(mm/s) OE	5,26 ± 1,67	6,16 ± 2,92	0,123
ML-Velocity (mm/s) OE	4,49 ± 1,80	5,53 ± 4,20	0,184
Sway path OE	184,31 ± 58,01	219,44 ± 132,15	0,158
Area of the Ellipse (mm2) OE	120,26 ± 72,64	265,88 ± 600,35	0,159
Romberg Perimeter CE ^/ OE	179,40 ± 71,16	164,56 ± 83,10	0,434
Romberg Area CE/ OE	229,91 ± 119,42	226,72 ± 210,30	0,939
X CoP (mm) CE	-0,46 ± 7,94	0,84 ± 9,45	0,543
Y CoP (mm) CE	-16,37 ± 12,03	-19,00 ± 18,96	0,497
AP-Standard deviation CE	4,49 ± 1,93	4,44 ± 1,98	0,920
ML-Standard deviation CE	3,14 ± 1,63	3,63 ± 2,95	0,405
AP-Velocity(mm/s) CE	10,34 ± 6,42	10,00 ± 5,49	0,816
ML-Velocity (mm/s) CE	7,37 ± 4,61	8,72 ± 6,92	0,348
Sway path CE	336,00 ± 202,45	355,56 ± 226,35	0,710
Area of the Ellipse (mm2) CE	297,83 ± 343,14	370,09 ± 538,90	0,511

***OA**: open eyes; **^OC**: close eyes; **: P<0.05 between-groups. T1 values of SF36. There are no significant differences between groups in standing balance at T1.*

Table IV. *SF36 values of Tai group and Control group and analysis between groups at T1.*

T1 – SF36 values (mean ± standard deviation)	Gruppo Tai (35 patients)	Control group (32 patients)	P-Level
Physical functioning	72,92 ± 20,51	61,00 ± 22,06	**0,021***
Role physical	58,33 ± 38,73	41,43 ± 45,35	0,095
Bodily pain	57,75 ± 21,02	49,37 ± 21,56	0,102
Gener Health	54,50 ± 15,99	47,69 ± 18,88	0,105
Vitality	57,50 ± 15,19	52,14 ± 19,56	0,201
Social functioning	68,61 ± 20,38	63,40 ± 22,89	0,314
Role emotional	57,44 ± 41,91	57,14 ± 46,16	0,977
Mental health	57,89 ± 14,26	57,94 ± 21,55	0,990
Physical Composite score	44,36 ± 7,36	38,37 ± 9,05	**0,003***
Mental Composite score	42,89 ± 7,81	43,94 ± 12,99	0,679
Physical Health Pain	62,97 ± 21,19	50,51 ± 22,93	**0,020***

*T1 values of SF36. The two groups show significant differences between groups in quality of life in Physical functioning (p level: 0,021), Physical Composite score (p level 0,003), Physical Health Pain (p level 0,020) with higher score in Tai group. *: P <0.05 between-groups.*

Table V. *Analysis within Tai group of stabilometric values at T0 and T1.*

Tai Group stabilometric values (Mean and standard deviation)	T0 tai group	T1 tai group	P-Level
X CoP (mm) OE*	-2,33 ± 7,50	-1,60 ± 7,51	0,489
Y CoP (mm) OE	-19,70 ± 15,38	-16,40 ± 15,59	0,565
AP-Standard deviation OE	3,00 ± 1,09	3,03 ± 1,01	**0,001****
ML-Standard deviation OE	2,30 ± 1,07	2,23 ± 0,77	**0,022****
AP-Velocity(mm/s) OE	5,38 ± 1,37	5,26 ± 1,67	**0,001****
ML-Velocity (mm/s) OE	4,40 ± 1,68	4,49 ± 1,80	**0,019****
Sway path OE	179,70 ± 56,85	184,31 ± 58,01	**0,001****
Area of the Ellipse (mm2) OE	133,18 ± 93,40	120,26 ± 72,64	**0,006****
Romberg Perimeter CE ^/ OE	173,88 ± 55,52	179,40 ± 71,16	0,903
Romberg Area CE/ OE	241,43 ± 141,53	229,91 ± 119,42	0,380
X CoP (mm) CE	-1,28 ± 8,62	-0,46 ± 7,94	0,886
Y CoP (mm) CE	-18,18 ± 14,89	-16,37 ± 12,03	0,802
AP-Standard deviation CE	4,28 ± 1,18	4,49 ± 1,93	0,718
ML-Standard deviation CE	3,13 ± 1,26	3,14 ± 1,63	1,000
AP-Velocity(mm/s) CE	9,68 ± 4,56	10,34 ± 6,42	0,372
ML-Velocity (mm/s) CE	6,95 ± 3,00	7,37 ± 4,61	0,403
Sway path CE	316,95 ± 127,39	336,00 ± 202,45	0,437
Area of the Ellipse (mm2) CE	260,93 ± 156,56	297,83 ± 343,14	0,598

***OA**: open eyes; **^OC**: close eyes; ****P**: <0.05 within –groups.*

women with osteoporosis in order to reduce risk of falling and prevent future fractures.

Groups of postmenopausal women were homogeneous at baseline. There were nosignificant differences between groups in standing balance at T1 but women practisING Tai chi showed better values of global stability of the CoP after 6 months of Tai chi, in within-group analysis. The improvement of perimeter and sway area values on the platform are representative of the centrality of the CoP. In literature, Motion analysis measured that Tai chi practitioners had a larger lateral body shift and distinct plantar pressure distributions compared with a control group. These data are similar to our results, also if they were obtained with different instruments. Significant results have been observed, in other studies lasting longer than ours have (6 months), after at least 10 months of Tai chi practice (10).

Few studies analyze the effect of Tai chi on quality of life in post-menopausal women. Authors underline that osteoporosis increases the risk of fractures, which are associated with higher mortality and lower quality of life (1).

The analysis of quality of life in our study showed interesting results. After 6 months of exercises, Tai chi group showed better results in all physical scores compared to control group. These results suggest better physical function, better social role and reduction of physical disability, with higher health status (1, 16).

Tai chi seemed to be effective in improving physical aspects of quality of life, in postmenopausal women with osteoporosis. Standing balance seems to increase after a 6 months Tai chi program, in post-menopausal women. Further studies will be useful to measure significant effects after a longer Tai chi practice as suggested by literature, and to analyze the long-term effects in postmenopausal women with osteoporosis in reduction of fall risks and fractures.

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ONSET OF RHABDOMYOLYSIS AND ACUTE RENAL FAILURE AFTER MINIMALLY INVASIVE SURGERY FOR TRAUMATIC SPINE FRACTURE: A CASE REPORT

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Letter to the editor:

Rhabdomyolysis (RM) is a clinical syndrome caused by muscle necrosis, characterized by the release of a large amount of electrolytes, myoglobin, and other sarcoplasmic proteins in the bloodstream; acute kidney injury (AKI) is a frequent and potentially fatal complication of this disease.

The diagnostic markers of RM are increased values of creatine phosphokinase and serum myoglobin.

Up to now, few cases have been reported of RM and consequent acute renal failure secondary to spinal surgery, and most of them are primarily among patients who underwent long time surgery (>4h) (1, 2). Moreover the association between minimally-invasive vertebral surgery and RM has not been reported yet.

Here we describe a case of rhabdomyolysis that occurred in a 26 year-old patient, who underwent vertebral stabilization surgery with a minimally invasive technique for post-traumatic L1 fracture.

Case report

Following a car accident with overturning of the vehicle, the patient was transferred to the local emergency room, where they took an X-ray of the lumbar spine, a CT of the skull and of the cervical spine, an ecoFAST of the abdomen and performed blood tests, which were normal. The lumbar X-Ray showed a fracture of L1, for which a targeted lumbar spine CT scan of D12-L2 was performed.

The scan showed an amyelic fracture of L1 classified as a type A.4, according to the AO classification and the patient was consequently transferred to our Emergency department (ED) for a more specialistic evaluation. Upon arrival the patient did not report any symptoms apart from the low back pain, and the neurological objective examination was normal. His anamnesis reported no notable disease.

Posterior lumbar stabilization was suggested. While waiting for surgery, the patient remained stationary with normal vital parameters, valid diuresis, regular bowel movements and standard blood parameters.

The patient was dehydrated at the time of admission to ED despite adequate hydration during the previous hospital stay. He underwent D12-L2 percutaneous stabilization 48 h after the trauma.

At the end of the intervention, no evidence of neurological disturbances was found. The patient was not catheterized for surgery, since the avarage operative time is around 45 mins. In the days following surgery, the patient had a progressive decrease in diuresis, and a progressive alteration of the renal functional indices, reaching values of creatinine as high as 8.37, ureic nitrogen of 56, and myoglobin of 1911 ng/mL. Ultrasounds of the abdomen and urinary tract, as well as upper and lower abdominal CT scans were performed. Both kidneys

Key words: complication, rhabdomyolysis, lumbar spine surgery

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appeared as globular with hyperechoic cortices, and showed diminished corticomedullary differentiation that excluded a renal etiology of the AKI (Fig. 1).

Because of the worsening renal function and the decreased diuresis, the patient was transferred to the nephrology department and was diagnosed with acute renal failure secondary to post-traumatic rhabdomyolysis. He began hemodialysis with a temporary right jugular CVC. The patient underwent daily dialysis sessions for 10 days and obtained a clear improvement in creatinine values, as well as resumption of diuresis with transient polyuria, and gradual weaning from the substitution therapy during the following 15 days. At discharge, the patient was in good clinical conditions, he was apyretic and renal function was markedly improved with an acceptable diuresis. In the subsequent outpatient check-ups, normalization of the renal function indices and improvement of the orthopedic clinical symptomatology were highlighted.

DISCUSSION

The post-operative phase is characterized by the onset of RM in the first post-operative days and by subsequent acute renal failure (IRA), in the absence of risk factors (3).

The most common causes of RM include crush injuries, excessive exercise, infections, muscular dystrophies, malignant hyperthermia, prolonged seizure activity, Lou Gehrig's disease, acute psychotic disorders, Reye's syndrome, intestinal ischemia, host-versus-donor disease, eosinophilic fascitis, muscular ischemia during vascular or orthopedic operations, compression in case of coma or immobilization, induced myopathies which can be either metabolic

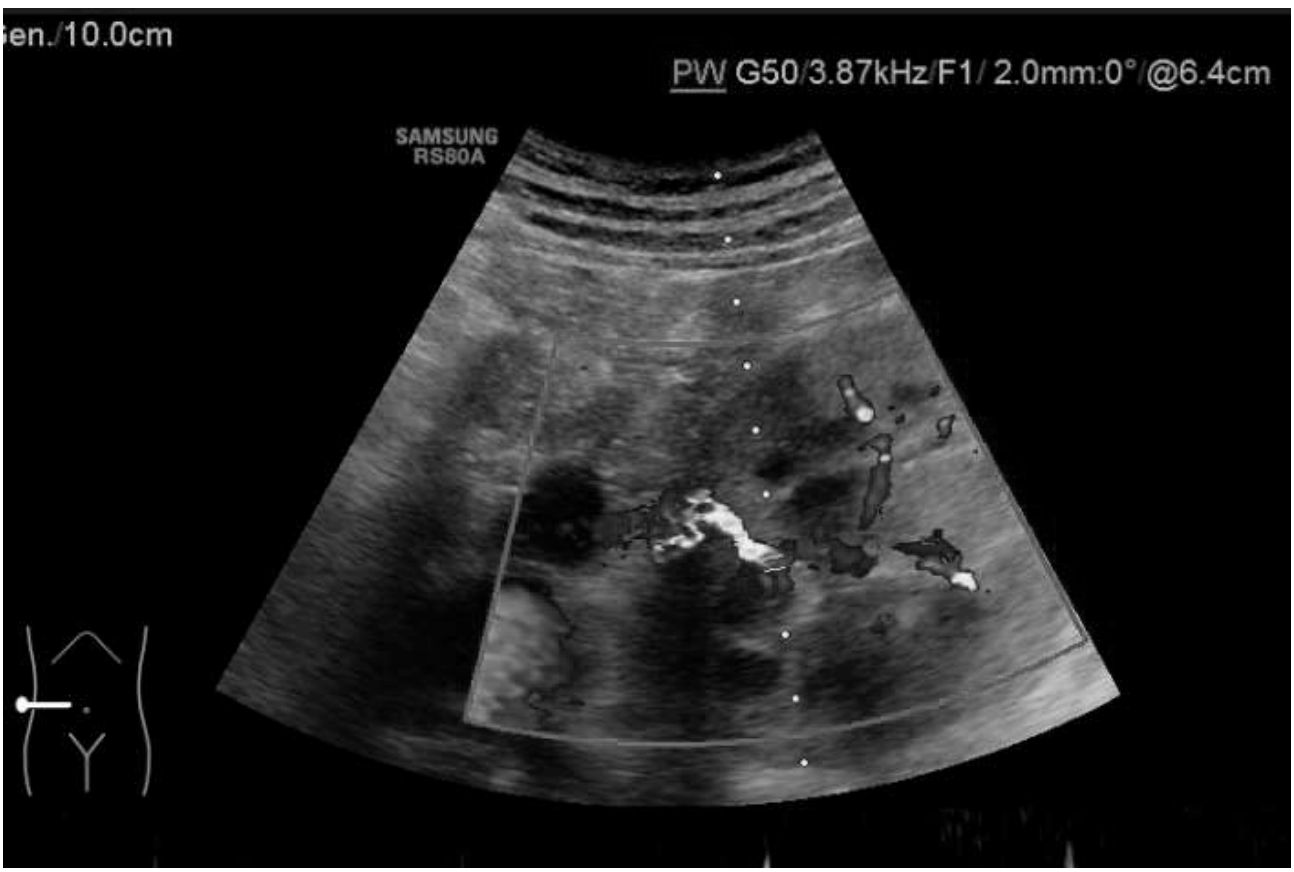

Fig. 1. *Abdominal-Ultrasound performed during AKI confirm the prerenal etiology.*

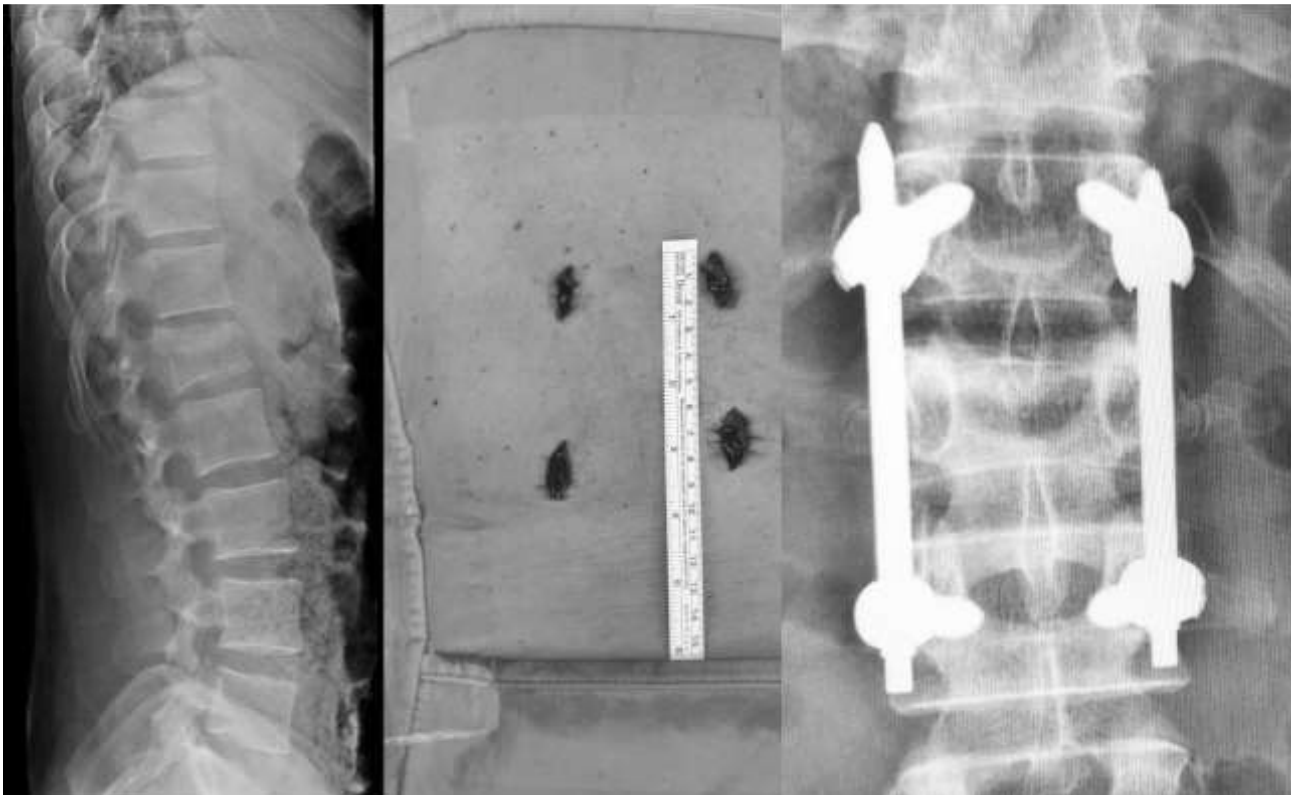

Fig. 2. *Preoperative X-Ray, the small access for the vertebral stabilization, postoperative X-Ray.*

(disorders of potassium or phosphate homeostasis) or inflammatory (4).

RM is a syndrome that must be promptly recognized and treated because of the serious consequences that may ensue, even when the clinical picture arises subtly (4).

In this particular case study, in the analysis of the anamnestic data, the type of trauma, the absence of major trauma of the limbs and the low invasiveness of the surgical treatment (Fig. 2), it is not possible to recognize an effective cause responsible for muscle damage. Even a possible pharmacological cause related to the use of anesthetic drugs and painkillers can not be hypothesized, because the intervention was short and the drugs used as pain relievers are not reported as potentially harmful to muscles.

Literature is limited to a few cases, but no case subsequent to vertebral surgery with percutaneous minimally invasive technique is reported (5). All cases of post-vertebral surgery rhabdomyolysis described in the literature were associated with open surgery with large muscle separation, which all lasted longer than 4 h. Other risk factors include obesity, as well as a sudden increase in CPK in the immediate post-operative period.

The literature also focuses on the position of the patient during surgery in order to avoid compressions at the level of the abdomen and at the root of the thighs and on the possible presence of myoglobinuria in the perioperative period.

In polytraumatized patients, dehydration and prolonged fasting before surgery, as well as diagnostic tests, occasionally lead to rhabdomyolysis. In this study, although the surgery was minimally-invasive, it ended up causing ARF.

Re-analyzing the greater dynamics of the trauma, as well as the various movements that the patient had to perform both for radiological examinations and for transfers between the two hospitals, an adequate hydration would be advisable, together with a total-body CT, both of which are recommended routinely in major traumas.

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SINGLE- VERSUS DOUBLE-INTEGRATED SCREWS IN INTRAMEDULLARY NAILING SYSTEMS FOR SURGICAL MANAGEMENT OF EXTRACAPSULAR HIP FRACTURES IN THE ELDERLY: A SYSTEMATIC REVIEW

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Approximately 50% of all hip fractures are extracapsular and typically treated with extramedullary or intramedullary fixation. Modern intramedullary nails used for internal fixation of extracapsular fractures are generally cephalomedullary nails secured by at least one cephalic screw. Different designs have been developed, varying in length, diameter, neck shaft angle, number of cephalic screws or blades, ability to slide and/or compress, ability to control rotation, construction materials and insertion-point. Articles published in all languages up to January 2019, are listed in PubMed and Scopus electronic databases about the association between the number of cephalic screws and the rate of complications and functional outcome. Twenty articles were included following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Sliding hip screws (SHS) were the standard of care for hip fractures from the 1950s to the 1990s, but presently intramedullary nails are more commonly used. There has been a more than 20-fold relative increase in the utilization of intramedullary nails since 1999. With the emergence of value-based healthcare, there is a growing interest of how best to provide high-quality care in a clinical and cost-effective manner, acknowledging limited healthcare budgets. The present systematic review assessed the long-term outcomes of the most commonly used nails using double cephalic screws compared with single screw devices in patients with unstable intertrochanteric fractures. The development of new technologies may allow a lower incidence of complications, a reduction in operative time and a lower intraoperative blood loss.

Approximately 50% of all hip fractures are extracapsular and treated with extramedullary or intramedullary fixation. The most common extramedullary implant is the sliding hip screw (SHS) (1). Modern intramedullary nails used for internal fixation of extracapsular fractures are generally cephalmedullary nails, inserted through the greater trochanter, and secured by a cephalic screw, which is passed up the femoral neck into the femoral head.

Different designs have been developed varying in length, diameter, neck shaft angle, number of cephalic screws or blades, ability to slide and/or compress,

Key words: hip fracture, InterTAN, nail, proximal femoral fracture, PFNA, screws

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ability to control rotation, construction materials and start-point. Examples include the Gamma Nail (Stryker Trauma GmbH), the InterTAN intramedullary hip screw (Smith and Nephew), the Proximal Femoral Nail (DePuy-Synthes) and the Proximal Femoral Antirotation Trochanteric Nail (DePuy-Syntes) (Table I). Extramedullary sliding hip screws (SHS) were the standard of care from the 1950s to the 1990s, but many surgeons now prefer intramedullary nails that interlock proximally in the femoral head (2).

There has been a more than 20-fold relative increase in the utilization of intramedullary nails since 1999. Approximately two-thirds of orthopaedic surgeons now use them routinely (3), although a recent study showed a 12.5% increase in the risk of 30-day mortality associated with the use of an intramedullary nail compared with a SHS in the treatment of trochanteric fractures (4).

With the emergence of value-based healthcare, there is a growing interest of how best to provide high-quality care in a clinically and cost-effective manner, acknowledging limited healthcare budgets (5, 6). The present systematic review assessed the long-term outcomes of the most commonly used nails using double cephalic screws compared with single cephalic screw devices in patients with unstable intertrochanteric fractures, thus assessing the effects of one or two cephalic screws in intramedullary nail systems in such elderly population.

MATERIALS AND METHODS

The review and its procedures were organized, conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (7) (Fig. 1). We wished to try to ascertain whether the number and the position of cephalic lag screws influenced the long-term outcome in elderly patients treated with intramedullary nail for hip a fracture.

A systematic search was performed (up to January 2019) in PubMed and Scopus electronic databases of scientific articles assessing the association between the number of cephalic screws and the rate of complications and functional outcome, with no restrictions of language. The search strategy covered the most common femoral nail and cephalic screw types used in clinical practice. In the search strategy, we used various combinations of the following key terms: dual head screws, dual lag screws, cephalic femoral screw, hip fracture, femoral nail, proximal femoral nail, nail fixation, and intramedullary nail.

We only considered for inclusion in the present study published articles that compared one and two screw nail systems, with no limit of year nor language. Case reports, editorials, technical notes, reply, narrative and systematic review articles were excluded.

Two orthopedic residents (LC, RA) performed the search and evaluated the articles independently. A researcher experienced (NM) in systematic reviews solved cases of doubt. Each investigator read the abstracts of all the articles, selected the relevant ones according to the inclusion and exclusion criteria previously determined, and then compared the results with the other examiner. After 4 weeks, the same studies were read again to establish the agreement of the researchers on the selection. No disagreement was observed among the investigators. One reviewer extracted the data from the full-text articles to Microsoft Excel software spreadsheet structured tables to analyze the study in a descriptive fashion. The second researcher independently double-checked the extraction of primary data from all the articles. Doubts and inconsistencies were solved by discussion (8-27).

RESULTS

After the initial literature search, 84 potentially relevant citations were identified. After removal of duplicate records, 51 articles were identified. After inspection of the title and the abstracts, 20 articles were not included, because they did not investigate the association between number of screws and complications or because they reported results and outcome about just one type of intramedullary nail. In addition, some of the excluded studies did not report the presence of a control group. After a further screening, another 11 articles were excluded because they did not comply with the inclusion criteria. Eventually, 20 articles were included in the present review (Fig. 1). The number of the reference, the methods and the data collected from the included articles are shown in the tables.

Intramedullary nails evaluated in the included studies

Single screw nails:

- Gamma Nail (Stryker Trauma GmbH, Schönkirchen, Germany):

The Gamma nail was introduced in the late 1980s for the treatment of extracapsular hip fractures. The implant consists in a sliding lag screw, which passes through a short intramedullary nail placed via the trochanteric entry point. One or two screws may be passed through the nail tip to secure it to the femoral shaft (distal locking). Theoretical advantages of this implant are its percutaneous insertion technique, and include reduced blood loss, minimal soft tissue trauma and short operating time, in common to all nails design. Modifications to the design of the Gamma nail and its instrumentation have occurred since its introduction. The long Gamma nail has a range of different lengths from 280 to 460 mm with two distal locking screw options (28). An Asian-Pacific version of the nail is available: it has reduced length, diameter and mediolateral angle to accommodate the small femur typical of this ethnic group (28).

- Gamma Nail 3 (Stryker Trauma GmbH, Schönkirchen, Germany):

The Gamma 3 nail is the third generation of the Gamma nail fixation system for proximal femoral fractures. It is a trochanteric entry nail with a reduced proximal nail diameter (15.5 mm versus 17 mm) to facilitate a shorter incision. Its length options range from 280 mm to 460 mm. Its neck shaft angle options include 120°, 125° and 130°. The lag screw shape has also been modified to provide superior cutting behaviour and greater resistance to cut-out (28).

- Proximal Femoral Nail Antirotational (PFNA) (DePuy-Synthes, Paoli, Pa., USA).

The PFNA, with lengths of 170 mm, 200 mm or 240 mm, is a modification of the PFN nail. It is similar to the PFN nail, but instead of two proximal lag screws, it accommodates on single helically-shaped blade designed to provide increased angular and rotational stability. The helical blade is designed to avoid the bone loss that occurs during drilling and insertion of a standard hip screw. The PFNA has two distal locking screw options for either dynamic or static locking. The blade shaft angle options include 125°, 130° and 135°. The PFNA II (Synthes Ltd) is a modification of the PFNA nail to address the different proximal femoral anatomy of Asian patients. The PFNA has a large proximal diameter (17 mm) which was thought to account for the increase in femoral shaft fracture, lateral cortex splitting and thigh pain reported in Asian patients. The PFNA II has a smaller proximal diameter (16.5 mm versus 17 mm) and a flatter lateral shape (5° *vs* 6°) (28).

Double screw nails:

- Proximal Femoral Nail (PFN) (DePuy-Synthes, Paoli, Pa., USA):

The PFN was introduced in 1998. Like the Gamma nail, it consists of a nail inserted via the greater trochanter into the medullary cavity. Two lengths are available, 200 mm and 240 mm. Two proximal lag screws are passed up the femoral neck to the head. Distal locking can be performed in static or dynamic mode via two distal locking screws (28).

- Double integrated screw nail IterTAN (Smith & Nephew, Inc. Memphis, Tennessee, USA):

The InterTan nail uses 2 cephalocervical screws in an integrated mechanism allowing intra-operative compression and rotational stability of the head-neck fragments. It has a cannulated set screw mechanism that allows for the device to be used in fixed angle mode or in sliding/compression mode. Its length ranges from 180 mm to 460 mm (28).

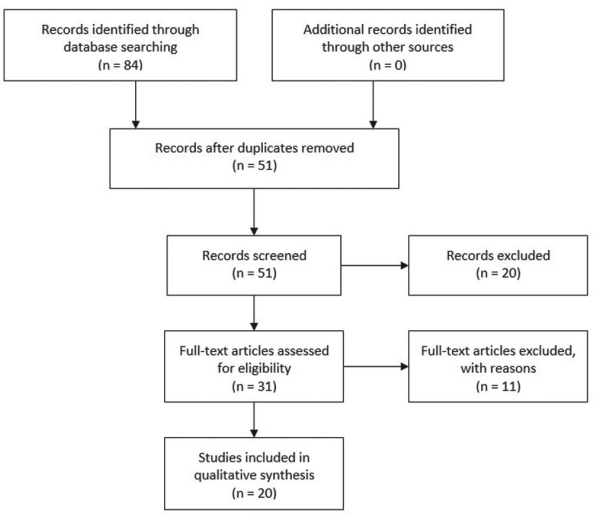

Fig. 1. *Prisma Flow diagram.*

Double cephalomedullary screw vs single cephalomedullary screw

- PFN vs PFNA

Sharma et al. compared the PFN to the PFNA (8) in a prospective comparative study with 48 participants (PFN=23, PFNA=25) and a mean follow-up of 18 months. There were no statistical differences in functional outcomes between the implants (p=0.83). Fewer complications were manifest in the PFNA group (p=0.02) (Table I).

- PFN vs Gamma Nail (GN)

The PFN was compared to the Gamma Nail in 3 different studies (9),(10),(11), with no significant differences between either nail in terms of the recovery of previous functional capacity, and time to fracture healing (12 weeks on average). Intra-operative blood loss was lower in the PFN (9-11). Shaft fractures and the cutting-out phenomenon were more common with the Gamma nail (9-11). Secondary varus occurred at a greater rate when using the PFN (9-11, 27). Functional outcome and consolidation were equal for both implants. Generally, the results of treatment of unstable trochanteric fractures were comparable for the PFN and GN (Table II).

Double integrated cephalomedullary screw vs single cephalomedullary screw InterTAN vs PFNA

The InterTAN was compared to the PFNA in 8 articles (12, 13, 17-22). There were no clinical and statistical significant difference regarding revisions, long-term implant-related failures and post-operative pain comparing the two implants. No differences were observed between InterTAN and PFNA for non-union and Harris Hip Score. Regarding intraoperative outcomes, there was a difference in blood loss in favour of PFNA, and there was no difference in operating times (Table III).

InterTAN vs Gamma Nail 3

The InterTAN was compared to the Gamma Nail 3 in 8 studies (14, 15, 23-25, 27). There were no significant differences between InterTAN and Gamma

Table I. *PFN vs PFNA.*

Author (year)	*Study design*	*Sample size*	*Percentage with tip-apex distance (TAD) ≥ 25 mm*	*Return to preinjury status*	*Complications (overall)*	*Operative time (average)*	*Cut-out*
Sharma et al 2017	Prospective comparative study	N=48 PFN=23 PFNA=25	PFN=4 (17.4%) PFNA=8 (32%)	PFN=34.7% PFNA=32%	PFN=8 (34.7%) PFNA=3 (12%)	PFN 40min > PFNA	PFN=7 (30%) PFNA=1 (4%)

Table II. *PFN vs Gamma Nail.*

Author (year)	*Study design*	*Sample size*	**Intra-operative blood loss/percentage of trasfusion**	*Operative time (average)*	*Return to preinjury status*	*Complications (overall)*	*Cut-out*
Herrera et al 2002	Prospective randomised study	N=250 PFN=125 GN=125	PFN=52% GN=37.6%	PFN=49 min GN=68 min	PFN=48% GN=52%	PFN=60 (48%) GN=73 (58.4%)	PFN=1 (0.8%) GN=5 (4%)
Schipper et al 2004	Multicentre prospective clinical study	N=424 PFN=211 GN=213	PFN=220 ml GN=287 ml	PFN=60 min GN=60 min	PFN=63% GN=60%	PFN=87 (41.2%) GN=84 (39.4%)	PFN=11 (5.2%) GN=13 (6.1%)
Marqùes et al 2005	Prospective randomised study	N=156 PFN=79 GN=77	PFN=37.7% GN=53.9%	PFN=45 min GN=40 min		PFN=42 (53%) GN=55 (71.4%)	PFN=7 (8.7%) GN=7 (8.7%)

Table III. *InterTAN vs PFNA.*

Author (year)	*Study design*	*Sample size*	**Mean blood loss**	**Operative time (average)**	**Complications (overall)**	**TAD (tip-apex d**
Huang et al (2013)	Comparative biomechanical study	N=16 ItT=8 PFNA=8				
Zhang et al (2013)	Retrospective Comparative study	N=113 ItT=57 PFNA II=56	ItT=235.3±124.6mL PFNAII=197.5±101.8mL	ItT=66.5±15.2min PFNAII=53.7±11.3min	ItT=38 PFNA II=44	ItT=23.7±2.1mm PFNA II=26.6±2
Makki et al (2015)	Retrospective comparative study	N=58 ItT=22 PFNA=36			ItT=0 PFNA=8	
Seyhan et al (2015)	Randomized controlled trial	N=75 ItT=32 PFNA=43		ItT=73.9±8.8min PFNAII=72.9±12.4min	ItT=6 PFNA=10	ItT=21.16 ±2.75 PFNA=23.53 ±3
Zehir et al (2015)	Retrospective comparative study	N=198 ItT=102 PFNA=96				
Wu et al (2016)	Retrospective comparative study	N=147 ItT=75 PFNA II=72	ItT= 190.6±6.0mL PFNA II=180.9 ± 10.8mL	ItT=71.9±6.8min PFNAII=52.3±4.0min	ItT=19 PFNA II=46	ItT= 23.2 ± 1.22 PFNAII=26.7 ± (
Zhang et al (2017)	Retrospective comparative study	N=174 ItT=86 PFNA II=88			ItT=11 PFNA II=33	ItT=26.00 ± 1.1(PFNA II=25.86 ±
Zhang et al (2017)	Retrospective comparative study	N=283 ItT=144 PFNA=139	ItT=180.7 ± 23.03mL PFNA=185.1 ± 18.96mL	ItT=67.2±3.9min PFNAII=68.9±4.2min	ItT=52 PFNA=81	ItT=19.9 ± 1.25r PFNA=20.2 ± 1.

Table IV. *InterTAN vs Gamma Nail 3.*

Author (year)	*Study design*	*Sample size*	**Mean blood loss**	**Operation time (average)**	**Complications (overall)**	**TAD (tip-apex distance)**	*Cut-out*
Hoffmann et al (2013)	Comparative biomechanical study	N=20 ItT=10 GN III=10					
Nuchtern et al (2014)	Comparative biomechanical study	N=24 ItT=12 GN III=12				ItT= 14.6 ± 1.5mm GNIII=10.2±1.2mm	
Wu et al (2014)	Retrospective comparative study	N=261 ItT=87 GN III=174	ItT= 87 ± 5mL GN III= 86 ± 6mL	ItT= 63.7 ± 10.4min GN III=59.9±11.8min	ItT= 16 GN III= 41		ItT= 1 GN III= 14
Berger-Groch et al (2016)	Randomized controlled trial	N= 104 ItT= 55 GN III= 49		ItT= 48 ± 28min GN III= 51 ± 20min	ItT= 12 GN III= 19	ItT= 10.4 ± 3.6mm GNIII=10.2±3.4mm	ItT= 1 GN III= 1
Hopp et al (2016)	Randomized controlled trial	N=78 ItT=39 GN III=39	ItT= 168.1 ± 151.25mL GNIII= 175.7±189.26mL	ItT= 78 ± 34min GN III= 64.6 ± 29min	ItT= 22 GN III= 29		ItT= 5 GN III= 4
Santoni et al (2016)	Comparative biomechanical study	N=22 ItT=11 GN III=11					
Serrano et al (2017)	Retrospective comparative study	N=413 ItT=283 GNIII=130					ItT= 2 GN III= 6

Nail 3 in terms of postoperative recovery, functional scores, hospital stay and the incidence of total complications. However, the incidence of cut-out and femoral shaft fracture were decreased in the InterTAN group comparing with the Gamma Nail 3 group. The InterTAN may result in better outcomes for patients with unstable trochanteric fractures (14, 15, 23-25, 27) (Table IV).

Double integrated cephalomedullary screw vs double cephalomedullary screw InterTAn vs PFN:

The InterTAN was compared to the PFN in 1 study (16). Better functional outcomes (Harris Hip Score) were observed in the InterTAN group when compared to the PFN group. There were better results in the InterTAN group when compared to the PFN group as 75% patients were found with no complications in comparison to 70%. The average fracture union time was shorter in the InterTAN group (ItT=17 weeks, PFN=19 weeks) (16) (Table V).

DISCUSSION

The 20 studies included in this review compared 5 different intramedullary nail systems. Nail design, lag screw design, and interlocking technique influenced the performance. The PFNA showed similar results in comparison with both double screw systems (12, 16-21). Equally, the Gamma Nail and Gamma Nail 3 showed similar results in comparison with the double screw systems.

The stronger statistically relevant differences were found in greater rates of intra-operative blood loss (9-11), greater rates of shaft fractures and the cutting-out phenomenon, all more common with the Gamma nail (9, 11, 14, 15, 23-27). The comparison between the 2 double screw systems (integrated, InterTAN, and non-integrated, PFN) showed a lesser number of complications in the InterTAN system (16). Particularly, the PFN system is associated with a statistically significant secondary greater rate of varus (9-11).

A potential explanation for the lesser number of complications of InterTAN arises from its design. This includes two integrated, interlocking lag screws that utilise a hybrid worm gear mechanism permitting better intraoperative fracture reduction and controlled compression of the intertrochanteric fracture. In addition, the trapezoidal proximal end of the nail may prevent uncontrolled shortening during fracture healing and limit varus collapse (5, 29).

This study had some limitations. Not all the many different kinds of intramedullary nails were evaluated, but only the most widespread. Moreover, the data collection could not be completely homogenous, given the many different parameters evaluated in the different studies. For the same reason, it was not possible to carry out a meta-analysis. Finally, only one comparative study compared the two double screw systems taken in consideration. This could not be enough to be able to express an evidence-based preference between the two nails. The development of new technologies that may allow a lower incidence of complications, a reduction in operative time and a lower intraoperative blood loss could represent an important step forward in the treatment of proximal femoral fractures.

The new Talon DistalFix femoral nail system (ODI Orthopedic Design North America, Inc), with an expandable locking mechanism, eliminates the need of distal locking screws. The Talon is associated with lower cut-out rates than the PFNA and shorter operative times than InterTAN (20). Further studies are warranted to clearly establish the potential advantages of Talon DistalFix over the other nails presently on the market.

Table V. *InterTAN vs PFN.*

Author (year)	*Study design*	*Sample size*	**Harris hip score**	**Complications (overall)**	**Z effect**	*Cut-out*	*Average fracture union (weeks)*
Mehta et al (2017)	Retrospective comparative study	N=40 ItT=20 PFN=20	ItT=18pz [80-100] PFN=16pz [80-100]	ItT= 5 (25%) PFN= 6 (30%)	ItT= 0 PFN= 1	ItT= 0 PFN= 1	ItT= 17 PFN= 19

The different devices showed different price ranges. The nail with the highest price in the market is the InterTAN with a cost of €1,650, followed by the PFNA at €1,000, the PFN at €960, the Gamma Nail 3 at €780, and the Gamma Nail at €583. Swart et al (30) calculated the cost of revision surgery from failure of fixation at approximately $30.000 [about twice the cost of the primary fracture surgery (31, 32)]. Considering the lower revision rate in terms of total complications and cut-out rate of the double integrated cephalic nail, it could represents a cost-saving solution compared to the other intramedullary nail systems.

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PUBIC OSTEOLYSIS SIMULATING A MALIGNANT LESION. A CASE REPORT WITH LONG-TERM FOLLOW-UP

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Pubic osteolysis is a rare pathology characterized by a painful radiographic destructive changes in the pubic rami, pubis or pubic symphysis that often follows a post-traumatic event. The etiology is unclear but it is a benign lesion, frequently misinterpreted as malignant. We report a case of a 54-year-old woman with pubic osteolysis mimicking a malignant lesion, diagnosed after open bone biopsy, conservatively treated without any sequelae and followed-up 10 years after the end of treatment. Although in the majority of the reported cases, a previous trauma has been commonly referred, in our case the patient did not refer to any cause before the onset of clinical symptoms. Knowledge of this entity is important to avoid invasive diagnostic procedures, costly investigations or overtreatment.

Pubic osteolysis is an uncommon lesion characterized by a painful bone resorption in the pubis, in the pubic rami or in the pubic synphysis (1). In this pathological condition, the osteolytic process presents a rapid progression that may be misinterpreted as a malignant lesion (2-5).

Despite the extensive and destructive aspect, pubic osteolysis is a benign lesion that heal without a specific treatment. However, it represent a rare disease that it is important to take into consideration in the differential diagnosis of a painful pubic lesion, in order to avoid unecessary procedures or costly investigations and consequently to exclude malignant lesion or other severe pathologies.

We report a 10-year follow-up of a case of pubic osteolysis in a 54-year-old female, diagnosed after open bone biopsy, conservatively treated and completely resolved in six months.

Case report

A 54-year-old female was admitted to our institution with right groin pain which had lasted one month. No history of trauma or radiation therapy of the pelvis was referred. At physical examination, the pubic region was mild painful to palpation and the patient had full range of motion of both hips, slightly painful especially to the right in flexion, abduction and internal rotation. The neurovascular evaluation and other physical findings were negative.

The radiographic examination of the pelvis did not show any significant abnormality of the pelvic bones (Fig. 1). The patient was treated by medication with Diclofenac, 150 milligrams once a day for 2 weeks, with a slight improvement of the symptoms. Two months later the same patient was admitted again to our institution, referring to a worsening of the right groin pain and limping. The symptoms worsened during daily activities and decreased at rest. At physical examination, the pubic region was very painful to palpation; the range of motion was restricted and painful in both hips, especially on the right side, without neurovascular deficit of the lower limb. Laboratory findings showed no significant abnormalities, they included blood count,

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sedimentation rate, C-reactive protein, serum calcium, serum phosphorus, alkaline phosphatase and serum parathyroid hormone (PTH) level.

A computed tomography of the pelvis showed an evident osteolysis of the right ileopubic ramus that was confirmed by CT-PET and MRI (Fig. 2). Since these appearances suggested a possible malignancy of the lesion, an open biopsy was performed. Biopsy samples revealed variably cellular and vascularized connective tissue, fibrocartilage and newly formed bone trabeculae consistent with reparative/reactive changes, without any evidence of malignancy (Fig. 3). At this point, a diagnosis of pubic osteolysis was done and the patient was treated conservatively with complete bed rest for four weeks followed by partial bed rest for another two months. At the end of treatment, the patient was pain free and progressively resumed any daily and physical activities. At follow-up, 10 years later, she was completely asymptomatic and radiographic examination of the pelvis showed a good remodeling of the right ileopubic ramus (Fig. 4).

DISCUSSION

Pubic osteolysis is a distinct diagnostic entity characterized by radiographic findings of osteolytic lesion of the pubis, pubic rami or pubic synphysis (1, 6). It is a painful lesion that generally occurs in post-menopausal women with radiographic evidence of osteoporosis, however an antecedent trauma has been commonly reported (4, 7-12). Some authors have suggested that pubic osteolysis is due to a stress fracture (1, 13), but some cases with no history of trauma have also been described (3, 6).

Pubic osteolysis is a benign lesion but, for the radiographic findings of destructive changes, is frequently misinterpreted as a malignant tumor, since the marked bone lysis present in the pubis or in the pubic rami may suggest a malignant lesion (2-4, 6-9, 14). The differential diagnosis include malignant lesions as chondrosarcoma, metastatic carcinoma, multiple myeloma and Hodgkin's disease; however a pubic osteomyelitis must be excluded (15, 16).

In the majority of the reported cases, the authors documented that pubic osteolysis healed with conservative treatment (1, 3, 4, 6, 9); on the contrary, Albertsen et al (7) reported a series of 14 patients with post-traumatic pubic osteolysis, in which bone healing did not occur in any of the patients.

Long-term follow-up studies of pubic osteolysis are very rare. Matsumoto et al (3) reported a case of pubic osteolysis in a 69-year-old woman with a long-term follow-up, in which the radiographic examination of the pelvis, taken 6 years after presentation, revealed

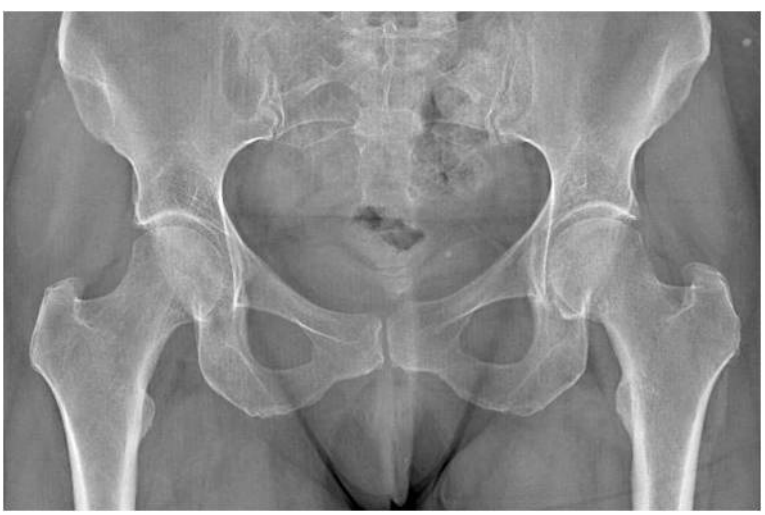

Fig. 1. *Radiographic examination of the pelvis in AP view, taken one month after pain onset, did not show any evident lesion of the pubic bones.*

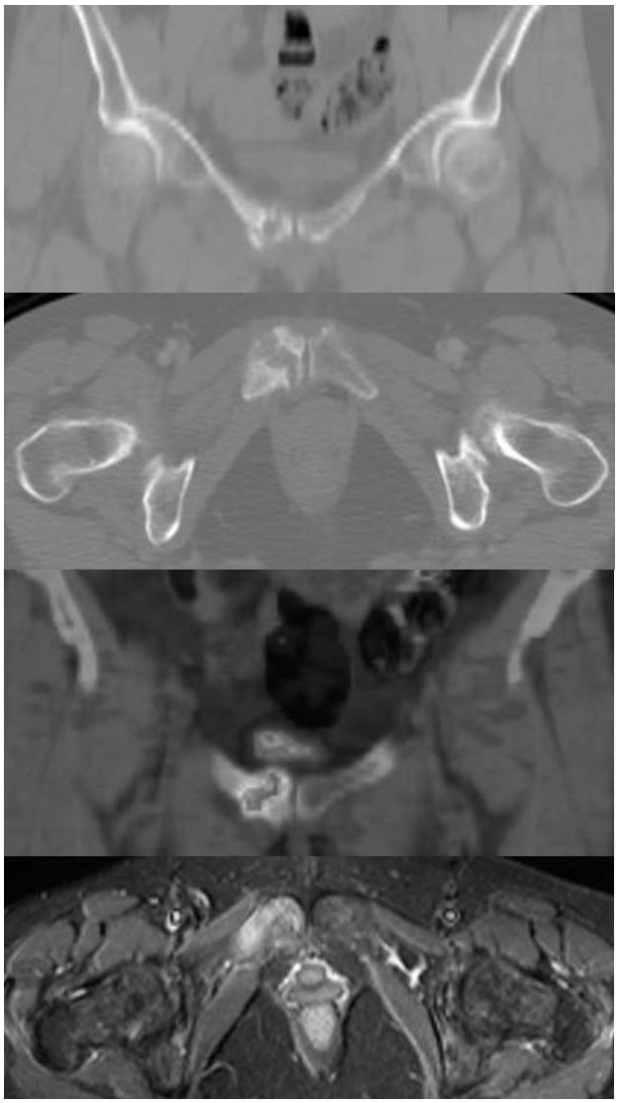

Fig. 2. *CT, CT-PET and MRI of the pelvis taken three months after pain onset, showed an evident osteolysis of the right ileopubic ramus.*

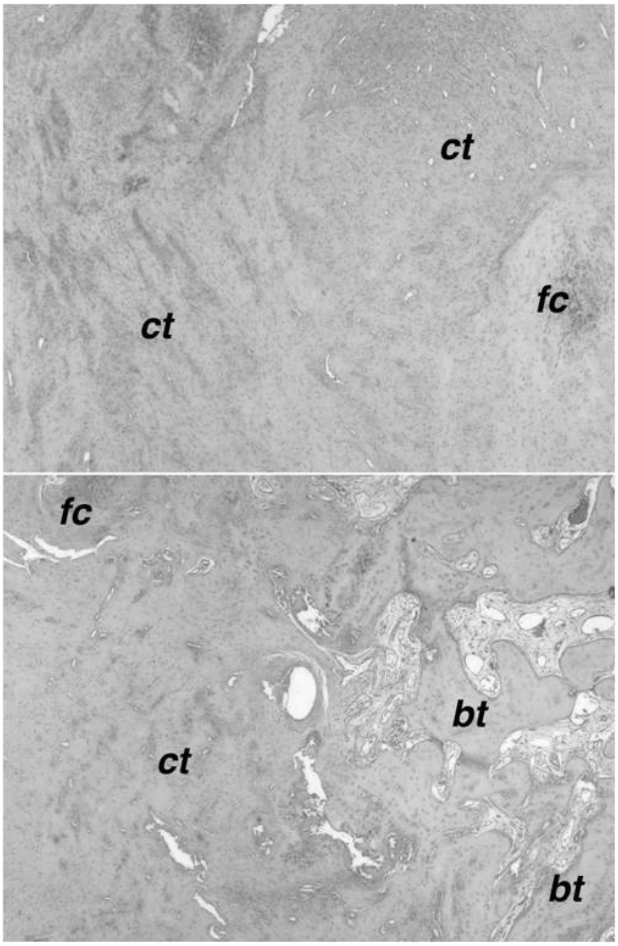

Fig. 3. *Biopsy samples revealed variably cellular and vascularized connective tissue (**ct**), fibrocartilage (**fc**) and newly formed bone trabeculae (**bt**) consistent with reparative/reactive changes.*

a complete healing of the lesion, confirming its benignity.

To the best of our knowledge, our reported case of pubic osteolysis has the longest follow-up. We do not think that our case is a post-fracture osteolysis, because the patient did not refer any trauma before the groin pain onset, but it is a different entity with spontaneous destruction of the pubic bones of uncertain etiology.

In conclusion, pubic osteolysis is an uncommon distinct pathology that cause groin pain and progressive walking impairment. From a radiographic point of view, it is characterized by rapid osteolysis in

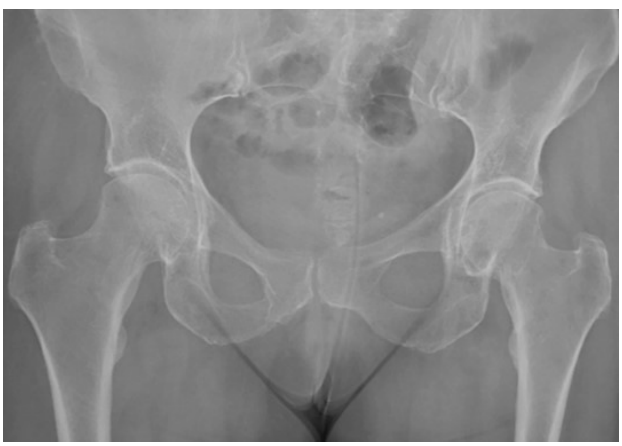

Fig. 4. *Radiographic examination of the pelvis in AP, taken at follow-up, 10 years after the end of treatment, showed a good remodeling of the right ileopubic ramus.*

the pubic bones, often misinterpreted as a malignant lesion. The etiology is still debated, the post-traumatic origin is often reported, but some case did not refer any specific cause. Conservative treatment usually solves the pathology within 4-6 months. Knowledge of this entity is important to avoid invasive procedures, costly investigations and overtreatment.

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CORRELATION OF PRE-OPERATIVE PLANNING TO SURGICAL CORRECTION OF OPENING WEDGE HTO: A RADIOGRAPHIC STUDY UTILIZING A MANUAL MEASUREMENT METHOD

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High tibial osteotomy (HTO) utilizing a medial opening wedge has become a common and effective surgical technique for treatment of isolated medial compartment knee osteoarthritis secondary to varus malalignment. To reduce the risk of under- or overcorrection, accurate preoperative planning is important. This is a radiographic study to evaluate the reliability of preoperative measurement on full-length weight-bearing X-rays (FLWBXr) compared to post-operative X-rays after healing. In addition, we calculated if the intraoperative opening wedge performed was consistent with the preoperative calculation and the postoperative correction. Three independent observers measured preoperative and postoperative FLWBXr at three different times. The angle of varus deformity; the angle to correct and the wedge needed to achieve desired alignment: the angle achieved postoperatively, and the postoperative mechanical axis deviation were measured. Intra- and inter-rater reliability showed high values for all the investigated parameters. The discrepancy between the calculated wedge and the wedge actually used in surgery ranged from 1 mm of over-correction to 3 mm of undercorrection, averaging -1.3 mm. The mechanical axis crossed the tibial plateau an average of 53% ±12.7. Clustering the data by the plate type statistically significant differences were found for preoperative varus alignment, advocated correction, intraoperative correction and post-op alignment. The Dugdale method can be considered highly reliable. Possible factors affecting the final correction are: surgeon's desire not to overcorrect in young patients and minimal osteoarthritis; measurement errors; variability in the method the FLWBXr is performed. In addition, the under correction could be the result of some collapse with time or the correction could be affected by the fixation system. Further investigation should include complete post-operative evaluation of outcomes and assess the role of these potential factors and their relationship to correction. Level of Evidence: Level III, Retrospective study.

High tibial osteotomy (HTO) utilizing a medial opening wedge technique has become a widely accepted and an effective surgical treatment for medial knee compartment overload secondary to varus alignment. Candidates for osteotomy include very active patients with isolated symptomatic medial compartment osteoarthritis or cartilage and meniscal loss, with intact lateral and patellofemoral compartment, varus metaphyseal deformity of tibia, age < 65 years, with good range of motion of the knee. (1-3). In addition to poor patient selection, inadequate preoperative planning, inaccurate correction during

Key Words: high tibial osteotomy, genu varum, mechanical axis correction, opening wedge

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surgery and postoperative loss of correction, ineffectively changing the knee load distribution, represent some of the most common causes for HTO failure (4)

(5, 6). Prior to surgery, to reduce the risk of under or overcorrection, accurate preoperative planning should be performed; an excessive correction can produce an unsatisfactory result as well as an inadequate correction can lead to relapse of symptoms. Degenerative status of medial and lateral compartment, patellar height and overall lower extremity alignment should be evaluated. Bilateral full-length weight bearing X-Rays, lateral views, tunnel views with the knee in 30° or Rosenberg views in 45° of flexion are helpful. Cartilage and soft tissue status can be examined by arthroscopy or MRI (3). Several methods to calculate preoperatively the optimal amount of correction have been developed and published. Both anatomical and mechanical axes have been used to measure preoperatively the angle to correct and to assess postoperatively the advocated result (5-11). As suggested by Miniaci et al (12), Noyes et al (13) and Dugdale et al. (4), the optimal outcome would be achieved transferring the weight bearing line to a point around 62.5% of tibial plateau (generally in the lateral compartment to the tip of the lateral tibial spine), aiming for a mechanical axis comprised between 3° and 5° of valgus. Moreover, recently, to improve the accuracy of correction in preoperative planning, dedicated software has been developed (14). The aim of this radiographic study is to evaluate the reliability of preoperative measurement on full-length weight bearing X-rays (FLWBXr) compared to post-operative X-rays after healing. In addition, we calculated if the preoperative correction is consistent with the size of the opening wedge performed and with the actual postoperative achieved correction.

MATERIALS AND METHODS

Sixty-five consecutive patients underwent to HTO by the same experienced surgeon (A.A.) for symptomatic medial compartment arthritis, either at the time of biologic cartilage or upon meniscal resurfacing, secondary to a varus deformity, from 2010 to 2013. The X-rays were taken in antero-lateral view of both the lower limbs with the patient in full weight bearing, knee fully extended, the patella and the feet facing forward. The x-rays were taken while the patient was asked to load both limbs equally. The surgical technique was performed according to the former description by the senior author (3). Postoperatively, for the first 6 weeks, the patients' knee was placed in a hinged brace with a 0-90° ROM, and a touch weight bearing was allowed; in the successive 6 weeks the brace was discontinued, and the patient allowed to progress gradually to full weight bearing. Three independent observers measured preoperative and postoperative FLWBXr at three different times separated by a two-week period. The angle of varus deformity; the angle to correct and the wedge needed (mm) to achieve desired alignment (according to the Dugdale method (4); the angle achieved postoperatively and the postoperative mechanical axis deviation was measured (Fig. 1, 2, 3).

Statistical Analysis

The intra-observer and inter-observer reliability were calculated with the Intra-Class Correlation Coefficient (ICC) 3.1, for continuous variables. Since a formula to calculate the sample size for ICC (3.1) is not available, the formula described by Doros and Lew for ICC (2.1) was used as a reference. Assuming that ICC is at least 0.7, then 32 (or more) subjects used by each of the three raters would be sufficient to assure an ICC 95% confidence interval smaller than 0.3. The difference between the calculated correction needed according to preoperative X-rays and the correction actually performed during surgery was calculated. Statistical significance was tested using a Mann–Whitney U-test for nonparametric values and t-test for continuous variables. Statistical significance was set at $P < 0.05$.

RESULTS

Thirty-one patients were excluded because of inadequate full-length weight bearing X-ray, therefore 34 patients were reviewed, and demographic data are shown in Table I. Postoperative weight bearing X-rays were taken in a median of 14 weeks after surgery. Two different implants were used, ContourLock HTO plate® (Arthrex) in 16 patients and iBalance® HTO system (Arthrex) in 18 patients. The preoperative deformity ranged from 2 to 13 degrees of varus, average of 7 degrees ±2.6. The calculated preoperative correction (62% from the medial tibial edge) ranged from 4 to 16 degrees (mean 9.5 degrees ±2.7) with the corresponding wedges ranging from 5 to 21 mm (mean 11.7mm ± 3.7). The size of the implants used in the surgery ranged from 6 mm to 17.5 mm (average 10.4mm ±3.3). The postoperative angles ranged from 7 degrees of varus to 7 degrees of valgus (mean 0.9±2.9 of valgus) and the mechanical axis crossed the

tibial plateau, in average, at 53% ±12.7 of the surface as measured from the medial plateau. This was 9% lower that the advocated value ($p<0.0001$).

Intra-rater reliability showed very high levels of agreement ranging from ICC 0.9404 to 0.9948 for angle of varus deformity, angle to correct, wedge size, and postoperative angle and postoperative mechanical axis location on the tibial plateau. Inter-rater reliability showed only slightly lower ICC, ranging from 0.8986 to 0.9580. The calculated angle to correct and the calculated corresponding wedge had ICC ranging from 0.9344 to 0.9471.

The mean preoperative calculated wedge was 11.7±3.7 while the mean intraoperative opening wedge was 10.4±3.3. Comparing the two groups of values, non-significant differences were found ($p=0.104123$, $U=445.5$). The discrepancy between the calculated wedge and the wedge actually used in surgery ranged from 1 mm of over-correction to 3 mm of under-correction, averaging -1.3 mm.

DISCUSSION

The intra- and inter-rater reliability for all the used measurements showed excellent results, therefore the radiographic measurement method utilized (4) for the purpose of this comparison study can be considered highly reliable.

Various methods of limb alignment measurement have been described. Some of them are based on the anatomical femoro-tibial angle [Coventry (9), Kettelkamp (8), Koshino (10)], others on the mechanical femoro-tibial angle [Hernigou (5), Ivarsson (15) and Myrnets (16)], the most recent on the weight bearing line (mechanical axis of the lower limb) [Dugdale (4), Miniaci (12) and Noyes (13)]. Kettelkamp (8) achieved good results with a correction leading to at least 5° of valgus, while Koshino et al. (10) recommend a 10° of valgus alignment, closer to what was previously stated by Conventry (9), which suggests to aim to 10° of anatomical valgus angulation (corresponding to 3 to 5° of mechanical-axis valgus angulation). The author also recommended that the patient should be in the standing position during the full length view X-rays, while Koshino suggests to weight bearing one limb at time. Hernigou et al. (5) used a full length limb X-ray with weight-bearing and aimed to achieve a

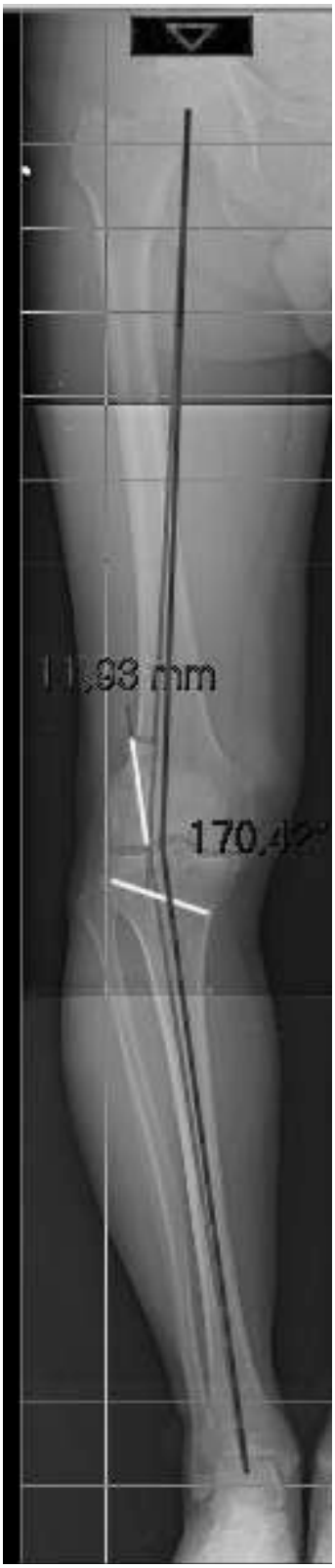

Fig. 1. *The blue line indicates the angle of varus deformity. The Red line indicates the amount of needed correction, according to the Dugdale method.*

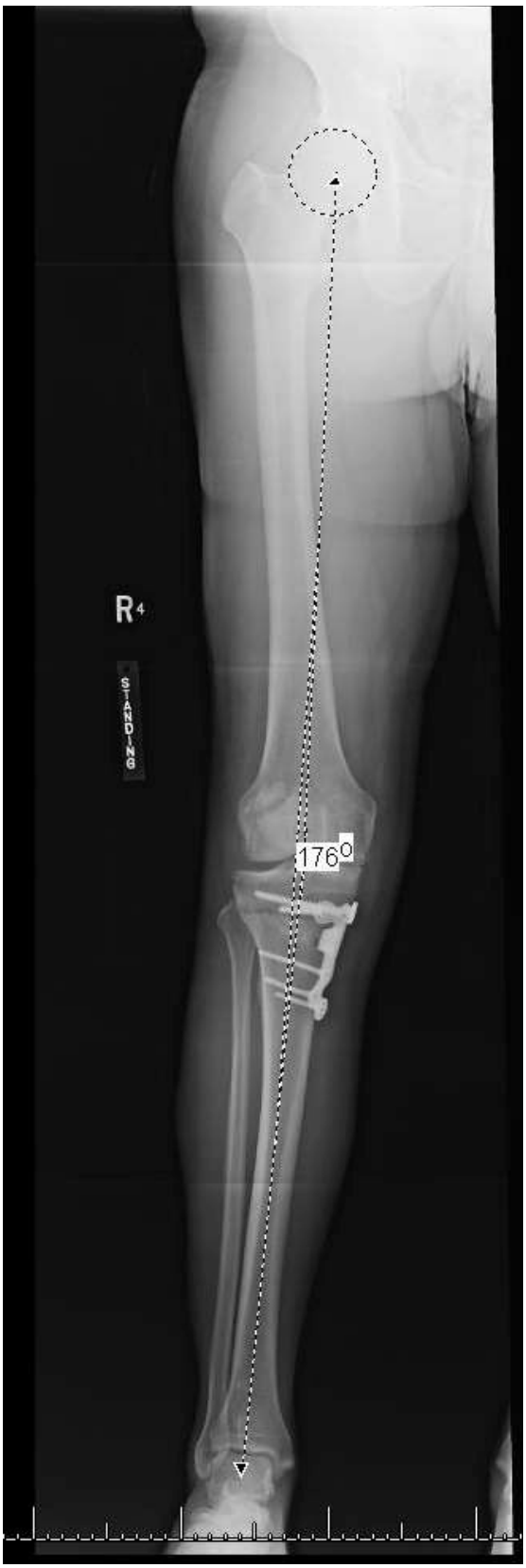

Fig. 2. *Angle achieved postoperatively.*

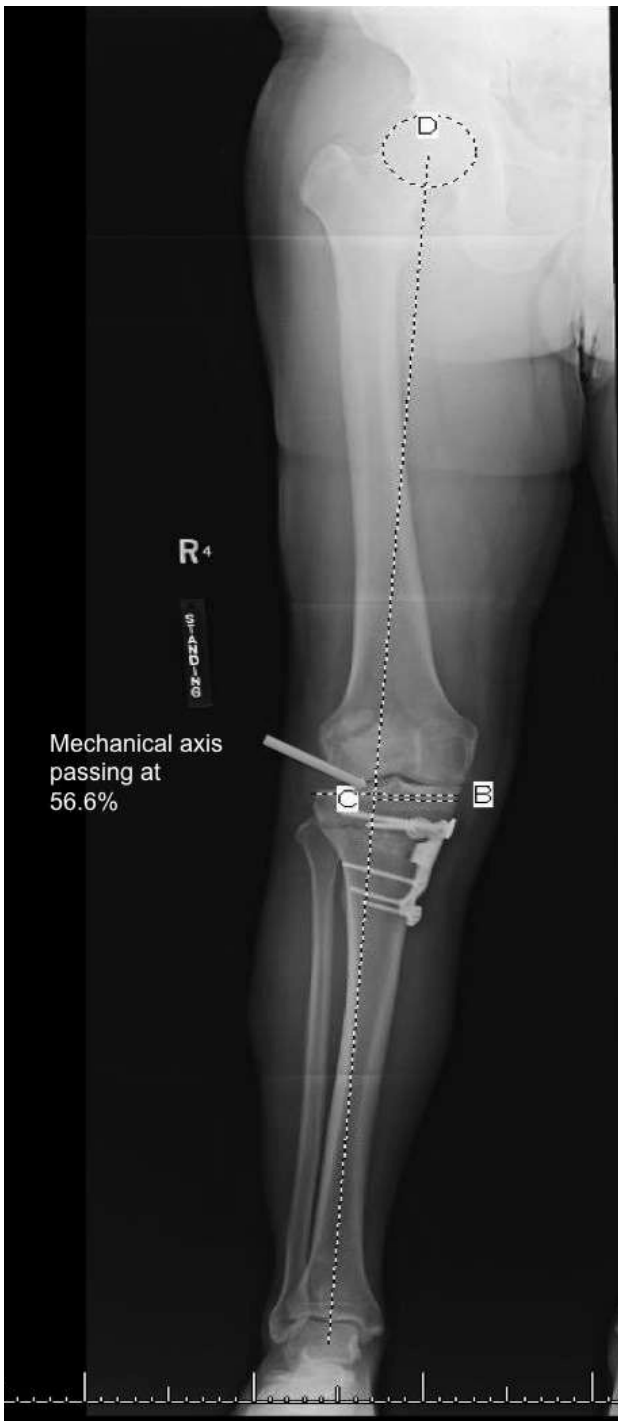

Fig. 3. *Postoperative mechanical axis.*

mechanical femoro-tibial angle in 3° to 6° of valgus.

Myrnerts (16) in 1980 reported better results in patients with a 3° to 7° valgus overcorrection compared to patients with a neutral correction, using mechanical femoro-tibial angle. Miniaci (12) suggested that the correction should result in a

mechanical axis that passes through a point 30%-40% the width of the lateral tibial plateau. Dugdale at al. (4) suggested to make the weight bearing line passing through a point 62 to 66% of the tibial width that approximates a 3°-5° valgus mechanical axis. The second aim of the study was to investigate if the amount of correction calculated preoperatively was consistent with the intraoperative opening wedge and the postoperative correction that was achieved. We found that there was a non-significant difference comparing these 3 measures, although there was a tendency towards under-correction. The postoperative X-rays showed that the mechanical axis crossed the tibial plateau, in average, at 53% ±12.7 of the surface as measured from the medial plateau, significantly lower than the value obtained with pre-operative planning. Various factors may have affected the final correction. First of all, the surgeon may have adjusted the correction amount in cases according to the age of the patient and to the osteoarthritis severity. Osteotomies were performed not only for medial compartment OA, but also for young patients with biologic resurfacing of the medial compartment. Therefore, overcorrection as advocated for osteoarthritic and older knees (5, 9, 10), may cause overcorrection and poor outcome in younger patients where the osteotomy was performed just to unload a meniscus transplant or cartilage resurfacing, while in young patients, maintain normal mechanics is important (17) . Other causes of undercorrection could be measurement error in the preoperative planning and the way the full-length X-ray is performed: a non-well balanced weight bearing on both legs could affect the actual varus alignment of the affected limb. All X-rays were taken in the same fashion by the radiology technician. Alignment X-rays were not performed on the day of surgery, and therefore the time between the pre-operative planning x-rays and the surgery may have caused a change in the amount of varus. We did not measure X-rays and alignment over time. In addition, the under-correction could be the result of some collapse with time. A recent study by Lee at al. (18) showed that the weight bearing line shifts progressively medially until 1 year post-operatively. Another possible cause of loss of correction is a break in the lateral cortex hinge. A lateral cortex breakage significantly compromises the stability of construct and the correction angle (12, 19, 20). The lateral hinge breakage may cause some osteotomy translation or instability that can lead to nonunion, malunion or implant failure (12, 19, 21-23). Corrections higher than 8° have an increased risk for lateral cortex fracture (24, 25). And finally, the fixation system could affect the stability of the osteotomy, favoring therefore an earlier medial shifting.

Stoffel et al (26) demonstrated in a biomechanical study as in case of lateral cortex fracture the TomoFix plate provides superior stability in both compression and torsion compared to the Puddu Plate. Another biomechanical investigation by Spahn et al. (27) showed that implants with a spacer that have superior biomechanical properties and angle stable plates may lower the risk for lateral cortex fractures. A retrospective study from Kim et al. (28) showed that at 2 years post-operatively, the correction angles differed significantly between wedge and locking plate.

Limits of the study are the short follow-up period and the lack of a regular series of full-length X-rays that were taken at different time points allowing measurement of change of over time. Moreover, the patient's symptoms and functional status were not correlated with the undercorrection, and the influence of the two different plates on providing and maintaining the amount of the advocated correction was not assessed. Strength of the study is the use of power analysis to determine the sample size. Further investigations should include complete postoperative evaluation of outcomes and relationship to correction.

The radiographic measurement technique utilized in this study (4) for pre and post-operative was found to be highly reliable. Based on this study, opening wedge HTO has a tendency to result in a postoperative under-correction based on the preoperative planning. Both a surgeon's tendency to under-correct during surgery to avoid overcorrection, as well as external factors may have affected the final alignment. There is a need for further studies assessing the role of each previously mentioned factors, including change in alignment over time, construct stability, and lateral cortex fracture. It is also necessary to objectively evaluate outcomes and relationship to the alignment achieved.

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TALAR EXOSTOSIS (EPIPHYSEAL DYSPLASIA): CASE REPORT OF POSTERIOR ARTHROSCOPIC EXCISION

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Letter to the editor,

Posterior ankle impingement is a syndrome characterized by discomfort or pain at the hind foot during plantarflexion. The etiology can be divided into three main categories: overuse, trauma and anatomic abnormalities. Regarding overuse, usually patients that complain of posterior ankle pain are ballet dancers, downhill runners, field athletes and soccer players secondary to flexor *hallucis tendinitis*.

Ballet dancers through repetitive exercises, especially the end point technique, will improve joint mobility, decreasing the distance between talus and calcaneus (1). Soccer players are at risk of developing posterior ankle because of repetitive ball kicking with hyper plantarflexion, resulting in excessive force on hind foot bones, as with runners during downhill running (2-4). Trauma-based posterior ankle impingement is generally due to hyper plantarflexion, supination, or their combination (5).

Anatomical abnormalities include an elongated lateral tubercle of the talus, the Stieda process (6), the os trigonum, a non-fused small bone on the posterolateral aspect of the talus coming from a different ossification center (7), or a talus bipartitus (8). Pain arises during hyper plantarflexion when soft tissue is pinched between bone tissues (9). A local infiltration with anesthetic can confirm the diagnosis if pain relief occurs. Although it is possible to diagnose it on a clinical basis, X-ray, MRI or CT scan are useful to differentiate among the possible etiologies.

We present a case of posterior ankle impingement syndrome in a 14-year-old male due to a congenital bony exostosis of the posterior edge of the talar dome; we addressed it surgically utilizing prone posterior ankle arthroscopic debridement. Although posterior arthroscopy has been utilized for posterior impingement, utilizing this technique for this congenital anomaly has not been described, is minimally invasive and effective.

History

A 14-year-old male student complained of long-standing right ankle pain with decreased motion. Patient and parents stated that he has limitations for as long as they can remember in pointing his foot in plantar flexion and pain after excessive activity and sports. Otherwise, he did not have significant symptoms in his routine activities of daily living. He had tried physical therapy without improvement. In addition, he had several other medical, including neurologic evaluation for limited plantarflexion without any underlying diagnosis.

Physical examination

The patient presented with limited hind foot and mid foot motion, limited plantarflexion on both

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ankles, but more on the right than the left. He has some forefoot adductus on the right compared to the left. The patient had regular gait with normal cadence with 5\5 throughout muscle testing all compartments. Standing examination revealed a slight varus alignment of the hindfoot with some varus alignment of the great toe. At tibiotalar range of motion patient was able to dorsiflex 15°, and plantar flex 15°, which was asymmetric compared to that of the left which had about 30° of plantarflexion. Patient did not complain of discomfort during palpation throughout the examination. The ankle had a firm bony endpoint in plantarflexion, and this did not produce significant pain or discomfort for the patient.

Radiological examination

Radiograph exams were largely unremarkable except for the apparent congenital bony deformity of the right talus with an asymmetric posterior dome that impinged on the posterior tibial plafond (Fig. 1, 2). Ankle and subtalar joint spaces were normal.

Surgical procedure

The patient underwent prone posterior ankle arthroscopy with extensive debridement of the posterior exostosis of the talus and posterior subtalar arthroscopic debridement. The patient underwent general anesthesia and local anesthetic neuromuscular block. A tourniquet was placed to his right proximal thigh and inflated to 275 mmHg. After establishing posteromedial and posterolateral portal using the nick and spread technique, a diagnostic arthroscopy was performed visualizing both the ankle and the subtalar joint above and below the exostosis.

A thick synovial tissue in the posterior aspect of his ankle was visualized, along with a large osteophyte vs congenital malformation of the posterior dome of the talus. A debridement and thickening of synovium at the posterior aspect of the ankle was removed. Talar dome prominence was taken down by a combined use of shaver and burr. Once this was removed, the cartilaginous edge was cleaned with a shaver and the thickened posterior capsule was taken down. Once this was done, the patient's range of motion improved markedly.

In regards to the subtalar joint, the shaver was used to identify the borders of the large posterior overhang, and then the large plantar overhang of the talus was taken down by a combined use of burr and shaver; once this was down to a stable base and the bony block was removed, a good exposure of the subtalar joint and improved range of motion was obtained. The area around the *Flexor Hallucis Longus* was debrided to ensure that it was not impeded by any part of the

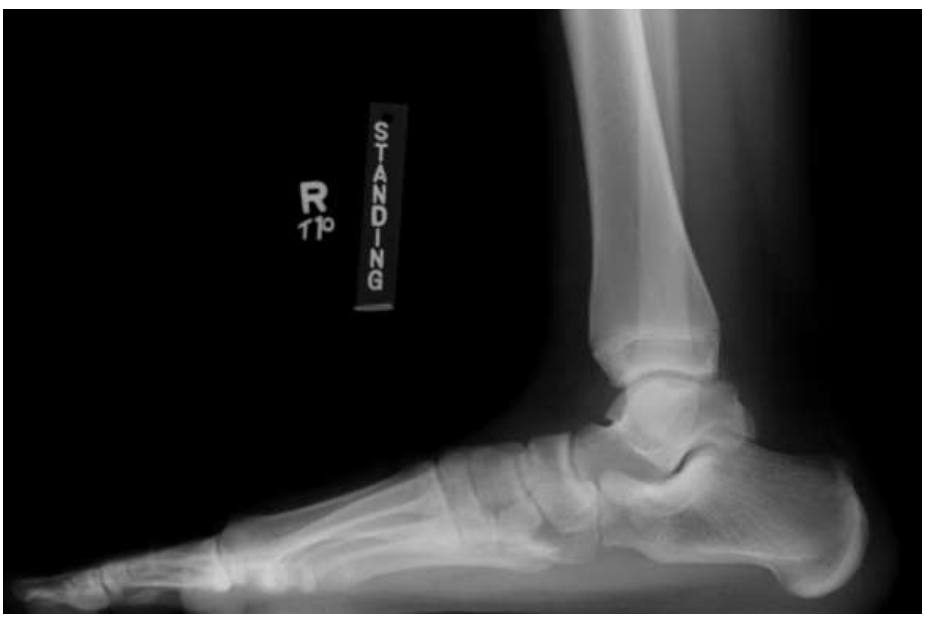

Fig. 1. *Pre-operative lateral X-Ray.*

talus during motion. Overall the patient's plantar range of motion was significantly improved following debridement of both joints without any visible bony impingement (Fig. 3-12).

Postoperative plan

The patient was weight bearing as tolerated in a postoperative boot. At postoperative day 3, he was able to remove the boot and begin early gentle range of motion. The patient returned to the orthopedic clinic at 10 days to begin physical therapy and range of motion exercises. He was clinically and radiographically followed up to 6 weeks after procedure. (Fig. 13-17). The last clinical follow up was 12 months from surgery and no complications were found.

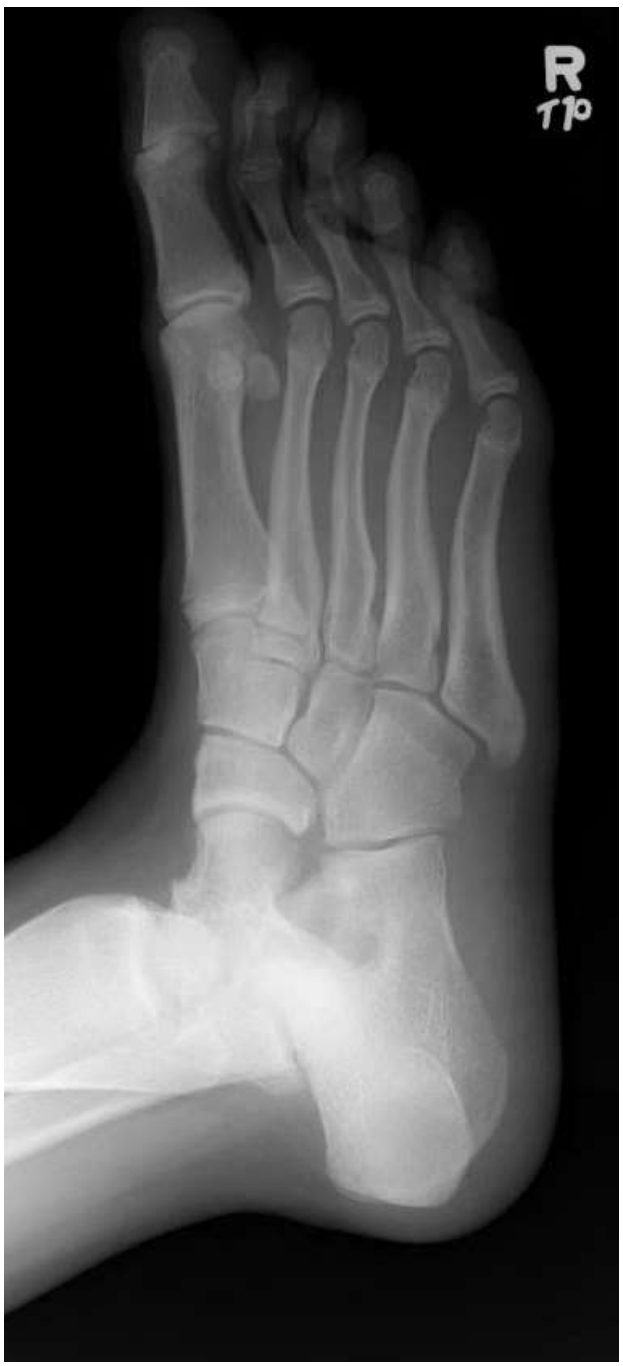

Fig. 2. *Preoperative oblique X-Ray.*

DISCUSSION

The first to describe posterior ankle pain due to bony impingement was Howse in 1982 (10) when he described the presence of a "bony block at the back of the ankle" determining pain during hyper plantar-flexion in dancers. A common cause of posterior ankle impingement is os trigonum (11-15). It is derived from a separate ossification center and it consists of a little piece of bone situated on the postero-lateral aspect of the talus. Generally, it mineralizes at 7- to 13-years-of-age, but in 7 to 14% of the population it remains as a separated ossicle. In 1.4% of the cases it is bilateral (16, 17). When this ossicle fuses with the postero-lateral aspect of the talus, but remains elongated, it is called Stieda's process. In this setting, the extended lateral tubercle of the talus may form a posterior block during hyper plantar flexion (2, 10). In some cases, Stieda's process can become inflamed secondary to micro trauma in chronic impingement, resulting in degeneration or thickening of the surrounding soft tissues (capsule, ligaments, and tendons).

Acute trauma during plantar flexion can also lead to fracture of the elongated postero-lateral process of the talus and result in impingement symptoms (15). The diagnosis of posterior ankle impingement is generally made on a clinical basis. The patient complains about chronic posterior deep pain during or exacerbated by hyper plantar-flexion. The patient may have a recent or remote history of ankle sprain (18, 19). The physical exam will show tenderness palpating the posterior aspect of the ankle joint, with or without associated swelling. Pain with passive hyper plantarflexion is a diagnostic test for posterior ankle impingement. If it is associated with pain during passive hallux dorsiflexion, a *flexor hallucis longus* tendon inflammation or impingement may be present (5).

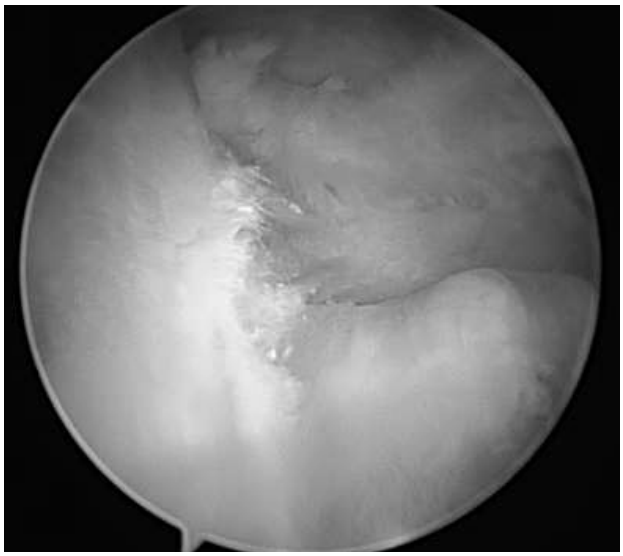

Fig. 3. *Arthroscopic posterior view of FHL tendon and bony prominence.*

Fig. 4. *Arthroscopic posterolateral view of ankle joint and edge of exostosis.*

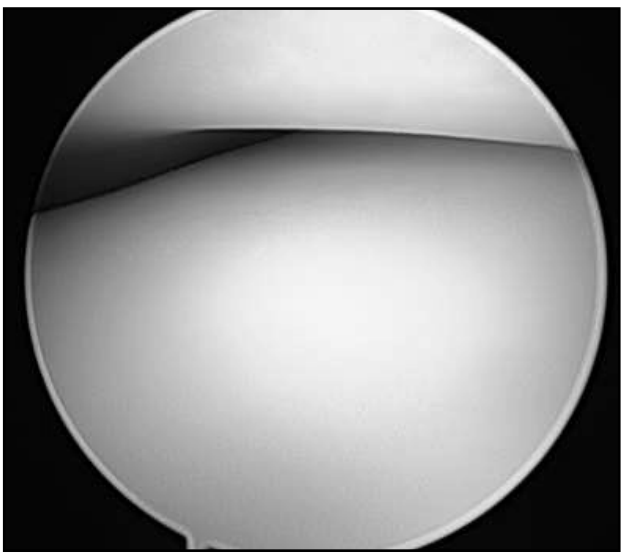

Fig. 5. *Normal ankle joint (Arthroscopic view).*

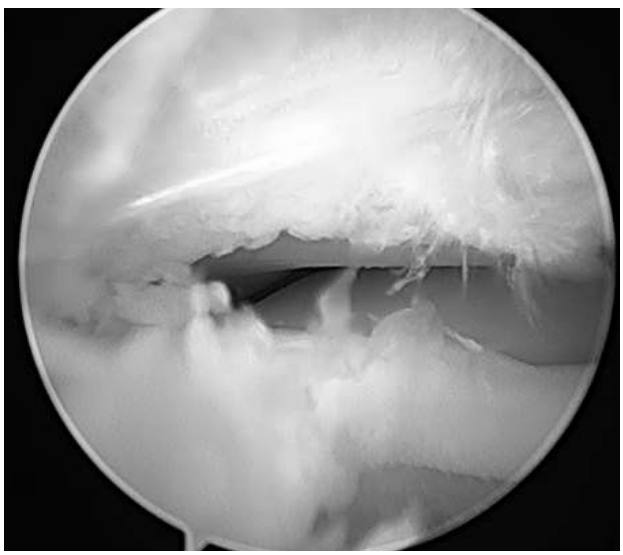

Fig. 6. *Arthroscopic posterior view of ankle joint and edge of exostosis.*

We describe the case of a patient suffering from posterior ankle pain due to the presence of a large exostosis of the posterior body of the talus. The history and the physical exam were consistent with the diagnosis of a posterior ankle impingement syndrome.

The intraoperative arthroscopic images clearly demonstrated the bony prominence covered by cartilage in continuity with the posterior talus. Exostosis is the most common bone tumor among children and it accounts for more than 30% of all benign bone tumors and 10-15% of all bone tumors (20). It consists of a bony projection with a bone marrow cavity in continuity with the one of the underlying bones and covered by cartilaginous tissue.

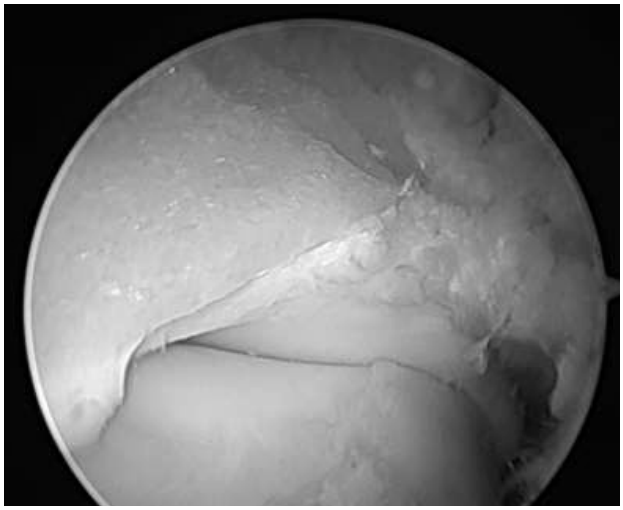

Fig. 7. *Partial removal of posterolateral aspect of exostosis (Arthroscopic view).*

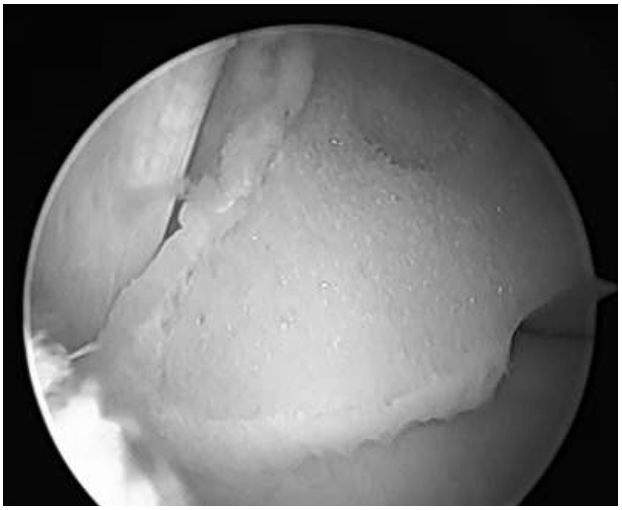

Fig. 8. *Partial removal of posteromedial aspect of exostosis (Arthroscopic view).*

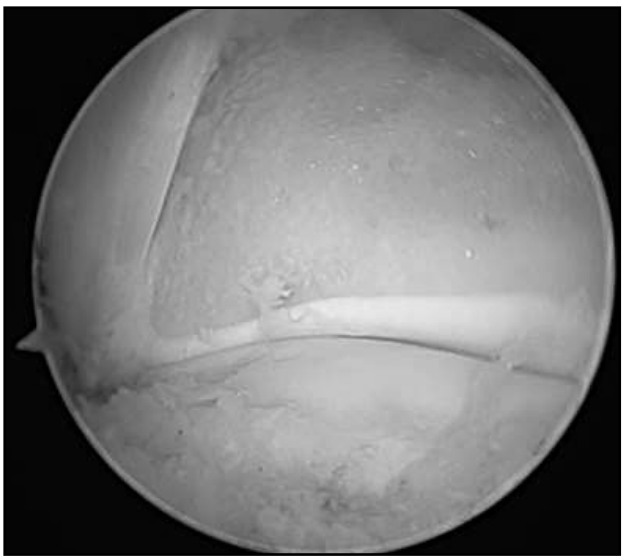

Fig. 9. *Full removal of exostosis (Posteromedial subtalar joint arthroscopic view).*

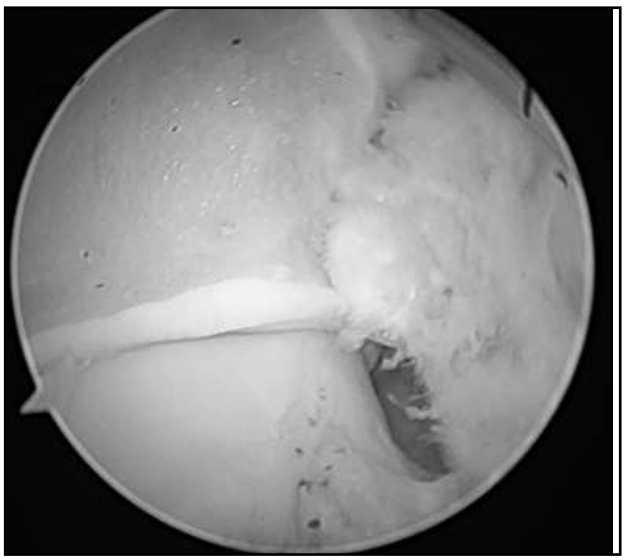

Fig. 10. *Full removal of exostosis (Posterolateral subtalar joint arthroscopic view).*

The lesions could be sessile or pedunculated, and they have the tendency to locate at the metaphysis of long bones, although every part of the skeleton could be affected (21-23). Most of the solitary exostosis are asymptomatic, while pain arises when the bony lesion hits the soft tissue, such as muscle or tendons or impinge with other bones (24, 25). Our patient was atypical, with a single lesion in an uncommon location, with radiological and gross feature of an exostosis. The initial approach was conservative with a course of physical therapy. Since the patient did not improve, it was decided to address it surgically through a posterior ankle arthroscopy. We opted for an arthroscopic technique since it has

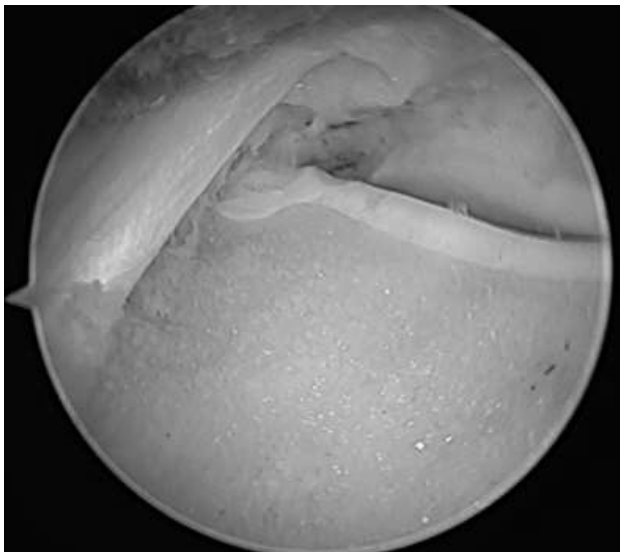

Fig. 11. *Full removal of exostosis (Posteromedial ankle joint arthroscopic view).*

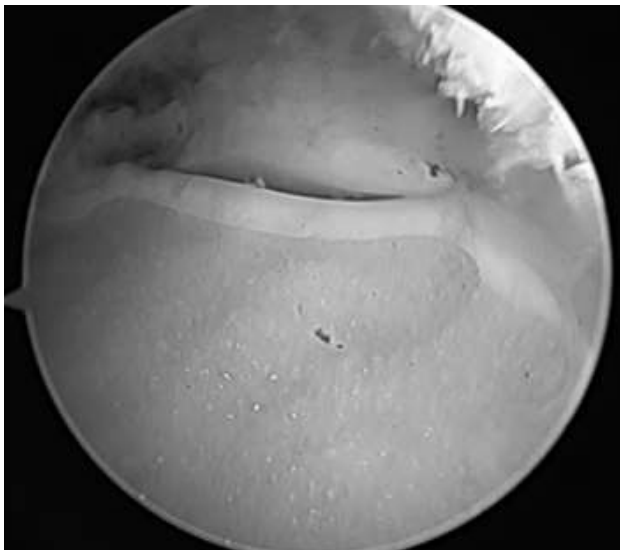

Fig. 12. *Full removal of exostosis (Posterolateral ankle joint arthroscopic view).*

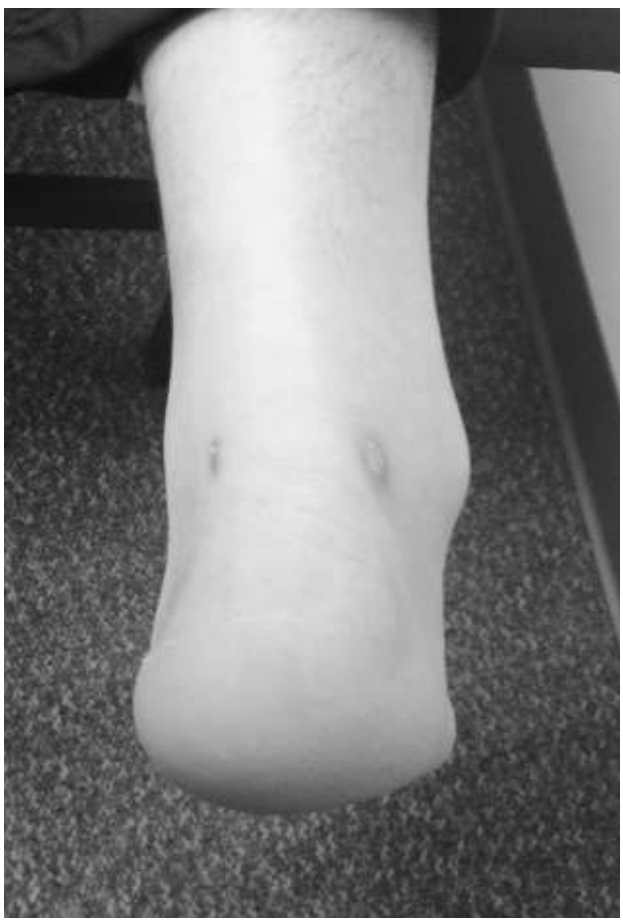

Fig. 13. *Postoperative picture (6 weeks).*

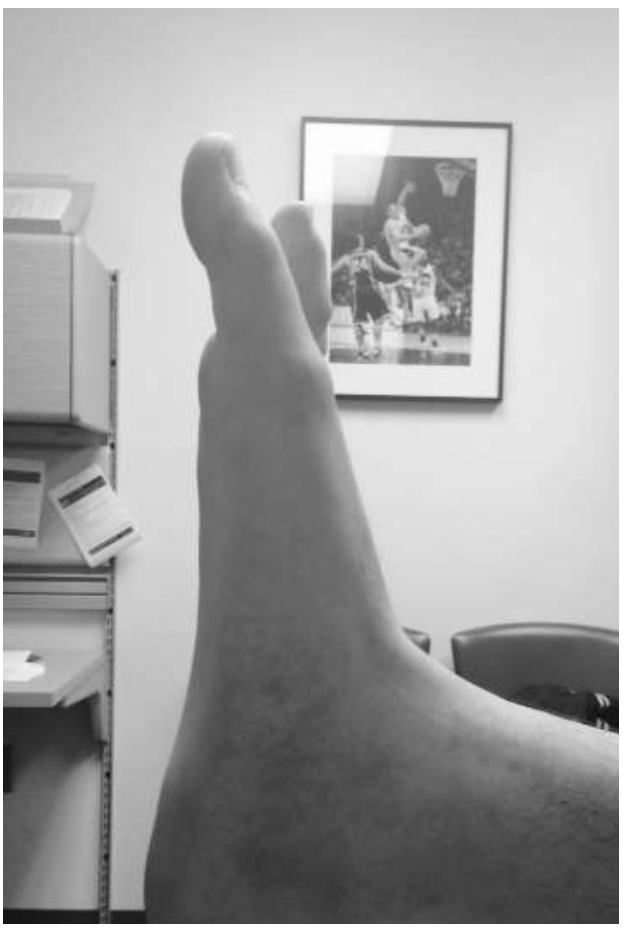

Fig. 14. *Postoperative picture (6 weeks).*

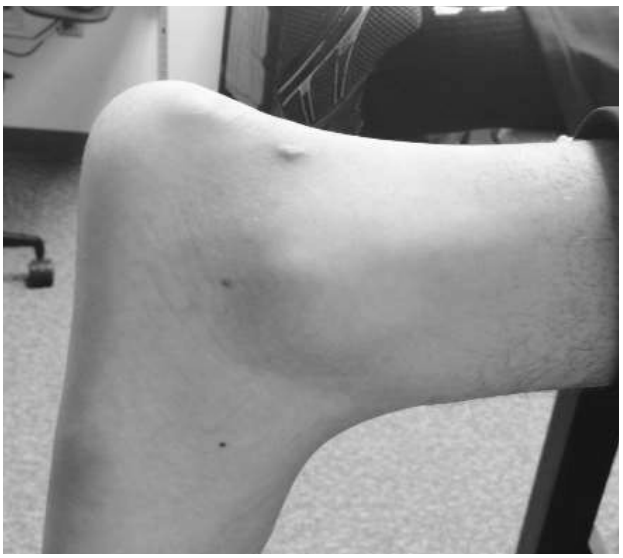

Fig. 15. *Postoperative picture (6 weeks).*

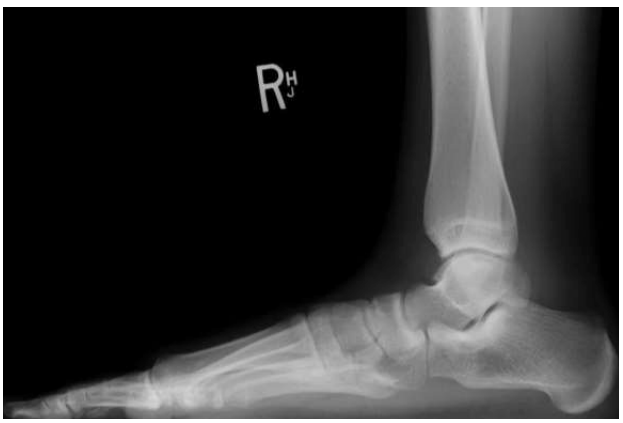

Fig. 16. *Postoperative lateral X-Ray (6 weeks).*

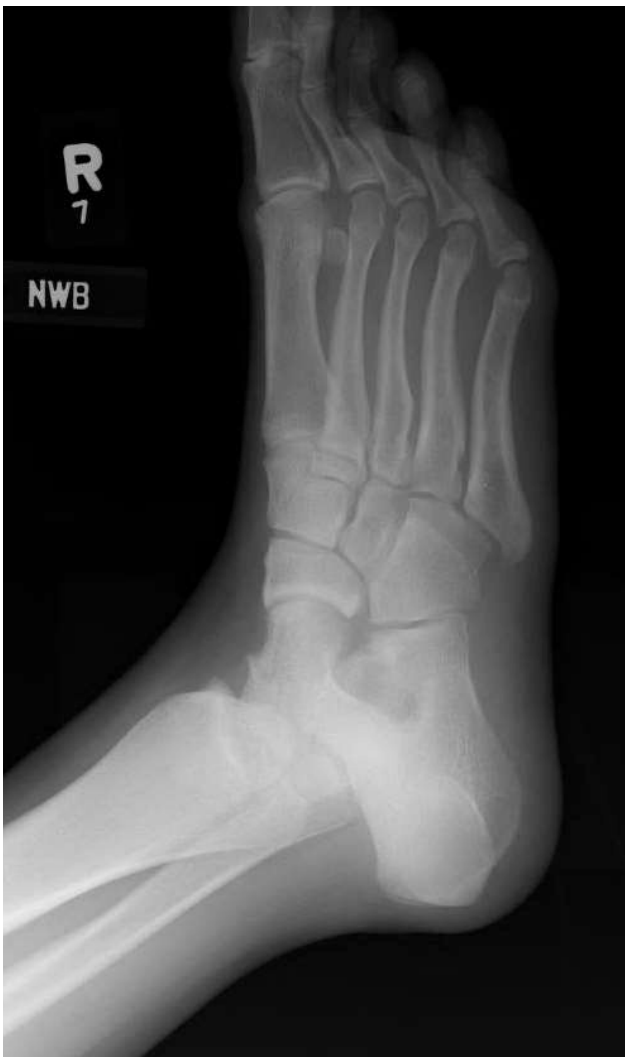

Fig. 17. *Postoperative oblique X-Ray (6 weeks).*

many advantages, i.e. lower infection rate, lower risk of wound dehiscence, less painful scars and nerve entrapment within the scar, minimal blood loss and shorter recovery time (26).

In this case report, the procedure resulted in a noticeable improvement both in pain and range of motion, without complications. Exostosis of the posterior talar dome is a rare condition. This patient presented with significant limitation of motion and bony posterior impingement, Posterior arthroscopic excision of the bony mass is a safe and effective option as presented in this case.

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ACUTE TREATMENT OF MEDIAL COLLATERAL LIGAMENT TEARS: SHORT TO MID-TERM RESULTS

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The aim of this study is to describe the results of a consecutive set of patients treated in acute for the surgical repair of medial collateral ligament (MCL) tears with a mean follow up of 63.78±43.25 months (4-136). This is a retrospective observational study. From January 2011 to December 2016, 56 patients within the average of 31.75±13.27 (13-55) years old at the time of injury underwent medial compartment repair in an acute setting. The sample size of our study is therefore made up of 26 patients. Patients have been evaluated with functional scores: IKDC (international knee documentation committee evaluation form), the KOOS (Knee injury and osteoarthritis outcome score) and clinical assessment. The Tegner Activity Score was evaluated retrospectively at the 12 months follow-up. The mean KOOS value at the final follow-up were 91.25±9.65 (72-100) for pain, 85.68 ± 12.34 (57-100) for the symptoms category, 94.5±8,07 (75-100) for the activity of daily life, 71.87±22.86 (35-100) for the sport category and 76.37±18.55 (38-100) for the quality of life. At the last follow up the mean IKCD value was 77.68±15.95 (55-98). The mean difference in the Tegner Activity Score between the preoperative time and the postoperative time was 1.06±1.12 with a 95% Confidence Interval 0.46-1.66. The functional outcomes underline how the surgical approach to the medial capsule-ligament compartment of the knee is a reliable treatment to restore excellent joint function. Level of evidence III retrospective observational study

The medial collateral ligament (MCL) injuries of the knee are one of the most common traumas of young athletes with an annual incidence between 0.24 and 7.3 x 1000 individuals (1). The most common rupture mechanism is a valgus stress trauma with or without external rotation (2). Usually, MCL injuries are graded based on Hughston's classification according to the medial knee joint space widening valgus stress with the knee in 30 degrees of flexion. Grade I width 5 mm, grade II width between 6 and 10 mm, and grade III more than 10 mm (3) (Table I).

Conservative treatment is universally accepted for grade I or II lesion (4). Grade III lesions are often associated with posteromedial structures tears, particularly the oblique posterior ligament (POL) involvement and are often treated surgically (Fig. 1). An undertreatment could determine a permanent instability and poor outcomes in the patient's daily life. Recently, many protocols have been introduced in the literature about surgical treatment of this kind of lesions and the management of this injury is a still a matter of concern (5-6-7). The debate also concerns when and how to treat MCL injuries. There is in fact paucity of literature about the surgical management

Key words: MCL, knee, instability, rehabilitation

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of these kind of lesions. The aim of this study is to describe the results of a consecutive set of patients treated in acute for the surgical repair of medial collateral ligament (MCL) tears with a mean follow up of 63,78±43,25 months (4-136).

MATERIALS AND METHODS

The present study is a retrospective observational study on a set of consecutive patient. All the patients signed aninformed consent before the surgery procedure. This study was performed according to the principles described in the 1964 Helsinki declaration and its later amendments.

From January 2011 to December 2016, 56 patients underwent medial compartment repair in an acute setting. Patients with PCL lesions, severe meniscal injuries, and chronic lesions were excluded from the study.

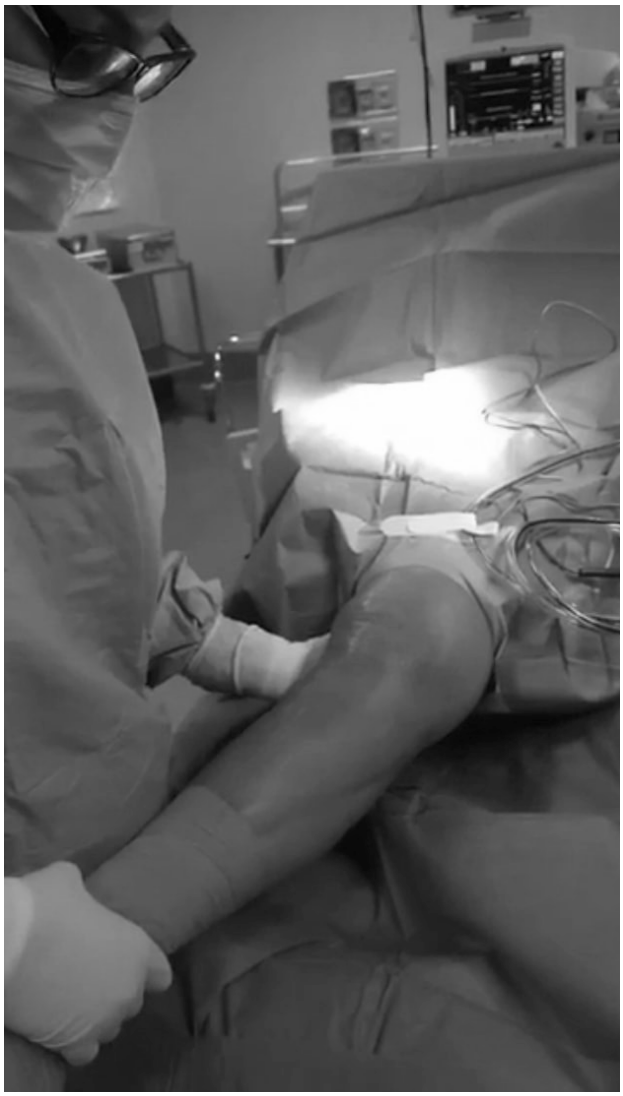

Fig. 1. *Intraoperative Knee Valgus Stress Test performed at 0° of flexion (extended knee).*

Our indications for surgical treatment were distal avulsion of the superificial MCL (SMCL) in "Stener like" lesions and lesions with deep-beam lesions with intra-articular displaced flap and meniscus capsular-lesions (Fig. 2). Surgical treatment was performed according to the type of lesion by a team of 2 senior knee surgeons with standardized technique adapted to the type of lesion. In case of an isolated "Stener like" lesion, the distal re-insertion of the superficial beam was carried out with a 5.5 mm titanium anchor. When possible, the original distal insertion site of SMCL has been restored.

In case of concomitant intra substance or distal pre-insertion injury, SMCL has been re-inserted proximally to the original seat just above pes anserinus, giving a manual tension to the surface beam to ensure excellent stability at 30 grade of knee flexion avoiding medial overconstrain.

In cases of deep MCL (DMCL), a reduction of the intra-articular flap was performed with a resorbable suture of femoro-meniscal ligament, femoro-tibial ligaments and a posteromedial capsule to retention the posteromedial compartment. Graft augmentation technique was never been performed.

Patients have been evaluated with functional scores: IKDC (international knee documentation committee evaluation form) (8), Tegner Activity Score (9), KOOS (Knee injury and osteoarthritis outcome score) (10) and clinical assessment. The Tegner Activity Score was assessed in the preoperative time and at the last follow up for each patient. Clinical assessment includes ROM, valgus stress at 0 and 30 degrees, Lachman test, anterior drawer, dysaesthesia in the territory of the infrapatellar branch of the saphenous nerve.

All patients underwent the same standardized rehabilitation protocol: knee brace at 30 degrees of flexion for fifteen days and subsequently increase of 30 degrees per week to reach complete articular excursion in 6 weeks. For 15 days, it was allowed a partial weight bearing with crutches and progressive weight bearing in the following weeks. As early as the first postoperative day, the patient is allowed to perform isometric strengthening of the quadriceps wearing the brace. The second rehabilitation step provides for static and later dynamic proprioception exercises and muscle strengthening with an open kinetic

chain. Return to sports activity, including pivoting and contact, is allowed at 3 months.

Statistical analysis was performed using the IBM SPSS Statistics for Macintosh (Version 22.0, IBM, Armonk, NY, USA). Variables are reported as mean, standard deviation and range. The difference between the preoperative and postoperative time in the Tegner Activity Score was analized with the paired sample t-test and a $p < 0.05$ was considered statistically significant.

RESULTS

The sample size of our study is therefore made up of 28 patients with an average age of 31.75±13.27 (13-55) years old at the time of injury. Four patients reported an associated ACL lesion, that was replaced in second surgical step (14.28%). Two patients sustained SMCL lesions (7.14%), 7 DMCL lesions (25%), 11 patients posteromedial capsule lesions (39.28%) and finally 6 patients an associated POL lesions (21.42%). The population of this study consists of 2 female (7.1%) and 26 male (92.9%), there was a prevalence of the left side (57.1%) and no bilateral lesions. The mean waiting time before the surgical intervention was 7.68±7.95 days (1-30). The affected side was the dominant lower limb in 62% of patients. The final average follow-up was 63.78±43.25 months (4-136). In 46% of the cases, the trauma mechanism results to be a knee sprain with a rotational component, in the other 54%, a direct valgus injury occurred. The mean preoperative Tegner Activity Score was 6.62±2.3 (3-10).

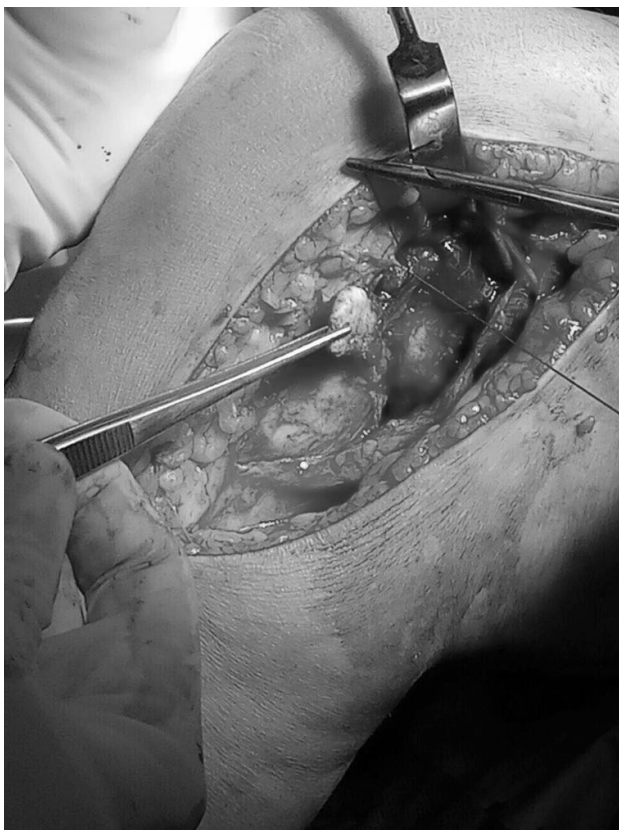

Fig. 2. *Intraoperative view of the superficial beam of MCL.*

The rehabilitation protocol was completed by 24 patients (85.71%). Four patients (14.28) needed a knee mobilization in narcosis or arthroscopic arthrolysis between the 35th and 75th postoperative days. At the final follow-up, 24 patients (85.71%) recovered a complete ROM (0-130°), in 2 patients (7.14%) there remained a deficit of 5 degrees, in another 2 (7.14%) a deficit of 10 degrees. No patient reported valgus subjective instability and no patient had valgus instability at 0 and 30 degrees of knee flexion; 2 patients (7.14%, developed a Pellegrini-Stieda Syndrome. Functional results were good or excellent in almost all patients.

The mean KOOS value at the final follow-up were 91.25±9.65 (72-100) for pain, 85.68±12.34 (57-100) for the symptoms category, 94.5±8.07 (75-100) for the activity of daily life, 71.87±22.86 (35-100) for the sport category and 76.37±18.55 (38-100) for the quality of life. At the last follow up, the mean IKCD value was 77.68±15.95 (55-98). The mean difference in the Tegner Activity Score between the preoperative time and the postoperative time was 1.06±1.12 with a 95% Confidence Interval 0.46-1.66 and a p value of 0.002.

DISCUSSION

The primary goal of surgical treatment is to restore joint stability of the knee; in our study, the cohort does not show instability at valgus stress tests at last follow up. What emerges from the study is that the primary purpose of the intervention is to regain the same activity level prior to the trauma.

According to the study by Hughston and Barret (11), the surgical treatment of isolated third degree

lesions of the MCL allows a return to the same sport activity as before injury in 71% of patients resulting therefore a reliable treatment in order to reach the objectives set.

Opposing opinions are those of Indelicato (12) and Sandberg (13); conservative treatment by immobilization and plastering allows a faster recovery of strength compared to surgical treatment, according to Indelicato, while Sandberg argues that the lesions of the MCL do not derive greater benefit from the surgical solution compared to the conservative one.

Particularly interesting work on the conservative treatment of isolated and complete lesions of the MCL, worthy of a comparison with our study, turns out to be that of Hastings (14), in which at the end of the follow-up, 23/29 patients (79%) are satisfied with the situation of their knee, although 4 of these (14%) present an objective laxity of the medial compartment. According to the literature (15), while isolated MCL injuries are frequently treated non-operatively, the III grade lesions, often associated with posteromedial structures tears, may result in a persistent posteromedial rotatory instability and therefore it needs a surgical management. In literature, there are not many studies comparing reconstruction and repair of medial knee compartment.

In a recent study, Hanley et al presented patients who obtained higher PROs (patient-reported outcomes) than those undergoing reconstruction by using IKDC and Lysholm score at a mean 6-year of follow-up in patients who underwent MCL repair in the setting of multi ligamentous knee injuries (16).

There are in fact several studies that support the benefit of early surgical intervention (17, 18, 19). Moreover, ligaments are amenable to repair only if there is sufficient and robust tissue, which may suggest that the patients had a less severe soft tissue injury, and thus, better results (16).

However, reconstruction offers a greater technical challenge over repair, as the restoration of native anatomic alignment is often not straightforward (15) and the graft type tensioning, attachments and the size in the reconstructive surgery are quite variable depending on the surgeon.

Finally Wijdicks et al demonstrated that both the anatomic SMCL augmented repairs and anatomic SMCL reconstruction in cadaveric knees were able to improve knee stability and provide less than 2 mm of medial joint gapping at 0° and 20° of flexion, without significantly different (20).

In his systematic review, Delong et al. (15) demonstrated that the repair might be an effective and reliable treatment for medial knee ligament injuries, resulting in improved valgus stability and patient-reported functional scores with low rates of secondary failure. Delong focuses on the evaluation of functional results with IKDC and Tegner activity score following the surgical treatment of MCL and posteromedial corner (PMC). Ninety percent of patients achieved a satisfactory IKDC score, while for the Tegner score the results were 4.76 (min 3.9 max 6.0). In Tzurbakis series (21), 12 of 44 patients presented an avulsion of the MCL and PMC were repaired. Total rupture of medial and posteromedial was repaired using sutures or anchors while the mid-substance tears of MCL were primarily sutured using nonabsorbable sutures. The author reported an IKDC grade A and B in 75% of patients while the overall average Tegner activity score decreased significantly at the re-examination compared to the activity score before an accident. Stannard et al (22) reported their experience in 25 patients with MCL tears treated with suture anchors repair of avulsed structures to their origin, with additional repair of the torn capsule as required. At 43 months of follow up, IKDC was grade A and B in 59% of patients; this date was lower than other studies because MCL was associated with tibial plateau fracture in 25% of cases. According to previous literature, that emphasizes the role of POL and posteromedial capsule as secondary stabilizers to rotational and valgus stress, our early repair aims to restore the anatomy of these structures. In fact, isolated repair of MCL may incompletely restore valgus stability and an anteromedial rotatory instability may persist. The clinical examination showed that more than 75% of patients are able to recover, with an adequate rehabilitation program, the complete articulation; in 16% of the remaining patients, there is a limitation between 5° and 10° that represent the last degrees of complete flexion during a squatting. Only 8% of patients have a minute joint range between 10° and 20° of flexion. All patients who did not have a

complete ROM recovery have undergone further surgery for the reconstruction of ACL. According to DeGrace et al. (23), this temporal distribution of the two operations would overall guarantee a good joint recovery with the lowest loss of ROM, reducing the percentage of arthroscopic re-operation for adherence lysis and joint mobilization under anesthesia from 15% to 3%. Primary repair of the MCL is usually performed within seven to ten days after the injury.

The indication for an acute surgical treatment are the presence of intraarticular entrapment of the end of the ligament, a large bony avulsion, a tibial plateau fracture, a complete tibial side avulsion in athletes, or, when anteromedial rotatory instability is present on physical examination. Finally, valgus-aligned knees with complete medial injury, since these knees do not tolerate the valgus laxity well (3).

After 3 months or more acute injury the ligaments have lost their healing potential and the anatomic repair of the traumatized tissue is no longer possible due to the contracture of the ligament ends and the formation of scar tissue. In these cases, the reconstruction of the superficial MCL with quadriceps tendon autograft, hamstring autograft, hamstring allograft, or Achilles allograft is required. (24, 25, 26)

The return to sport and its timing have shown variability. For example there is no consensus about rehabilitation protocols due to the complex anatomy of the medial knee and because MCL injuries are often associated with lesions of other structures. Furthermore, prospective comparative studies are limited about rehabilitation programs (27).

The return to play depends also to grade of injury, the type of sports and the psychological readiness of the player. In fact, sports, such as hockey or skiing may require more time of rehabilitation because place extra stress through the knee as the foot and ankle are locked in a boot. Other sports, such as wrestling, place high rotational forces across the knee during various maneuvers. The return to play is also influenced by how the athlete feels psychologically in the early return period. Very common in fact is the use of brace although there is lack of evidence as to whether or not it in case of isolated MCL injuries (28).

However, Logan et al. (4), in patients who underwent a repair or reconstruction of MCL, propose a 5-step rehabilitation process: for 6 weeks with a knee brace in full extension with the exception of during passive range of motion with physical therapist and no weight bearing; 90% of flexion is achieved in 2 weeks, progressing to full ROM. The return to sport is estimated at around 20 weeks; there is no specific test that evaluates the function of the medial compartment, but there are specific sports tests , for example Vail Sports Test (29) . The conservative approach is also proposed by other studies, such as that of Ballmer and Jakob (30), which identify non-surgical treatment as the best choice to achieve complete ROM. Although Kannus (31), showed that a long-term outcome for grade III injuries treated conservatively are worse than the I- and II-grade lesions, because medial instability persists in a high percentage of cases with muscular weakness and secondary progressive development of ACL instability.

In our experience of acute MCL repair, the rehabilitation protocol is faster. The knee is blocked for 2 weeks at 30 degrees for initial scarring of the tissues in the resting position of the medial joint capsule. The weight bearing was allowed 2 weeks and the complete weight bearing is achieved after 4 weeks. Return to sport is possible at 3 months, after an isokinetic test that highlights less than 20% of strength loss in extension and flexor muscular compartment of the injured leg compared to opposite side.

Approximately 70% of patients complaining of alterations affecting tactile sensitivity: hypoesthesia, dysaesthesia, cutaneous hyperalgesia and associations between these. Surgical examination in the event of incidents in the medial ligamentous capsule compartment of the knee is considered by the classic “hockey stick” incision, although the surgeon pays attention to isolate and preserve the sensitive infrapatellar branches of saphenous nerve, which often suffer lesions that hesitate in the described dysesthesia.

Only two patients claim to be conditioned daily by this type of sensitivity alteration. The remaining patients who presented changes in sensitivity had no repercussions either on daily life or on sporting activity due to this deficit. During the rehabilitation program, a limitation of ROM recovery may occur with joint stiffness. These patients require the joint mobilization

under anesthesia or arthroscopic lysis; in our case series, 4 patients (15%) developed this complication despite an accelerated rehabilitation protocol.

According our study, Owens et al. (32) reports that a repair of an MCL could hesitate in a joint stiffness up to the complete block of the work. They have shown that 27% of patients treated for complex ligaments involving the MCL because of knee dislocations, hesitate in post-operative stiffness requiring subsequent manipulation treatments or arthroscopic interventions for adherent lysis.

Another unpleasant complication that may occur after the surgical and conservative treatment of MCL lesion is the Pellegrini-Stieda syndrome. McArthur et al. (33) claim that it is correlated to a trauma of soft tissue without highlighting a specific cause. In 2 out of 26 patients, Pellegrini-Stieda syndrome occurred in 8% of our case series (all male) and in all cases, there were reductions of ROM of about 20°.

From the literature, there are no complete data regarding the incidence of Pellegrini-Stieda syndrome, but this condition is more common in adult males than in women, children and the elderly patients and its presence is closely linked to a reduction in the articular range of motion, determined by joint stiffness and pain.

The outcomes obtained with functional scores are excellent in almost 40% of patients. Another important parameter obtained by completing the questionnaires is the Tegner Activity Score whose average value is 5.7 while the average reduction in the level of activity (D average loss) is less than a unit and in 54% of cases, there is no difference compared to the pre-injury level. It means that the patient, after completing the rehabilitation process, returned to the same level of activity before the accident.

Our study has some limitations: it is a retrospective study, it does not have a control sample, heterogeneous population for sport activity level, and the long-term follow-up, in patients older than 40 years old, may affect the return to sport results due to the physiological aging of the population that involves a relative deterioration of sport performances.

The comparison between patient activity level before and after injury highlights that the surgical treatment can guarantee the return to the same pre-injury activity levels to a slightly inferior degree in almost all patients. However, the type of treatment, either surgical or conservative, reserved for grade III lesions of the MCL, is still a matter of concern.

Complications of surgical treatment, although rare, could be very disabling and lead to a long and painful postoperative period. Results that are surely more complete will come from a prospective randomized clinical trial comparing surgical and conservative treatment. The functional results underline how the surgical approach to the medial capsule-ligament compartment of the knee is a reliable treatment to restore excellent joint function.

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