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COVID-19 infection and survival in patients with spontaneous intracerebral haemorrhage

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SARS-CoV-2; neurosurgery

Spontaneous intracerebral haemorrhage in patients with COVID-19 infection can negatively affect their clinical outcome. From an overview of the current literature, the most common reported comorbidities were hypertension, diabetes, and cardiovascular disease. A Glasgow Coma Scale (GCS) < 8 at presentation affects clinical outcome in all patients; however, it seems that mortality for intracerebral haemorrhages in patients with COVID-19 infection is higher (consistent in more than half of patients) than patients without infection. Published data support accumulating evidence that patients with COVID-19 infection tend to develop extensive intracerebral haemorrhages that can increase in size more quickly than usual and lead to deadly bleeding.

The current COVID-19 pandemic caused by SARS-CoV-2 has spread worldwide with over 47.000.000 reported cases. Patients typically present with fever, shortness of breath and cough. In addition, some patients with COVID-19 presented neurologic manifestations, such as headache, loss of sense of smell, stroke and seizures, suggesting that SARS-CoV-2 displays neurotropism and enters the central nervous system (1-3). Some of these neurological symptoms, like headache and fatigue, were related to COVID-19 infection, as they are flu-like symptoms. However, more severe neurological symptoms can be related to more severe intracranial diseases like ischemic stroke, spontaneous intracerebral haemorrhage (ICH) or subarachnoid haemorrhage (SAH) due to aneurysms or other arteriovenous malformations.

Keywords: COVID-19; intracerebral haemorrhage; intraparenchymal haemorrhage; overall survival;

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It is reported that when ICH occurs in patients with COVID-19 infection, the diagnosis results are more challenging to reach, especially in patients with ARDS, which require endotracheal intubation and neurological examination is more challenging to do (2, 3). ICH has a mortality rate of almost 50% when associated with intraventricular haemorrhage within the first month and an 80% dependency rate at 6 months from onset (4). ICH itself can negatively affect the clinical outcome of patients with laboratory-confirmed COVID-19 infection, as often they are old and present several comorbidities. Furthermore, severe COVID-19 infection can lead to critical illness as ARDS and multi-organ failure as its primary complications, eventually followed by intravascular coagulopathy (5), that can worsen the initial neurological clinical presentation. Continuous observation and daily clinical practice by physicians and surgeons and scientific published research can improve long-term all patient outcomes (6-36).

From an overview of the current literature, the most common reported onset symptoms in patients with Covid-19 are fever, cough, myalgia, or fatigue (37,38). Neurologic manifestations in patients with COVID-19 are common too (39-41). The occurrence of a broad spectrum of neurologic complications in hospitalized patients with laboratory-confirmed COVID-19 infection supports the possible neuroinvasive potential of SARS-CoV-2 (3). However, a direct link between neurological symptoms and the clinical condition cannot be drawn at the current state of knowledge. Zhou *et al.* (42) confirmed that COVID-19 uses the same receptor for cell entry as other coronaviruses, ACE2.

ACE2 has been demonstrated to be expressed in neurons and endothelial and arterial smooth muscle cells in the brain (43), potentially allowing SARS-CoV-2 to cross the blood-brain barrier and affect the CNS. Published papers (37, 44) on COVID-19 infection postulated that cerebrovascular diseases resulted from a cytokine storm during the infection, as monocytes and tissue cells activated, causing the release of cytokines and the expression of cytokines tissue factors, which led to altered coagulation activity. It is difficult to ascertain that all ICHs reported were directly related to the COVID-19 infection; however,

it is possible that in those patients without any significant risk factors or comorbidity, the cytokine storm, coupled with the sympathetic drive-in attempt to combat the infection, may have had a role in the development of ICH. Platelet count is a simple and readily available biomarker, independently associated with disease severity and risk of mortality in the ICU (45,46). Lippi *et al.* (5) investigated if thrombocytopenia may be associated with severe COVID-19, concluding that low platelet count is associated with increased risk of severe disease and mortality in patients with COVID-19.

As other cases with isolated severe thrombocytopenia in patients with COVID-19 infections were reported (47,48), some patients developed severe immune thrombocytopenia due to COVID-19 infection and subsequently had ICH due to coagulopathy. Some patients with COVID-19 infection underwent extracorporeal membrane oxygenation, which required therapeutic anticoagulation to maintain therapy but predisposed patients to additional bleeding complications (49,50,51). Recent studies (37,52) showed that up to 20% of COVID-19 patients have abnormal coagulation function and that COVID-19 infection could also manifest in significant abnormal coagulation parameters, notably more prolonged PT and aPTT. Another study involving 1099 patients showed that 82.1% of patients had lymphopenia, 36.2% had thrombocytopenia, and 33.7% had leukopenia (53). Due to the high tendency of patients with COVID-19 infections to develop alteration in coagulation, the surgical outcome for ICH of those patients will be poor.

It is common to find that ICHs occurred in intubated patients due to COVID-19 breathing difficulties or ARDS. These patients were difficult to evaluate neurologically and, in these patients, ICHs were often detected with CT scans performed after nonreactive fixed and dilated pupils had been observed. Other clinical symptoms reported were loss of consciousness, headache and hemiparesis and GCS at presentation was higher than 12 only in 21.1% of patients (1). Hypertension and cardiovascular disease, comorbidity associated with a worse health outcome, more complex clinical management and increased health care in patients with COVID-19 infections were

present in 54.4% and 20% of patients, respectively (1). Jain *et al.* (54) also reported in their study that COVID-19 patients who had sizeable ischemic stroke or ICHs on imaging have a 50% mortality. Zhou *et al.* (55) concluded that ICH in admitted COVID-19 patients is one of the most substantial prognostic factors of poor outcome, even more than age and other previously reported comorbidities such as hypertension and obesity.

These data support accumulating evidence that patients with COVID-19 infection tend to develop large ICHs that can increase in size more quickly than usual and lead to deadly bleeding. In addition, patients with COVID-19 infection could develop ICHs that are difficult to treat surgically due to coagulation abnormalities and a high risk of rebleeding. We cannot speculate on ICH incidence in patients with COVID-19 infections; however, ICHs in patients with COVID-19 infection increase the risk of mortality in these patients (56-117). The ICHs and COVID-19 infection pathophysiology is still under investigation and warrants additional studies.

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High-grade glioma and oral microbiome: association or causality? what we know so far

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In recent years, a growing body of evidence supports the role of the oral and gut microbiome in human physiology and biological activity under homeostatic and pathological conditions. However, the relationship between the gut-brain axis and glioma development has been only recently investigated, reporting an association between oral microbiome and grade of glioma and examining the relationship between malignancy-related oral microbial features and the isocitrate dehydrogenase (IDH) mutation in glioma. The microbiome seems to affect brain tumors by altering the development and function of immune cells and producing the metabolites accumulated in the tumor microenvironment in the brain. The immunosuppressive environment in glioma has numerous interrelationships with the oral microbiome, such that the oral microbiome

functions in the initiation, development and treatment of glioma. Investigating the composition of the oral microbiome can provide insights into immunotherapies for glioma. Therefore, further studies are needed to evaluate the relationship between the oral microbiome, brain axis and glioma.

Glioblastoma multiforme (GBM) is the most common primary malignant brain tumor in adults (1). Despite recent advances in diagnosis and treatment of the disease (2-6), the prognosis of patients with GBM remains poor, with a median overall survival and progression-free survival of 22 and 10 months, respectively (2, 7).

In recent years, a growing body of evidence supports the role of the oral and gut microbiome in human physiology and biological activity under homeostatic and pathological conditions

Keywords: brain tumor; oral microbiome; microbiome; oral microbiota; glioma; glioblastoma

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(8-23). Recently, it has been described that the oral microbiome can influence acute central nervous system diseases, such as stroke (24), or neurodegenerative disorders such as Parkinson's disease (25), multiple sclerosis (26), and Alzheimer's disease (27). However, the relationship between the gut-brain axis and glioma development has been only recently investigated (8, 14, 28-36).

Evidence from human studies has indicated that the oral and gut microbiome is closely related to cancers; however, whether the oral microbiome plays a role in glioma malignancy remains unclear (37). Evidence now suggests that some microbes may confer susceptibility to certain cancers and influence response to therapies (38, 39). D'Alessandro *et al.* (14) summarized the effects of neurotransmitters on the proliferation and differentiation of neuronal precursor cells in the adult brain and brain gliomas. They discussed the hypothesis that modulation of neurotransmitters by oral and gut microbiome might impact the development and progress of brain tumors, specifically glioma. The oral and gut microbiome can spread to the brain through cranial nerves or cellular infections or produce specific metabolites to affect the brain by both direct and indirect means (40, 41).

The gut-brain axis is the bidirectional conversation link among the gastrointestinal and central nervous systems (42). In this complex gut-brain axis, a growing understanding of the oral microbiome's role reveals the extent to which the gut influences the brain (43).

Wen *et al.* (44) reported the first study examining the role of the oral microbiome in glioma malignancy. First, they investigated the association between oral microbiome and grade of glioma. They examined the relationship between malignancy-related oral microbial features and the isocitrate dehydrogenase (IDH) mutation in glioma, reporting that the shift in oral microbiome β -diversity was associated with high-grade glioma (HGG) (44). We *et al.* (44) identified five oral microbial features (*Porphyromonas*, *Haemophilus*, *Leptotrichia*, *TM7x*, and *Capnocytophaga*) that accurately discriminated patients with HGG from those with low-grade glioma (LGG). They reported that the abundance of *Patescibacteria* decreased significantly with

increasing glioma malignancy from LGG to HGG, compared with healthy controls (44); otherwise, the genera *Capnocytophaga* and *Leptotrichia* were inversely associated with glioma grade. Moreover, the abundance of the phylum *Firmicutes* was significantly negatively correlated with IDH-mutant samples, whereas the genera *Bergeyella* and *Capnocytophaga* were significantly positively correlated with IDH-mutant samples (44).

Similarly, Patrizz *et al.* (8) reported that mice and glioma patients demonstrated significant differences in β -diversity and Firmicutes/Bacteroides (F/B) ratio and an increase of *Verrucomicrobia* phylum and *Akkermansia* genus compared to healthy controls, demonstrating a significant glioma-induced change in the F/B in young mice following glioma development (8).

Patrizz *et al.* (8) showed that *Verrucomicrobia* phylum and *Akkermansia* genus abundance increased after glioma growth in a mouse tumour model, which was not observed in the TMZ treatment setting. Furthermore, glioma development was associated with a significant decrease in *Firmicutes* and an increase in the *Verrucomicrobia* phylum, of which the predominant genus is *Akkermansia* (45). Similarly, it seems that the intake of *Bifidobacterium* in mice decreases tumor growth by influencing the immune environment of glioma, involving dendritic cells maturation, CD8 +T cell stimulation and immune cells recruitment (46).

The IDH1-mutant plays an essential role in glioma cell glucose induction, glutamine metabolism, lipid synthesis, and cell redox regulation (47,48). Recent studies have found that lipid metabolism reprogramming plays a crucial role in the progression of cancer cells, such as in membrane synthesis, energetic production, and signal transduction (49). In addition, the oral microbiome influences the cellular level of α -KG by glutamate and altered α -KG level affects DNA methylation (43). A mutation in the genes for IDH has been identified as an essential biomarker for gliomas. The microbiome affects brain tumors by altering the development and function of immune cells and producing the metabolites accumulated in the tumor microenvironment in the brain (50). In a syngeneic glioma mouse model, ABX was reported

that affect tumor growth by changing both the oral microbiome and immune microenvironment of glioma (28).

Although further animal and cell experiments are needed to determine the causality of IDH1 mutation on the oral microbiome under glioma status, Wen *et al.* (44) showed that the abundance of *Firmicutes* was significantly lower in the IDH-mutant samples compared with that of the IDH-wild-type samples at the phylum level. In addition, the genus-level profiling showed that the abundance of *Bergeyella* and *Capnocytophaga* was significantly positively correlated with the IDH-mutant samples (44).

Inflammation and immune suppression along with the microbiome can lead to the induction and sustaining of brain tumors (51). Mehrian-Shai *et al.* (51) proposed that specific gut microbiota in concert with the host's background may affect the body's immune system and metabolism through an interaction model leading to cancer. These interactions, in turn, may result in altered and specifically suppressed immune function, allowing some cells to escape immune surveillance (51). This scenario may encounter fertile ground in potential tumor cells because of somatic mutation accumulation in their genomes and may lead to the establishment and/or development of brain cancer and other tumors in a multistep process (51). Physicians' and surgeons' continuous observation and daily clinical practice, and continuous scientific research can improve long-term patient outcomes and provide further insights and discoveries (52-66). Further investigation on the mechanisms involved in the bidirectional gut-brain communication is required to identify new molecular and cellular targets involved in the dysregulation of brain homeostasis occurring in glioma.

Understanding the interactions between glioma and the oral microbiome is vital as a particular microbiome composition may enhance the effects of existing therapies (chemotherapies, targeted therapies, immunotherapies), which have not yet been effective in glioma (8, 67-129). The immunosuppressive environment in glioma has numerous interrelationships with the oral microbiome, such that the oral microbiome functions in the initiation, development and

treatment of glioma. Investigating the composition of the oral microbiome can provide insights into immunotherapies for glioma. Therefore, further studies are needed to evaluate the relationship between the oral microbiome, brain axis, and glioma.

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Oro-facial pain in Chiari type 1 malformation

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The symptom of facial pain is one of the most common reasons for referral to a dental centre or an oral maxillofacial treatment centre. Orofacial pain is a common symptom with many causes. However, oro-facial pain is rarely the only symptom of Chiari type 1 malformation (CM1), a disease characterized by an anatomical defect at the base of the skull where the cerebellum and the spinal cord herniate through the foramen magnum into the cervical spinal canal. Approximately 20% of patients with CM1 may also experience facial hypesthesia, trigeminal or glossopharyngeal neuralgia, paralysis of the vocal cords, soft palate weakness. In the literature, proposed mechanisms to explain the trigeminal neuralgia and CM1 correlation are vascular compression at the nerve root entry zone, which could be affected by hydrocephalus or anatomic factors related to the CM1, demyelination, micro-ischemic changes and direct brainstem compression. However, further investigation on the mechanisms involved in orofacial pain in patients with CM1 is needed.

The symptom of facial pain is one of the most common reasons for referral to a dental centre or an oral maxillofacial treatment centre (1). Orofacial pain is a common symptom with many causes. Dental and facial pain bring great discomfort and damage the quality of life.

Symptomatic apical periodontitis is identified as the most frequent cause that triggers dental pain and usually arises from an infection or inflammation in the pulpless root canal structure (2-10). Diagnosis of orofacial pain can be difficult and require multiple examinations and histories provided by the patient

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(11-16). Most common acute painful craniofacial conditions are easily recognized and well managed, but others, especially chronic, represent a clinical challenge. The trigeminal nerve is the part of the nervous system responsible for sending sensations of pain, touch and temperature from the face to the brain. The increased understanding gained of the physiological and pathological processing of nociception in the trigeminal system has provided new perspectives for the mechanistic understanding of acute craniofacial pain conditions and the peripheral and central adaptations related to pain chronification (17-21). In addition, an oro-facial pain may rarely be the presenting or only symptom of Chiari 1 malformation (CM1), which is a disease characterized by an anatomical defect at the base of the skull where the cerebellum and the spinal cord herniate through the foramen magnum into the cervical spinal canal (22-25).

Some people with CM1 live their entire lives experiencing mild symptoms or none, whereas other people with CM1 have severe disabilities. People who experience symptoms tend to present in adolescence or early adulthood with headaches, neck pain, and sometimes cerebellar symptoms (26-28). The condition may be complicated by the development of hydrocephalus or syringomyelia (26). The most frequent clinical findings observed in CM1 patients are suboccipital headache, weakness in the extremities, facial numbness, loss of temperature sensation, ataxia, diplopia, dysarthria, dysphagia, vomiting, vertigo, nystagmus and tinnitus (29). In addition, approximately 20% of patients with CM1 may experience symptoms such as facial hypesthesia, trigeminal or glossopharyngeal neuralgia, paralysis of the vocal cords, soft palate weakness (22, 29-34). Urbizu *et al.* (35) analyzed the oropharynx and oral cavity morphological features in 76 patients with CM1 and identified significant anatomical differences for several oropharynges and oral cavity measures, primarily involving the length and thickness of the soft palate.

Atypical facial pain, often diagnosed as trigeminal neuralgia, can occur in patients with CM1, often associated with severe headaches that often worsen with coughing or sneezing. Trigeminal neuralgia

(TN) is characterized by recurrent episodes of sudden, intense, usually unilateral, lancinating pain confined to the distribution of one or more branches of the trigeminal nerve (36, 37). It seems that pain along the course of the trigeminal nerve may be associated with changes in intracranial pressure and may affect the trigeminal tract that runs dorsolateral to the spinal cord (22, 38-40), consequently mimicking the signs and symptoms of the temporomandibular joint disorder (TMJ) (22), that leads the patient refers to the dentists or maxillofacial surgeons. In addition, the various clinical problems that affect the masticatory muscles and the TMJ may be concomitantly associated with a primary disease or disorder (41-43).

CM1 should widen the spectrum of orofacial pain and facial hypesthesia for all these reasons and should be included in the differential diagnosis among craniofacial pain disorders. TN is usually associated with vascular compression of the trigeminal nerve, but some cases are associated with central lesions such as tumors, aneurysms, arteriovenous malformations and sometimes also with CM1 (44). Recently, several papers that relate CM1 with TN have been published (1, 36, 44, 45). Understanding possible mechanisms that lead to this kind of pain could help clinicians and oral and maxillofacial surgeons understand this uncommon condition and help diagnose patients with similar physical characteristics by referring them to a neurosurgeon (22). Papanastassiou *et al.* (44) proposed 4 possible mechanisms to explain the TN and CM1 correlation: vascular compression at the nerve root entry zone, which could be affected by hydrocephalus or anatomic factors related to the CM1, demyelination, micro-ischemic changes and direct brainstem compression.

González-Bonnet & Piquer (46) bring the pathophysiology of TN in CM1 back to the anatomy of the trigeminal nerve and trigeminal nucleus, that descending, form the spinal tract of the trigeminal nucleus, which parallels the spinal trigeminal nucleus until the C2 level. These pain and temperature fibres are poorly myelinated or unmyelinated, they are very vulnerable because of their low myelin and dorsal localization (46).

Several authors (1, 39, 44, 40, 47) reported that CM1 could cause progressive headache, trigeminal

dysesthesia and oral pain, with a resolution of all the symptoms after decompression of the foramen magnum. Peñarrocha *et al.* (48) reported the case of a patient with orofacial pain and CM1 who underwent dental treatment, but he did not report clinical improvement; a subsequent neurosurgical treatment resulted in improved orofacial symptoms. Similarly, Uldry *et al.* (49) reported a patient presented with TN and peripheral facial paralysis caused by CM1 with hydrocephalus, who underwent ventriculoperitoneal shunt with complete and rapid regression of the symptoms. Therefore, continuous observation with daily clinical practice by physicians and surgeons, continuous scientific research and further discoveries and the use of 3-dimensional virtual reality can improve long-term patient outcomes and provide relief with the resolution of pain (50-72). On this basis, patients with oro-facial pain at times may be underdiagnosed, underscoring the importance of awareness of this malformation on the part of clinicians, general dentists, oral and maxillofacial surgeons. Thus, it is important for clinicians who examine patients with painful symptoms in the orofacial region to consider any comorbidity (22). Further investigation on the mechanisms involved in orofacial pain in patients with CM1 is needed.

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Periodontal inflammation and the role of C-reactive protein

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Periodontitis is a chronic and infectious inflammatory disease that leads to the destruction of the supporting structures of the teeth and includes local inflammation (1-6). Periodontal disease can induce a systemic inflammatory response associated with increased C-reactive protein (CRP) levels (7-12). Periodontitis is a multifactorial disease that occurs in bacteria, and genetic and environmental factors influence it. Proinflammatory cytokines are involved in the host immune response to periodontal pathogens through association with the inflammation phenomenon (13-20). Increased CRP levels are associated with various

diseases such as cardiovascular diseases, periodontal diseases, spine and other inflammatory diseases and can be an effective biomarker for predicting future risks of periodontal diseases (21-45).

Even in healthy subjects, higher levels of serum CRP are associated with a greater risk of atherosclerosis and cardiovascular complications. CRP is one of the nonspecific mediators produced in various inflammatory situations. Its concentration increases rapidly following inflammation (1-3). It is calculated that about 10% of the adult population and about 30% of people over 50 suffer from severe

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periodontitis (1, 4, 6). As CRP is considered a major biomarker of systemic inflammation, its positive association with periodontal disease has been explored by several epidemiological, clinical and microbiological analyses (9, 10, 46, 47).

Sargolzai et al. (48) conducted a case-control study to investigate the relationship between the acute-phase reaction molecule and periodontal status, showing higher plasma concentration of CRP in the periodontal status compared with periodontally healthy subjects (control group) ($p = 0.008$). As the infective nature of periodontal diseases can affect the amount of plasma CRP, the severity of periodontitis has been positively associated with levels of CRP ≥ 0.3 mg/dL (48).

Similarly, Jayaprakash et al. (15) compared three groups (individuals with periodontitis, gingivitis and healthy group). They proved that the periodontitis group was associated with a higher mean CRP level (2.49 ± 0.47 ng/mL) than the other 2 groups (1.40 ± 0.32 ng/mL and 0.56 ± 0.20 ng/mL, respectively). In addition, an interestingly significant discrepancy in CRP was observed between the gingivitis subjects and the healthy group (15).

A recent review (49) reported that chronic and aggressive periodontitis diagnoses were consistently associated with higher levels of CRP and high-sensitivity-CRP ($p < 0.001$). Patients with aggressive periodontitis exhibited an average of more than 50% higher levels of CRP ($p = 0.0039$) than patients with chronic periodontitis. Intensive non-intensive non-surgical periodontal treatment induced an immediate increase of high-sensitivity-CRP followed by a progressive decrease, whilst non-intensive non-surgical periodontal treatment consistently decreased high-sensitivity-CRP after treatment up to 180 days ($p < 0.001$). Therefore, continuous observation with daily clinical practice by physicians and surgeons, continuous scientific research, and further discoveries can improve the long-term outcome of patients with periodontitis and other similar diseases and give them the correct clinical value for the CRP marker (50-77). Rahmati et al. (78) linked periodontal disease to systemic inflammation by showing a positive correlation between levels of CRP and immunoglobulin G of *Porphyromonas gingivalis* (*P. gingivalis*), a major bacterium colonized in the subgingival environment (79, 80).

Furthermore, limited reports suggested that control of local periodontal infection was associated with a decrease in levels of serum inflammatory markers (78). Noack et al. (18) found out that the extent of increase in CRP levels in periodontitis patients depends on the severity of the disease. They conducted a study on 174 subjects, reporting statistically significant increases in CRP levels in subjects with periodontal disease when compared to healthy controls (18). Rapone et al. (81) demonstrated significant reductions in CRP in patients who received non-surgical periodontal treatment compared with control group individuals (81). These findings provide robust evidence that periodontitis is associated with systemic inflammation as measured by serum CRP levels.

The extent of increase in CRP levels in periodontitis patients depends on the severity of the disease after adjusting for age, smoking, body mass index, triglycerides and cholesterol (18, 82-132). Investigations emphasized the role of moderate elevated CRP plasma levels as a risk factor for cardiovascular disease. Therefore, the positive correlation between CRP and periodontal disease might be a possible underlying pathway in the association between periodontal disease and the observed higher risk for cardiovascular disease in these patients. However, further studies are needed to confirm this correct association.

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Periodontal inflammation in patients with chronic kidney disease

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Periodontitis is a common occurrence in maintenance hemodialysis patients, characterized by susceptibility and a high degree of comorbidity. A significant proportion of hemodialysis patients suffer chronic inflammation due to their increased susceptibility to diseases, and many inflammatory reactions may originate from other sites, including graft or fistula infections, not biocompatible dialysis membrane, dialysate, endotoxin exposure, back filtration. Individuals with periodontitis display an increased production of CRP (1-3,15,50,54). The findings that periodontal inflammation intensifies the

release of positive immunoregulatory cytokines have critical repercussions for systemic health. Although the role of periodontal infection in promoting systemic inflammation is widely considered, the underlying pathophysiological mechanisms behind the relationship between periodontitis and hemodialysis condition is only partially understood, which requires further studies

Periodontal disease, a chronic and infectious inflammatory disease that leads to the destruction of the supporting structures of the teeth and includes local inflammation, can induce a systemic inflammatory

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response, which is associated with increased C-reactive protein (CRP) level (1, 2).

Chronic kidney disease (CKD), defined by abnormalities in kidney structure or function, characterized by permanent nephron loss and an eventual decline in the glomerular filtration rate, can be classified into glomerular, vascular, renal tubulointerstitial, cystic and other congenital diseases (3). Over the last 10 years, CKD's prevalence and incidence have constantly increased (4-7). Many hemodialysis patients suffer chronic inflammation due to their increased susceptibility to diseases, and many inflammatory reactions may originate from other sites, including graft or fistula infections, not biocompatible dialysis membrane, dialysate, endotoxin exposure, back filtration (8). Furthermore, in hemodialysis patients, CRP is a strong predictor of adverse cardiac events, as inflammation is implicated in the pathogenesis of cardiovascular diseases (CVD), the leading cause of morbidity and mortality in individuals undergoing hemodialysis (9-10).

Periodontitis is a common occurrence in maintenance hemodialysis patients, characterized by susceptibility and a high degree of comorbidity. Epidemiologically, periodontitis, CVDs, CKD have been moderately linked with elevated serum CRP levels (e.g., >2.1 mg/L) (11). The immune pathogenesis of periodontitis might explain the positive correlation with the inflammatory status of patients undergoing hemodialysis, and the CRP might be the identifier marker of this association. Epidemiologically periodontitis, CVDs, CKD have been moderately linked with elevated serum CRP levels. (e.g., >2.1 mg/L) (11-24). Since periodontitis is associated with CVDs, CKD, diabetes and other systemic diseases, there is an increasing interest in studying the relationship between periodontitis and CRP (1,25-34).

As continuous observation of physicians' daily clinical practice and scientific and laboratory research could provide further discoveries (35-47), fluctuations in CRP circulating levels in hemodialysis patients have deleterious effects and represent an active factor in the pro-atherosclerotic phenomenon. It has been reported that increased odds of cardiovascular diseases among subjects undergoing hemodialysis by 1.73 times

in serum CRP levels ≥ 0.6 mg/dL. Hemodialysis condition has multiple exposures to traditional risk factors (age, diabetes, hypertension and obesity) that may be involved in the pathogenesis of CVD in hemodialysis patients (48-56). It has been proposed that during chronic renal failure, the gradual decline of kidney function might be responsible for CRP increase because of the promotion of the synthesis of oxidative stress mediators. In humans, there is evidence that periodontitis promotes systemic levels of proinflammatory cytokines network, including IL-1, IL-6, and TNF- α (14,50,51,54).

Individuals with periodontitis display an increased production of CRP (1-3,15,50,54). The findings that periodontal inflammation intensifies the release of positive immunoregulatory cytokines have critical repercussions for systemic health (4-6,16). Thus, periodontitis may trigger or contribute to the onset of several disorders with an inflammatory genesis (50,57-79). The detrimental effect of this oral pathology on general health has been demonstrated in individuals undergoing hemodialysis.

Elevation in CRP values in hemodialysis patients might be multifactorial and associated with previous or concomitant periodontal inflammation. The relationship between periodontitis and CRP level in hemodialysis patients might be explained by applying the conceptual model developed by Fisher et al. (80), which combines clinical evidence by identifying a causal inflammatory pathway from clinical outcome parameters and pointing out the relationship between PD with CVD and CKD who are on maintenance hemodialysis treatment.

Given that periodontitis may be reflected in CRP serum concentration, many studies observed this biomarker to infer the relationship between periodontitis and inflammatory status in subjects in maintenance hemodialysis. In addition, researchers have reported an increased risk of CVD with exposure to non-traditional risk factors, including periodontitis (50,51,54,81-141). Although the role of periodontal infection in promoting systemic inflammation is widely considered, the underlying pathophysiological mechanisms behind the relationship between periodontitis and hemodialysis condition is only partially understood, which requires further studies.

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The C-reactive protein level in hemodialysis patients as a predictor factor for cardiovascular disease

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Recent studies showed that plasma ROS levels were significantly increased in hemodialysis (HD) patients compared with healthy controls, a condition explained by the prominent dysfunction of the mitochondrial respiratory system in chronic kidney disease (CKD) and HD patients. Chronic inflammation in CKD patients may be detected by high pro-inflammatory cytokines, such as interleukin-6 (IL-6) and C-reactive protein (CRP). Several studies have shown that plasma IL-6 and CRP levels are strong predictors of cardiovascular mortality in dialysis patients (19). Even poor oral, dental and periodontal health in HD patients can be a source of inflammatory reactions (32-40). Periodontitis and the presence of *p. gingivalis* are

associated with an enhanced inflammatory response expressed by higher CRP levels in HD patients.

Several studies reported that in HD patients, low-grade inflammation decreases the efficiency of cardiovascular therapeutic interventions and participates in the persistence of cardiovascular hemodynamic overload; however, further studies are needed to better understand the pathophysiological mechanisms underlying the relationship between CRP, HD and cardiovascular disease.

Cardiovascular disease (CVD) is the major cause of morbidity and mortality in patients with end-stage renal disease on hemodialysis (HD). CVD is present in >50% of patients undergoing dialysis, and the relative risk of death due to CVD events in

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HD patients is reported to be 20 times higher than in the general population (1-4). HD patients have disease-related risk factors such as oxidative stress, malnutrition and chronic inflammation (1,5-18). Oxidative stress is an imbalance in reactive oxygen species (ROS) production. Recent studies showed that plasma ROS levels were significantly increased in HD patients compared with healthy controls, a condition explained by the prominent dysfunction of the mitochondrial respiratory system in chronic kidney disease (CKD) and HD patients (19). Chen et al. (20) showed that severe periodontitis is associated with poor nutritional status, such as lower albumin, BUN, Cr and transferrin levels (20-25). Malnutrition and inflammation complex syndrome (MICS) are strong predictors of the degree of sickness and morbidity and mortality in HD patients (26-31).

Chronic inflammation in CKD patients may be detected by high pro-inflammatory cytokines, such as interleukin-6 (IL-6) and C-reactive protein (CRP). Several studies have shown that plasma IL-6 and CRP levels are strong predictors of cardiovascular mortality in dialysis patients (19). Even poor oral, dental and periodontal health in HD patients can be a source of inflammatory reactions (32-40). Periodontitis and the presence of *p. gingivalis* are associated with an enhanced inflammatory response expressed by higher CRP levels in HD patients (4). Even in healthy subjects, higher levels of serum CRP are associated with a greater risk of atherosclerosis and cardiovascular complications (41-44). Serum CRP concentration does not change with the changes in kidney function but in the early stage of kidney disease, and it may be related to serum albumin levels which are affected by an inflammatory response. Thus, high sensitivity-CRP has a greater predictive ability for primary prevention of cardiovascular risk. The association between inflammatory markers and cardiovascular events, coronary artery disease and its complications occur with high frequency in patients with CKD and substantially it is contributing to cardiovascular morbidity and mortality in this population (4). Among the risk factors that may provide a rationale for the prevalence of vascular disease in HD patients, inflammation has been recognized as a key element in promoting vascular injury (45-51).

Available data reveal that the pro-inflammatory cytokines play a key role in the genesis of cardiovascular diseases in HD, as reported by Iseki et al. (52). Their study underlined a significantly increased mortality risk for HD patients with CRP levels ≥ 10 mg/L over a follow-up of 5 years. Furthermore, they concluded that CRP is a significant predictor of death in chronic dialysis patients, independent of serum albumin and other possible confounders (53-55).

Similarly, Liu et al. (56) concluded that in a population with a low normal range of serum CRP levels, chronic periodontitis is associated with increased CRP levels and decreased HDL cholesterol concentrations, which suggests some relationship between periodontal inflammation and CVD (56). Therefore, dialysis patients with high CRP levels should be carefully evaluated and monitored regardless of serum albumin concentrations in the normal range (52). Furthermore, the increased risk of periodontitis associated with maintenance hemodialysis is recognized and indisputable. Therefore, physicians' continuous observation with daily clinical practice and scientific research could provide further discoveries and improve long-term patient outcomes in all medical and surgical specialities (57-71). Hence, it was proposed that CRP might be used as a surrogate marker for periodontal inflammation. Additionally, the higher incidence of periodontitis in the follow-up period in hemodialysis patients supports the theory that the chronic inflammatory status may be affected by periodontitis and may explain the epidemiological evidence concerning an increased risk of periodontal inflammation in subjects undergoing hemodialysis (72-81). In addition, serum CRP levels predict cardiovascular disease and mortality in hemodialysis patients and predict the development of vascular access thrombosis in chronic hemodialysis patients (82-89).

Several studies reported that in HD patients, the presence of low-grade inflammation decreases the efficiency of cardiovascular therapeutic interventions and participates in the persistence of cardiovascular hemodynamic overload (86-134) however, further studies are needed to better understand the pathophysiological mechanisms underlying the relationship between CRP, HD and CVD.

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Neurosurgical and craniofacial surgery during the Covid-19 pandemic

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The pandemic of coronavirus disease (COVID-19) resulted in an unprecedented global public health crisis and impacted all spheres of life, including all economic activity, travel, governance, education, surgery and, of course, healthcare. Neurosurgery, dentistry, and maxillofacial surgery are also not spared. Surgeons operating near the aerodigestive tract are at particularly high risk of being infected, and consequently, they shifted their practices toward more protective personal protective equipment. In the present digital era, surgeons use more and more web, teleconsulting, and virtual reality to effectively communicate with patients and their relatives on treatment strategies and appointments for surgical works. The COVID-19 situation also provides a novel opportunity to learn, update our knowledge, and update ourselves such that we continue to save lives. In conclusion, it seems appropriate to request that every healthcare institution receives well-researched and documented protocols for dealing with future inevitable global pandemics.

The pandemic of coronavirus disease (COVID-19) resulted in an unprecedented global public health crisis and impacted all spheres of life, including all economic activity, travel, governance, education, surgery and, of course, healthcare. Neurosurgery, dentistry and maxillofacial surgery are also not spared

(1-5). Owing to the well-known major risk factors and the onset of neurological deficit, craniofacial and oral cancer can be detected in the early stage, also due to easy access to neuroimaging (2, 6-13).

The COVID-19 pandemic has upset health care organizations, requiring a deep reorganization in

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many respects and adequate management protocols to reduce hospital viral spread, improving safety for both patients and health care professionals (1-3, 14). COVID-19 has disrupted the normal delivery of healthcare for neurosurgeons and maxillofacial surgeons across the world, who are trying to improve the optimization and treatment of their pathologies during the ongoing global pandemic. Oral and oropharyngeal cancer represents a major public health concern worldwide, accounting for 447,571 new cases and 228,389 deaths in 2015 (14).

The COVID-19 pandemic has raised concerns about healthcare worker exposure risk. Although infrequent, severe respiratory infection and death caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are disproportionately high among healthcare providers such as craniofacial surgeons who work in the head and neck region. Surgeons operating near the aerodigestive tract are at particularly high risk of being infected, and consequently, they shifted their practices toward more protective personal protective equipment (5,8,15-23). Factors that impact SARS-CoV-2 transmission include high viral loads in the mucosa of the oral and nasopharynx, limited and/or imprecise disease screening/confirmation testing, and access to and appropriate use of personal protective equipment (24).

Recent recommendations for surgeons engaging in cranial and maxillofacial procedures have been proposed, for example, to limit cranial and maxillofacial procedures to urgent and emergent cases or to treat craniofacial patients, requiring surgery who cannot undergo COVID-19 testing as they are infected (3-5, 25-27). When managing patients undergoing surgery, some principles must be followed. Prior to admission to the hospital, screening for SARS-CoV-2 infection should be performed, by a nurse-directed triage, to exclude respiratory symptoms or recent contact with affected people. The morning before surgery, each patient should undergo an RT-PCR test on nasopharyngeal swabs. Then, the patient should be immediately hospitalized to avoid the infection with SARS-CoV-2 after having undergone the test (28)

In the present digital era, surgeons use more and more web, teleconsulting and virtual reality

to effectively communicate with patients and their relatives on treatment strategies and appointments for surgical works (25, 26, 29-39). Neurosurgery and maxillofacial surgery represent an example of a speciality that has had to adapt to this outbreak because of the subspecialties of oncology and traumatology (27, 36, 37, 40-48). Maxillofacial surgeons, dentists and neurosurgeons, as well as others who perform procedures in the head and neck region, are at high risk of being exposed to and infected by COVID-19 (25, 36, 49-55). These specialties provide such specific treatment options for patients that it is almost impossible to transfer these activities to other specialties for management. This necessitates the management of head and neck patients presenting for treatment and the development of new protocols to ensure provider, personnel and patient safety from the virus during that treatment (56).

Protecting healthcare workers from high-risk infection hazards is vital to ensure their safety while delivering care and avoid a healthcare system collapse (56). As the number of COVID-19 cases continues to rise throughout the world, there is a growing concern that health care systems may reach surge capacity and be unable to care for patients with moderate to severe symptomatology, particularly patients requiring mechanical ventilation. By delaying elective procedures, spine surgeons can help preserve several hospital resources, including health care providers who would otherwise be in the operating room, inpatient beds, intensive care unit, ventilators, blood bank reserves and personal protective equipment that would normally be consumed during surgery (31, 49, 57-73). The most daunting pandemic the world has faced in over a century presents the opportunity to harness the field's multidisciplinary training and step into crucial frontline roles (15, 18,19, 49, 74-131). The COVID-19 situation also provides a novel opportunity to learn, update our knowledge, and update ourselves such that we continue to save lives.

In conclusion, it seems appropriate to request that every healthcare institution receives well-researched and documented protocols for dealing with future inevitable global pandemics. These should be developed and vetted by both local and coordinated international healthcare-based organizations (56).

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Surgical multidisciplinary for precision medicine: the challenge for the future

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Multidisciplinary care has been shown to improve patient outcomes, and interprofessional collaboration has been shown to improve one’s medical knowledge. Multidisciplinary interventions in the field of surgery are designed to address a specific problem occurring in a particular patient population and/or within the context of an individual hospital system. The importance of multidisciplinary and interdisciplinarity at all levels, including clinical oncology, craniofacial trauma, and brain abscess caused by dental peri-implantitis, is well established. The challenge for future research is to further develop and validate medical team performance assessment instruments; this will help improve medical and surgical team training efforts and aid the design of clinical work systems supporting effective teamwork and safe patient care.

Multidisciplinary care has been shown to improve patient outcomes, and interprofessional collaboration has been shown to improve one’s medical knowledge. Multidisciplinary interventions in the field of surgery are designed to address a specific problem occurring in a particular patient population and/or within the context of an individual hospital system (1-10).

Tree et al. (2) highlighted the importance of

multidisciplinary and interdisciplinarity at all levels, including clinical oncology. Harmonious interactions between oncologists, surgeons, radiologists and radiotherapists, and other members of multidisciplinary teams, including biomedical engineers, are essential for optimising patient care in oncology (2). This multidisciplinary approach is particularly important in the current landscape,

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in which standard-of-care approaches to cancer treatment are evolving towards highly targeted treatments, precise image guidance and personalized cancer therapy (13-18).

The surgical management of complex patients with the craniofacial oncological disease is a challenge that must be conducted by trained, experienced and multidisciplinary teams (neurosurgeon, maxillofacial surgeon, ENT surgeon and plastic surgeon). For example, a wide resection with craniectomy and reconstruction with microvascular free tissue transfer provides safe and reliable treatment of recalcitrant invasive scalp skin cancers, when performed by an experienced team (19-32). Communication across different specialties remains a core element of cancer care. Communication skills are important in establishing a good relationship with patients, but in the increasingly complex field of cancer treatment, oncologists and surgeons need to be equally skilled at communicating with and learning the art of those focused on other specialties (2).

Similarly, the treatment of facial fractures also requires a multisystem approach, as all bony and soft tissue injuries should be diagnosed, and reconstitution of all tissue layers should be performed, if possible (13, 22, 30, 33-41). The advancement of technology has enabled rigid fixation to become the standard of care for the fixation of most facial fractures (42). More precise stability and fixation of fractures have become possible, and intermaxillary fixation is used less frequently. Well planned incisions minimize scarring. Adequate exposure, precise reduction, and stable fixation remain the hallmarks of the treatment of facial fractures (43-46). The main principles of middle face trauma are an accurate and complete lesions evaluation; a mixed surgery team with an ENT, maxillofacial, neurosurgeons, and ophthalmology surgeon (42).

Complex spine surgery carries a high complication rate that can produce suboptimal outcomes for patients undergoing these extensive operations; however, multidisciplinary pathways introduced at multiple institutions have demonstrated promising potential for reducing the burden of complications in patients treated for complex spinal diseases (47-56). Similarly, in patients with brain abscess

caused by dental peri-implantitis, multidisciplinary treatment, performed by neurosurgeons, dentists and maxillofacial surgeons (57-68), includes broad-spectrum antibiotics, craniotomy for abscess drainage, sinus surgery and the removal of the implant (69-80).

Although many multidisciplinary care teams have been described in the field of surgery, few studies to date have examined whether or not these team-based interventions are generally cost-effective (1,81-84). Davis et al. (1) examined cost savings attributable to multidisciplinary care across all surgical fields, concluding that multidisciplinary surgical care is beneficial in patient and provider outcomes and its cost-effectiveness. In addition, hospital length of stay has been proposed as a key indicator of appropriate resource use in the North American healthcare system (81, 82), whereas a prolonged hospital length of stay is associated with poor clinical outcomes and increased costs to patients (82, 83). Sterbenz et al. (84) examined the implementation of business strategies in clinical research to increase productivity and help a research team remain competitive, summarizing the model of an effective research team and presenting an approach that can be used to derive strategies that foster productivity in a surgical research setting.

Literature on teams identified shared mental models, mutual respect and trust and closed-loop communication as the underpinning conditions required for effective teams. Educational interventions can promote a better understanding of the principles of teamwork, help staff understand each other's roles and perspectives and help develop specific communication strategies (85). Well-designed multidisciplinary teams tend to optimize perioperative care for all involved parties. Therefore, improving surgical care should employ multidisciplinary teams to promote quality and cost-effective care.

Future research challenges further developing and validating medical team performance assessment instruments; this will help improve medical and surgical team training efforts and aid the design of clinical work systems supporting effective teamwork and safe patient care (86-131).

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Augmented and virtual reality as training tool for maxillofacial surgeons and neurosurgeons: is it the future?

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Recent biotechnological advances, including three-dimensional microscopy and endoscopy, virtual reality, surgical simulation, surgical robotics, and advanced neuroimaging, have moulded the surgeon-computer relationship. For developing neurosurgeons and maxillofacial surgeons, such tools can reduce the learning curve, improve conceptual understanding of complex anatomy, and enhance visuospatial skills. However, current clinical trials in dental virtual reality must still be experimental.

Recent biotechnological advances, including three-dimensional microscopy and endoscopy, virtual reality, surgical simulation, surgical robotics, and advanced neuroimaging, have moulded the surgeon-computer relationship. For developing neurosurgeons and maxillofacial surgeons, such tools can reduce the learning curve, improve conceptual understanding of complex anatomy, and enhance visuospatial skills (1-13). Craniomaxillofacial surgery comprises multiple surgical disciplines, including neurosurgery, plastic surgery, otolaryngology, ophthalmology, and oral

and maxillofacial surgery. These specialties are performing surgery in an era of evolving technology, cost containment, reduced resident work hours, and a focus on patient safety (14-18).

Robotic surgery is a promising field in neurosurgery and craniofacial surgery, which can currently also be used to train residents. However, before robotic assistance becomes commonplace in the neurosurgical and maxillofacial field, improvements and breakthroughs must occur in minimally invasive and endoscopic robotics-assisted surgical systems (19-34).

Keywords: augmented reality; computer simulation; dentistry; maxillofacial surgery; neurosurgery; virtual reality; training

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Therefore, communication across different specialities remains a core element of cancer care. Communication skills are essential in establishing a good relationship with patients, but in the increasingly complex field of cancer treatment, oncologists and surgeons need to be equally skilled at communicating with and learning the art of those focused on other specialities (2).

The increasing techno-manual complexity of procedures and time constraints necessitates practical neurosurgical and maxillofacial training (12, 15, 35). Approaches including 3D printed brains, gelatin composite models, and virtual environments have been published (33). However, the quality of brain surgery simulation is limited due to discrepancies in visual and haptic experience, especially in brain tumor resection and following head and spinal injuries (36-48). In addition, the increasing interest and advancements in robotic spine surgery parallel a growing emphasis on maximizing patient safety and outcomes, as an increasing interest in minimally invasive spine surgery has further fueled robotic development, as robotic guidance systems are aptly suited for these procedures (49-63).

Similarly, clinical research related to virtual reality technologies in dental medicine revealed that these were predominantly used for educational motor skill training in university settings, for clinical analyses of complex maxillofacial surgical protocols, and to reduce surgical complications (64-128). Furthermore, virtual reality technology was also applied to investigate human anatomy and treat patients with dental phobia. However, current clinical trials in dental virtual reality must still be experimental (64).

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Early functional orthodontic treatment of bad oral habits with AMCOP® bio-activators

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Genetic and environmental factors influence craniofacial growth. The presence of bad habits such as finger or pacifier sucking, atypical swallowing, oral breathing, nail-biting and abnormal postures play an essential role in developing malocclusions. The severity and type of malocclusion are related to the age of the patient and the frequency, duration and intensity of the spoiled habit. The most common malocclusions are: posterior crossbite, transverse contraction of the palate, anterior open bite, and augmented overjet. Eliminating oral habits with an interceptive functional treatment allows for restoring the correct development of the bone bases and normal occlusion. Elastodontic devices represent a valid tool to correct neuromuscular dysfunctions and re-educate respiratory, swallowing, speech and masticatory functions, performing a functional, orthopaedic action.

Craniofacial growth is the result of two components: heredity and muscle function. The functional pillars of facial morphogenesis are: breathing, chewing, sucking and swallowing. The close relationship between form and function of the stomatognathic system begins in the first week

Keywords: interceptive orthodontics; elastodontics; elastodontic therapy; elastodontic appliances; bad oral habits; atypical swallowing; oral breathing; finger sucking

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of gestation, increases significantly during the fetal period and makes part of the early period of human ontogenesis (1, 2) upper and lower. Function and structure are highly correlated; the structure determines a correct function, and function generates a good structure (3).

Recently many authors have applied the functional matrix growth theory and noted that neither bone nor cartilage is a determinant for the growth of the craniofacial skeleton by inferring that development and control should be attributed to adjacent soft tissues. Furthermore, some authors have pointed out that the response to functional needs can determine facial growth assisted by the soft tissues surrounding the jaw. Together with the soft tissues, bone and cartilage also grow in a consecutive and functional phase. Therefore the development of the craniofacial skeleton is mainly determined in tissues, organs or non-skeletal spaces, defined as matrices (4, 5) providing functional, developmental and evolutionary information. Bone articulations in the skull arise due to interactions between genetic regulatory mechanisms and epigenetic factors such as functional matrices (soft tissues and cranial cavities).

Dental and skeletal relationships are harmonious in the presence of eugenic skeletal growth with physiological neuromuscular development (6). Unfavourable factors can alter this growth, and bring about various malocclusions, as often evidenced by the maxillary, mandibular and dental anomalies secondary to lingual disorders or bad habits in which repeated abnormal muscle action causes periosteal alterations, which modify the subject's bone growth (7).

All spoiled habits lead to alterations in the neuromuscular balance, especially when the subject already tends to non-physiological growth (8, 9).

Bad oral habits

A "bad oral habit" is a negative and repetitive behaviour pattern that makes part of a child's daily life, which, by making muscles and joints work incorrectly, leads to an alteration of the shape and development of the dental arches and skeletal structures (10).

The presence of bad habits such as atypical swallowing, oral breathing, an incorrect posture of the

tongue, prolonged sucking of the finger, lip sucking, and nail biting represents an important environmental risk factor for the onset of malocclusions (11, 12). These habits exert a force on the dento-skeletal structures which, if of sufficient frequency, duration and intensity, can cause deformations at the dental or skeletal level such as increased overjet, openbite, posterior crossbite or increased facial height (13). The duration of the force is more important than its intensity; resting pressures of the tongue, lips and cheeks have a great impact on the position of the teeth, as they are protracted most of the time (14). The fluctuating severity of the disease may be linked to changes in behavioural patterns such as a more unhealthy way of eating and drinking, as well as harmful oral hygiene habits (15, 16). There is also a correlation between bad oral habits and fatigue due to lack of sleep, interrupted by oral breathing and frequent sleep apnea, attention deficit disorder (ADD) and hyperactivity. Thus it is possible to note that there is a combination of proportional negative effects between bad oral habits and lack of sleep in babies (17).

Sucking habits

In infants, we can divide sucking habits into nutritive and non-nutritive (18). Breast-feeding or bottle-feeding are considered nutritive sucking habits, while sucking off a finger, pacifier, or other objects is among the non-nutritive sucking habits (19, 20). Data show that the type of diet in the first year of life and the activity of non-nutritive sucking activity are the main risk factors for the development of deciduous dentition malocclusion (21).

Breast-feeding, unlike artificial feeding, has a protective effect on the correct craniofacial development through the physiological stimulation of the orofacial muscles, as it promotes a correct lips closure, stimulates the correct jaw position and correct tongue position against the palate (22). The tongue and lips exert a "squeezing" action to withdraw the milk, and the jaw remains in a more advanced position. On the contrary, in artificial feeding, a sucking activity on the part of the lips and cheeks prevails with less stimulation of the orofacial structures (23). Additionally, bottle-fed babies have been found to have an increased risk of developing non-nutritive sucking habits after the first year of life

(24, 25). The latter were significantly correlated with malocclusions in both deciduous and permanent dentition. The damage caused by these spoiled habits is associated with several factors: duration, frequency, intensity and modality, facial biotype, hereditary substrate, development of secondary functional anomalies and individual predisposition to some types of malocclusions (26-28).

Finger sucking

Finger sucking is a flawed primary habit, already present in the prenatal period, considered physiological up to the age of two years (29). Babies have natural rooting and sucking ability anyway; sucking is a primary child need and makes part of his psycho-physical development. Sucking habit is generally hard to solve because of the soothing and calming effect. Finger sucking has a reassuring, relaxing effect and becomes an antidote to fear and a sense of loneliness (30). The factors that drive children to feel the need to suck their thumbs or fingers stem from family life, emotional instability, expressing rules and accepting solutions to problems.



Fig. 1. Thumb sucking



Fig. 2. Intraoral effect of finger sucking

Most children spontaneously stop finger sucking between the age of 2 to 4 (31). However, if this habit persists beyond 4-5 years of age, the risk of causing damage to the stomatognathic system increases (32).

In the most common form, the child presses the thumb on the palate and the hand on the jaw. The force of the thumb between the arches, together with the pressure of the peri-oral muscles not counterbalanced by the action of the tongue, will cause upper jaw transverse contraction, narrow palate, posterior crossbite, anterior open bite and upper incisors pro-inclination. The pressure of the hand on the mandible can cause mandibular retrusion and lingual inclination of the lower incisors. Finally, the lips will not reach adequate competence, and while swallowing, the child interposes the tongue to obtain the anterior seal, developing secondary atypical swallowing (33, 34) (Fig. 1 and Fig. 2).

Pacifier sucking

The need to suckle is vital in all healthy babies, and even before birth, fetuses could be seen sucking their thumbs while still in the mother's womb. Sucking is a natural reflex; it is the first coordinated muscle activity; it is an essential skill for survival with relaxing and beneficial effects such as calming the pain during diagnostic procedures, including blood tests (35) focusing on the consequences to occlusion, breathing, and children's oral motor aspects.

SOURCES: A literature review based on Medline database from the early 60s up to 2001 was performed taking into consideration the following topics: pediatrics, dentistry and speech language pathology.

SUMMARY OF THE FINDINGS: Based on this review of literature, we could verify that early weaning may lead to a proper oral motor development rupture, which may cause negative consequences to swallowing, breathing and speaking activities as well as malocclusion, oral breathing and oral motor disorders.

CONCLUSIONS: In addition to several benefits of breastfeeding, it contributes to a proper oral motor development and also avoids speech-language disorders, regarding oral motor system."

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Even non-nutritive breast-feeding is a particular sucking practice used to calm the baby and has been recognized as capable of generating general, immunological, nutritional and oral benefits for the baby. In a functional sense, the action of sucking involves muscle activity and promotes oral motor development. In addition to the aforementioned benefits, sucking confers a sense of security found in the use of the pacifier associated with the protection of Sudden Infant Death Syndrome (36, 37) and (2).

The use of pacifiers is widespread among babies and children all over the world. Pacifier sucking has great emotional value, promotes sleep, helps to overcome the distress of maternal detachment, increases the well-being of parents and babies, and prevents thumb or finger sucking. Pacifier use for more than 6 months and baby bottle feeding for over 1 year reduces chewing capacity and function (19).

However, the teat affects the upper part of the anterior and central portion of the mouth and forces the tongue to occupy a low posture preventing it from exerting its pressure on the palate, causing a reduced transverse width of the upper arch and posterior crossbite (38). Pacifier sucking is more clearly related to a posterior crossbite in the deciduous dentition than finger sucking. The anterior open bite is also usually more noticeable and visible earlier in pacifier suckers than in finger suckers. In both cases, the open bite is associated with the thrust of the tongue between the arches during swallowing (33, 39). Increased overjet is significantly associated with finger sucking rather than pacifier sucking (40) study models were obtained for 372 children at 4 to 5 years of age and assessed for posterior crossbite, anterior open bite, and overjet. The subjects were grouped according to the duration and type of habit (pacifier or digit, for less than 12 months or more than 48 months).

Atypical swallowing

Swallowing is a complex oral function that during life evolves in different stages: fetal, neonatal, mixed and, finally, adult swallowing around the age of 7. In infant swallowing and in the newborn, the main role is played by the lips, which create negative pressure inside the mouth to allow sucking, while the tongue is

low and moved forward. In the transition from infant to adult swallowing, with the eruption of teeth and the weaning, there is a modification of the muscle structure involved in swallowing (41, 42). It has been found that there is a modification of the muscle structure involved in swallowing during the transition from infantile to adult swallowing, and during these phases, there is the appearance of teeth and weaning (43).

In adult swallowing, the main role is played by the tongue, whose apex points to the hard palate (44). Atypical swallowing occurs when there is no transition from infantile to adult swallowing (43); this is a myofunctional problem characterized by an altered lingual posture during the act of swallowing. Consequently, the transit times of food are lengthened, muscle contractions occur improperly, and the tongue makes an incorrect movement during the act of swallowing (45) (Fig. 3).

The aetiology is multifactorial: hereditary factors, eating habits, prolonged and protracted use of baby bottles, delayed weaning and a low solid foods diet, the abuse of the pacifier, thumb or tongue sucking, biting the nails or small objects, and allergic diseases can all be involved in its onset (46).

Most of the interest shown in the literature concerns the effects of the tongue on the oral environment, demonstrating that alterations in size (47, 48), function (49) and posture (50) of the tongue could influence not only teeth position (51) but also oral development (1). Persistent infantile swallowing can cause pro-inclination of the anterior teeth, narrow palate, open bite, as well as speech disturbances and postural alterations (52).



Fig. 3. *Atypical swallowing*

Mouth breathing

Breathing through the nose represents the correct breathing pattern. The mouth can be used to breathe only in occasional circumstances, such as, for example, in low temperatures or following intense physical exertion. Breathing should normally take place effortlessly through the nose, with competent lips, barely touching or 2 mm apart, and with relaxed facial muscles (53). The air that passes through the nasal cavity is heated, humidified and purified through the hair cells and tonsils (pharyngeal and palatine).

The term “Oral Breathing” refers to an abnormal condition in which the passage of air inside the body occurs mainly through the oral cavity and may be due to an obstruction (adenoid hypertrophy, pharyngeal tonsil hypertrophy) or a bad oral habit (54). Because oral breathing does not allow enough oxygen to be introduced, children are pale, apathetic, lack concentration and often get tired. Hypoxia can cause sleep disturbances, such as snoring, frequent awakenings, nocturia, and difficulty falling asleep. Oral breathing predisposes the subject to subacute inflammatory processes affecting the pharynx, larynx, trachea and bronchi since nasal stasis and congestion cause rhinitis, rhino-pharyngitis, tracheitis, adenotonsillar hypertrophy, sinusitis and otitis with possible hearing loss. In addition, the subject can suffer from constipation and/or colitis (55, 56). The causes of oral breathing can be local (tumors, cysts, inflammation of the paranasal sinuses, polyposis, pharyngitis, deviations of the nasal septum, bad habits, allergic and non-allergic rhinitis) and general (asthma, endocrine diseases, allergies, muscular hypotonus) (57, 58).

Clinical manifestations of oral breathing also appear in the craniofacial structures. Oral breathing in infancy can compromise dental occlusion and, consequently, the functions performed by the stomatognathic system, as the growth of the maxilla is associated with nasal breathing and dysgnathic growth with oral breathing. These subjects often suffer from dental malocclusions and craniofacial bone abnormalities (55, 59). Usually, by oral breathing child has typical facial features that in medicine go under the name of adenoid facies: the

eyes have dark skin circles due to the periocular venous stasis caused by the congestion of the nasal mucosa, and the nostrils are narrow (microrhinia), the incompetent lips, a short and hypotonic upper lip, a lowered jaw, a low lingual posture and a long, narrow face. There is, therefore, “deformation” of the skeletal and muscular structure, ogival and high arched palate, with a possible crossbite, tendency to anterior open bite (60), mandibular post-rotation, class II and III class malocclusion, posterior crossbites (unilateral or bilateral), dental crowding, chronic gingivitis, periodontitis, candida infections and halitosis (61).

Nasal airway obstruction with oral breathing in growing children is related to clockwise rotation of the growing mandible, with a disproportionate increase in the lower anterior vertical face height and a decrease in the posterior face height (54, 62).

Interposition or lip sucking habit

This habit is often secondary to finger sucking or atypical swallowing and to a marked overjet that causes the lower lip to be placed behind the upper incisors, worsening the situation. These patients show superior dentoalveolar protrusion, retro-inclination of the lower incisors, mandibular retrusion, deep bite, labial incompetence and hypertonus of the mental muscle. During swallowing, the muscles create many small dimples on the skin of the chin and this aspect is called a “golf ball chin” (63).

Bad posture

Abnormal external postural pressures can also cause dentoskeletal deformations and facial asymmetries. For example, the habit of sleeping by placing the face on the hand or head on one side or in the supine position places the weight of the head on that side and the tissues of the jaw region of that side, causing asymmetry and unilateral crossbite. The habit of resting the chin on the palm of the hand for many hours a day causes a lateral force on the mandible, which in the long run can cause facial asymmetry with mandibular deviation. Instead, in wind instrument players, variations in the overjet and overbite are frequently found, and the mandible is pushed in a posterosuperior direction (64).

Onychophagia and lispiphagia

Onychophagy, which is the habit of biting nails, and lispiphagia, the habit of nibbling pens or pencils, occur in association with anxiety disorders, insecurity, and stress. During these performances, the tongue provides in a pushing position against the lower incisors. In addition, they can cause dentoalveolar open bite, dentoalveolar malposition, as well as dental abrasions, gum damage, and viral and bacterial infections (65) (Fig. 4).

Early interception

The first dental visit is recommended after the appearance of the first tooth in the arch and, in any case, no later than 18 months. On this occasion, it is possible to discuss with parents the prevention of malocclusion problems and the interception of any bad oral habits (32, 66).

Primary prevention refers to the elimination of risk factors and is achieved with early orthodontic visits, medical history and objective examination in search of bad oral habits. Interceptive preventive therapy is “the set of measures aimed at avoiding malocclusion or limiting the effects on normal craniofacial growth” (American Association of Orthodontists AAO) (67, 68). It is necessary to early intervention in the malocclusion etiological factors to prevent its development or, if already developed, to correct it with an early orthodontic treatment to restore a proper skeletal growth (69, 70).

The early interception of bad oral habits is, therefore, essential in preventing the onset of structural alterations (71, 72). When oral dysfunction is left untreated or worse diagnosed, severe orofacial myofunctional disorder can occur (67,

73). The methods of treating an oral habit include behaviour modification techniques, myofunctional therapy, treatment with orthodontic devices and a multidisciplinary approach between orthodontist, paediatrician, speech therapist, psychologist, or otolaryngologist may be required (32, 74, 75).

The restoration of a nasal breathing pattern, obtainable using orthodontic devices, affects the patient’s respiratory situation in various ways, including nasal obstruction. In addition, the restoration of the respiratory defences related to the use of nasal airways constitutes prophylaxis that positively affects the patient’s general respiratory health (76). Interceptive therapy will allow re-educating functions such as swallowing, breathing, chewing, respiratory problems and sleep disturbances (77-79).

Functional rehabilitation with AMCOP® devices

Elastodontic therapy represents a new approach to interceptive functional orthodontic treatment in children and uses light and biological forces of an elastic type to correct malocclusions. It is based on the rationale that the signs of various malocclusions are often detectable already in deciduous or early mixed dentition and that many forms of malocclusion do not correct themselves spontaneously with growth; contrariwise, they tend to get worse (80)acquired craniofacial disorder and contribute to generational dysfunction, disorder and disease.\nINTRODUCTION: Baseline orthodontic consultations are generally recommended beginning age seven. However, the dysmorphic changes that result in malocclusion are often evident years earlier. Similarly, following orthodontic treatment, patients require permanent retention when the bite is not stable, and without such retention, the malocclusion can return.\nSETTING AND POPULATION: Narrative review article including research on infants, children and adults.\nMATERIALS AND METHODS: This review is a brief survey of the symptomology of orofacial myofunctional disorder and outlines 10 areas of oral function that impact occlusal and facial development: breastfeeding, airway obstruction, soft tissue restriction, mouth breathing, oral resting posture, oral habits, swallowing, chewing, the



Fig. 1. Intraoral effects of onychophagy

impact of orofacial myofunctional disorder (OMD).

Elastodontic devices represent a valid opportunity to manage orthodontic treatment in an early phase in a simple, comfortable way, with significant reductions in therapy times (81, 82) second class malocclusion, deep bite and lower arch crowding from the deciduous dentition to permanent one.

CASE REPORT

At first, the 5-year-old patient was treated with an elastodontic device known as "Nite-Guide". When the patient was 7 years old, during her first permanent molars and incisors eruption and after optimal house-practices, an Occlus-o-Guide Series G was placed at night and on daylight (two hours a day. Treatment is easy, short and rarely requires a second phase of orthodontic therapy, avoiding the problems resulting from a classic mobile (83) or fixed (84-89) orthodontic treatment.

They are especially indicated in preschool age, an era in which skeletal structures are characterized by remarkable plasticity and adaptability, to restore harmonious dentoskeletal development by correcting any neuro-muscular dysfunctions and re-educating swallowing, respiratory, speech and masticatory functions (90-92).

It should be emphasized that the elastodontic approach offers the opportunity to anticipate the timing of interceptive intervention even towards the age of 3, not so much for exclusively orthodontic purposes, but above all for respiratory and functional ones, which can often constitute a pediatric problem early (93) we will shed some light on the causes, symptoms, and diseases correlated with mouth breathing. The second article, defined as part-two, will introduce forms of therapy to encourage nasal breathing, one of which will focus on the Butevko® breathing method."

container-title": "International Journal of Orthodontics (Milwaukee, Wis.. Functional re-education aim at the normalization of the muscle tone of the structures involved in the relative functions: lips, tongue, and cheeks (94, 95).

The AMCOP[®] Bio-Activators (cranio-occlusion-postural morphostructural harmonizers) are preformed elastodontic devices made of a certified, biocompatible thermoplastic material that derives

from a polymer-elastomer mixture (96-100). This elastic material does not create irritation or pain, allowing easy adaptability in the oral cavity and making it comfortable even for the smallest patients. Furthermore, the choice of device size can be made by measuring the distance between the vestibular cusps of the upper sixths on a wax bite or directly in the mouth, making it unnecessary to take impressions, which is a procedure not well tolerated by very young patients (101-107) orthopedic and dental effects. Thus, these devices are useful in the developmental age, when skeletal structures are characterized by important plasticity and adaptation capacity, allowing to remove factors responsible for malocclusions. Elastomeric devices are generally well tolerated by patients requiring simple collaboration and management. This work can be useful to update all orthodontists already adopting these appliances or for those who want to approach them for the first time. This study aimed to describe four cases treated with new elastomeric devices called AMCOP Bio-Activators and to provide an overview of elastodontics, its evolution, indications and limits. Methods: A total of four clinical cases were presented after a treatment period of 16–20 months to evaluate the clinical and radiological effects of the elastodontic therapy. Results: The effectiveness of Bio-Activators on clinical cases was evidenced with a significant improvement in skeletal and dentoalveolar relationship, and malocclusion correction in a limited treatment period (16–20 months).

The elastodontic devices work in a three-dimensional way on all the structures of the stomatognathic system, bones, alveoli, teeth, masticatory muscles, lips, tongue, cheeks, temporomandibular joint, exerting a remodelling action of the dento-cranial-facial structures and of neuromuscular re-education. These devices act as shields by neutralizing the centrifugal (tongue) and centripetal (lips and cheeks) forces and, at the same time, exert a stretching action on the peri-oral and chewing muscles in order to lengthen the muscle fibres (108). Devices are available with different chewing planes according to the type of malocclusion and with four different arch shapes (109). They are characterized by:

- High vestibular flanges which have the function of removing the peri-oral muscles and of proprioceptive stimulation of the bone matrix;
- Lingual ramp that directs the tongue upwards on the palate;
- Lingual button that facilitates the correct positioning of the tongue on the palate;
- Absence of indentations allows the teeth to freely place themselves in the elastodontic space, that is, the area of equilibrium between the strength of the tongue and that of the cheeks and lips.

In addition, the device requires nasal breathing, which is favoured by the expansive transverse action and the presence of a high vestibular flange. The AMCOP® Bio-Activators also present a line for the little ones still in deciduous dentition, indicated for early and atraumatic therapies in dysfunctional problems and neuro-muscular, osteopathic, orthopaedic and psycho-affective lesions. They are particularly suitable for children suffering from transverse maxilla deficiency with dental open bite due to dysfunctional tongue interposition and/or prolonged use of the pacifier.

The pacifier model has a shield and support for the grip, similar to a baby pacifier. In this way, the use of the device is more acceptable, especially from a psycho-emotional point of view. It can be considered a dental-skeletal growth stimulator capable of acting on the interferences and the determining causes of malocclusions for early and interceptive action. The occlusal plane is perfectly flat (no Spee and Wilson curves). Therefore the AMCOP® Bio-Activator used in deciduous dentition:

- performs a functional, orthopaedic-osteopathic action
- corrects the deviations of the midlines
- corrects bilateral and unilateral crossbites
- corrects the anterior open bites
- corrects dysfunctional spoiled habits
- places the tongue on the palatine spot
- improves swallowing and nasal breathing in oral respirators
- is indicated for infantile nocturnal grinding
- is indicated for the expansion of the dental arches
- is indicated for thumb sucking
- is indicated for the removal of the pacifier (110-170).

CASE REPORTS

Case 1

Three-year-old female patient with pacifier sucking habit. On intraoral examination, contraction of the upper arch, anterior open bite with a tendency to the third class and interposition of the tongue between the arches were observed. The interceptive therapy was carried out with the AMCOP® DC device, characterized by the pacifier grip. The 16 months of treatment allowed the correction of the bad habit, the resolution of the anterior open bite and the achievement of a harmonious relationship between the upper and lower arch (Fig. 5).

Case 2

Eight-year-old female patient with finger sucking habit. This bad behaviour caused a contraction of the upper arch, ogival palate, increased overjet and reduced overbite. The cephalometric analysis (Deltadent® software) revealed skeletal class II with mandibular retrusion. The patient was treated for 18 months with the AMCOP® Integral device characterized by a flat chewing surface. This device was worn overnight and for one hour during the daytime for the first 6 months and then only during nighttime. At the end of the treatment, expansion of the upper arch, correct intercuspation and normal overbite and overjet values were obtained (Fig. 6, Fig. 7 and Table I).

CONCLUSION

Oral habits represent risk factors for disorders of craniofacial growth and malocclusions, and their presence should be intercepted and corrected at an early age. A functional orthodontic approach with elastodontic devices allows re-educating the muscles and restoring a harmonic development of the stomatognathic system.

Patents

Invention patents:

Title: dispositivo ortodontico-elastico-armonizzatore dento cranio-facciale, scope: Ita-lian, granted under n° 102015000057082

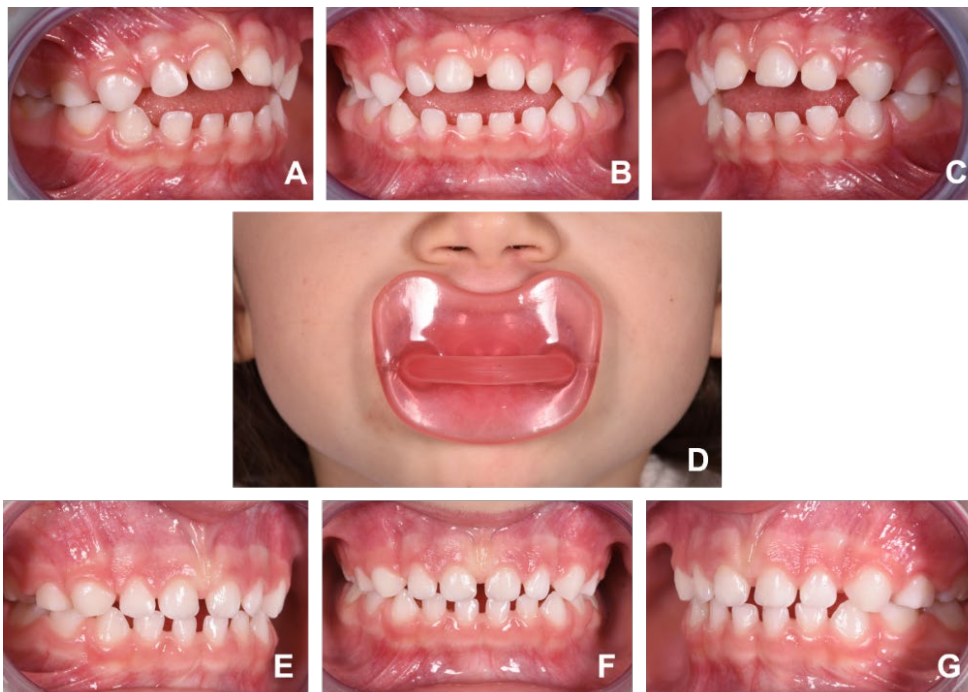


Fig. 1. Intraoral photos before treatment: right (A), frontal (B) and left (C); Patient wearing AMCOP® DC device (D); Intraoral photos after treatment: right (E), frontal (F) and left (G)



Fig. 1. Intraoral photos before treatment: right (A), frontal (B) and left view (C). Patient during thumb sucking (D). Upper (E) and lower (F) jaw occlusal views. Lateral Teleradiography before treatment (G); Patient wearing AMCOP® INTEGRAL device (H); Intraoral photos after treatment: right (I), frontal (K) and left view (L). Upper (M) and lower (N) jaw occlusal views; Lateral Teleradiography after treatment (O).

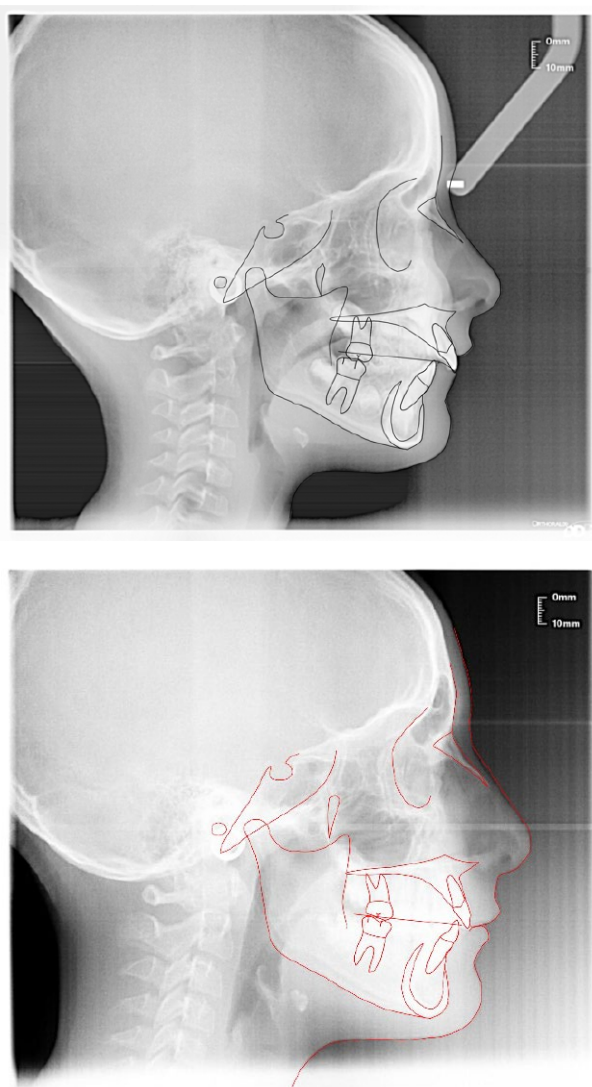


Fig. 7. Cephalometric traces (DeltaDent software) before (A) and after (B) treatment

Title: dispositivo ortodontico-elastico-armonizzatore dento cranio-facciale, scope: International, n° WO 2017/056010

Institutional Review Board Statement

The present clinical study was based at the University of Bari (Italy), in full accordance with ethical principles, including the World Medical Association Declaration of Helsinki and the additional requirements of Italian law. Furthermore, the University of Bari, Italy, classified the study as exempt from ethical review as it carries only negligible risk and involves using existing data that

Table 1. Cephalometric report (DeltaDent software®) before and after treatment

Parameters	Before	After
SNA	82.8°	79.5°
SNB	74.7°	75.3°
ANB	8.1°	4.2°
Wits	5.9	1.6
OVJ	7.8	4
OVB	3.9	2.8
IS^II	124.4°	132.4
sna-snp^Go-Gn	24.4°	26.2°
S-N^sna-snp	8.2°	8.7°
S-N^PO	17.5°	19.2°
S-N^Go-Gn	32.6°	34.9°
SNBa	136.9°	140.7°
SND	71°	72°
IS^II	124.4°	132.4°
IS:N-A	1.8	2.1
II:N-B	2.1	2.6
II:A-Pog	-1.4	0.3
Ls:S Line	-2.4	-1.8
Li:S Line	-4.7	-4.8
Cvm:S-Gn	-0.3	-2.1
Upp Mol^P. Occl	78.3°	101.7°
N-S-Cop	129.6°	135.1°
S-Cop-Go	139.1°	132.6°
Cop-Go-Gn	123.9°	127.1°
Cop-Go-N	53.3°	53.9°
N-Go-Gn	70.6°	73.2°
II^Go-Gn	102.5°	97.2°
SOr:sna	51	59.6
sna:Me	54	60.1
S:N	60.4	63.9
snp:A	42.6	41.8
Go:Me	53.2	59.6
IS^N-S	100.4°	95.6°
Pog:N-B	0.8	0.9
Pog:N-B - II:N-B	-1.3	-1.7

contain only non-identifiable data about human beings. The patient signed a written informed consent form.

Informed Consent Statement

Informed consent was obtained from the subjects involved in the study. Written informed consent has been obtained from the patient to publish this paper.

Data Availability Statement

All experimental data to support the findings of this study are available by contacting the corresponding author upon request.

Conflicts of interest

The authors declare no conflicts of interest.

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Navigation systems in maxillofacial surgery and neurosurgery and their potential advantages

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Operating microscopes, navigation systems and intraoperative neurophysiological monitoring are essential in modern neurosurgical and maxillofacial procedures. Advances in surgical planning in neurosurgery and maxillofacial surgery led to the more common navigation system that helps surgeons know more information and ultimately do more for their patients. The benefits of a contemporary navigation system in the complicated brain, skull-base, maxillofacial and spine surgery are undeniable. Workflow analyses and cost-benefit evaluations must be carried out to increase the efficiency of neuro-navigation systems in the next future.

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procedures (1-8). Advances in surgical planning in neurosurgery and maxillofacial surgery led to the more common use of navigation systems that helps surgeons

Key words: neuronavigation; maxillofacial surgery; neurosurgery; virtual reality; neuronavigation system; technology

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to know more information and ultimately do more for their patients (9-16). All intraoperative navigation systems incorporate a computer digitizer to track the location of the patient and instruments in space. Four different digitizer modalities have been developed: optical, electromagnetic, electromechanical, and ultrasonographic. Optical tracking is most used (17). Registration is accomplished by identifying specific fiducial markers on the virtual patient, as seen on the navigation system monitor (17).

Innovation in the medical equipment industry led to the update of navigation equipment such that the systems are now more user friendly, have dynamic referencing and offer multiple tracking capabilities, including 3D imaging (18). In addition, the systems can also be integrated with external devices like microscopes, endoscopes and ultrasound (18-27).

The benefits of the contemporary navigation system in the complicated brain, skull-base and spine surgery are undeniable (28-37). For example, small lesions in eloquent brain areas can be operated on more radically with less morbidity than the pre-neuro-navigation era (18, 24, 38-40). Similarly, in the case of external drainage and small ventricles, navigation can be helpful (41-43).

Craniofacial approaches with intra-operative neuro-navigational guidance in a multidisciplinary setting allow safe resection of large tumors of the upper clivus and the paranasal sinuses involving the anterior skull base (18, 44-46). Complex skull base surgery with the involvement of bony structures appears to be an ideal field for advanced navigation techniques, given the lack of intraoperative shift of relevant structures (47-50). Also, in oral surgeries, the usefulness of the navigation system has been indicated by its surgical applications in craniomaxillofacial trauma, orthognathic surgeries, head and neck pathological resections, complex skull base surgeries and surgery involving temporomandibular joints (9, 51-63).

In maxillofacial surgeries, open reduction and internal fixation for the treatment of facial fractures remains the standard of care for most facial fractures. However, symmetric repair of complex facial fractures remains extremely challenging (17, 64-71). The use of a navigation system permits to treat

of complex facial fractures, reducing the risk of a discrepancy between symmetrically opposite facial bones. It has the benefits of combining 3D computed tomography (CT) and computer-aided design technology for the development of custom-designed prostheses are applied in the repair of posttraumatic and congenital facial contour deficiencies (64, 72-86).

Although primarily developed for a neurosurgical application, intraoperative navigation has gained acceptance even in maxillofacial surgery with an increasing field of indications (87). Heiland et al. (87) showed one of the best examples of the benefit of navigation in secondary orbital reconstruction in maxillofacial surgery.

Computer-assisted surgery has evolved from its earliest introduction with utility in the neurosurgical field. Within the past twenty years, optical navigation systems have emerged and developed into a great tool for dentistry and craniomaxillofacial surgery (88). Currently, computer-assisted surgery is useful for orthognathic and temporomandibular joint surgery, facial trauma, maxillomandibular reconstruction, implantology, and restorative dentistry (88). Similarly, ablative tumor surgery and orbital and midface reconstruction, as much as orthognathic surgery, require detailed planning using CT or magnetic resonance imaging (MRI) (89). These techniques also allow the simulation of complex surgeries preoperatively. Proper reconstruction depends on reliable information to choose the correct type of grafts and to predict the outcome.

Hohlweg-Majert et al. (89) reported in their study the benefit and indications of computer-assisted surgery in the treatment of 107 patients who underwent craniomaxillofacial surgery, showing that intraoperative navigation makes tumor and reconstructive surgery more reliable by showing the safety margins, saving vital structures, and leading the reconstruction to preoperatively planned objectives.

In spine surgery, the navigation system significantly reduces intraoperative radiation time, puncture time, and operation time, reshapes the learning curve, and improves percutaneous surgical treatment of spine fractures (90-99). Workflow

analyses and cost-benefit evaluations must be carried out to increase the efficiency of neuro-navigation systems in the next future (18).

Advances and innovations in neuroimaging, surgical techniques and medical equipment over the last decades have given an enormous boost to the improvement and success of contemporary neurosurgery and maxillofacial surgery. One of these advances has been image-guided surgery which can be defined as any method that uses imaging technology to enhance brain, maxillofacial and spine surgery (100). However, more and more assessments of neuro-navigation from the perspective of health care system efficiency, effectiveness, and economy are required (18).

With the opportunity to perform preoperative planning, surgical simulation and postoperative prediction, computer-assisted navigation shows great value in improving the accuracy of maxillofacial surgery and neurosurgery, reducing operational risk and postsurgical morbidity, and restoring facial symmetry (101-138).

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Functional breastfeeding: from nutritive sucking to oral health

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Functional breastfeeding plays a key role in the correct psychophysical and neuromotor development of a child, and it has repercussions on craniofacial complex growth and functioning. The consequences of not breastfeeding seem to have not only aesthetic complications but can cause significant functional orthodontic repercussions. Each study on breastfeeding has shown how breast milk protects against acute otitis media, pneumonia, syncytial virus, bronchitis, asthma, gastroenteritis, Sudden Infant Death Syndrome (SIDS), leukaemia, obesity, allergies and even constitutes a protective factor against habitual infant snoring and in reduction of the risk of obstructive apnea. By exercising his muscles, the child strengthens his zygomatic processes so that nasal airways have good drainage capacity and consequently a low predisposition to sinus and respiratory infections. Dentists have a fundamental role in the prevention of maternal-infant oral health, and by assisting its management, they can even implement the best development of a child's immune system. The “primary” function of the dentist which is concretized in encouraging the planning of the first early visits of the interception of spoiled habits and incorrect lifestyles, together with the “internal” one of the intestinal and oral microbiota of the child together with breastfeeding have an indirect yet significant consequence of favoring the harmonic growth of the orofacial complex.

Key words: functional breastfeeding; oral microbiota; malocclusions; oral health; bad oral habits; early childhood caries

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Nutritive sucking and nonnutritive sucking, together with breathing, swallowing, speech articulation and posture, participate in the growth and development of the oro-facial and maxillo-mandibular complex (1–3). The Ministry of Health, following the indications of the World Health Organization (WHO), recommends exclusive breastfeeding for at least 6 months from birth. In addition, the use of teats is recommended using only from the moment breastfeeding is established (4–7).

It is evident that breastfeeding is important for health and well-being; favoring it within 30 minutes of birth promotes its exclusivity (8,9). The lack of breastfeeding can represent the etiopathogenesis of problems of odontostomatological interest that occur in early childhood, such as bad habits and malocclusions, which require collaboration between various specialists, in a particular paediatrician, pediatric dentist and orthodontist (10–12).

In addition to satisfying nutritive needs, breastfeeding has benefits on the cognitive, emotional and relational development of the child as it is a form of communication with the mother called “bonding”. Furthermore, it is a type of relationship, of body heat exchange between mother and child, a caregiving and protection support (13, 14). After childbirth, there is a reduction in estrogen and progesterone levels, but an increase in:

- Prolactin: released from the adenohypophysis, it acts on the epithelial cells of the alveolus and stimulates milk production, inhibits ovulation, has an immunomodulating effect and an anti-stress action; and

- Oxytocin: released from the neurohypophysis, it acts on the myoepithelial cells surrounding the alveolus, pushing the milk towards the nipple. Oxytocin is produced in greater quantities due to visual, tactile, and auditory stimuli associated with the child, while its secretion is inhibited by pain, stress and psychophysical discomfort (15, 16).

Breast milk and oral microbiota

Breast milk is a species-specific food and comprises numerous components, including stem cells, macrophages, 88% water, sugars (mainly lactose), fats, proteins, vitamins (Vitamin A, B12

and K), carbohydrates, minerals, hormones and antibodies. In addition, it has a bifidogenic effect and ensures proper maturation of a child’s immune system (17–21).

Human Milk Oligosaccharides (HMOs) from breast milk is considered the most important of the prebiotic group, essential for developing and maintaining the intestinal and oral microbiota of the unborn child. Furthermore, they facilitate *Bifidobacteria*’s growth, the predominant species in the microbiota of breastfed infants, resulting in the production of microbial metabolites characteristic of carbohydrate fermentation (22). From the fourth month of life, the oral and intestinal microbiota is specific to each person, interacting with all organs. Furthermore, the intestinal and oral microbiota of vaginal delivery and breastfed newborn that exhibits low biodiversity is considered eubiotic, taking on a more complex composition between the first and second years of life, when it becomes similar to the intestinal microbiota of the adult (23). From the maternal microbiota, the microbiota of each future individual develops in a constant natural exchange.

With a vaginal birth, there is a vertical maternal-neonatal transmission. When the child crosses the birth canal, the maternal vagino-rectal flora colonizes the tissues of the child himself. At the same time, intestinal colonization occurs by the newborn’s ingestion of the mother’s vaginal secretions, and with subsequent breastfeeding and sucking, colonization extends. This exchange of natural fluids creates an unrepeatable bond that unites the mother and her child from the first moments of birth. And the effects of this exchange are amplified until they determine the subsequent and new colonization of the skin, starting from the maternal skin itself, and of the neonatal oral cavity, through the few traces, even involuntary, of the mother’s saliva. Therefore it is essential to maintain the health of the mother’s vaginal and oral fluids; otherwise, maternal-fetal colonization during delivery would not occur; if *Streptococcus agalactiae* was present, the mother could involuntarily transfer colonies of *Streptococcus mutans* and *Actinomyces* of oral derivation to the child from the first moments of his contact (24). Precisely in this sense, move the improvement of maternal oral eubiosis that

aims, therefore, to implement the best oral eubiotic condition of the newborn.

In correlation, the idea of a “sterile uterus” is also known, i.e. until a few years, it seemed certain (but it is not today) that it was a bacteria-free uterus (25). Today, this scientific concept is outdated and particularly the object of attention; in fact, it is known that there is real access of microorganisms to the amniotic cavity at least in pathological pregnancies.

This access would be guaranteed by the existence of three possible natural paths:

- ascending (cervix, vagina);
- peritoneal (tube);
- hematogenous (pyelonephritis, pneumonia and periodontitis) (24).

It should be noted that during pregnancy, even in physiological conditions, a woman partially changes her microbiota to implement the verticalization of it towards the child. Therefore, the vaginal microbiota reduces α and β biodiversity and increases ecological stability through a numerical increase in the lactobacillary population; in addition, it is highlighted that, at the colonic level, microbiota reduces biodiversity α to the detriment of that β and increases both genus *Bifidobacterium* and those belonging to proteobacteria phylum, in this case to the detriment of *Faecalibacterium*, which, on the contrary, are reduced (24).

It is also interesting to investigate that vaginal and colon changes pay a “duty”, and a “transit cost”, and this “payment” occurs at the oral level. Here microbiota tends to a substantial worsening characterized by a general increase in bacterial load and by an increased presence of Gram-negative bacteria, potential pathogens, such as *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans*. On the other hand, the presences, quantitatively unchanged, of *Prevotella intermedia* and *Fusobacterium nucleatum* remain. *Candida* species also appear more represented in the oral cavity than final stages of pregnancy (24, 26).

Microbiota, particularly oral microbiota, plays a fundamental role in susceptibility to oral infections and will strongly affect the entire respiratory tract (27, 28). There is also evidence of a synergistic effect between viruses and bacteria in oral and respiratory

pathogenesis; in fact, recurrent infections can cause virus-induced immune dysfunction and can lead to a vicious cycle of recurrent respiratory tract infections (RRI) with bacterial superinfections, exacerbation of cough, and increased risk of developing asthma (24, 29–31).

Therefore, microbiota significantly affects typical upper respiratory tract infections such as sinusitis, chronic tonsillitis, and inflammation of the adenoids, in which most viral infections are activated and are often complicated by bacterial infections involving more common respiratory pathogens such as *Streptococcus pneumoniae*, *Mycoplasma pneumoniae* and *Streptococcus pyogenes*. Without forgetting that *Streptococcus* is the dominant genus in the oral cavity, and *Streptococcus salivarius* was the most protective of infections among the various species (32–34).

Oral cavity is the main area in which the microbial communities implement their colonies with widespread effects in the respiratory tract down to the intestinal tract; the state of health of the oral cavity has a significant impact on these effects (32, 35).

Caries and saliva are the clearest spies in the oral cavity, which is still a little explored source of individual health. The diagnosis of cario-receptivity preceding the diagnosis of caries is determined by fundamental factors such as nutrition, fluoroprophylaxis and oral hygiene (24, 36, 37). In a complementary way, the approach for modulation in the intestinal microbiota is the use of strains of viable bacteria orally (probiotics), indigestible carbohydrates (prebiotics), or synergistic combinations of a probiotic and prebiotic (synbiotic). For example, *Streptococcus salivarius* K12 is a probiotic strain antagonist to the growth of *Streptococcus pyogenes*, and the most important bacterial cause of pharyngeal infections in infants. Recent studies report that a daily administration to children showed a reduction in streptococcal pharyngitis and acute otitis media; this created a strong link between the administration of probiotics and respiratory and oral microbiota (24, 38–40).

The oral pathology of caries has a multifactorial aetiology with the relevance to sugars and time and the presence of food residues, even microscopic,

with a polysaccharide structure, on the tooth surface. Saliva with amylase, that is, ptyalin, can break down sugar into simple sugar (monosaccharide) so that it can be transformed into lactic acid by lactic acid bacteria, which are the natural pro-active inhabitants of the oral cavity (24, 41–43).

The mother's oral health is fundamental to the health of the baby's oral cavity. Maintaining oral health in the perinatal period consists of the correct transmission of the microbiota from mother to child before and during childbirth. The third, the most important phase of intestinal and oral colonization of the infant occurs during breastfeeding (38).

Protection mechanisms of breast milk

For the baby, breast milk protects against (24):

- infections: acute otitis media
- lower respiratory tract diseases: pneumonia, syncytial virus, bronchitis, asthma
- gastroenteritis
- Sudden Infant Death Syndrome (SIDS)
- Leukaemia
- Obesity
- Allergies
- Malocclusions

Breastfeeding for mothers reduces the risk of (24):

- Post partum bleeding and haemorrhages
- Breast cancer: thanks to reduced exposure to estrogen by elimination through the maternal fluid, delayed ovulation
- Ovarian cancer: thanks to the decrease in gonadotropin levels
- Osteoporosis

Association between breastfeeding and malocclusions

Breastfeeding is a dynamic process which

requires coordination of the baby's jaw movements, tongue waving, and breast milk ejection reflex (44). The maternal nipple, together with part of the areolar tissue, is actively stimulated with the peristaltic movement of the tongue, which presses it against the palate at the level of the retroincisal spot, an area intended to accommodate the lingual support in the physiological swallowing pattern (45–47). Tongue motility is impaired in children with impaired lingual frenum, so breastfeeding problems may arise in such patients (46).

The lips actively participate in each feed, creating a seal around the areola. The lip seal and the lingual location on the palatine lines represent the cornerstones of the correct resting position (48).

The short duration of breastfeeding (never or less than 6 months) is directly associated with a posterior crossbite, which causes detrimental effects on the chewing cycle and normal growth of the orofacial system (49–51). Furthermore, by alternating the feeding to the right and left breast, one avoids consolidating the unilateral and laterally deviated postures and consequently ensures a harmonious craniomandibular development of the baby (52–54).

Several scientific studies agree that longer periods of breastfeeding have reduced the incidence of posterior crossbite and anterior open bite (55) (Fig. 1). Furthermore, breastfeeding for 12 months or longer protects against the development of class II malocclusion (48, 56, 57).

Early complementary feeding could lead to insufficient perioral muscle activity, with repercussions on swallowing, breathing and speech, as well as malocclusions (12, 49). Therefore, in many cases, an early orthodontic intervention will be required (58–61).



Fig. 1. Posterior Crossbite (left) and Anterior Open Bite (right)

Furthermore, infants who are breastfed for less than 6 months are more likely to develop pacifier sucking habits than those who are breastfed for more than 6 months (62, 63). Theories attempting to explain this effect suggest that naturally breastfed babies meet their psychological and emotional needs while sucking in close, intimate contact with the mother and therefore have less need to use the pacifier, finger or other objects (49).

Breastfeeding and sleeping respiratory disorders

Many studies claim that breastfeeding is a potentially protective factor against infant snoring, bruxism and sleep breathing disorders (64). In addition, breast milk provides immunoglobulin A which protects against the risk of contracting infections and inflammation of the respiratory tract with adenotonsillar hypertrophy (65). On the other hand, it has been hypothesized that breastfeeding promotes the correct development of the oropharyngeal area by preserving the oropharyngeal volume and making this area less susceptible to collapse during sleep (44, 66). Therefore, breastfed infants are less predisposed to the development of oral respiration, as they have a vector of transverse growth of the palate, large dental arches and normal mandibular position (67, 68).

Use of the pacifier

Sucking represents part of the development of the fetus, the neonatal period and further on into childhood (69). It is an innate instinct; it has a fundamental function for orofacial development; it is also part of two neonatal reflexes that remain only in the first months of life. Therefore, the “pacifier” is a transitional object and could have

several benefits and utilities: (i) calming effect: pacifier has an analgesic effect and is used from birth to reduce anxiety and pain; and SIDS. Among the recommendations of the American Academy of Pediatrics (AAP), the use of the pacifier was introduced to reduce the risk of SIDS; the correct mechanism is not clear, but probably the pacifier promotes the supine position during sleep, increases the patency of the airways, reduces gastropharyngeal reflux and sleep apnea and increases respiratory drive by reducing carbon dioxide (70).

The pacifier could also prevent “rebreathing” by avoiding direct face contact with the sheets. It has also been seen that it lowers the awakening threshold and determines a greater production of arousal in case of hypoxia. Even the information given to parents about its protective role increases their attention to ensure that the child does not lose the pacifier while sleeping. Furthermore, some theories believe that nonnutritive sucking may regulate the control of the infant’s autonomic nervous system (70, 71): i) premature children: a review of the literature has shown that in premature babies, nonnutritive sucking is related to a reduction in hospital stay, favours a faster transition from enteral feeding and improves bottle feeding (72); ii) infections: numerous studies have reported that *Candida*, *Streptococci* and other microorganisms often colonize pacifiers. In particular, latex pacifiers are more frequently colonized by *Candida*, *Staphylococcus* and pathogens commonly responsible for otitis media than silicone ones (73); iii) medium otitis: The American Academy of Family Physicians (AAFP) and the American Academy of Pediatrics (AAP) have issued guidelines regarding otitis media recommending limiting the use of pacifiers from six months to prevent the risk



Fig. 2. Overjet increase: front view (left) and occlusal view (right)

of such pathology. Two mechanisms could explain the correlation between the use of the pacifier and otitis media: reflux of nasopharyngeal secretions in the middle ear during sucking or dysfunction of the Eustachian tube due to alteration of the dental structures (74); and iv) malocclusions: protracted and prolonged use after two years of age can predispose to the development of malocclusions. The pacifier could also disadvantage breastfeeding if it is used in the first month of life, before breastfeeding is consolidated (48, 75, 76).

It should be borne in mind that prolonged and protracted use even of the so-called traditional pacifiers could cause damage, similar to the vitiated habit of finger sucking. The pressure of the thumb or the inadequate pacifier directs the growth of the base of the maxilla downwards, delaying the eruption of the anterior teeth while the posterior ones continue to erupt. In the vertical plane, this results in the formation of an anterior open bite (23, 77, 78).

On the sagittal plane, on the other hand, thumb sucking or inappropriate use of the traditional pacifier predispose to a molar and canine II class relationship and increased overjet (Figures 4 and 5); the latter factor is due to the pro-inclination of the upper incisors due to the advancement of the premaxilla. The endo-inclination of the lower incisors can also worsen Overjet due to external pressure. The predisposition to class II, on the other hand, could be related to the advancement of the base of the upper jaw (79–81).

In addition, a significant correlation was observed between prolonged sucking of the traditional pacifier and a significant reduction in the mean intercanine and intermolar amplitude in the maxillary arch and an increase in the incidence of cross bite (77, 82).

Baby bottle use

Breastfeeding promotes proper craniofacial development thanks to the intense muscle activity required, which promotes a correct lip seal, stimulates mandibular function and correctly positions the tongue on the palate. Several mechanisms have been hypothesized through which bottle feeding can contribute to the development of malocclusions (49):

- Traditional bottle feeding requires less muscle

activity, and this involves less exercise of the chewing and perioral muscles with consequent hypotonus;

- The tongue and lips during bottle-feeding could play a passive role, leading to the establishment of altered swallowing patterns and lingual pushing habits;
- Over 60% of bottle-fed babies present with oral or mixed breathing.

Early childhood caries

The term “early childhood caries” (ECC) refers to early childhood caries (first three years of life). They represent a serious problem for children’s health and have a serious social impact, resulting in:

- pain and discomfort
- reduced appetite resulting in malnutrition and possible delayed physical development
- speech joint disorder
- impairment of social relationships due to reduced self-esteem
- difficult and ineffective dental treatments due to poor collaboration (83).

Traditional baby bottles can predispose to ECC because they block the access of saliva to the upper incisors; the lower incisors, on the other hand, being close to the main salivary glands, are protected by saliva and tongue. The use of traditional bottles during the night is also associated with the reduction of salivary flow and the ability to neutralize saliva, which would cause the accumulation of food on the surface of the teeth with consequent prolonged exposure to fermentable carbohydrates. Furthermore, it has been shown that children with ECC sleep less at night, receive more feedings with conventional bottles, and wake up more frequently (24, 84).

According to a recent study, about 47% of babies with ECC were bottle-fed before falling asleep, and in particular, 10% of their parents reported adding sugary substances to their milk. 70% habitually made use of the pacifier with the addition of sugar, honey or the like (85).

For human breast milk, cariogenicity has never been extensively examined in vivo; however, animal studies have suggested that human breast milk has higher cariogenicity than cow’s milk but lower

than infant formula at high-frequency exposures. Therefore, breastfeeding could be a protective factor against ECC for babies compared to formula milk. However, the association between breastfeeding and ECC is potentially prone to confusion by other factors such as nighttime breastfeeding, brushing habits, frequency of eating sweets, parental education level and socioeconomic status (86-162).

CONCLUSION

Ideal timing to set correct nutritive needs is concentrated in the first 1,000 days of the child's life, which is essential to ensure his physical well-being and neuro-intellectual development in the short and long term. Growing organism health is determined not only by the genetic background but also by nutritive needs.

Dentists can play a fundamental role in the prevention of maternal and child health. They must manage mothers' oral health from pregnancy, encourage breastfeeding, and promote the first dental visit between 12-18 months to intercept bad habits and incorrect lifestyles and guide the development of the deciduous dentition. They must also discourage the use of a pacifier after two years of age associated with the use of sugar substances to prevent the onset of early childhood caries; the latter have a serious social impact. Therefore, it is necessary to intensify information, prevention, and follow-up campaigns. According to current scientific evidence, breastfeeding for up to six months is a protective factor for the correct overall development of the baby. The use of prolonged pacifiers or thumb sucking often occurs in children who have never been breastfed and lead to a greater risk of developing class II malocclusions, open bites and cross bites.

The challenge of future dentistry and orthodontics is to create personalized prevention programs to make patients aware of correct lifestyles from early childhood and intervening on the risk factors of dental diseases and not on overt pathologies. A healthy lifestyle and a peaceful pregnancy surrounded by a favourable relational environment are the foundations for guaranteeing the best starting conditions and greater possibilities for the child's well-being.

Institutional Review Board Statement:

The present clinical study was based at the University of Bari (Italy), in full accordance with ethical principles, including the World Medical Association Declaration of Helsinki and the additional requirements of Italian law. Furthermore, the University of Bari, Italy, classified the study to be exempt from ethical review as it carries only negligible risk and involves the use of existing data that contain only non-identifiable data about human beings. The patient signed a written informed consent form.

Informed Consent Statement:

Informed consent was obtained from the subjects involved in the study. Written informed consent has been obtained from the patient to publish this paper.

Data Availability Statement:

All experimental data to support the findings of this study are available by contacting the corresponding author upon request.

Conflicts of Interest:

The authors declare no conflicts of interest.

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Periodontal disease and clinical association with COVID-19 infection

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SARS-CoV-2 infection can cause long-standing damage to the immune system characterized by increased inflammatory cytokine activation. Maintaining periodontal health may reduce host susceptibility to COVID-19 and prevent COVID-19 aggravation in infected patients. There is sufficient evidence in the literature to warrant an association between the presence of PDs and the development and course of respiratory illnesses. Optimum oral health, maintaining good systemic health, and elimination of smoking habits may be beneficial for the prevention and management of COVID-19 infections. Future studies on the periodontal status of patients with COVID-19, including from mild to severe forms, could allow the opportune identification of people at risk of severe illness and generate relevant recommendations. The connection, if any, between the oral microbiome and COVID-19 complications is urgently required to establish the importance of oral hygiene and pre-existing oral disease in the severity and mortality risk of COVID-19.

Key words: COVID-19; periodontitis; pneumonia; respiratory diseases; periodontal disease; brain; spine; coronavirus

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COVID-19 is a disease caused by the recent coronavirus named SARS-CoV-2 that triggers damage to the lungs and other organs. Most COVID-19 patients present mild symptoms; however, other patients could develop severe illnesses having pneumonia, pulmonary oedema, acute respiratory distress syndrome (ARDS), multiple organ dysfunction syndromes, or even die (1-5). Additionally, patients with COVID-19 can present neurologic manifestations, such as headache, loss of sense of smell, stroke and seizures, suggesting that SARS-CoV-2, like MERS-CoV and SARS-CoV-1, displays neurotropism and enters the central nervous system (6,7). Many neurological disorders and conditions affect individuals' functioning, result in disabilities, limit activities, and restrict participation, representing an important global public health (8-22).

SARS-CoV-2 infection can cause long-standing damage to the immune system characterized by increased inflammatory cytokine activation (23-27). Vaccines provide a significant reduction in breakthrough infections with COVID-19 (23). While 80% of patients with COVID-19 infections have mild symptoms, 20% have a severe form of infection associated with higher inflammatory markers (IL-2, IL-6, IL-10), bacteria neutrophil-to-lymphocyte count (28). Optimal oral hygiene and treatment of periodontal diseases (PDs) can reduce ACE2 expression, inflammatory cytokines, and aspiration pneumonia (29-33). Maintaining periodontal health may reduce host susceptibility to COVID-19 and prevent COVID-19 aggravation in infected patients (34). PD therapy also improves systemic diseases such as COPD and diabetes (3,16,35-39). Pitones-Rubio et al. (40) proposed that although some of the known risk factors have not been strongly associated with PDs or their causal relationships are not completely established, it is convincing to propose an association between PDs and COVID-19, where the latter could be affected by the intervention of periodontopathogenic bacteria outside its ecological niche and cause chronic inflammation. Additionally, the association between PDs and severe COVID-19 illness could be non-causal, suggesting that prevention or treatment of PDs does not prevent a worse progression and outcome of COVID-19 (40).

Periodontitis is a chronic inflammatory disease

that progressively affects the integrity of the tissues supporting the teeth and is associated epidemiologically with several chronic disorders, such as cardiovascular disease, type 2 diabetes mellitus, rheumatoid arthritis and spine, inflammatory bowel disease, Alzheimer's disease and certain cancers (41-63). PD comprises a group of diseases involving inflammatory aspects of the host and dysbiotic events that affect periodontal tissues and could have systemic implications (40). Diverse factors and comorbidities have been closely associated with PDs, such as diabetes, obesity, ageing, hypertension and brain disease (40).

This oral disease remains a major public health and socioeconomic burden and affects, in its severe form, about 10% of adults (53). PDs are among the most common diseases that affect adults. It is estimated that about 42% of those above 30 years-of-age and 60% of those above 65 years-of-age have periodontitis (64-67). Severe stages of periodontitis are the sixth most common disease in older adults, affecting about 11% of the global adult population (23,64). PD should also be considered a pandemic, with the reported case load exceeding COVID-19 (5,65-69). Among other chronic inflammatory diseases and conditions, periodontal inflammation may influence COVID-19 susceptibility and pathogenesis (70,71-80).

There is sufficient evidence in the literature to warrant an association between the presence of PDs and the development and course of respiratory illnesses (81). These mechanistic links range from a direct aspiration of these pathogens into the lungs to more indirect mechanisms wherein virulence factors and enzymes released by periodontopathogens may modify mucosal surfaces to make them more amenable to colonization, destroy bacterial salivary pellicle to inhibit their subsequent clearance or modify the respiratory epithelium via cytokines to promote infection (28,82-86). COVID-19 patients with PD have a higher mortality risk than patients without periodontitis (88). In addition, the immune cellular release of cytokines, including IL-1 and TNF in periodontitis, may exacerbate the recognized "cytokine storms" associated with COVID-19 infections (71).

Marouf et al. (89) found a significant association between PDs and COVID-19-related outcomes.

However, no clinical assessment of their periodontal status at the time of suffering from the COVID-19 infection was made and hence patients with previous bone loss but no active disease at the time of the study might have been grouped along with those experiencing an active disease. On the other hand, Gupta et al. (5) did not conduct a real-time clinical examination of all the patients involved and made the important distinction of assessing active PDs and their relation to COVID-19-related outcomes.

Sampson et al. (28) reported that the four main comorbidities associated with an increased risk of complications and death from COVID-19 are also associated with altered oral biofilms and PDs, hence the link between poor oral health and COVID-19 complications is suggested. Periodontopathic bacteria are implicated in systemic inflammation, bacteremia, pneumonia, and death. Epigenetic mechanisms contribute to many aspects of the SARS-CoV-2 replication cycle, including expression levels of viral receptor ACE2, cytokine genes as part of the host immune response and the implication of various histone modifications in several aspects of COVID-19 (90). SARS-CoV-2 proteins physically associate with many different host proteins throughout infection, and notably, there are several interactions between viral proteins and epigenetic enzymes such as HDACs and bromodomain-containing proteins, as shown by correlation-based studies (90).

Several studies give credence to the association between the COVID-19 and PDs since the beginning of the pandemic. For example, a recent publication has reported that the patients with COVID-19 have higher dental plaque scores and gingival oedema than their matched SARS-CoV-2 negative controls (85). In addition, Larvin et al. (87) analyzed the data on surrogates of periodontitis from 13,253 participants in the United Kingdom Biobank, which included 1,616 COVID-19 positive cases, observing significantly higher mortality in the patients with COVID-19 with periodontitis.

In another retrospective study, Sirin and Ozcelik (91) analyzed the dental records and panoramic radiographs of 137 patients with COVID-19 and found a remarkable connection between dental damage and the prognosis of viral disease. Also,

Marouf et al. (88) conducted a case-control study by collecting the electronic health records, medical as well as dental, of the patients with COVID-19 and analyzed them for the associations between the presence of periodontitis and the severity of COVID-19 infections, reporting a significant association was observed between the presence of periodontitis and COVID-19 complications, such as death, ICU admission, or need for assisted ventilation. However, as PD is both reflective and deterministic of systemic health, it might also play an indirect role in worsening the status of comorbidities more directly associated with a poorer prognosis of COVID-19-related adverse outcomes (5). The use of telemedicine can be an essential tool to avoid unnecessary travel to hospitals and clinics, reducing the potential risk of COVID-19 infection and continuous observation and daily clinical practice by physicians and surgeons, continuous scientific research and new technologies can improve long-term patient outcomes and provide further insights and discoveries (92-105).

Survival against SARS-CoV-2 infection may partially depend on periodontal health, good oral hygiene and access to dental care. Optimum oral health, maintaining good systemic health, and elimination of smoking habits may be beneficial for the prevention and management of COVID-19 infections (71). Future studies on the periodontal status of patients with COVID-19, including from mild to severe forms, could allow the opportune identification of people at risk of severe illness and generate relevant recommendations (106-153). The connection, if any, between the oral microbiome and COVID-19 complications is urgently required to establish the importance of oral hygiene and pre-existing oral disease in the severity and mortality risk of COVID-19.

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The effect of casein phosphopeptide-amorphous calcium phosphate on chemical-induced enamel erosion: an in vitro study with ESEM analysis

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AIM: Chemical exogen acids effect can be considered in terms of the loss of hard tissue of teeth or potential loss. When the remineralization does not antagonize the demineralization, the dissolution of hard tissues arises. Significant among physical processes is degeneration in enamel structure due to the chemical processes of acidification and alkalization. There are also several underlying determinants of enamel erosion. The enamel erosion induced by chemical exogen acids causes the dissolution of the hard tissues of teeth. The aim of this study was to analyze the erosive effect of three different soft drinks on the enamel surface and the potential remineralizing effect after applying casein phosphopeptide-amorphous calcium phosphate.

MATERIALS AND METHODS: Fifteen human third molar teeth specimens were analyzed to assess the effects of the topical cream containing 10% w/w casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) nanocomplexes on enamel teeth lesions. Morphological characterization of teeth was performed using Environmental Scanning Electron Microscope (ESEM). In addition, the surface of specimens was examined before and after immersion into three recipients containing three different soft drinks and after the remineralization process for comparison.

RESULTS: Environmental Scanning Electron Microscopy analysis showed enamel morphology alterations after acidic soft drink exposure and superficially repair of teeth enamel after remineralizing treatment.

CONCLUSION: This in vitro study demonstrated that the casein phosphopeptide-amorphous calcium phosphate treatment was effective in remineralizing demineralized subsurface lesion enamel in vitro after having caused alterations by exogen acids.

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Dental erosion can be defined as the chemical dissolution of tooth minerals resulting in the loss of hard tissues but without the involvement of bacteria. Chemically-induced enamel erosion is a multifactorial condition and is recognized as being triggered by exogen acid exposure. Several diet agents have been associated with enamel erosion. The consumption of the adverse diet causes characteristic abnormalities of hard tissues of teeth, primarily with the dissolution. It is well known that this lesion results from the dissolution of the tooth by extrinsic or intrinsic acids or chelator acids when the surrounding aqueous phase is undersaturated concerning tooth minerals (1-7). The exogen acid introduction in the oral cavity is the leading cause of dental erosion as a result of a chemical reaction between hydrogen ions in the acid with dental hydroxyapatite $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ that promote the release of mineral ions (Ca^{2+} , OH^-) and PO_4^{3-} (8-9).

Furthermore, the enamel demineralization causes a substantial decrease in microhardness (10-17), increasing the vulnerability of the surface to mechanical impacts (18). The enamel erosion influences the occurrence of cervical lesions. Indeed, when the enamel is exposed to chemical insult, a process defined as “softening” begins, consisting of the loss of a mineral layer extending a few micrometres below the surface (19). In the early stages, this process is reversible. If the softening evolves, it results in complete loss of enamel. The high consumption of acidic beverages as diet components in childhood explains the most prevalence of these lesions among children (18-21). The consumption of acidic drinks has changed through the decades, increasing exponentially (22-26). There is strong evidence that the chemical composition and properties of the demineralizing solution are implicated in the dental erosive process caused by acidic drinks (27-30). Indeed, conventional soft drinks also consist of titratable acidity and chemical preservatives. In addition to lower PH value, these agents increase the erosive potential of these beverages. In other risk factors, this phenomenon is associated with a high incidence and progression of dental erosions, mainly in children and adolescents

(31-33); this may compromise the dentition and lead to expensive restorations in adulthood (34-37). Therefore, interest in early child development and recognition of its lifelong impacts grows. Preventive measures to counteract enamel erosion are imperative.

One result, in recent years, has been a substantial increase in numerous treatment regimens, including a new formulation of toothpaste containing casein phosphopeptide – amorphous calcium phosphate (CPP-ACP), which studies in vitro have demonstrated to be effective in inhibiting cariogenic activity and reducing demineralization of the altered tooth surfaces. The casein phosphopeptide – amorphous calcium phosphate (CPP-ACP) is a bioactive agent with a base of milk. It has been demonstrated that the anti-cariogenic property of CPP-ACP due to its ability to stabilize calcium and phosphate in an amorphous state, also due to the presence of two cluster sequences in CPP, Ser (P)-Ser (P)-Ser (P)-Glu-Glu from casein (38-41). Moreover, ACP separates from CPP in an acidic environment, thereby enhancing salivary calcium and phosphate concentrations (39-43). Furthermore, CPP can become constant with the level of ACP in saliva by inhibiting the precipitation of calcium and phosphate and stabilizing the calcium level. Our study aimed to analyze the potential remineralizing of paste containing casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) after demineralization process induced by exogen acids, using a well-known chemical process. Three predisposing factors (soft drinks) were selected based on available data present in the literature (44-52).

MATERIALS AND METHODS

Fifteen third human molar teeth were included in the study. All were extracted for orthodontic reasons, and written informed consent was obtained from all participants to use their teeth for scientific purposes. Inclusion criteria were teeth caries lesions free. Biological samples were handled by one of three different procedures before ESEM (Environmental Scanning Microscope Quanta 200, FEI Company, Philips Electron Optics, Eindhoven, Netherlands) observation. Analysis of specimens for

morphological characterization was performed using an ESEM, set in low vacuum mode (120 Pa), at pressures that were ca. 0.6 Torr lower than the pressure of maximum brightness. The ESEM technology allows the analysis of biological samples in their natural state and without metal coating (Danilatos 1988, Goldstein et al. 1992, Johnson et al. 1993). The instrument allows a resolution of 3.0 NM @ 30kV, with a high signal to noise ratio both in high/low vacuum and ambient mode. The acceleration voltage (200V÷30 KV) and the filament current (up to 2µA) are constantly adaptable. Stehr and Oestlund (2000) showed that ESEM is an essential tool in studying the surface condition and acceptable machining deformations without the risk of artefacts in specimen preparation. This microscope was equipped with the following facilities: SED Everhart-Thornley secondary electrons detector, LFD (large field secondary electrons detector, GSED (secondary gaseous electrons det., in ESEM mode), BSED/CLD detector for photocathodoluminescence electrons, Thermostatic Peltier heating/cooling stage (20°-5°C) (in ESEM mode) with external chiller, Eucentric goniometer stage with R = 360° continuous and repeatability: 2µm, Digital video recording.

Preparation protocol for ESEM

Before the treatments, samples were handled by the following procedure: (1) the teeth specimens were thoroughly cleaned of all residual debris with mechanical instruments and then stored in physiological saline solution for three weeks; subsequently, each sample was mounted on stubs with double-adhesive. No metallization of the samples was necessary. (2) The teeth were untreated to evaluate the enamel surface before the effect of exogen acids; (3) the chamber conditions were set at 5° and 6.0 Torr (humidity in the specimen chamber was about 85%); and (4) the samples were observed and photographed. Therefore, after undergoing ESEM observation, all specimens were divided into three groups and then immersed in different acid solutions for thirty minutes a day for 7 days to simulate a typical daily assumption of soft drinks. In Group A, each specimen was immediately washed with normal saline and then immersed into individual containers of Coca Cola (having phosphoric acid) with PH 2,53. After washing with normal saline in group B, the teeth were placed into containers of RED BULL (having citric acid) with PH 3,41. Samples of Group C were rinsed with sterile saline and then immersed into individual containers of orange juice (having

citric acid about 0.2-0.004 M) with PH 3.5. Subsequently, each sample was treated with casein phosphopeptide-amorphous calcium phosphate for three minutes for 10 days to evaluate the remineralizing effectiveness. After each treatment, the teeth specimens were cleaned and washed with distilled water and then stored in normal saline until further treatment was stored in physiological saline solution up to the time they were analyzed. Therefore, morphological analysis was performed. Samples were analyzed using secondary electrons with SS Detector (Solid State detector) or LFD (Large Field Detector).

RESULTS

In vitro morphological ESEM evaluation

The images obtained from the treated samples at different conditions were compared with images observed after treatment with casein phosphopeptide-amorphous calcium phosphate. Before the treatments, samples were handled by the following procedure: to prepare these samples, (1) the teeth specimens were thoroughly cleaned of all residual debris with mechanical instruments and stored in physiological saline solution for 3 weeks; (2) the deposition of a conductive layer on the specimens was not necessary. Samples were mounted on stubs with double adhesive. The teeth were untreated to evaluate the effect of the exogen acids on the enamel surface; (3) the chamber conditions were set at 5°C and 6.0 Torr (humidity in the specimen chamber was about 85%); and (4) the samples were observed and photographed using an SR stereomicroscope (Carl Zeiss AG, Oberkochen, D-73446, Germany). The images obtained from the treated samples in different solutions were compared with images observed after treatment with casein phosphopeptide-amorphous calcium phosphate. Teeth were examined at magnifications of (×100, ×250, ×500 and ×1000) with the ESEM. All teeth specimens were shown at the ESEM about the same appearance.

The enamel is more evident than the root to the rear-scattered electrons or the secondary electrons. Representative ESEM images of the retrodiffused electrons, at the low empty ESEM, of the teeth before treatment with the soft drinks were revealed. The ESEM image from Group A showed the regular enamel prisms' ends. The enamel surface was fairly

uniform, with longitudinal grooves and fracture lines. The morphological analysis showed a jagged root, specifically at the dental-enamel junction, and the level can be either jagged or uniform. The ESEM image from group A showed standard prisms' ends with few surface deposits and no surface enamel roughness after immersion into Coca Cola. The ESEM image from group B showed surface deposits with mild enamel surface roughness after casein phosphopeptide-amorphous calcium phosphate treatment. The ESEM image from group C showed low surface deposits and no surface roughness. The ESEM image from group D showed severe enamel surface roughness with no surface deposits. The ESEM showed deep fissures and damaged enamel prisms in the sample treated with Coca Cola. The ESEM image from Group B, treated with RED BULL, showed surface deposits with mild enamel surface roughness. The ESEM image from group C showed scarce surface deposits and no surface roughness. The ESEM image from group D showed severe enamel surface roughness with no surface deposits. After treatment with Coca Cola, at a magnification of 500 $\times$, the dental surface showed numerous extended fractures on the enamel, with more uniform portions and others more susceptible to the erosive action of the drink. The prisms were damaged, showing more eroded than the sheaths, with more uniform portions and others more susceptible to the effect of the drink. At a low magnification of 250 $\times$, before the treatment with Coca Cola, the surface of the enamel appeared sufficiently uniform, with some slight longitudinal groove and some lines of surface fracture. The root occurred at the ESEM with a frayed surface, especially near the amelo-cementitious junction and some fracture lines. The treatment with casein phosphopeptide-amorphous calcium phosphate revealed the almost total absence of scratches and grooves, filled and levelled. After treatment with casein phosphopeptide-amorphous calcium phosphate, it was shown clearly how the level of the prisms of the enamel was settled, occluding the cavities produced by the erosive action of Coca Cola. After treatment with Red Bull, the ESEM sample presented an accentuated erosive damage; the surface was more eroded at the enamel level, with newly formed fracture lines. Taking as a reference the same

surface, treated first with Red Bull and then with casein phosphopeptide-amorphous calcium phosphate, we noted slight improvements, especially on the enamel, with the presence of casein phosphopeptide-amorphous calcium phosphate deposits, which had the characteristic of chemically binding to it. Near the root, we saw the casein phosphopeptide-amorphous calcium phosphate bound to the surface, and the fracture lines occurred with less thickness than in the previous image. Before being treated with Red Bull, the surface had depressions of the prisms in specific sites; in others, the homogeneous glaze was observed. Near the amelite-cementitious junction, the appearance of the surface was frayed. In order to analyze an area of the larger surface at lower magnification, it is highlighted how the Red Bull does not have uniform effects on the prisms but produces irregular excavations. Analyzing at the same magnification, the same surface area, following the treatment with Red Bull and subsequently with casein phosphopeptide-amorphous calcium phosphate, we found how erosion defects were reduced, showing a more compliant surface. After the treatment with Red Bull, at a higher magnification, the enamel presented porous. The drink changed the appearance of the surface, producing irregular excavation of prisms and generalized microlesions. After the treatments with Red Bull and casein phosphopeptide-amorphous calcium phosphate, it was possible to notice the improvement of the enamel surface. The change in its appearance highlighted the reparative action of the casein phosphopeptide-amorphous calcium phosphate.

At a magnification of 500 $\times$, the casein phosphopeptide-amorphous calcium phosphate treated surfaces appeared covered by a uniform layer of material. Enamel micro-cavities are filled. Before being treated with 100% orange juice, the sample was presented to the ESEM with a fringed pattern near the enamel-cement junction, with marked soft wear at the level of the enamel, where longitudinal and horizontal furrows prevailed, associated with abrasions with hard materials, and a slight presence of prism depressions. The root, because of its composition more susceptible to external insults yet presented jagged already departing. There were numerous microfractures, particularly accentuated at the cement-enamel

junction and when the same site was brought to 500x magnification to better highlight erosion from the juice. Depressions of the prisms already present were noted but aggravated by the drink's erosive effect, which also damaged the formation of new furrows.

DISCUSSION

It is generally accepted that the physicochemical properties of exogenous chemical soft drinks increase the risk of teeth enamel erosion. Reynolds and co-workers demonstrated that formulations of professionals containing casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) could significantly affect the remineralizing process. (10-17, 53, 54) The authors found that increasing the duration of exposure to casein phosphopeptide-amorphous calcium phosphate increased the levels of calcium and phosphate ions and promoted the remineralization of enamel subsurface lesions *in situ* (55-61). Based on a comparison of the physicochemical properties of the various remineralizing agents, the authors showed the synergistic effect of 2% CPP-ACP in conjunction with 1100 ppm fluoride in reducing the enamel dissolution because of the formation of CPP-stabilized amorphous calcium fluoride phosphate, which results in the increased incorporation of fluoride ions into plaque (62-64). Similar findings have also been reported by Cai et al. in a randomized, controlled, double-blind trial showing that CPP-ACP significantly reduced the caries experience when the fluoride was added (65). The concentration employed in this study reflects the level of agent required to exert a clinically beneficial effect on the enamel surface when applied topically (66-68).

Furthermore, work is required on these systems to make a definitive comparison of the effect of solvent volatility and penetrant lipophilicity upon their penetration into the skin (34-39, 69). Microradiography of the remineralized lesions demonstrates that the 2% CPP-ACP paste generated homogenous remineralization of the lesion. This effect is attributable to the ability of the CPP to concentrate and fix the ions at the tooth surface in the correct molar ratio [Ca:PO₄:F = 5:3:1]. In several different studies, the effectiveness of CPP-ACP technology

has been demonstrated in promoting the levels the remineralization of enamel subsurface lesions via increasing the level of calcium and phosphate ions in supragingival plaque (70-78). Barbour *et al.* demonstrated that CPP-ACP bound to bacterial and produced a reservoir of bioavailable calcium ions (79). In another randomized clinical study, Lussi et al. examined 152 visible white-spot lesions on 60 incisors and canines immediately after orthodontic debonding (80). They were assigned to different remineralizing treatments, which comprised a tooth cream containing CPP-ACP with a fluoride dentifrice or a daily topical application of a 0.05% sodium fluoride mouthwash in conjunction with fluoride dentifrice (81-90). The lesions were observed, and the authors reported a significant difference between the treatment ($p < 0.01$), registering a regression of about 64% of white spots for the CPP-ACP group in comparison with the fluoride group, which reported a 23% of regression (91-134).

The present *in vitro* study demonstrated that the casein phosphopeptide-amorphous calcium phosphate treatment was effective in remineralizing demineralized subsurface lesion enamel *in vitro* after having caused alterations by exogen acids.

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Salivary markers quantification of oxidative stress in patients with periodontitis, before and after intensive periodontal treatment: a one-blinded, randomized, clinical trial

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AIM: Periodontitis is one of the most common inflammatory and infectious diseases, significantly associated with circulating levels of oxidative stress biomarkers. A network of interacting molecular pathways comprising proinflammatory mediators and reactive oxygen species (ROS) are involved in the progression of periodontitis. The aim of the trial was to determine the effects of intensive periodontal treatment on the salivary levels of oxidative stress in patients with moderate periodontitis.

MATERIALS AND METHODS: A randomized, one-blinded, controlled clinical trial was conducted with 3 months of follow-up. A total of 58 patients were included in the study and randomized to receive intensive periodontal treatment (Group Test) or conventional adult prophylaxis (Group Control). Salivary samples for determination of total antioxidant status (TAS), total oxidant status (TOS), nitric oxide (NO), myeloperoxidase (MPO), glutathione (GSH), malondialdehyde (MDA) levels, and 8-hydroxy-2'-deoxyguanosine (X8-OHdG) concentrations were collected from each patient prior to the periodontal treatment and at 3 months after the therapy.

RESULTS: A significantly decreased NO, and MDA levels were registered in the Test Group compared to the Control Group ($p < .0001$), and the concentration of GSH was found to be significantly increased in the test group compared to the control group.

CONCLUSION: Intensive periodontal treatment mitigates salivary oxidative stress in patients with moderate periodontitis.

Key words: periodontitis; oxidative stress; salivary markers; prophylaxis; periodontal treatment

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Periodontitis is a common inflammatory chronic disease affecting the hard and soft tissues around the teeth and is the primary cause of tooth loss in adults (1-6). Periodontitis is due to a complex interaction between the host immune system and pathogenic bacteria that leads to the loss of attachment of the connective tissue from the root cementum and alveolar bone (7-12). Oxidative stress plays an essential role in the pathophysiology of the destruction of periodontium during inflammation (13-15). Oxidative stress is an imbalance of pro-oxidants and oxidants (16-18). An oxidative stress condition is established if homeostasis is disrupted in favor of ROS (19-23). The effect of oxidative stress in periodontitis can be explained by the increase in levels of systemic and local release of Tumor Necrosis Factor- α (TNF- α) and Interleukin 6 (IL-6) (24-29). ROS production is mandatory in all aerobic organisms with a complex antioxidant defence system (30-33). The critical biomarkers of oxidative stress are the total antioxidant status (TAS), total oxidant status (TOS), nitric oxide (NO), myeloperoxidase (MPO), glutathione (GSH), malondialdehyde (MDA) levels, and 8-hydroxy-2'-deoxyguanosine (X8-OHdG) (34-40). MDA biomarker is the main product of lipid peroxidation. It has been demonstrated that ROS directly impacts fibroblast and osteoblast cells and might be responsible for decreased collagen production in extracellular matrix producing cells (41-45). Several clinical trials have demonstrated that total salivary antioxidant status is decreased in patients with chronic periodontitis and that periodontal treatment improves this condition (46-49). The aim of this trial was to evaluate the impact of intensive periodontal treatment on oxidative stress of patients diagnosed with moderate periodontitis.

MATERIALS AND METHODS

This prospective, one-blind controlled clinical trial randomized 58 patients with moderate periodontitis to receive standard periodontal treatment plus gaseous ozone therapy (Test Group) or periodontal treatment alone. The study protocol was approved by the Institutional Review Board at the University of Tetovo in Macedonia (PR. NR. 09-154/3) and conformed with the ethical standards established in the Declaration of Helsinki. Informed

consent was obtained prior to randomization from study subjects. Patients who had at least 4 teeth with one or more sites exhibiting probing pocket depth (PPD) ≥ 4 mm, clinical attachment level (CAL) ≥ 4 mm, full-mouth plaque score and full mouth bleeding score $>35\%$ were enrolled in this study. In addition, patients were included in the trial if they met the following criteria: age >18 years; diagnosis of moderate periodontitis; ability to provide written informed consent. Patients who received periodontal treatment within 12 months prior to the start of the study were excluded, as were patients who received systemic antibiotics within the last 6 months, had uncontrolled hypertension, were pregnant, had a history of heart disease or stroke, or breast-feeding women, and patients unable to make informed consent.

Sample size calculation

A power analysis was conducted prior to the study based on preliminary data (1-4). Using an approximate two-sample proportion test, two-sided and $\alpha = 0.05$, we estimated $>80\%$ power with 25 patients per group to detect a significant difference (<0.001) in oxidative status.

Salivary markers assessment

Participants' clinical periodontal examination and oxidative stress assessment were performed at baseline and during a 3-month follow-up. Salivary samples were taken at baseline in non-fasting conditions and stored at -80°C for all patients. Then, they were transferred to the University of Tetovo for analysis. Salivary concentrations of glutathione (GSH), malondialdehyde (MDA), (X8-OHdG), total antioxidant status (TAS), and total oxidant status (TOS), nitric oxide and (NO) were measured by employing a Sciex API 3000 triple quadrupole mass spectrometer as described previously.

Statistical analysis

Data were expressed as means $\pm$ SEM or median or median and range. Shapiro-Wilk tests were conducted to determine whether a normal distribution could have produced dependent variables for each group (Razali & Wah, 2011). The result of the Shapiro-Wilk test was significantly based on an alpha value of .05, $W = 0.81$, $p < .001$. This result suggests that the variables are unlikely to have been produced by a normal distribution. Levene's test was conducted to assess the homogeneity of variance. The result of Levene's test

was significant based on an alpha value of .05, $F(1, 85) = 13.73$, $p < .001$. This result indicates that the assumption of homogeneity of variance was violated. The Mann-Whitney U test assessed differences in GSH levels. All entered data were analyzed using SPSS software (Statistical Package for the Social Sciences version 15 USA).

RESULTS

Fifty-eight patients were enrolled. All participants completed the study. Group Test had an average of age of 58.25 ($SD = 8.46$, $SE_M = 1.28$, Min = 39.00, Max = 70.00). The observations for age for Group Control had an average of 47.26 ($SD = 8.50$, $SE_M = 0.91$, Min = 32.00, Max = 54.00). At baseline, about the variable X8-OHdG, the two-tailed Mann-Whitney U test was not significant based on an alpha value of .05, $U = 726$, $z = -1.87$, $p = .062$. The mean rank for group A was 39.00, and the mean rank for group B was 49.12; this suggests that the distribution of X8-OHdG for group A ($Mdn = 4,789.00$) was not significantly different from the distribution of X8-OHdG for the group B ($Mdn = 4,890.00$) category. Fig. 1 presents a boxplot of the ranks of X8-OHdG by the group. About the variable TOS, the result of the two-tailed Mann-Whitney U test was not significant based on an alpha value of .05, $U = 996.5$, $z = -0.43$, $p = .667$. The mean rank for group A was 45.15, and the mean rank for group B was 42.83, suggesting that the distribution of TOS at baseline for group A ($Mdn = 15.75$) was not significantly different from the distribution of TOS at baseline for group B ($Mdn = 15.50$) category. Figure 1 presents a boxplot of the ranks of each variable at baseline by the group. Regarding the variable NO, the result of the two-tailed Mann-Whitney U test was not significant based on an alpha value of .05, $U = 1109.5$, $z = -1.39$, $p = .165$. The mean rank for group A was 47.72, and the mean rank for group B was 40.20, suggesting that the distribution of NO at baseline for group A ($Mdn = 25.35$) was not significantly different from the distribution of NO for group B ($Mdn = 24.50$) category. The result of the two-tailed Mann-Whitney U test was significant based on an alpha value of .05, $U = 1331$, $z = -3.27$, $p = .001$. About the variable MDA, the mean rank for group A was 52.75, and the mean rank for group B was 35.05, suggesting that the distribution of MDA for group A was

significantly different from the distribution of MDA at baseline for the group B. The median for A ($Mdn = 233.84$) was significantly larger than the median for B ($Mdn = 190.34$). The two-tailed Mann-Whitney U test about the variable TAS was not significant based on an alpha value of .05, $U = 954$, $z = -0.07$, $p = .946$. The mean rank for group A was 44.18, and the mean rank for group B was 43.81; this suggests that the distribution of TAS at baseline for group A ($Mdn = 4.32$) was not significantly different from the distribution of TAS for the group B ($Mdn = 4.32$) category. Table I presents the result of the two-tailed Mann-Whitney U test. Fig. 1 presents the boxplot of the ranks of each variable at 3 months by the group.

At 3 months, the two-tailed Mann-Whitney U test for X8-OHdG was not significant based on an alpha value of .05, $U = 726$, $z = -1.87$, $p = .062$. The mean rank for group A was 39.00, and the mean rank for group B was 49.12, suggesting the distribution of X8-OHdG for group A ($Mdn = 4,789.00$) was not significantly different from the distribution of X8-OHdG for the B ($Mdn = 4,890.00$) category. TOS of the two-tailed Mann-Whitney U test was not significant based on an alpha value of .05, $U = 996.5$, $z = -0.43$, $p = .667$. The mean rank for group A was 45.15, and the mean rank for group B was 42.83; this distribution of TOS for group A ($Mdn = 15.50$) was not significantly different from the distribution of TOS for the group B ($Mdn = 15.50$) category. The two-tailed Mann-Whitney U test regarding the variable NO was not significant based on an alpha value of .05, $U = 1109.5$, $z = -1.39$, $p = .165$. The mean rank for group A was 47.72, and the mean rank for group B was 40.20, suggesting that the distribution of NO for group A ($Mdn = 25.35$) was not significantly different from the distribution of NO for the group B ($Mdn = 24.50$) category. The two-tailed Mann-Whitney U test about the MDA variable was significant based on an alpha value of .05, $U = 1331$, $z = -3.27$, $p = .001$. The mean rank for group A was 52.75, and the mean rank for group B was 35.05, suggesting that the distribution of MDA for group A was significantly different from the distribution of MDA for group B. The median for A ($Mdn = 233.84$) was significantly larger than the median for B ($Mdn = 190.34$). The two-tailed Mann-Whitney U test for TAS was not significant based on an alpha value of .05, U

= 954, $z = -0.07$, $p = .946$. The mean rank for group A was 44.18, and the mean rank for group B was 43.81, suggesting that the TAS distribution for group A ($Mdn = 4.19$) was significantly different from the distribution of TAS for the group B ($Mdn = 4.32$) category. Table II presents the two-tailed Mann-Whitney U test results at 3 months. Fig. 2 presents the boxplot of the ranks of each variable at 3 months by the group.

DISCUSSION

Periodontal tissue damage results from several pathologic mechanisms involving the immune response, direct stimulation of the pathogenic

microorganism, and the host system in response to this trauma (50-56). The primary etiologic agent is specific, predominantly gram-negative or facultative anaerobic bacteria within the subgingival biofilm; most periodontal tissue destruction is caused by an inappropriate host response to microorganisms and their products (41-44, 57-59). More specifically, a lack of balance between the proteolytic enzyme, inhibitors, reactive oxygen species (ROS), and antioxidant defence systems causes oxidative stress (60-68). Oxidative stress is believed to cause cellular and molecular damage, which further leads to tissue destruction. (69-74) ROS cause tissue damage through several mechanisms, which include

Table I. Two-Tailed Mann-Whitney Test for all variables at baseline

Mean Rank					
Variable	A	B	<i>U</i>	<i>z</i>	<i>p</i>
X8-OHdG	39.00	49.12	726.00	-1.87	.062
TOS	45.15	42.83	996.50	-0.43	.667
NO	47.72	40.20	1,109.50	-1.39	.165
MDA	52.75	35.05	1,331.00	-3.27	.001
TAS	44.18	43.81	954.00	-0.07	.946

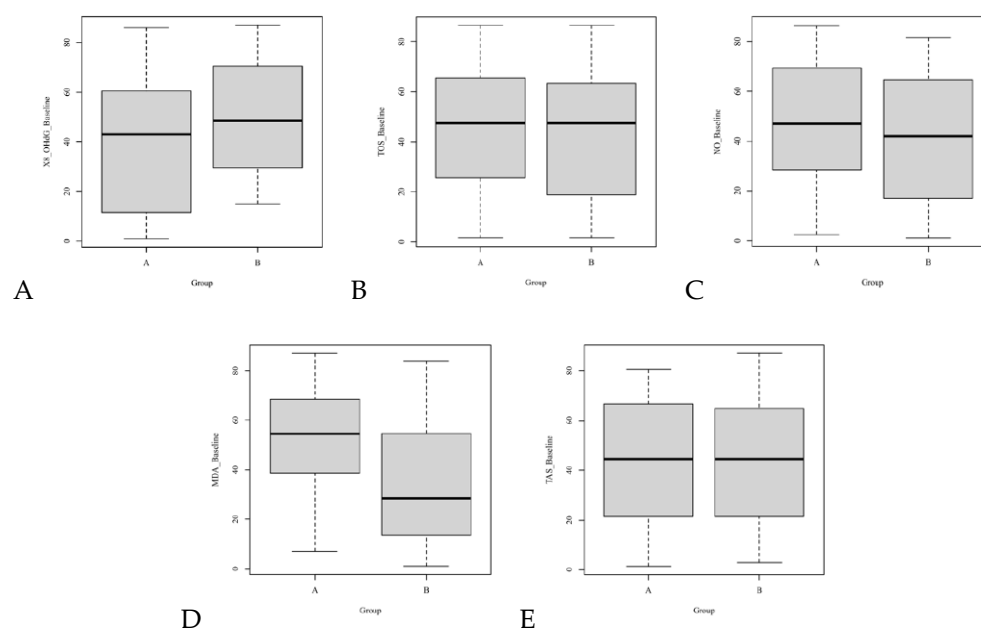


Fig. 1. Ranks of X8-OHdG (A), TOS (B), NO (C), MDA (D), TAS (E) at baseline by Group

DNA damage (75-80), lipid peroxidation (through activation of cyclooxygenases and lipoxygenases) (76), damage to proteins including gingival hyaluronic acid and proteoglycans, and oxidation of important enzymes (e.g., antiproteases, α -antitrypsin, stimulation of proinflammatory cytokine release by monocytes and macrophages by depleting intracellular thiol compounds and activating nuclear factor) (81-86). Oxidative stress generally appears after exposure to a relatively high concentration of ROS and/or a decrease in the antioxidant defence system against ROS (87). It has been implicated as a major contributor to more than 100 disorders and,

more recently, to periodontitis. Our study observed that oxidative stress levels in patients with moderate periodontitis were significantly decreased after intensive periodontal treatment compared with the control group. These results are consistent with other studies that have shown significant improvement in periodontal condition in conjunction with the reduction in oxidative stress (88-129).

Within the limitations of this study, it can be concluded that patients with periodontitis demonstrate a high level of oxidative stress, and intensive periodontal treatment reduces the salivary concentration of the key biomarkers.

Table II. Two-Tailed Mann-Whitney Test for all variables at 3 months

Mean Rank					
Variable	A	B	<i>U</i>	<i>z</i>	<i>p</i>
X8-OHdG	39.00	49.12	726.00	-1.87	.062
TOS	45.15	42.83	996.50	-0.43	.667
NO	47.72	40.20	1,109.50	-1.39	.165
MDA	52.75	35.05	1,331.00	-3.27	.001
TAS	44.18	43.81	954.00	-0.07	.946

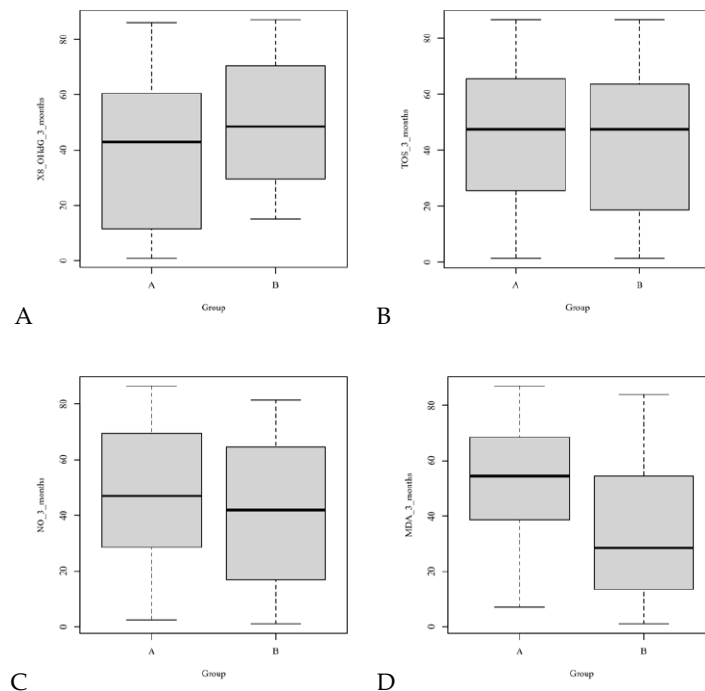


Fig. 2. Ranks of X8-OHdG (A), TOS (B), NO (C), MDA (D), TAS at 3 months by Group

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Temporomandibular joint (TMJ) and cervical spine: is there any relationship between them?

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Many studies supported the clinical, anatomical and functional relationship between the cranial region, the temporomandibular joint (TMJ) and the cervical spine; however, the mechanism of this relationship remains unclear, and the relation between temporomandibular disorders (TMDs) and the head and neck posture changes are still controversial. The understanding of the complex interrelations between the stomatognathic system, cervical spine, pain and dysfunctions in other areas of the body is useful in order to be able to treat patients more efficiently and effectively at the initial stage, when painful symptoms appear, and to cure them much swifter and in a more efficient way. On the other hand, the increased severity of temporomandibular disorders also could lead to a compensatory or antalgic posture of the neck. The function of the masticatory system should be evaluated in patients with neck complaints to rule out the possible involvement of the masticatory system. In addition, to be able to make successful therapeutic interventions, dental surgeons should cooperate in an interdisciplinary fashion with neurologists, orthopedists or neurosurgeons

Keywords: temporomandibular disorders; cervical spine disorders; orofacial pain; temporomandibular joint; musculoskeletal system

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Head and orofacial pain originate from dental, neurologic, musculoskeletal or oncologic diseases, and they are treated by many health care practitioners, such as dentists, oral surgeons, neurosurgeons and physicians who specialize in these pathologies. Many studies supported the clinical, anatomical and functional relationship between the cranial region, the temporomandibular joint (TMJ) and the cervical spine (1-15); however, the mechanism of this relationship remains unclear, and the relation between temporomandibular disorders (TMDs) and the head and neck posture changes are still controversial (1,16-21). One of the possible explanations for these controversial results is the heterogeneity of TMDs, a multifactorial entity without a well-defined etiopathogenesis that encompasses several conditions, such as temporomandibular joint pain, mastication muscle pain, or a combination of both (2,22-31). The understanding of the complex interrelations between the stomatognathic system, cervical spine, pain and dysfunctions in other areas of the body is useful in order to be able to treat patients more efficiently and effectively at the initial stage, when painful symptoms appear, and to cure them much swifter and in a more efficient way.

Temporomandibular disorders are often associated with headaches and neck pain. In the literature, cervical posture is related to different body factors, such as craniofacial morphology and functional factors such as nasorespiratory function and temporomandibular dysfunction (1,2,32-46). Several studies focused on the relationship between the cervical spine and the skeletal class of the subjects (2,22,30,47), but the results were contrasting. Kraus (39) reviewed the musculoskeletal system, including the TMJ and muscles of mastication, in correlation to TMDs and cervical spine disorders. Along with cervical postural changes, neck pain is also common among patients with TMDs (39,48-59). Visscher et al. (30) concluded that patients with craniomandibular pain more often showed cervical spinal pain than those without craniomandibular pain. In addition, chronic craniomandibular pain patients with coexistent cervical spinal pain showed more psychological distress than patients with only a local craniomandibular pain and asymptomatic persons (30). Paço et al. (2), in their study, evaluated the

craniocervical posture in participants with a TMDs diagnosis who underwent orthodontic treatment, reporting that cervical physiotherapy was effective in pain management. Walczyńska-Dragon et al. (60) showed a significant association between TMDs treatment and reduction of cervical spine pain, as far as improvement of cervical spine mobility. Some studies found a correlation between symptoms of craniocervical dysfunction and temporomandibular disorders (2,30,61-73).

On the contrary, others found no relationship between TMD and head-neck posture (74-78). For example, Iunes et al. reported that, despite the biomechanical relationships between TMJ, cervical spinal column and head position and the common presence of changes in these segments among individuals with TMDs, posture should not be interpreted as an etiological factor predisposing TMDs. On the other hand, Weber et al. (79) showed the coexistence of cervical spine dysfunction, and TMD signs and symptoms appear to be more related to the common innervations of the trigeminocervical complex and hyperalgesia of the TMD patients than to craniocervical posture deviations. Furthermore, considering that craniocervical dysfunction can contribute to TMDs, it is reasonable to assume that the physician should evaluate any changes in the craniocervical region during orthodontic treatment and any changes in TMDs (2,21). The increased severity of temporomandibular disorders also could lead to a compensatory or antalgic posture of the neck, as confirmed by the literature (16,80,81).

TMDs are associated with an imbalance of the whole body (60). Moreover, the close relationship between the craniomandibular and craniocervical systems has been described, showing their functional, biomechanical, neurodynamic, and physiological interrelationship as potentially influencing each other (2, 56, 71). Considering this, it seems possible that the mechanical effects of orthodontics may lead to muscular and articular adaptations on the cervical spine. However, the issue of relationships between TMDs and body posture is still a source of speculations. The knowledge about connections between distant body districts must be proven by appropriate diagnostic procedures and instruments.

TMDs are musculoskeletal disorders needing a multidisciplinary effort to manage with other professionals (60,82-84). Segmental limitations of the cervical spine and tender points in neck muscles were shown to be more frequent in patients with TMDs than in those without any TMDs (50,85). Furthermore, cervical sagittal malalignment and deviation from normal sagittal cervical alignment are also common in TMD patients. Average values for cervical lordosis were postulated as 21–34° in the literature (86). Values above 40° and below 20° were found to be correlated with cervicogenic symptoms (74). Kim et al. (87) concluded that associations between upper cervical spine characteristics and treatment outcomes in patients with TMD exist, suggesting such parameters as a possible radiographic index in TMD diagnosis and treatment. However, it is also true that neck pain might play a major role in cervical malalignment in TMDs, as the accompanying neck pain might itself explain the malalignment of the cervical spine in a patient with TMDs (50).

Therefore, continuous observation with daily clinical practice by physicians and surgeons, continuous scientific research and further discoveries, the use of 3-dimensional virtual reality and new technologies can improve patient outcomes and provide relief with the resolution of the pain of these diseases (88-118). Although the aetiology of cervical spine pain very often remains unexplained, reported papers in many cases report the comorbidity of dysfunctions in the stomatognathic system and the pain syndrome in the cervical spine (119-165).

It is evident that the function of the masticatory system should be evaluated in patients with neck complaints in order to rule out the possible involvement of the masticatory system (60). To be able to make successful therapeutic interventions, dental surgeons should cooperate in an interdisciplinary fashion with neurologists, orthopedists or neurosurgeons.

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Chewing and cognitive performance: what we know

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In recent years, chewing has been discussed as producing effects of maintaining and sustaining cognitive performance. It is reported that mastication improves cognitive function by activating cerebral cortical activity, and it is important to demonstrate the cognitive effects of masticatory training using various interventions. Recent studies emphasized that chewing gum can attenuate reductions in alertness, suggesting that chewing gum enhances worker performance. Several mechanisms have been proposed to account for the facilitation in performance observed when the gum is chewed during cognitive testing. Chewing gum during exposure to stress decreases plasma and salivary cortisol levels and reduces mental stress, although other studies report no such effect. In addition, chewing reduces stress-induced changes in central nervous system morphology, especially in the hippocampus and hypothalamus. However, further research on the alerting effects of chewing gum and possible improved test performance in these situations is needed.

Key words: temporomandibular disorders; chewing; cognitive performance; swallowing, attention

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In recent years, chewing has been discussed as producing effects of maintaining and sustaining cognitive performance. It is reported that mastication improves cognitive function by activating cerebral cortical activity, and it is important to demonstrate the cognitive effects of masticatory training using a variety of different interventions (1-10). Smith (11) showed that chewing gum increases alertness and, in contrast, no significant effects of chewing gum were observed in the memory tasks. Intellectual performance was improved in the gum condition (11-32).

Several papers reported that chewing might improve or recover the process of working memory; however, the mechanisms underlying these phenomena are still to be elucidated. Recent investigations have shown how chewing can exert a stimulating effect on cognitive performance. Gum chewing enhances alertness and attention (33-49), speed of neural processing (51), and learning and memory (11). The gum was associated with higher alertness regardless of whether performance tasks were completed and altered sustained attention.

The rate of chewing and subjective force of chewing seems not to alter mood but have some limited effects on attention (41-54). Chewing gum during the workday was associated with higher productivity, and fewer cognitive problems raised cortisol levels in the morning and did not affect heart rate. Recent studies emphasized that chewing gum can attenuate reductions in alertness, suggesting that chewing gum enhances worker performance (41). Several mechanisms have been proposed to account for the facilitation in performance observed when the gum is chewed during cognitive testing (55-65). For instance, Stephens and Tunney (66) argued that the improved performance of those who chewed gum was due to the increased availability of glucose in the brain associated with increased metabolic activity. Hirano et al. (50) investigated the effect of chewing on aspects of attention and cognitive processing speed, testing the hypothesis that this effect induces higher cognitive performance in 17 healthy adults and concluding that chewing induced an increase in the arousal level and alertness in addition to an effect on motor control and, as a consequence, these effects could lead to improvements in cognitive performance.

Recent investigations showed that an asymmetry in electromyographic (EMG) masseter activity during clenching is detrimental to cognitive performance and is associated with pupil asymmetry (anisocoria) (67). A very significant correlation was observed between anisocoria and EMG asymmetry, pupil size being larger on the side of higher EMG activity (hypertonic side). Correction of the trigeminal imbalance by an orthotic splint leads to a great reduction of the anisocoria, with an associated improvement in performance

It is well known that chewing gum is used for sleepiness prevention during work, learning, and driving (50). In addition, it has been shown in the elderly that a decrease in the number of residual teeth is related to dementia onset (50). Moreover, the changes induced by bite wearing in pupil size and anisocoria were significantly related to the corresponding changes in EMG activity and asymmetry during clenching: this finding underlines the importance of sensorimotor trigeminal activity in determining the LC discharge level and the degree of its left-right imbalance. It has to be stressed that bite placement did modify pupil size and anisocoria only when the arches were in contact, so its action was related to its effectiveness in correcting the occlusion, not barely to the stimulation of oral mechanoreceptors (67).

Several longitudinal studies show that masticatory ability is correlated with cognitive function (68-78). Cardoso et al. (79) reported that the Mini-Cognitive Examination scores increased with more occlusal contacts, and higher functional masticatory ability is predictive of individuals with no cognitive impairment. Lexomboon et al. (80) also found that the risk of cognitive impairment was determined not by the teeth loss but by chewing difficulty. Kim (1) showed that Mini-Mental State Examination was used to assess general cognitive function, and a significant improvement was confirmed as a result of the intervention. Although previous studies supporting the direct causal relationship between masticatory exercise and cognitive function are not available, correlation studies on the effects on masticatory ability and cognitive function support our results. Therefore, continuous observation with daily clinical practice by physicians and surgeons, continuous scientific research and further discoveries, the use of

3-dimensional virtual reality and new technologies can improve patient outcomes and provide relief with the resolution of the pain of these diseases (81-111). Chewing gum during exposure to stress decreases plasma and salivary cortisol levels and reduces mental stress, although other studies report no such effect. Chewing reduces stress-induced changes in central nervous system morphology, especially in the hippocampus and hypothalamus (112-161). However, further research on the alerting effects of chewing gum and possible improved test performance in these situations is needed.

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Electric toothbrush vs. sonic toothbrush, the effectiveness on gingival inflammation: a randomized clinical trial

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AIM: The aim of the study is to evaluate the efficacy of electric or sonic toothbrushes on periodontal inflammation.

MATERIALS AND METHODS: A randomized, controlled, one-blind study was conducted. Patients in the test group used sonic toothbrushes (Sonicare FlexCare with ProResults brush head, HX6011, Philips Oral Healthcare Inc, Bothell, Wash), whereas those in the control group used electric toothbrushes (Oral B Professional Care Triumph 4000, Procter & Gamble, Cincinnati, Ohio). Periodontal status was recorded at baseline and 3 months. In total, 60 patients were recruited for the study at baseline. Plaque Index (PI) and Loe and Silness Gingival Index (GI) were used. Student's t- test repeated was used to compare the mean PI and GI scores obtained between the test and control groups at each time point.

RESULTS: In total, 56 subjects completed the study. Significant differences were recorded between the two groups for periodontal parameters at 3 months. In addition, the indices of group *Sonic* were significantly reduced at 3 months compared to the *Roto-oscillatory* Group ($P < .005$).

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CONCLUSION: Sonic toothbrush reduced parameters of periodontal inflammation more effectively than the electric toothbrush.

Keywords: electric toothbrush; sonic toothbrush; gingival inflammation; powered toothbrush; manual toothbrush

Oral hygiene aims to modify the bacterial flora and promote periodontal and dental tissue health. Tooth brushing and floss are the standard methods employed in domiciliary oral hygiene (1-8). However, it has been largely demonstrated that the mechanical action of toothbrushing is more effective than the traditional devices. Although the oscillating-rotating electric toothbrush is the most common tool commercialized, recently, several trials have reported the effectiveness of sonic toothbrush technology (9-16). Oscillating electric toothbrush technology rotates in a clockwise-counterclockwise motion, while the sonic toothbrushes move laterally in a side-to-side motion (17-22). The advantages of both systems consist of a significant reduction of bacterial plaque amount compared with manual toothbrushing, the flexibility of use, and many physical benefits deriving from the oscillatory movement of bristles (23-30).

This trial aimed to evaluate the effectiveness of sonic toothbrushes in reducing the indices of gingival inflammation.

MATERIALS AND METHODS

A one-blinded randomized clinical trial was performed. Prior to starting the study, the protocol was approved by the Institutional Review Board of the University of Tetovo in Macedonia (Nr 09-154/6) and is in line with the principles of the Declaration of Helsinki. Each participant provided signed informed consent. Subjects were screened before study entry, and their medical and clinical anamnesis were assessed. In order to participate, patients were required to be at least 18 years of age. Subjects were trained not to use their usual toothbrush, interdental devices, and mouthwashes. Each patient was randomized to receive the oscillating-rotating electric toothbrush (Oral B Professional Care Triumph 4000, Procter & Gamble, Cincinnati, Ohio) or the sonic toothbrush (Sonicare FlexCare with ProResults brush head, HX6011, Philips Oral Healthcare Inc, Bothell, Wash). Patients were asked to use a roto-oscillating or

sonic toothbrush for 3 months. Randomization was done by assigning random numbers from a random number table to the treatment conditions and translating the random number into the treatment assignment. A single blinded examiner performed all measurements and clinical examinations.

Statistical analysis

Shapiro-Wilk tests were conducted to determine whether a normal distribution could have produced GI and PI for each group category. In addition, a two-tailed Independent Samples t-Test was conducted to examine whether there were significant differences in GI and PI between the levels of the group and carried out at a significance level of .05. The data were analyzed using SAS software (SAS Institute Inc., Cary, NC, USA).

RESULTS

A total of 60 patients were recruited. All participants concluded the study. The Shapiro-Wilk test for GI at baseline in the Test Group category was not significant based on an alpha value of .05, $W = 0.94$, $p = .296$. This result suggests that a normal distribution cannot be ruled out as the underlying distribution for GI in both categories. The Shapiro-Wilk test GI in the roto-oscillatory toothbrush category was not significant based on an alpha value of .05, $W = 0.91$, $p = .058$. This result suggests that a normal distribution cannot be ruled out as the underlying distribution for GI at baseline in the sonic toothbrush category. The Shapiro-Wilk test was significant for either the roto-oscillatory or sonic toothbrush categories, indicating the non-normality assumption was met. Levene's test was conducted to assess the homogeneity of variance between the group categories. Levene's test for GI was not significant based on an alpha value of .05, $F(1, 38) = 0.05$, $p = .832$, indicating the assumption of homogeneity of variance was met. The two-tailed independent samples t-test was not significant based on an alpha value of .05, $t(38) =$

0.11, $p = .916$, indicating the null hypothesis cannot be rejected. This finding suggests the means of GI and PI at baseline were not significantly different between the toothbrush categories of the group. The results are presented in Table I.

The findings at 3 months suggested that the means of GI and PI were not significantly different between the roto-oscillating and sonic toothbrushes categories of the group. The results are presented in Table II.

DISCUSSION

Several studies evaluated the efficacy of a Powered Toothbrush (PTBs) in comparison with a Manual Toothbrush (MTBs) on plaque removal (31-43). The efficacy of PTBs and MTBs was analyzed by comparing pre-brushing and post-brushing plaque scores. Renton-Harper *et al.* reported no statistically significant differences between the 3 brush treatments (44). The authors showed that post-brushing plaque indices overlapped for both groups at baseline and after a few days of investigation (45-60). Our findings disagree with Grender *et al.* (61), which review the efficacy of six comparative clinical trials on oscillating-rotating power toothbrushes. The purpose of this review was to report a summary of the differences in post-brushing plaque removal in the different areas of

the oral cavity by oscillating-rotating toothbrushes, sonic toothbrushes, and manual toothbrushes (62-70). The chosen studies were single-centre, randomized and controlled, and examiner-blind. Healthy subjects were enrolled (71-80). Plaque evaluations were via the Turesky Modification of the Quigley-Hein Plaque Index (TMQHPI) or the Rustogi Modification of the Navy Plaque Index (RMNPI). Subjects brushed with a randomly assigned O-R power brush [Oral-B Professional Care Series 4000 (Triumph) or Oral-B Vitality with Floss Action or Precision Clean brush head] or a controlled brush [Sonicare FlexCare with ProResults brush head] or an American Dental Association (ADA) 462 subjects completed the trials and were evaluable. Results confirm that all toothbrushes furnish a significant post-brushing versus baseline plaque removal efficacy. The result of O-R power brush was superior compared to the sonic power or manual brushes (81-122). The O-R brush demonstrate superior results compared to the sonic brush statistically significant on lingual surfaces ($P < \text{or} = 0.044$), lingual approximal surfaces ($P < 0.001$), lingual mandibular and lingual mandibular anterior regions ($P < \text{or} = 0.005$) Post-brushing with O-R brush of whole oral cavity indicates reduction of RMNPI or TMQHPI. The O-R brush compared to the manual brushes were statistically significant on lingual

Table I. Two-Tailed Independent Samples *t*-Test for GI and PI by Group

	Oral B		Philips				
Variable	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>t</i>	<i>p</i>	<i>d</i>
GI	58.21	17.53	57.75	18.32	0.11	.916	0.03
PI	61.43	7.12	49.45	12.34	0.10	.898	0.02

Note: Degrees of Freedom for the *t*-statistic = 38. *d* represents Cohen's *d*.

Table II. Two-Tailed Independent Samples *t*-Test for GI and PI at 3 months by Group

	Oral B		Philips				
Variable	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>t</i>	<i>p</i>	<i>d</i>
GI	2.80	3.45	2.30	3.75	1.41	.166	0.45
PI	3.25	3.56	2.56	2.34	1.34	.163	0.39

Note: Degrees of Freedom for the *t*-statistic = 38. *d* represents Cohen's *d*.

surfaces ($P < \text{or} = 0.001$), on lingual approximal surfaces ($P < \text{or} = 0.001$), lingual gingival margin regions, respectively ($P < \text{or} = 0.001$). Our randomized, controlled, one-blind study recorded periodontal status at baseline and 3 months. 56 subjects completed the study. Significant differences were recorded between the 2 groups at 3 months. The sonic toothbrush plaque removal was significant at 3 months compared with the roto-oscillatory toothbrushes ($P < .005$).

Sonic toothbrush reduced parameters of periodontal inflammation more effectively than the electric toothbrush.

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Oral health and brain connection: is there any relationship?

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Several studies reported the association between periodontal diseases, a persistent inflammatory process and other chronic ailments such as cardiovascular diseases, diabetes mellitus, Alzheimer's disease and cancer. Although many epidemiologic data support these associations, a cause-and-effect relationship has not been established. Numerous articles reporting oral bacteria in samples collected directly from brain abscesses confirmed the association between brain abscess and odontogenic infection. Dental diseases can be treated with ambulatory care rather than hospitalization and emergency care. Older adults should establish daily oral hygiene care routines during the early stages of Alzheimer's disease.

Several studies reported the association between periodontal diseases, a persistent inflammatory process and other chronic ailments such as cardiovascular diseases, diabetes mellitus, Alzheimer's disease and

cancer (1-14). Other conditions such as low birth weight and premature delivery due to chorioamnionitis are also known to be linked to poor periodontal health. Although many epidemiologic data support these associations, a

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cause-and-effect relationship has not been established (15-21). Numerous articles reporting oral bacteria in samples collected directly from brain abscesses confirmed the association between brain abscess and odontogenic infection. Upper molars were the teeth most often associated with brain abscesses (22-29). Spontaneous brain abscesses and intracranial empyema are rare but life-threatening diseases. They can result from potential complications of chronic oral infections. Given the similarity between germs commonly found in cerebral abscesses and the oral cavity and its anatomic proximity, the oral cavity represents a significant source of cerebral infections (30-52).

The oral microbiota has been implicated in various neurologic conditions, including autism spectrum disorder and Alzheimer's disease. Recent data propose the etiopathogenetic role of intestinal microbiota in autism spectrum disorder (52-62). Oral cavity pathogens may reach the brain in various ways: 1) direct contiguity spread (notably upper jaw teeth), 2) systemic hematogenous bacteremia (after an invasive oral procedure or even spontaneous), 3) direct venous drainage (52,63-72). Cerebral abscesses linked to oral infection are usually polymicrobial: streptococci, staphylococci, *Actinomyces* sp, *Actinobacillus* sp, and *Fusobacterium* sp (52). Researchers found that bacteria associated with gum disease can be passed into the bloodstream through everyday routines like brushing teeth. When the brain gets repeated exposure to these germs, responses are triggered that can kill brain cells.

Dementia is one of the leading causes of disability among older adults. It is a progressive neurodegenerative disease that affects older adults' ability to perform daily living activities. Alzheimer's disease is the primary subtype of dementia and causes declining memory, reasoning, and communication skills. They also have behavioural and psychological symptoms, such as depression and aggression. Therefore, it is essential for them to maintain good oral health, as oral health is an essential and integral part of their general health (73). However, dental diseases can be treated with ambulatory care rather than hospitalization and emergency care. Therefore, older adults should establish daily oral hygiene

care routines during the early stages of Alzheimer's disease. (73).

Therefore, continuous observation with daily clinical practice by physicians and surgeons, continuous scientific research and further discoveries, 3-dimensional virtual reality, and new technologies can improve patient outcomes and provide new solutions (74-89). Poor oral hygiene, difficulty in wearing dentures, and the inability to self-care, including carrying out oral hygiene procedures, are the most probable cause of impaired oral health in Alzheimer's disease. Collecting information on oral/dental conditions from Alzheimer's disease patients or their caregivers/relatives is often tricky and scientific literature on the topic is sparse (90-155). The problem of awareness of good oral health for keeping quality of life more acceptable in adult-onset dementia disorders is discussed.

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Safety of commercial airlift in patients with craniofacial diseases

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The potential risk of pressure changes during commercial air travel causing the expansion of trapped intracranial air in post-operative patients is known. Current studies reveal that it is safe for patients with space-occupying brain lesions to fly various distances. Nevertheless, in patients with pre-flight symptoms thought to be due to mass effect or cerebral oedema, the administration of dexamethasone and anticonvulsants may help minimize the risk of further brain swelling and possible seizures during air flight.

Besides other oral manifestations of barometric pressure changes, such as barodontalgia, clinicians should be familiar with this entity, take preventive measures, and periodically examine patients who fly planes. Clinicians should also search for occult pathologies such as leaking restorations or secondary caries lesions. Nevertheless, pneumocephalus is not a contraindication to early post-operative flying. More significant, prospective, multi-institutional studies will be necessary to validate these recent results.

The potential risk of pressure changes during commercial air travel causing the expansion of trapped intracranial air in post-operative patients is known and

well documented (1-10). Zrinzo et al. (3) reported that patients with intracranial mass lesions might be at risk for neurological deterioration when exposed to

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cabin conditions commonly present on commercial flights and prophylactic steroid agents, acetazolamide supplementary O₂ should also be considered during flying. Ascent to higher altitude with regulated but lower air pressure occurs on commercial airline flights, exposing passengers to changes in cabin pressure, posing a potential risk for individuals with space-occupying brain lesions (11). However, many patients with intracranial tumors often fly to tertiary care facilities without deleterious events (11-37). It is generally recommended to avoid air flight for patients with intracranial tumors or mass lesions as there is concern that the air pressure differentials experienced can induce further cerebral oedema or mass effect, worsening symptoms (1).

The air pressure changes typically experienced on commercial jet aeroplanes vary but are equivalent to being at an elevation of 8000–10,000 ft (2400–3000 m); this is partly dependent on the make of the aircraft (Boeing vs Airbus) (1). In their study, Phillips et al. (1) reported that 24.4% of patients developed worsened symptoms during an air flight, including headaches, fatigue, dizziness and ear pain, and one patient had an onset of seizures in flight. In addition, there was no correlation between tumor size, volume, location or flight duration and with development of neurological symptoms (1).

Current studies reveal that it is safe for patients with space-occupying brain lesions to fly various distances. Nevertheless, in patients with pre-flight symptoms thought to be due to mass effect or cerebral oedema, the administration of dexamethasone and anticonvulsants may help minimize the risk of further brain swelling and possible seizures during air flight (1). After surgery, “When can I fly?” is a frequent question encountered while discharging a patient after intracranial surgery; however, the answer is not always the same (38-45). The main concern regarding flying post intracranial surgery is that the presence of any residual air in the cranium may potentially expand, converting a simple pneumocephalus into a life-threatening tension pneumocephalus. In practice, however, there is little evidence to support this. Other concerns about flying post-surgery may be related to the risk of deep vein thrombosis, severe headache in the air, or a post-operative complication away from home (38,46-51).

Donovan et al. (52) looked retrospectively at the air transport of military casualties during the conflict in Iraq, with patients with confirmed intracranial air on CT scan 24 hours prior to air travel from the Middle East to Germany at cabin pressures equivalent to an altitude of 5000–8000 feet. In that study (52), none of the patients with ICP monitoring during flight, either by an external ventricular drain and transducer or an intra-parenchymal ICP monitor, sustained elevations of their ICP during flight. In addition, no patient suffered a temporary or permanent neurological deficit due to air travel (52).

In addition to air pressure, flying can affect the spine too. De Oliveira & Nadal (53) reported that cyclic compressive force due to helicopter vibration could potentially increase the load imposed on the spines of pilots during flight; this might explain the incidence of back pain and other injuries to the spine within these categories of professionals. The high incidence of back pain in helicopter pilots (HP) has been attributed to vibration and the in-flight pilot's posture (53-66). Similarly, Byeon et al. (66) studied the relationship between whole body vibration induced helicopter flights and degenerative cervical and lumbar spine changes.

Degenerative changes in the cervical spine were significantly more prevalent in the helicopter pilots than in the control group. Accumulated flight hours were associated with degenerative cervical and lumbar spine changes in helicopter pilots (66). The cervical spine multivariate model and accumulated flight hours (per 100 hours) were associated with degenerative changes. In the lumbar spine multivariate model, accumulated flight hours (per 100 hours) and age were associated with degenerative changes (66). Therefore, continuous observation with daily clinical practice by physicians and surgeons, continuous scientific research and further discoveries, and the use of 3-dimensional virtual reality and new technologies will provide new solutions (66-73).

Besides other oral manifestations of barometric pressure changes, such as barodontalgia (barometric pressure-related oral pain), clinicians should be familiar with this entity, take preventive measures, and periodically examine their patients who fly planes (9). Clinicians should also search for occult

pathologies such as leaking restorations or secondary caries lesions. In addition, clinicians should be aware of the possible influence of pressure changes on the retention of prosthetic devices and plan treatment accordingly (74-167). It seems that pneumocephalus is not a contraindication to early post-operative flying (52); however, more extensive, prospective, multi-institutional studies will be necessary to validate these recent results.

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Amantinomatous craniopharyngiomas and odontogenic epithelial differentiation

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The origin of the craniopharyngioma has been the subject of several publications. Theories of the genesis of this tumor include remnants of the craniopharyngeal duct, squamous metaplasia of anterior pituitary cells, and misplaced tissue of the embryonic enamel organ. Because embryology of the adenohypophysis and the teeth indicated that all of the epithelia in this tumor emerged during the normal development of the stomodeum, it was believed that an “embryonal form of craniopharyngioma” would characterize this organoid neoplasm. Pertinent to understanding the theories of the origin of craniopharyngioma, a direct

review of the development of the tooth and pituitary is necessary. Given the rarity of these tumors, efforts to optimize infrastructure and international collaboration should be research priorities.

Craniopharyngioma is considered the most typical intracranial tumor of childhood and adolescence, accounting for 8.3% of intracranial tumors and 14.5% of all supratentorial tumors (1). The origin of the craniopharyngioma has been the subject of several publications (1-13). Theories of the genesis of this tumor include remnants of the craniopharyngeal duct, squamous metaplasia of anterior pituitary

Keywords: craniopharyngioma; intracranial tumor; spine; teeth

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cells, and misplaced tissue of the embryonic enamel organ (2,14-19). Tooth development begins at about the seventh week of embryonic life (2,3,20-25). An epithelial plate, the dental lamina, arises from the gum surface and grows into the underlying mesenchyme (26-36). The histological subtypes, adamantinomatous craniopharyngiomas (ACPs) and papillary craniopharyngioma (PCP), differ in genesis and age distribution. ACPs are diagnosed with a bimodal peak of incidence (5–15 years and 45–60 years), whereas PCPs are restricted to adults mainly in the fifth and sixth decades of life (37-41). Pediatric ACPs are histologically benign brain tumors that often follow an aggressive clinical course. Arising in the sellar/suprasellar region, they grow close to critical neurological and vascular structures and can result in significant neuroendocrine morbidity (42-55). First-line treatment often involves surgical resection with or without radiotherapy and has been associated with significant morbidity and poor quality of life outcomes (42).

Recent years have witnessed significant progress in the knowledge base regarding the genomic, transcriptomic, and proteomic makeup of ACPs, moving the field closer to implementing novel therapies (42,56-61). Some of these molecules and pathways of interest include pro-inflammatory actors such as interleukin-6 (IL-6) and indoleamine 2,3-dioxygenase-1 (IDO-1), as well as other pathways such as the programmed cell death protein 1/ligand (PD-1/PD-L1), the mitogen-activated protein kinases/extracellular signal regulated kinases (MAPK/ERK) pathway, and cellular senescence (42). ACPs resemble histologically some odontogenic tumors, such as ameloblastoma and calcifying odontogenic cyst. However, there has been no evidence that ACPs differentiate functionally as odontogenic epithelium (62). Among normal human tissues, enamel proteins are expressed exclusively in teeth, and lymphoid enhancer factor 1 (LEF1), in cooperation with β -catenin, plays a significant role in tooth development (62). Therefore, the expression of these proteins indicates odontogenic epithelial differentiation (62). The origin of the craniopharyngioma from primitive stomatodeum theoretically facilitates odontogenesis. Theories of the genesis of this tumor include remnants of the craniopharyngeal duct,

squamous metaplasia of anterior pituitary cells and misplaced tissue of the embryonic enamel organ (1, 2, 63-68). A literature review documents six cases of craniopharyngioma with tooth formation, although none appear to be as extensive as the case presented (1). Craniopharyngioma should be added to teratoma in the differential diagnosis of suprasellar odontogenic elements demonstrated by imaging studies (69-72). Therefore, continuous observation with daily clinical practice by physicians and surgeons, continuous scientific research and further discoveries, and the use of 3-dimensional virtual reality and new technologies will provide new solutions (73-135). Many theories have been postulated regarding the origin of these tumors and include: epithelial rests and craniopharyngioma arising from a portion of an incompletely obliterated craniopharyngeal duct; a metaplastic process where squamous cells might arise from other cell types; tumors could arise by an enrolling of dental elements into the tuberal process of the developing pituitary (1,136-164). Whether the tumor arises from embryonic residues or metaplasia, the similarity to the adamantinoma of the jaw is valid only if the embryonic ductal epithelium remains competent to differentiate in this direction (8,137). Because embryology of the adenohypophysis and the teeth indicated that all of the epithelia in this tumor emerged during the normal development of the stomodeum, it was believed that an “embryonal form of craniopharyngioma” would characterize this organoid neoplasm best (137,165-187). Pertinent to understanding the theories of the origin of craniopharyngioma, a direct review of the development of the tooth and pituitary is necessary. Given the rarity of these tumors, efforts to optimize infrastructure and international collaboration should be research priorities.

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Immediately restored single post extractive implants: clinical outcomes of a retrospective analysis with 8- 10 years follow-up

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BACKGROUND: This study evaluated retrospectively the outcomes of immediately restored single post-extractive implants over a period of 8–10 years. The clinical records of 62 consecutive patients (mean age 53.2 years; range 40–77 years), rehabilitated with single implants placed in fresh extraction sockets (40 maxillary/22 mandibular) were analyzed. All implants were functionalized using an immediate protocol. Outcome measures were implant failure, peri-implant radiographic bone level changes, peri-implant mucosa conditions and gingival aesthetics.

RESULTS: The final follow-up interval was 9.1 years (range 8–10.6 years). Three implants (4.8% of total) failed, one implant in mandible and two implants in maxilla. No difference in implant failures was registered between maxillary and mandibular implants ($p=0.967$). Mean marginal bone levels at implant placement and at the last follow up were 0.02 ± 0.04 mm and 1.23 ± 0.43 mm, respectively. Mean marginal bone remodeling averaged 1.21 ± 0.52 mm. Peri-implant mucosa was healthy for the most (98.3%) of implants. At 10 years, patients had mesial and distal papilla index scores of 2 or 3 for 84.8% and 81.4% of implants, respectively.

CONCLUSION: The results of this retrospective long-term study proved excellent survival rate of immediately restored single post-extractive implants as well as favorable marginal bone response and soft tissue conditions.

Osseointegrated dental implants are placed traditionally following a two-stage protocol (1). This approach involves healing periods of several weeks to months between tooth extraction and implant insertion and again between implant insertion and loading. Successful osseointegrated dental implants are anchored directly to the bone. However, in the presence of micromovement, a soft-tissue interface may encapsulate the implant, causing its failure (2). To minimise the risk of soft tissue encapsulation, some clinicians have recommended keeping implants unloaded. This conventional approach requires longer treatment periods, multiple surgeries, increasing

cost. Early attempts to load implants earlier were associated with increased failure rates (1). In 1990, the first longitudinal study was published showing that implants could be loaded immediately (3). Recently, a Cochrane systematic review suggested that there was no convincing evidence of a clinically important difference in prosthesis failure, implant failure or bone loss associated with different loading times of implants (4). In order to contain micromovements and avoid soft tissue encapsulation, implants should be splinted together and/or implants should gain a high level of primary stability (5). Since rigid splinting is possible in multiple unit restorations, several

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articles have evidenced good long-term success of immediately loaded implants rigidly splinted together both in mandible and maxilla (6, 7). Instead, rigid splinting is not possible in single-tooth restoration and the immediate loading applied to a single implant leads to higher risk of failure.

Recently, it has been shown that placing implant in single tooth gap fresh extraction socket and immediately restored entail both implant success and hard- and soft- tissue outcomes. Immediate implant placement reduces the number of surgical procedures and healing time, preserves hard tissue, and could help maintain alveolar architecture through decreased resorption (8, 9). A meta-analysis of 16 studies found a small but significant difference in crestal bone levels that favoured immediately placed implants compared with those placed in healed or native bone, suggesting that immediate placement could possibly preserve bone level (10). The effects of immediate placement on soft tissue has been mixed, with one systematic review showing higher variability in soft-tissue outcomes and a higher frequency of gingival recession following immediate placement compared with early placement (11), whereas other systematic reviews and meta-analyses reported no differences in soft-tissue outcomes between immediate and delayed loading (12, 13). So there are multiple treatment options that could lead to similar results. Long-term clinical outcomes could help the clinicians to take decisions in their practice. The aim of this unicentric retrospective cohort study was to evaluate the outcomes of immediately restored single implants placed in fresh extraction sockets over a period of 8–10 years.

MATERIALS AND METHODS

The present retrospective study was based on the analysis of clinical records of patients that underwent implant surgery between September 2009 and February 2012. The principles outlined in the Declaration of Helsinki on clinical research involving human subjects were adhered to. All the surgeries and prosthetic rehabilitations were carried out in the same dental clinic and by the same surgeon (TG), skilled in implant surgery and prosthetic procedures. The selection of the patients' clinical records was based on the following inclusion criteria: (1) patients with one single

immediately loaded post-extractive implant in the maxilla or mandible, between two natural teeth (or crowned teeth); (2) attendance at all planned follow-up visits; and (3) availability of radiographic documentation at both implant insertion and long-term follow up. Only one implant/crown per patient was entered in the study. Pre-operative clinical assessment included periapical radiographs and cone beam computed tomography (CBCT) scans.

Exclusion criteria were: (1) heavy smokers (more than 20 cigarettes daily); (2) lack of opposing occluding dentition; (3) patients with periapical lesions on adjacent teeth; (4) patients with incomplete demographic (age, gender) or clinical data reporting (eg, implant outcomes, smoking status, implant size). Flapless tooth extraction was performed with particular attention to not damage the alveolar bone walls. If present, all granulation tissue was removed. The alveolar bone walls were carefully sounded with a probe to assess the absence of bone dehiscence. The implant site was prepared with sequential drilling under copious irrigation according to the manufacturer's instructions (JDentalCare, Modena, Italy). Tapered titanium screw-shaped design implants (JDEvolution®, JDentalCare) with sand blasted and acid-etched treated surface up to the neck were placed flapless (Fig. 1). The JDEvolution implant has an internal connection characterized by a 2 mm deep internal hex and a 45-degree internal bevel. Final insertion torque was measured using a calibrated torque wrench (JDTorque®, JDentalCare). The wrench used was able to perform torque measurement within a range of 15–80 Ncm, with 5% precision.

The implants should attain insertion torque of at least 45Ncm to be immediately loaded. If the implant did not



Fig. 1. External macro-design of the implant used in the study (JDEvolution, JDentalCare)

reach an insertion torque of at least 45Ncm, a delayed loading protocol was performed and the patient was not included in the study. In all patients, the gap between implants and the surrounding bone was filled with granules 0.25 – 1 mm of anorganic bovine bone (Geistlich Bio-Oss, Geistlich Pharma AG, Wolhusen, Switzerland). A piece of collagen (Condress, Euroresearch, Milano, Italy) was placed over the graft and under the margins of the labial gingiva. An impression was immediately taken after surgery with a conventional open tray impression technique. Then a resin screw-retained provisional crown fabricated in the lab was placed the day after surgery and all the centric and eccentric contacts were excluded by to the interposition of 200 μ articulating paper. Verbal and written post-operative and oral hygiene instructions were given and patients were instructed to have a soft diet for 8 weeks. The screw-retained metal-ceramic definitive crowns were placed 4 months after surgery with full occlusal contacts (Fig. 2).

The primary outcome measures were:

- Crown/implant failure: evaluated as implant mobility (assessed with metallic handles of two instruments) and

removal of stable implants (due to progressive marginal bone loss or infection).

- Peri-implant marginal bone level changes: evaluated on intraoral radiographs taken with the paralleling technique at implant insertion and at the longest follow-up postsurgery. All measurements were taken by an independent blinded assessor. Radiographs were scanned, saved and stored as images in JPG format in a personal computer, than converted to TIFF format with a 600 dpi resolution. Peri-implant marginal bone levels were measured using Image J 1.42 software (National Institute of Mental Health, Maryland, USA). The software was calibrated for all the images using the known implant diameter. Measurements of the mesial and distal crestal bone levels adjacent to each implant were made to the nearest 0.01 mm and averaged at patient level. The measurements were taken parallel to the implant axis. Reference points for the linear measurements were the most coronal margin of the implant collar and the most coronal point of bone-to-implant contact. Baseline radiographs were taken after

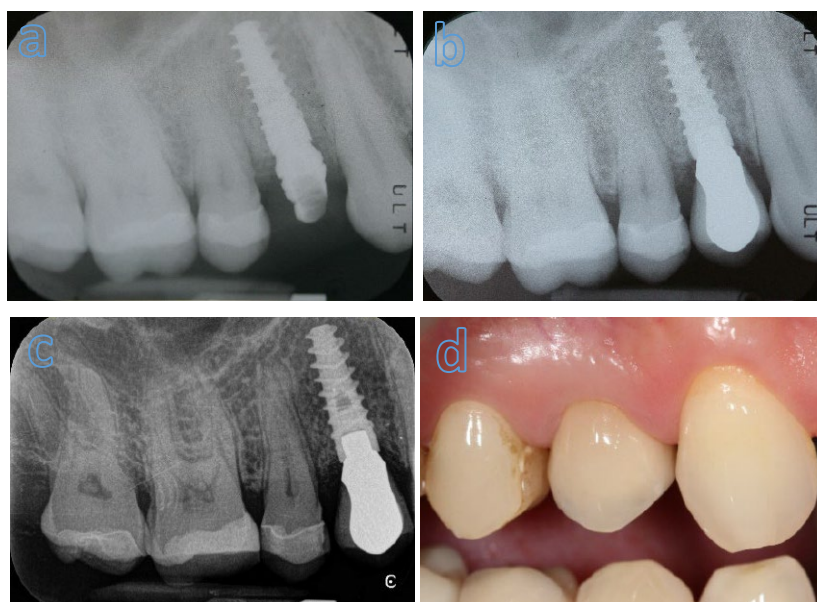


Fig. 2. Representative clinical case images from 43-year-old male patient requiring replacement of his first premolar (position 14). **A)** Radiograph of the JDEvolution 4.3 x 13 mm implant at insertion following placement into a fresh extraction socket with a torque of 60 Ncm. The implant was immediately loaded with a screw-retained temporary crown. **B)** Radiograph of implant and final metalceramic crown placed 4 months after initial surgery. **C)** Radiograph of implant showing osseointegration and excellent bone levels at 10 years after insertion. **D)** Clinical view of definitive prosthesis showing healthy soft-tissues at last follow up.

the bone augmentation procedure.

The secondary outcomes assessed included:

- Bleeding of the peri-implant mucosa: (0: no bleeding, 1: bleeding on probing, 2: spontaneous bleeding);
- Assessment of gingival aesthetics: Vestibular pictures including the two adjacent teeth, taken at implant loading and at the longest follow-up postsurgery were evaluated on a computer screen. In order to ensure comparability between the baseline and follow-up photographs, the following lines were drawn on a graphic tablet: a straight apico-coronal vertical line from the most coronal portion of the crown edge to the gingival zenith and a mesio-distal horizontal line at the gingival zenith of the teeth (Fig. 3).

The classification described by Jemt (14) was used for the assessment of interproximal gingival papillae. In order, the values were the following: 0 = no papillae, 1 = less than one half of the gingival embrasure, 2 = at least one half of the height, 3 = complete closure of the proximal space, and 4 = overgrowth. The mid-buccal gingival level was assessed by measuring the difference with the buccal gingival outline of the adjacent teeth using Image J 1.42 software (National Institute of Mental Health, Maryland, USA). The software was calibrated for all the images using the known mesio-distal width of the implant crown. The classification ranged from 0-4, representing 0 = no difference in gingival level, 1 = less than 1 mm difference, 2 = less than 2 mm difference, 3 = less than 3 mm difference, and 4 = differences in buccal gingival outline greater than 3 mm.

Statistical analyses were performed using the statistical package StatView (version 5.01.98, SAS Institute Inc, Cary, North Carolina) by an independent statistician with

expertise in Implant Dentistry. When necessary, prevalence was compared by contingency tables and the Chi square test. The patient was the statistical unit of the analyses. Differences in the proportion of patients with implant failures and complications (dichotomous outcomes) were compared between the groups using the Fisher's exact probability test. Differences of means at patient level for continuous outcomes were compared by t-tests. For all analyses, the null hypothesis was rejected at a two-tailed p value < 0.05 . Parametric results were expressed as the mean $\pm$ standard deviation (SD).

Descriptive statistics were performed by an independent statistician in the software SPSS v23 (IBM). Data are presented as mean $\pm$ SD.

RESULTS

Data from 64 implants placed in 64 patients were analyzed in this report. Five patients treated with a single immediate implant between September 2009 and February 2012 were not included in the study because implants did not reach an insertion torque of at least 45Ncm and consequently a delayed loading protocol was performed. All these five implants were placed in the premolar area of the maxilla. Two patients (2/64, 1.6%) died during the study follow up and were excluded from the analysis. The final follow-up interval ranged from 8 to 10.6 years (mean 9.1 ± 1.2 years, $n=62$), for which data for 62 implants were available. At the time of implant insertion, the patients ranged in age from 40 to 77 years (mean 53.2 ± 6.9 years). Patients' and interventions' characteristics are summarized in Table I.

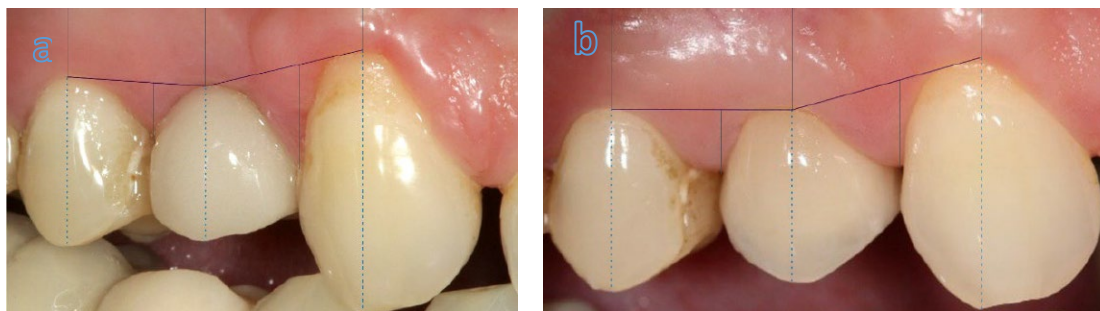


Fig. 3. Photographic measures by Image J at implant loading (A) and at the longest follow-up (B) to assess the interdental papilla (distance between the top of the papilla and projection of the gingival zenith) and the buccal mucosal level measuring the difference with the buccal gingival zenith of the adjacent teeth.

Patients were generally healthy, though 6/62 (9.7%) patients suffering from controlled non-insulin diabetes were included and 21/62 (33.9%) with drugs-controlled hypertension. Of the 62 implants, 40 (64.5%) were placed in the maxilla and 22 (35.4%) were placed in the mandible. The opposing dentition was natural teeth in 49 cases (79.1%) and ceramic/crown bridge in 13 cases (20.9%).

The reasons for teeth extraction are illustrated in Table II. Twelve immediate post-extractive implants were placed in sites with chronic periapical lesion. Seating torque values and the dimensions (diameter and length) of the inserted implants are listed in Table III. Implant diameters ranged from 3.7 to 5.0 mm, and implant lengths ranged from 11.5 to 15 mm. Average insertion torque was 68.8 ± 11.3 Ncm.

Three implants (4.8% of total) failed, two implants in maxilla (2/40, 5.0% of maxillary) and one implant in mandible (1/22, 4.5% of mandibular). No difference in implant failures was registered between maxillary and mandibular implants ($p=0.967$). Two implants

(3.2% of total) failed within one month from loading. The implants were painful at the 1-week control and then also at the 3-week control; when tested for stability the implants were mobile and were removed. No immediate post-extractive implants placed in sites with chronic periapical lesion failed. One implant (1.6% of total) was removed after 4 years for peri-implantitis with pus and mobility.

The mean marginal bone levels at implant insertion and at the last follow up were 0.02 ± 0.04 mm and 1.23 ± 0.43 mm, respectively, as shown in Table IV. The estimated marginal bone remodelling averaged 1.21 ± 0.52 mm.

At the last available follow-up, a healthy, noninflamed peri-implant mucosa was observed at the large majority of implants. The bleeding score was 0 in 47 cases (79.7%), 1 in 11 cases (18.6%), and 2 in 1 case (1.7%).

At provisional prosthesis loading, 96.7% and 93.5% of the implants had a papilla index of 2 or 3 for the mesial and distal side, respectively. At the last

Table I. *Patients' and interventions' characteristics*

	Study group
Male	28/62 (45.2%)
Mean age at implant insertion $\pm$ SD	53.2 $\pm$ 6.9
Smoking up to 10 cigarettes/day	7/62 (11.3%)
Smoking more than 10 cigarettes/day	4/62 (6.5%)
Controlled type 2 diabetes	6/62 (9.7%)
Hypertension	21/62 (33.9%)
Natural teeth in the opposite jaw	49/62 (79.1%)
Ceramic/crown bridge in the opposite jaw	13/62 (20.9%)
Maxillary implants	40/62 (64.5%)
Implants placed in incisor sites	12/62 (19.4%)
Implants placed in canine sites	5/62 (8.1%)
Implants placed in premolar sites	41/62 (66.0%)
Implants placed in molar sites	4/62 (6.5%)

Table II. *Reasons for teeth extraction*

Reason for tooth extraction	Total n=62
Endodontic failure	12 (19.4%)
Periodontal disease	14 (22.6%)
Tooth fracture	31 (50.0%)
Caries	5 (8.0%)

Table III. *Dimensions (diameter and length) and final seating torque of the inserted implants*

		Total n=62
LENGTH	11.5	13 (21.0%)
	13	34 (54.8%)
	15	15 (24.2%)
DIAMETER	3.7	29 (46.8%)
	4.3	18 (29.0%)
	5	15 (23.2%)
INSERTION TORQUE (Ncm)	45	3 (4.8%)
	50	3 (4.8%)
	55	2 (3.2%)
	60	6 (9.7%)
	65	3 (4.8%)
	70	6 (9.7%)
	75	8 (13.0%)
	80	31 (50.0%)

Table IV. *Mean radiographic peri-implant marginal bone levels and changes (mm)*

	Implant placement	Last control (mean 9.1 years)	Difference placement (last control)
	Mean±SD (95% CI)	Mean±SD (95% CI)	Mean±SD (95% CI)
Marginal bone levels	N=62 0.02±0.04 (-0.02; 0.06)	N= 59 1.23±0.43 (0.80;1.66)	-1.21±0.52 (-1.69; -1.73)

follow up, 84.8% and 81.4% of the implants had a papilla index of 2 or 3 for the mesial and distal side respectively (Table V).

DISCUSSION

Although many short-term clinical reports are available showing favorable results for immediately restored single post-extractive implants (15-22), scarce documentation exists on the long-term success of these implants. The present retrospective study, performed with 62 patients, suggests that single post-extractive implants immediately loaded achieve excellent clinical performance up to 10 years of function. The implant survival rate was 95.2% and mean marginal bone remodelling was 1.21 ± 0.52 mm.

Given the extensive debate on immediate implant placement and loading protocols, the outcomes of numerous studies using these protocols, both independently and in combination, have been extensively scrutinized in systematic reviews and meta-analyses. Survival and hard tissue outcome are critical factors for implant success, and differences between placement and loading protocols could have a profound impact on implant performance. A systematic review by Kinaia and colleagues¹⁰ of crestal bone level changes around immediately placed implants included 57 studies, 16 with comparable control groups. The meta-analysis showed crestal bone levels of immediately placed implants were better preserved at 12 months compared with those of implants placed in healed or native bone; however, the magnitude of the difference may not have a clinical impact.

Further, both immediate and delayed implant loading had no differences in crestal bone level changes. A systematic review by Weigl and colleagues (23) involved 17 studies analyzing tapered, moderately rough-surfaced implants in the esthetic zone that were immediately placed and restored. The results showed a high survival rate (98.25%) after a mean follow-up of 31.2 months and a difference less than 1 mm for crestal bone level and interproximal mucosa level compared with baseline.

A systematic review and meta-analysis by Benic (12) and colleagues scrutinized different loading protocols for single implants, including 10 randomized controlled trials (RCTs), and resulted in no significant differences in implant survival or marginal bone loss comparing immediate and conventional loading. A systematic review by Yan and colleagues (13) included 13 RCTs evaluating changes in hard and soft tissue around single-tooth implants placed in the esthetic area using both immediate and conventional protocols. There were no differences in hard tissue outcomes between immediate and conventional placement and between immediate loading and delayed loading.

To decrease the risk of early failures of immediately loaded implants, various clinical 'tips' have been suggested such as the under-preparation of the implant site to achieve high primary stability and the use of a non-occluding temporary prosthesis during the first 2 months of healing (24). Two RCTs were published comparing immediately loaded single implant-supported crown in occlusion or not in occlusion (25, 26). The results, also summarised in a meta-analysis of a Cochrane systematic review (4), did not show any trend in favour of crowns not placed

Table V. *Assessment of interdental papilla according to Jemt (14)*

Score			Provisional prosthesis loading (n=62)	Last control (mean 9.1 years) (n=59)
2	At least one half of the height	mesial	8 (12.9%)	8 (13.6%)
		distal	7 (11.3%)	5 (8.5%)
3	Complete closure of the proximal space	mesial	52 (83.8%)	42 (71.2%)

in occlusion during the implant healing phase. The lack of difference could be explained by the fact that even if the crowns were not put in direct occlusion, patients used them functionally when chewing. The most relevant factor which may explain the positive results obtained in this trial is the high insertion torque at implant placement. To qualify for immediate loading, implants had to be inserted with torque superior to 45 Ncm. To achieve this in medium and soft bone, tapered self-tapping/self-condensing implants were placed in underprepared osteotomies which were one to two sizes smaller than the final implant diameter. The implants used feature also a progressive increase in the thickness of the threads to help stabilize the implant while going inside the osteotomy. Using this approach, high insertion torque was predictably achieved, and the fact that the cases were consecutively treated reflects the high degree of predictability in achieving high insertion torque using the described protocol. This explanation is in agreement with the findings of two trials (27, 28). In a controlled clinical trial of split-mouth design where single undergoing either immediate non-occlusal loading or conventional loading, the authors found a strong correlation between insertion torque and implant failures for immediately loaded implants. In fact, out of 10 single implants placed with an insertion torque of 20 Ncm, nine failed, whereas only one implant failed out of 10 implants inserted with a 32 Ncm (27).

The other split-mouth RCT showed a statistically significant difference with more failure (seven failures) of immediate non-occlusally loaded single implants when inserted with torque between 25 and 35 Ncm than implants (no failure) placed with an insertion torque superior to 80 Ncm (28). It can be concluded that immediate loading of single implants can be successful if some clinical precautions are taken. Such precautions may include: under-preparation of the implant sites particularly in the presence of soft bone, use of implant design favouring achievement of high insertion torque and an accurate control of loading. Some authors also advocate the use of specific implant surface modifications to reduce the healing time (29), but no evidence support this hypothesis (30).

In addition to survival and marginal bone remodelling, soft-tissue outcomes are critical for both the health and satisfaction of the patient. Unlike hard tissue outcomes, soft-tissue outcomes of immediately placed and loaded implants seem to have higher controversy between studies. A systematic review by Chen and Buser of 50 studies investigating aesthetic outcomes following immediate or early implant placement in the anterior maxilla showed higher variability in soft tissue outcomes and a higher frequency of gingival recession following immediate placement compared with early placement, although these outcomes may be related to deficiencies in facial bone (11). Benic and colleagues demonstrated no significant differences in changes in papilla levels or aesthetics comparing immediate and conventional loading (12). The study presented here had mesial and distal papilla indexes of 2 or 3 for 84.8% and 81.4% of implants, respectively, at the 10-year follow up, possibly because buccal bone walls were kept intact after tooth extraction and patients were strongly encouraged to maintain good oral hygiene at all follow ups.

The patient biotype was not examined in this study. The effect of gingival biotype on peri-implant tissue response seemed to be limited only to facial gingival recession and did not influence interproximal papilla or proximal marginal bone levels (31). Twelve post-extractive implants were placed in sites with chronic periapical lesion in this study. None of these implants failed resulting that implants inserted into fresh and infected extraction sockets is not a risk factor for implant survival, as reported previously in other studies (32-37).

The main limitation of this trial is that the study design was retrospective, which reduces the quality of the evidence. However, this limitation is offset some by the long-term follow up. Photographs for assessment of gingival aesthetics were taken trying to keep the same perspective and inclination, but, as for the radiographs, no individualised templates were used to standardized the images and this could lead to less precision in measurements. Another limitation of the present investigation is the small sample size. Prospective studies with a larger number of implants evaluated are needed to confirm these findings.

In conclusion, the results of this retrospective long-term study proved excellent survival rate of immediately restored single post-extractive implants as well as favourable marginal bone response and soft tissue conditions.

Ethics approval and consent to participate

The present retrospective study was based on the analysis of clinical records of patients that underwent implant surgery at practice between September 2009 and February 2012. The principles outlined in the Declaration of Helsinki on clinical research involving human subjects were adhered to. Patient recruitment, surgeries and prosthetic rehabilitations were performed in a single dental clinic. The same surgeon, with experience in implant surgery and prosthetic procedures, performed all interventions. The study design was completely observational (i.e., without any modification of the routine clinical practice), and all data were obtained from the electronic database and anonymised before analysis. Every patient was required to sign a written informed consent.

Competing interests

There are no potential conflicts of interest relating to the manuscript (for each author), and there were no extramural sources supporting this research. The study is original and the manuscript has not been published yet and is not being considered for publication elsewhere in any language either integrally or partially. All authors have agreed with the submission in its present (and subsequent) form.

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Three-year outcomes of tilted dental implants in patients with low bone density

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The aim of this retrospective study was to report the mid-term outcome (3 years) of standard implants with 20 to 24 mm of length in immediate function with bicortical anchorage for prosthetic rehabilitation of complete edentulous jaws with low-density bone. To this end, clinical, instrumental and 3-year outcome data of 27 patients with complete edentulous arches and low bone density treated with long implants were investigated. Follow-up examinations were performed at 10 days, 2, 4, 6 months, 1 year, 2 years, and 3 years after implant placement. Marginal bone was evaluated at baseline (before surgery) and after 1, 2, and 3 years. The survival of the prosthesis was evaluated in terms of function. A prosthesis that needed to be substituted was considered a failure. A 100% survival rate was observed. All prostheses were in function during the follow-up period. No patient was lost during the follow-up. Regarding the short implants, the average marginal bone remodelling was 0.09 ± 0.21 at the baseline time point, 0.71 ± 0.32 after 1 year and 1.48 ± 0.28 at 3-year follow-up. Similarly, a constant and significant increased average marginal bone was observed at the sites of long implants. In conclusion, the data reported improved evidence about the clinical success of using long implants (≥ 20 mm) in immediate function with bicortical anchorage to treat patients with low bone density and partial or complete edentulous fixed prosthetic rehabilitation.

The dental rehabilitation of areas affected by low bone density currently represents a clinical challenge in clinical dental research. Several approaches have been proposed in this scenario, including the sinus lift and/or bone substitute materials (1-5). It is important to note that these techniques are not fully supported by scientific literature. Numerous authors report confusing and debated data (6). In any case, dental practitioners commonly apply these clinical methods with controversial results. Therefore, it is clear the need to use alternative and less invasive rehabilitation approaches to improve the management of patients with low bone density (7-12). Recent studies demonstrated that bone graft techniques in the rehabilitation of the maxilla are both more expensive and technically more

demanding concerning long implants, also showing similar or even lower implant success rates (12-15). In addition, it is important to note that the use of short implants may negative influences the long-term implants' survival in patients with low bone density by considering the crestal portion of the implant body load-bearing capacity, the pattern of distribution of prosthetic loads to the bone-implant interface, and the restorations' augmented crown (16-18).

Despite this evidence, the association between the length of the implant and the success rates is not entirely understood yet, especially for mid-long term follow-up (19-20).

From a mechanistic point of view, a significant reduction in implant-associated bone stress was

Keywords: dental implantology; bone tissue; dental rehabilitation

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demonstrated in patients treated with long implants both in immediate and delayed implant loading (20). In this context, a study by Kinsel et al. (21) demonstrated that a reduction in the length of dental implants is a solid predictor of implant failure.

An alternative method for the rehabilitation of atrophic jaws is tilted implants. This surgical approach is suggested for patients with partial (18, 22-25) and total edentulism of the maxilla (26-29). The tilting of the posterior implants enables the positioning of longer implants providing a larger bone-implant contact area, which ensures a very stable primary anchorage. In addition, the use of tilted implants allows a better load distribution and maintains a greater distance between implants, thus eliminating or decreasing cantilevers in the prosthesis (26-27, 29-30).

As a result, the use of tilted implants in immediate function can partially reduce the risk of dental implant failure in patients with poor bone quality (31, 32).

Thus, mid-long term studies focused on the implants' survival rate of tilted long implants in immediate function are needed to improve the clinical practice in patients with low bone density.

From these considerations, this retrospective study aimed to report the mid-term outcome (3 years) of standard implants with 20 to 24 mm of length in immediate function with bicortical anchorage for prosthetic rehabilitation of complete edentulous jaws with low-density bone.

To this end, clinical, instrumental and 3-year outcome data of 27 patients with complete edentulous arches and low bone density treated with long implants were investigated.

MATERIALS AND METHODS

In this retrospective cohort study, 27 patients (17 males and 10 females) with complete edentulous arches and low bone density were consecutively enrolled (average age 62.33 ± 1.70 years; min 46 max 82 years). The study was performed according to the last Helsinki Declaration for human subjects research. All patients were informed about the study and any possible alternative treatments during the first visit. Written informed consent was obtained for each patient.

Inclusion criteria:

- edentulous fixed prosthetic rehabilitation supported by implants in immediate function;
- low bone density determined preoperatively;
- bone atrophy that made it mandatory to use tilted implants of the longer length to be able to install the most posterior implant using bicortical anchorage.

Exclusion criteria:

- incomplete rehabilitation protocol at the rehabilitation centre;
- oncological treatment in the last six months;
- the presence of adequate marginal bone in the posterior segments to insert dental implants for partial restoration.

Clinical and anamnestic data were collected for each patient, including panoramic radiographs and cone beam computerised tomography (before surgery and at 1, 2 and 3 years after surgery). A total of 115 implants were placed; 35 long implants (study implants) with 20 to 24 mm of length (JDNasal®, JDentalCare) and 80 (control/short implants) with 11.5 to 18 mm of length (JDEvolution®, JDentalCare). The opposing dentitions were implant supported prosthesis, natural teeth, or both.

Surgical Protocol

Two surgeons performed the surgery under local anesthesia (articaine chlorhydrate -72 mg/1.8 ml- with epinephrine (0.018 mg/1.8 ml) 1:100,000). Antibiotic therapy (amoxicillin 875 mg + clavulanic acid 125 mg) started 1 hour before surgery and continued for the next 6 days. Post-surgery therapies included cortisone medication (prednisone 5 mg), anti-inflammatory treatment with ibuprofen 600mg and clonixine 300 mg as an analgesic. Lastly, antalgic medication was performed with 20 mg/day with omeprazole for 6 days post-surgery.

In order to obtain a total rehabilitation, a mucoperiosteal flap was raised at the ridge crest with relieving incisions on the buccal aspect. Next, rehabilitation of the maxillary started by opening a small-sized window to the sinus; to identify the exact position of the anterior sinus wall, a round bur was used. Next, abutments and the implants were placed, starting with the posterior ones. Finally, a special guide was placed into a 2 mm osteotomy made at the midline of the jaw; to follow the occlusal centerline of the opposing jaw, the titanium band was bent.

Standard procedures were used to place the implants. According to the manufacturer's protocol, the preparation was performed by full drill depth with a 2 mm twist

drill followed by twist/step drills. The implant head (JDentalCare) was placed at bone level. All long implants were 4 mm in diameter, ranging from 20 to 24 mm. Long implants were tilted distally following the anterior sinus wall or anterior to the mental foramen up to 45 degrees of inclination. Thirty-degree angulated abutments were connected to the implant correcting the inclination to a maximum of 15 degrees. Thanks to tilting the posterior implant, it was possible to position the implant head in the second premolar/first molar region instead of in the canine/first premolar region. A guide pin allowed to place the axial implants. All conventional nonstudy implants were JDEvolution®. The anterior implants were placed in the canine or first premolar positions. After closing and suturing the flap with 4-0 and 3-0 non-resorbable sutures, the abutments were accessed using a punch if needed, and impression copings were placed.

Immediate Prosthetic Protocol

On the day of surgery, full arch acrylic resin prostheses were inserted. After suturing, an impression with putty material (Elite HD+ Putty Soft Fast; Zhermack, Badia Polesine, Italy) was made in a custom open tray. In order to support the peri-implant mucosa during the fabrication of the prosthesis, healing caps were placed. High-density acrylic resin prosthesis with titanium cylinders was inserted 2 to 3 hours post-surgically. During lateral movements, anterior occlusal contacts from canine to canine and canine guidance were preferred in the provisional prosthesis.

A metal-acrylic resin implant supported a fixed prosthesis with a titanium framework, and acrylic resin prosthetic teeth were used to replace the provisional prosthesis. The abutment position was then chosen at the laboratory and was adjusted in the patient's mouth. In this final prosthesis, the occlusion mimicked natural dentition. The final prosthesis was delivered 6 months post-surgically.

Follow-Up

Follow-up examinations were performed at 10 days, 2, 4, 6 months, 1 year, 2 years, and 3 years after implant placement. For the intraoral technique, a conventional radiograph holder was used, which was adjusted manually to ensure orthogonal film positioning. In addition, a blinded operator examined all radiographs of the implants for marginal bone remodelling (reflecting the remodelling due to the surgical and prosthetic procedures). Each periapical

radiograph was scanned at 300 dpi with a scanner, and the marginal bone level was assessed using Image J analysis software (Image J version 1.40 g for Windows; National Institutes of Health, Bethesda, MD, USA).

The reference point for the reading was the implant platform (the horizontal interface between the implant and the abutment), and marginal bone remodelling was defined as the difference in marginal bone level relative to the bone level at the time of surgery.

Primary and Secondary Outcome Measures

Prosthesis and implants' survival represent the primary outcome measures. The survival of the prosthesis was evaluated in terms of function. A prosthesis that needed to be substituted was considered a failure.

The following criteria were used to define the implant survival:

- the implant satisfied its function as a support for reconstruction;
- the implant showed stability if individually and manually tested;
- an absence of pain
- no evidence of infection (abscess or fistulae);
- an absence of radiolucent areas next to the implants;
- good aesthetic satisfaction according to both patient and prosthodontist outcomes;
- the implant allowed the construction of the implant-supported fixed prosthesis.

All implants that did not meet all the criteria mentioned above were considered failures. The secondary outcome measures were:

- The marginal bone loss (MBL) was evaluated at baseline, 1, 2 and 3-years after surgery;
- The incidence of both mechanical and biological complications;

Periapical radiographs were performed on the day of surgery and 1, 2 and 3-years of follow-up by using a parallel technique with a film holder (Super-Bite, Hawe Neos Dental). The MBL evaluation was performed on both the distal and mesial areas. Average values were calculated. The level of the marginal bone evaluated 1, 2 and 3-years after surgery were compared with the values assessed on the day of surgery (baseline). This analysis allowed obtained the MBL value. The following complications were classified as biological complications:

- fistulae formation;

- peri-implant disease;
- the presence of peri-implant pockets ≥ 5 mm;
- bleeding on probing;
- clinical attachment loss with concurrent presence of MBL

The following complications were classified as mechanical complications:

- loosening of any prosthetic component
- fracture of any prosthetic component

Statistical Analysis

The differences between control implant sites and implant study sites were evaluated using the one-way ANOVA method.

RESULTS

This study enrolled 27 consecutively patients characterised by complete edentulous arches and low-bone density. A 51.87% were non-smokers, and an 18.51% smoked more than 10 cigarettes/day. As concern, the main investigated co-morbidities, 51.87% of patients had no associated pathologies. Diabetes was found in 7.41% of patients, 18.51% were hypertensive whereas 7.14% were affected by glaucoma. After surgery, complications were recorded in 22.22% of patients. Specifically, 7.41% showed

bleeding after surgery, whereas in 4 patients (14.81), a breakage of the definitive prosthesis composite was observed (Fig. 1, 2). Also, one patient showed an abutment loosening 2 months after surgery. The problem was amended by retightening the abutment and correcting the occlusion. No further mechanical complications occurred during the follow-up of the study. There were no biological complications registered during the follow-up of the study.

Noteworthy, a 100% survival rate was observed. All prostheses were in function during the follow-up of the study. No patient was lost during the observational period.

Regarding the control implants, the average marginal bone remodelling was 0.09 ± 0.21 at the baseline time point, 0.71 ± 0.32 after 1 year and 1.48 ± 0.28 at 3-year follow-up. Similarly, a constant and significant increased average marginal bone was observed at the sites of study implants (baseline time point 0.20 ± 0.26 ; 1 year 0.92 ± 0.42 ; 3-year 1.71 ± 0.38) (Table I-III).

DISCUSSION

The results of this retrospective study about the use of long implants (≥ 20 mm) placed in a tilted position for the rehabilitation of patients affected by complete

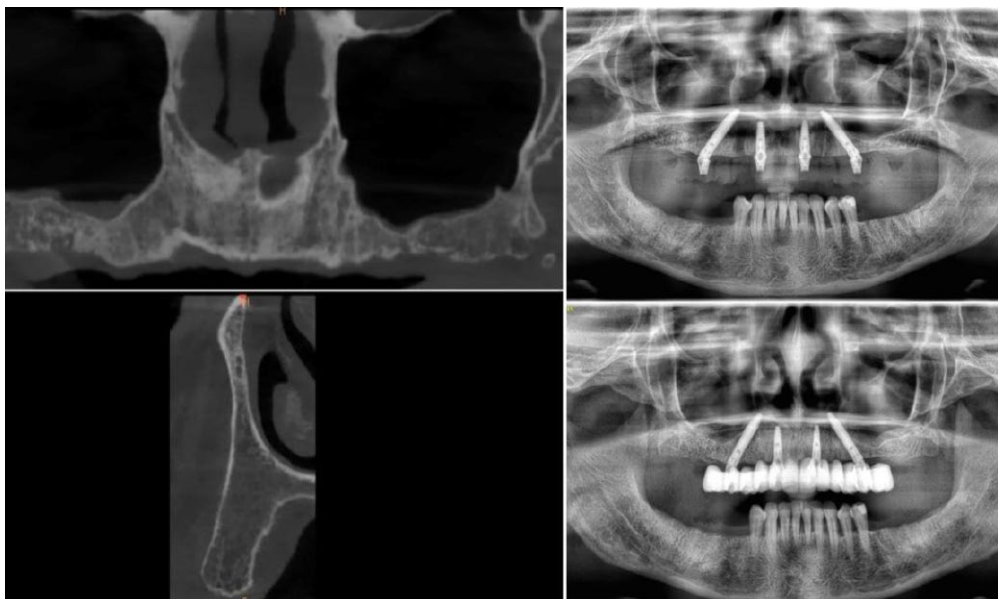


Fig. 1. Composite figure of a successful clinical case with the new implant-surgery protocol.

Table I. *Baseline patients' and implants' characteristics.*

Patient	Gender	Age	Clinical condition	Position	Implant	Diameter	Length	Torque	Drop out
1	M	77	edentulous	15	JDNasal	4	20	35N	after 2 years
				13	JDEvolution	3.7	15	45N	
				11	JDEvolution	3.7	15	45N	
				21	JDEvolution	3.7	15	30N	
				23	JDEvolution	3.7	15	45N	
				25	JDNasal	4	20	35N	
2	F	57	terminal dentition	15	JDEvolution	3.7	15	80N	no
				12	JDEvolution	3.7	15	80N	
				22	JDEvolution	3.7	15	80N	
				25	JDNasal	4	24	80N	
3	F	56	edentulous	16	JDNasal	4	20	80N	no
				11	JDEvolution	3.7	13	80N	
				21	JDEvolution	3.7	13	80N	
				23	JDEvolution	3.7	15	80N	
				26	JDEvolution	3.7	18	80N	
4	M	63	terminal dentition	15	JDNasal	4	20	60N	no
				12	JDEvolution	3.7	15	80N	
				22	JDEvolution	3.7	15	80N	
				25	JDEvolution	3.7	13	80N	
5	M	68	edentulous	16	JDNasal	4	20	80N	no
				12	JDEvolution	3.7	18	80N	
				22	JDEvolution	3.7	18	80N	
				26	JDNasal	4	20	80N	
6	F	54	terminal dentition						no
				15	JDNasal	4	22	60N	
				12	JDEvolution	3.7	15	80N	
				22	JDEvolution	3.7	15	80N	
				24	JDEvolution	4.3	18	80N	
				26					
7	M	75	terminal dentition	16	JDNasal	4	22	80N	after 1 year
				12	JDEvolution	3.7	15	80N	

				22	JDEvolution	3.7	15	80N	
				26	JDEvolution	4.3	18	80N	
8	F	63	terminal dentition	15	JDNasal	4	20	60N	no
				21	JDEvolution	3.7	15	60N	
				23	JDEvolution	3.7	13	60N	
				25	JDEvolution	3.7	15	60N	
9	F	71	terminal dentition	15	JDEvolution	3.7	18	45N	no
				12	JDEvolution	3.7	13	45N	
				22	JDEvolution	3.7	13	45N	
				25	JDNasal	4	22	45N	
10	M	68	terminal dentition	16	JDNasal	4	20	80N	no
				11	JDEvolution	3.7	13	80N	
				21	JDEvolution	3.7	13	80N	
				25	JDEvolution	3.7	18	80N	
11	M	64	terminal dentition	15	JDNasal	4	20	60N	no
				12	JDEvolution	3.7	18	80N	
				21	JDEvolution	3.7	15	80N	
				25	JDNasal	4	20	80N	
12	M	53	terminal dentition	16	JDEvolution	3.7	18	80N	no
				13	JDEvolution	4.3	18	45N	
				11	JDEvolution	3.7	15	45N	
				21	JDEvolution	3.7	15	60N	
				23	JDEvolution	4.3	15	45N	
				26	JDNasal	4	20	80N	
13	M	58	terminal dentition	15	JDEvolution	4.3	15	80N	no
				12	JDEvolution	3.7	15	80N	
				22	JDEvolution	3.7	15	80N	
				25	JDNasal	4	22	80N	
14	M	62	terminal dentition	15	JDNasal	4	20	80N	no

				12	JDEvolution	3.7	15	80N	
				22	JDEvolution	3.7	15	80N	
				25	JDEvolution	3.7	18	80N	
15	M	63	terminal dentition	15	JDEvolution	3.7	18	45N	no
				12	JDEvolution	3.7	11.5	60N	
				22	JDEvolution	3.2	11.5	60N	
				25	JDNasal	4	20	15N	
16	M	47	terminal dentition	25	JDEvolution	4.3	15	80N	no
				12	JDEvolution	3.7	15	80N	
				22	JDEvolution	3.7	15	80N	
				25	JDNasal	4	22	60N	
17	F	68	terminal dentition	15	JDNasal	4	20	80N	no
				12	JDEvolution	3.7	13	80N	
				22	JDEvolution	3.2	13	80N	
				25	JDEvolution	4.3	18	80N	
18	F	64	edentulous	15	JDNasal	4	22	80N	no
				12	JDEvolution	3.2	15	80N	
				22	JDEvolution	3.2	15	80N	
				25	JDNasal	4	22	80N	
19	F	74	terminal dentition	15	JDNasal	4	20	80N	no
				12	JDEvolution	3.7	15	80N	
				22	JDEvolution	3.7	15	80N	
				25	JDNasal	4	20	80N	
20	F	60	terminal dentition	14	JDNasal	4	20	80N	no
				12	JDEvolution	3.7	15	80N	
				22	JDEvolution	3.7	15	80N	
				25	JDEvolution	4.3	18	80N	
21	M	46	edentulous	15	JDNasal	4	22	45N	no
				12	JDEvolution	3.7	13	80N	
				22	JDEvolution	3.7	13	80N	

				25	JDEvolution	4.3	18	40N	
22	M	53	terminal dentition	15	JDNasal	4	22	25N	no
				11	JDEvolution	3.7	15	80N	
				21	JDEvolution	3.7	15	80N	
				25	JDEvolution	4.3	15	80N	
23	M	58	terminal dentition	15	JDEvolution	3.7	18	80N	no
				13	JDEvolution	3.7	15	80N	
				11	JDEvolution	3.7	15	80N	
				21	JDEvolution	3.7	15	80N	
				23	JDEvolution	3.7	15	80N	
				25	JDNasal	4	20	80N	
24	M	66	terminal dentition	15	JDNasal	4	20	45N	no
				12	JDEvolution	3.7	13	30N	
				22	JDEvolution	3.7	13	30N	
				25	JDNasal	4	20	45N	
25	M	82	edentulous	15	JDNasal	4	20	80N	no
				11	JDEvolution	3.7	15	45N	
				21	JDEvolution	3.7	15	45N	
				25	JDNasal	4	20	80N	
26	M	59	terminal dentition	15	JDEvolution	4.3	18	80N	no
				12	JDEvolution	3.7	13	80N	
				22	JDEvolution	3.7	13	80N	
				25	JDNasal	4	20	80N	
27	F	54	terminal dentition	15	JDNasal	4	20	80N	no
				12	JDEvolution	3.7	13	80N	
				22	JDEvolution	3.7	13	80N	
				25	JDNasal	4	20	80N	

edentulous are in line with both the preliminary data of Malò and colleagues (33-36) and the three years outcomes of the use of conventional implants in patients with similar characteristics (28).

At the state art, the short-term outcome of using long implants placed in a tilted position reported a survival rate between 97.6% and 100% (28, 35, 37). In the same studies, a marginal bone remodelling between 0.9 mm and 1.6 mm as described (28, 35, 37). However, only a few studies reported solid and mid-long-term follow-up data about using these implants in patients with complete edentulous. In 2013, Malo et al. (36) reported 100% survival for the short-term outcome (one year) of prosthetic rehabilitation of patients with low bone density using implants of 20 to 25 mm in length in immediate function.

This study reported three years of follow-up data of a cohort of 27 patients with low bone density treated with long lengths tilted implants confirming the high implant survival (100%) described by Malo et al. 1-year after surgery (36). Therefore, the use of longer lengths tilted implants in patients with low bone density can represent a powerful clinical option for treating with complete edentulous arches and low bone density. It is important to note that no biological and mechanical complications have been observed. The absence of mechanical complications can be related to the use of implants in immediate function (38). In fact, the immediate load force may contribute to bone regeneration, thus improving the stability of both implants and prostheses.

In this context, several researchers hypothesised

Table II. Control implants versus study implants: comparison of mean bone levels (means $\pm$ SD) at different time intervals.

Follow up		Mean bone level (mm)				
Baseline	Control implants (n=80)	0.09 $\pm$ 0.21	Control vs study implants Mean difference			
12 months		0.71 $\pm$ 0.32				
36 months		1.48 $\pm$ 0.28	0-12 mo	0-36 mo		
					0.10 $\pm$ 0.31	0.12 $\pm$ 0.35
Baseline	Study implants (n=35)	0.20 $\pm$ 0.26	p=0.235	p=0.336		
12 months		0.92 $\pm$ 0.42				
36 months		1.71 $\pm$ 0.38				

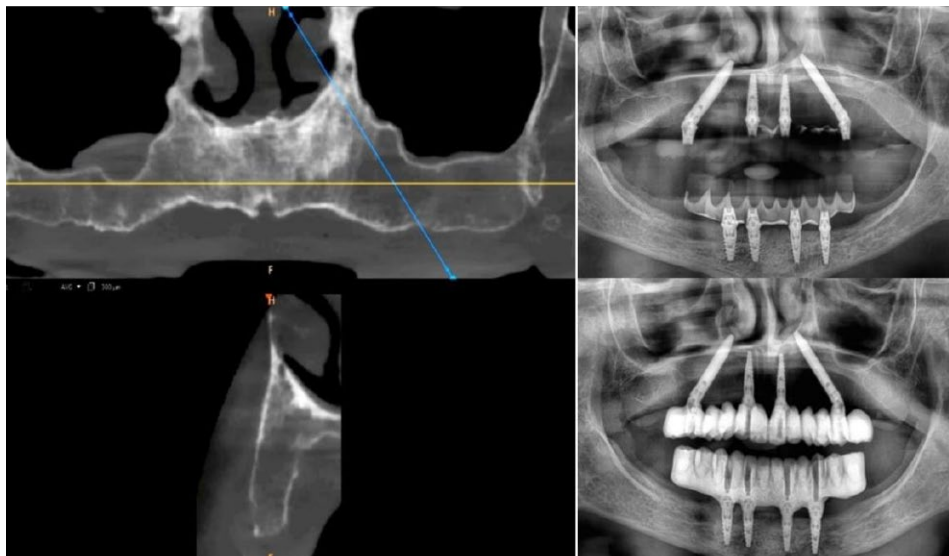


Fig. 2. Composite figure of a successful clinical case with the new implant-surgery protocol.

Table III. Marginal bone remodeling (MBR) for the study implants after 1 and 3 years of follow-up using the patient as the unit of analysis.

	Baseline Bone Level	MBR 1 year	MBR 3 years
Average (mm)	0.21	0.72	1.51
Standard deviation (mm)	0.14	0.34	0.46
Number	35	34	32

that the increase of bone contact surface associated with the use of longer implants could be more advantageous due to the increase of bone implants (39-41). The better stabilisation of the longer implants at the bone site may significantly improve the management of patients with complete edentulous arches and low bone density by reducing the occurrence of implant failure, especially for what concerned the mechanical complications (31, 32). Indeed, the loss of implant stability is the first cause of implant failure in patients with complete edentulous arches and low bone density treated with conventional implants (no longer implants). According to this, Georgiopoulos et al. (19) demonstrated that implant length and diameter can influence the stress applied by implants of the bone sites. In particular, the increase in implant length seems to be associated with bone stress reduction in both immediate and delayed loading (21). In order to increase the implant stability in patients affected by complete edentulous arches and low bone density, it is important to achieve a bicortical anchorage using the maxilla and nasal cortical. Thus, the increase in implant stability can be possible by using implants length ≥ 20 mm since the head of these implants may anchor on the maxilla cortical positioned on the 1st/2nd premolar and the implant apex anchored on the nasal cortical.

This method of implant placement aims to strengthen the bicortical anchorage, which in turn provides a significant benefit in terms of implant-supported immediate function rehabilitations performed in patients showing very low bone density. In any case, some disadvantages and advantages associated with the applications of dental implant

bicortical anchorage have been described. One of the main disadvantages is the increased risk of screw loosening and/or component fracture due to their capability of the long implant to support a larger load share due to their stiffer anchorage (42). Conversely, short implants are associated with a lower risk of screw loosening and/or component fracture because of the greater bone flexion (42).

Despite the evidence of higher stress induced by long bicortical implants on the bone sites with respect to the short ones, the transmission of more considerable stress to the bone by short implants increases the rate of implant failures, thus representing a further a potential advantage for long implants inserted with bicortical anchorage (43). A more detailed characterisation of the physical, molecular and biological interaction between bone and dental implants could improve our knowledge about the implant integration allowing improvement of the management of patients affected by complete edentulous arches and low bone density.

Data here reported improved evidence about the clinical success of using long implants (≥ 20 mm) in immediate function with bicortical anchorage for the treatment of patients with low bone density and partial or complete edentulous fixed prosthetic rehabilitation. The main limitation of this investigation is that only one clinical centre was involved.

Conflicts of interest

The authors declare no conflict of interest.

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Alteration of the perception of cold, heat and texture of food in association with taste dysfunction in COVID-19

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COVID19 is characterized by alteration of smell and taste perception. It was investigated the presence of alteration for cold, heat, and food consistency perception in COVID-19 patients and the possible correlation with the most commonly used biomarkers in a routine way (CRP, IL-6, IL-1, PSP, PCT) to show if the local inflammatory process may induce alteration of cold, heat, and food consistency perception in COVID-19. From March 2020 to April 2021, a survey about taste and oral tactile/thermal sensitivity dysfunction was carried out on 1155 patients with mild or moderate COVID-19, while patients admitted to intensive care were excluded because they could not answer questions from health professionals. Positive RT-PCR confirmed all diagnoses. CRP, IL-6, IL-1, PSP, and PCT were detected for each patient. Taste and Smell Questionnaire Section of the US NHANES 2011–2014 protocol (CDC 2013b) was used for gustatory function assessment. The study was approved by the Ethics committee of AOU Policlinico Consorziale di Bari (No. 6388 COVID19 DOM - protocol number 0034687/12-05-2020), and written informed consent was obtained.

A total of 208 patients referred only to alteration to taste (208/821). 75/208 ageusia, 71/208 ipoageusia, 21/208 fantageusia, 19/208 dysgeusia, 22/208 parageusia. Significant correlations between CRP, IL-6, IL-1, PSP, PCT levels and type of dysfunctions about the perception of heat, cold and food consistency have not been found ($P > 0.05$). Loss of taste can be due to the action of inflammatory mediators on gustatory buds, while alteration of cold, heat and food consistency perception may be due to direct damage of filiform papillae, allowing virus binding through the spike protein to ACE2 receptors of filiform papillae cells.

Since the pandemic due to Sars-CoV-2 was declared in early 2020, anosmia and ageusia are among the most common COVID-19 symptoms (1-3). In addition, severe alteration of taste and smell without rhinorrhea or nasal obstruction can be prodromal symptoms in the

early stage of the disease (4, 5). Some epidemiologic studies reported prevalence ranging from 68% to 85% for olfactory disturbances and from 71% to 88.8% for taste disturbances (78.9% for hypogeusia/ageusia and 21,1 % for parageusia) in mild-to-moderate

Key words: COVID-19; CRP; IL-6; IL-1; PSP; PCT; taste dysfunction; SARS-CoV-2

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forms of coronavirus disease (6, 7). In comparison, two meta-analyses showed a prevalence of olfactory dysfunction of 41.0–61.0% and gustatory dysfunction of 38.2–49.0% (8) and Tong et al. In a meta-analysis of 9 studies from Europe, North America, China, and the Middle East reported gustatory dysfunction ($n = 1390$) in 43.93% (95% confidence interval 20.46%–68.95%) of patients with COVID-19 (9).

Cell entry receptors of Sars-CoV-2 are angiotensin-converting enzyme 2 (ACE2) receptors and transmembrane protease serines 2 (TMPRSS2) (10, 11). ACE2 receptors have been identified in salivary glands (12) and the oral epithelium (oral tongue and gingival tissue) (13). ACE2 was found in a subpopulation of epithelial cells in the basal region of nongustatory filiform papillae but not in the taste papillae (14). TMPRSS2 proteases were identified in the tongue epithelium, mesenchyme, and epithelium of the soft palate in mice (mice and humans have shared similar gene expression patterns for ACE receptors TMPRSS2 proteases) (14).

Different probable mechanisms for the ageusia/hypogeusia during Sars-CoV-2 infection have been suggested: i) retronasal olfactory loss linked to the intimate functional correlation between smell and taste system (15), ii) neurotrophism and neuroinvasiveness of Sars-Cov-2 even if still lacks enough evidence (16, 17), iii) the ability of Sars-CoV-2 to bind sialic acid receptors on the taste buds, with interference with glycoprotein-mediated transport of taste substances before they can be detected with increase of taste threshold and consequent taste dysfunction (18, 19), iv) changes in cellular zinc homeostasis of gustatory cells (20), v) local and/or systematic immune responses (21, 22), vi) inflammatory reaction (4) that could alter taste or may disrupt taste bud homeostasis (23). Recent studies have showed that taste loss in COVID-19 patients is likely not caused by a direct infection of Sars-CoV-2 to taste bud cells but by a lesion of the epithelial cells of the non-gustatory filiform papillae due to inflammatory process (14).

During Sars-CoV-2 infection there was an important inflammatory reaction with the release of different inflammatory cytokines and other chemical mediators secreted by immune and non-immune cells (cytokine release syndrome-CRS) (24, 25). CRS is

responsible for serious systemic complications with consequent dysfunctions multi-organ which, if not adequately and promptly treated, can lead to the death of the patient (25, 26).

The inflammatory response could damage some receptors of oral cavity: in particular GPRC (G-protein-coupled receptor) receptors involved in the perception of sweet, umami and bitter tastes, (27), amiloride-sensitive ion channels ENAC (epithelial Na channel) and ASIC (acid sensing ion channel) involved in the perception of sour, salty (28) and ionic receptors involved in the transmission of the tactile (Merkel cells, Ruffini endings, Meissner corpuscles and free nerve endings) (29) thermal (TRP ion channels: TRPV1, TRPV2, TRPV3, TRPV4 for heat and TRPM8, TRPA1 for cold) (30, 31) and painful sensitivity (32) through the trigeminal nerve endings (33). TRP thermo-receptors contribute to the modulation of taste perception by enhancing some flavours: TRPV1 for the perception of capsaicin, TRPM8 for menthol, TRPM5 for the perception of sweet, bitter and umami (34). Filiform papillae contain trigeminal nerve endings that conduct information on the temperature, texture and pain (27).

Different biomarkers are used to evaluate the evolution of the inflammatory process during COVID-19 disease, for example C reactive protein (CRP), interleukin-6 (IL-6), interleukin-1 (IL-1) procalcitonin (PCT), presepsin (PSP), etc., but none of these present sensitivity and specificity sufficient to be used in clinical practice to assess disease status (35). Therefore it is more appropriate, given the complexity of the process, do not refer about a single marker, but rather to a combination of biomarkers able to describe the course of the disease.

Elevated values of CRP have been found in COVID-19 patients when compared to other viral infections (36).

IL-6 is the main cytokine of the inflammatory cascade with central and peripheral action (37). It stimulates the proliferation and the differentiation of cells involved in immune responses and in the inflammatory response (38). can induce the differentiation of B-cells, monocytes, cytotoxic T lymphocytes, and can enhance NK cell activity (39). Viral infection may induce the production of IL-6

(38). Elevated levels of IL-6 have been found in serum of patients during different human influenza virus infections (1918 H1N1 influenza virus, 2009 H1N1 influenza virus and HPAI H5N1 virus) (40, 41) and during COVID-19 disease (35). It is related to severe clinical manifestations in critically ill patients with respiratory failure and poor prognosis (42).

IL-1 is another cytokine playing a dominant role in a cytokine storm in COVID-19 patients (43). It is the main mediator of the “acute phase” inflammatory produced in response to various infectious, inflammatory and immunologic stimuli by blood monocytes, tissue macrophages, T and B lymphocytes, various epithelial, endothelial and some mesenchymal cells (44). Biological activities of IL-1 is mediated by IL-1 α and IL-1 β : specifically, IL-1 α is released by dying epithelial and endothelial cells whereas IL-1 β is produced by infiltrating monocytes, macrophages, and neutrophils (45).

PCT, widely used in recent years, is considered as a validated serological marker for the identification of microbial infection (46) and predictor for evolution towards a more severe form of disease (47, 48). Recent published systematic review showed that PCT was significantly associated with prognosis. This data was further endorsed by various subsequent publications (49, 50).

PSP is a soluble peptide produced from CD14 which interact with T and B lymphocytes and control immune responses. PSP allows during the early stages to identify COVID-19 patients with more severe disease (51) predict disease aggravation in order to determine early-stage treatment strategies (52).

The aim of this study was to evaluate i) whether there was a difference in the most commonly used biomarkers in a routine way (PCR, IL-6, IL-1, PSP, PCT) between COVID-19 patients with taste dysfunction and COVID-19 patients without taste dysfunction; ii) if COVID-19 patients with taste dysfunction had other chemosensory disturbances (disturbances in the perception of cold, heat and food texture); iii) if there was a difference in CRP, IL-6, IL-1, PSP, PCT between patients with alteration in the perception of cold, heat and food texture (APCHFT) and patients with only alteration in the perception of heat and cold (APCH) in order to evaluate the

involvement of the different receptor systems to identify early the possible evolution of the disease. The evaluation of taste dysfunction, of the alteration of cold, heat and perception of the texture of the food was carried out through the use of a validated questionnaire.

MATERIALS AND METHODS

This study was conducted from March 2020 to June 2021 following the provisions of the Declaration of Helsinki. A survey about taste dysfunction and alteration of oral tactile and thermal sensitivity in 1155 patients with mild or moderate COVID-19 at the time of diagnosis was carried out. Patients admitted to intensive care were excluded because not able to answer questions from health professionals. All patients tested positive to RT-PCR test for Sars-CoV-2. Criteria of exclusion were indicated in Table I.

In a sample of 1155 COVID-19 patients, 821 (71%) presented chemosensitive dysfunctions: of them, 208 (25%) patients (118 men age 59 $\pm$ 13 and 90 women age 56 $\pm$ 12) - showed like prodromic symptoms only taste dysfunctions, 286 (35%) showed like prodromic symptoms only smell dysfunctions and 180 (22%) presented smell and taste disorders. 147 (18%) patients were excluded because 37 (25%) refused to answer, 35 (24%) required intensive care admission (critical patients), 13 (9%) presented allergic rhinitis, 4 (3%) finished chemotherapy and 2 (1%) radiotherapy of oral and oropharyngeal cancer recently, 15 (10%) presented diabetes, 15 (10%) were affected by liver diseases, 10 (7%) by kidney diseases, 9 (6%) by hyperthyroidism, 7 (5%) by neurologic and psychiatric diseases.

The study was approved by Ethics committee of the AOU Policlinico Consorziale di Bari, Italy (No. 6388 COVID19 DOM - protocol number 0034687/12-05-2020) and written informed consent was obtained. Taste and Smell Questionnaire Section of the US NHANES 2011–2014 protocol (CDC 2013b) was used as reference for gustatory function assessment (53). The validated questionnaire was integrated with quick questions (yes/no) which investigated the presence of disturbances in the perception of heat, cold and the texture of food.

All patients underwent a venous sample for laboratory tests at the admission. Samples for IL-6, PCT, CRP and IL-1 β were collected in 5 mL Vacutainer tubes without

Table I. General characteristics, associated symptoms, associated pathologies of COVID-19 patients

Inclusion criteria	Exclusion criteria
- age > 18 years; / - laboratory-confirmed COVID-19 infection (reverse transcription-polymerase chain reaction, RT-PCR); / - patients with only taste dysfunction like prodromic symptom	- patients without a laboratory-confirmed diagnosis of COVID-19 infection; / - patients with taste dysfunctions before the epidemic (congenital ageusia, side effects of drugs, previous surgery of ear and of wisdom teeth, radiotherapy of the oral and pharyngeal cavities, chemotherapy, diabetes mellitus, increasing age and institutionalization or acute hospitalization); / - nutrient deficiency; / - insufficient hydration; / - head trauma; / - hyperthyroidism; / - heart disease; / - liver diseases; / - kidney diseases; / - malignancies (oral and tongue carcinoma); / - ear infection; / - patients with neurodegenerative and psychiatric disorders (Parkinson's disease, Major depression and Alzheimer disease); / - upper respiratory infections; / - allergic rhinitis, asthma; / - oral cavity infections (related to the use of dental prostheses, candidiasis); / - poor oral hygiene; / - Burning Mouth Syndrome; / - smoke
General characteristics	
Gender	Age (years)
Male 118 (57%)	59 ± 13
Female 90 (43%)	56 ± 16
Days from COVID-19 symptoms onset	4 ± 1
Clinical classification	
MILD 127 (61%)	54 ± 13
Male 62 (4.9%)	53 ± 15
Female 65 (51%)	49 ± 14
MODERATE 81 (39%)	62 ± 12
Male 56 (69%)	69 ± 11
Female 25 (31%)	66 ± 12
Associated symptoms	
Cough	176 (85%)
Muscle or joint pains	194 (93%)
Stuffy nose	97 (46%)
Chest pain	144 (69%)
Fever	196 (94%)
Felt tired	153 (73%)
Problems breathing	66 (80.4%)
Asthenia	185 (89%)
Headache	102 (49%)
Abdominal symptoms	29 (14%)
Sore throat	131 (63%)
Vomit (1-2 episodes in the days before hospitalization)	59 (28%)
Nausea	91 (44%)
Diarrhea	31 (15%)
Loss of appetite	159 (76%)
Associated pathologies	
Gastroesophageal reflux disease	101 (48%)
Hypertension	99 (47%)
Thyroid disease (Hypothyroidism)	52 (25%)
Respiratory insufficiency	29 (14%)

anticoagulants while PSP was collected in a lithium-heparin anticoagulant tube.

IL-1 β (v.n. < 13.6 pg/ml) assay was performed with ELISA (Diasource ImmunoAssay S.A. Rue du Bosquet, Belgium). The IL-6 (v.n. 0–7 pg/mL) assay (kit Elecsys IL-6, Roche, Mannheim, Germany) and PCT assay (v.n. 0.0–0.05 ng/mL) (kit Elecsys BRAHMS PCT, Roche, Mannheim, Germany) were performed with the chemiluminescence assay using Cobas e801 (Roche, Mannheim, Germany), Presepsin (v.n. 20–200 pg/mL) assay (kit PATHFAST Presepsin CARTRIDGE, Mitsubishi Chemical Europe GmbH, Düsseldorf, Germany) with chemiluminescence assay using PATHFAST® Presepsin, CRP (v.n. 0–3 mg/L) nephelometric assay (kit CRP Flex reagent cartridge SIEMENS, Munich, Germany) using Siemens Dimension Vista 1500 (SIEMENS, Munich, Germany).

using MedCalc for Windows, version 19.4 (MedCalc Software, Ostend, Belgium). Age, sex, symptoms associated and taste disorders variables are reported in numerals and percentages of the total. Descriptive statistics for quantitative variables are given as the mean $\pm$ SD.

The statistical analysis of biomarkers IL-6, CRP, PCT, PSP, IL-1 β was performed using Mann Whitney U test to evaluate the difference between independent groups of mild and moderate patients in perception of cold and heat and of food texture. Welch two test was used to compare the mean values of the biomarkers studied in the APCFT group and in the APCH group.

Pearson's linear correlation coefficient was used to correlate these biomarkers in two groups mild and moderate patients.

RESULTS

Statistical analysis

Statistical analyses were performed were performed

Totally 334/1155 (29%) patients did not complain of any taste/smell alteration and 821/1155 (71%)

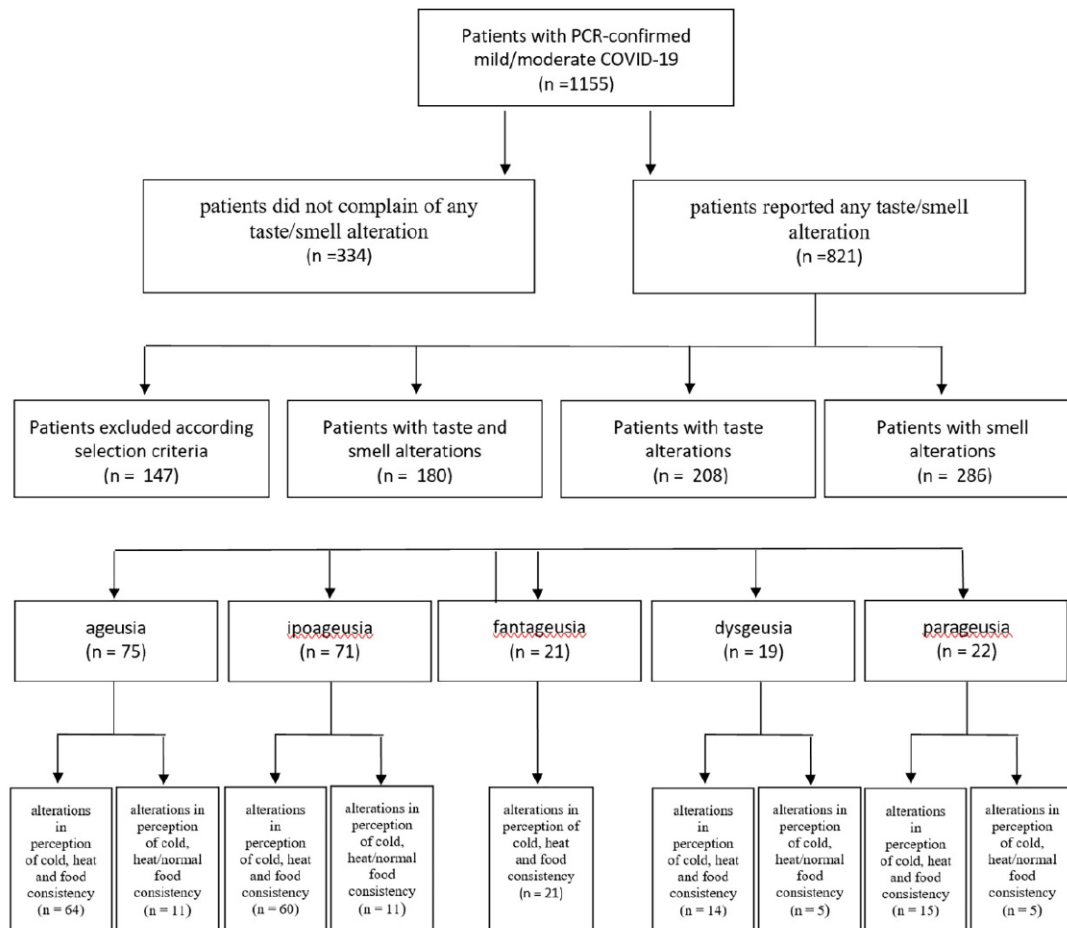


Fig. 1. Flowchart of the study with major results

reported chemosensory disturbances (taste and/or smell disorders, and disturbances affecting oral tactile and thermal sensitivity) (Table II).

Totally 147/821 (18%) were excluded according to exclusion criteria and 674 (82%) patients showed smell/taste alterations: only taste (208/821, 25%), 286 only smell (286/821, 35%), 180 both taste and smell (180/821, 22%).

Patients with taste alteration alone (118 men - 57%, with mean age of 59 years; 90 women - 43%, with mean age of 56 years) have been examined in order to verify what type of taste alteration was present together to somato-sensorial alterations (cold, heat and food consistency) (Fig. 1).

Totally 75/208 (36%) patients (39 women - 52%, 36 men - 48%) referred ageusia: 64/75 (85%) associated to alterations in perception of cold, heat and food consistency, 11/75 (15%) associated to alterations in perception of cold, heat, but perception of food consistency was normal.

Totally 71/208 (34%) referred ipoageusia: 60/71 (84%) associated to alterations in perception of cold, heat and food consistency, 11/71 (16%) associated to alterations in perception of cold, heat but perception of food consistency was normal.

Totally 21/208 (10%) referred phantageusia (gustatory perception in the absence of gustatory stimulation) associated to alterations in perception of cold, heat and food consistency.

Totally 19/208 (9%) referred dysgeusia: 14/19 (74%) associated to alterations in perception of cold, heat and food consistency, 5/19 (26%) associated to alterations in perception of cold, heat, but perception of food consistency was normal.

Totally 22/208 (10%) referred parageusia: 17/22 (77%) associated to alterations in perception of cold, heat, and food consistency, 5/22 (23%) associated to alterations in perception of cold, heat, but perception of food consistency was normal (Table II, Fig. 1).

The time spent on average for the onset of somatosensory disorders was for all groups of 4 ± 1 days from the appearance of the first symptoms (Table I). Mann Whitney U test in mild and moderate patients showed that the two samples were statistically different and that in the moderate the values were higher (Table III).

Welch Two test showed that at least in the early stages there were no statistically significant differences in the mean values of the biomarkers studied in mild patients between those without taste dysfunction and those with taste alteration ($p > 0.05$) while there were statistically significant differences in the mean values of biomarkers in moderate patients between patients without taste alteration and patients with taste dysfunction ($p < 0.05$) (Table IV). The distribution of the parameters in mild and moderate patients with taste dysfunction is shown in Fig. 2.

Pearson's linear correlation coefficient showed that in mild patients there was no statistically significant correlation between CRP and PCT ($p > 0.05$) and between PCT and PSP ($p > 0.05$) (Table IV). Probably in the initial clinical stages of COVID-19 disease there is no important inflammation involving all mediators and there is no concomitant bacterial infection since PCT and PSP are not released. Pearson's linear correlation coefficient in mild patients showed that there is no statistically significant correlation between CRP and PCT ($p > 0.05$) and between PCT and PSP

Table II. Taste disorders are associated with alterations in the perception of cold, heat, and food consistency. All patients with taste disturbances also showed alterations in the perception of cold and heat

	N. of cases	Alterations in perception of cold, heat, and food consistency	Alterations in perception of cold, and heat, but perception of food consistency was normal.
Ageusia	75	64	11
Ipoageusia	71	60	11
Phantageusia	21	21	0
Dysgeusia	19	14	5
Parageusia	22	17	5
Total	208	176	32

($p>0.05$) (Table V). Pearson's linear correlation coefficient in moderate patients showed that there was an excellent correlation between the parameters considered ($p<0.05$). (Table VI)

Mann Whitney U test showed that there were no

statistically significant differences in IL1 β , IL6, CRP, PCT, PSP levels between patients with alterations in perception of cold, heat and food texture and patients with alterations in perception of cold, heat and without alteration of food texture ($p>0.05$). These

Table III. Mann Whitney U test in mild and moderate patients with taste dysfunction

Variable	P-value	Mean value
IL1 β mild vs IL1 β moderate	<0.05	15.14 vs 23.7
CRP mild vs RCP moderate	<0.05	7.51 vs 38.2
IL6 mild vs IL6 moderate	<0.05	11.5 vs 54.3
PCT mild vs PCT moderate	<0.05	0.11 vs 0.68

Table IV. Welch Two test in mild and moderate patients with and without taste dysfunctions

Variable	P value	Mean value
IL1 β in mild patients without taste dysfunction vs IL1 β in mild patients with taste dysfunction	>0.05	14.9 vs 15.14
CRP in mild patients without taste dysfunction vs RCP in mild patients with taste dysfunction	>0.05	6.81 vs 7.71
IL6 in mild patients without taste dysfunction vs IL6 in mild patients with taste dysfunction	>0.05	10.8 vs 11.5
PCT in mild patient without taste dysfunction vs PCT in mild patients with taste dysfunction	>0.05	0.12 vs 0.11
IL1 β in moderate patients without taste dysfunction vs IL1 β in moderate patients with taste dysfunction	<0.05	43.2 vs 23.7
CRP in moderate patients without taste dysfunction vs RCP in moderate patients with taste dysfunction	<0.05	63.9 vs 49.3
IL6 in moderate patients without taste dysfunction vs IL6 in moderate patients with taste dysfunction	<0.05	54.9 vs 26.4
PCT in moderate patients without taste dysfunction vs PCT in moderate patients with taste dysfunction	<0.05	0.68 vs 0.31

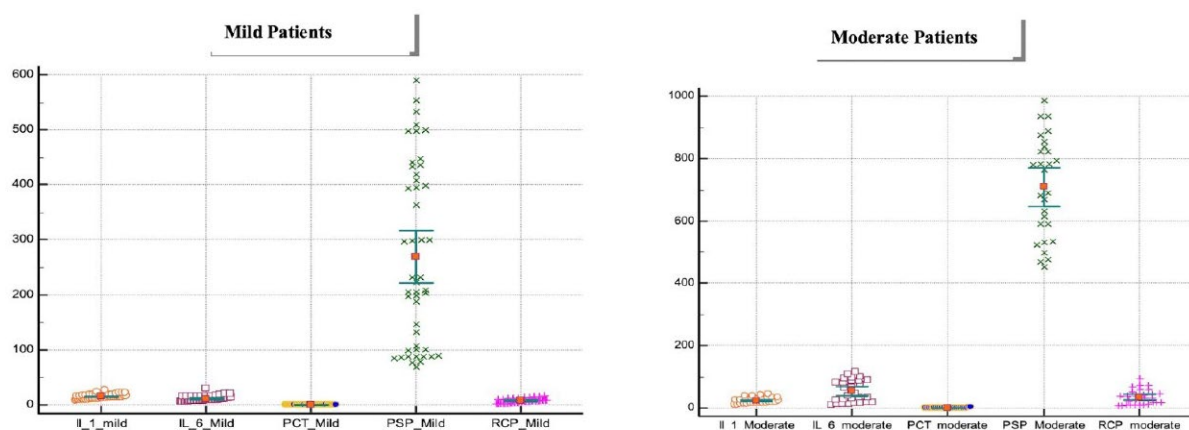


Fig. 2. Distribution chart of parameters considered for mild and moderate patients

data indicated that increased levels of biomarkers were present in both groups (Table VII).

DISCUSSION

Different papers investigated the occurrence of anosmia/hyposmia and dysgeusia/ageusia in

COVID-19 patients correlating them with different biomarkers. To date, no papers have correlated the presence of these disorders with the most commonly used biomarkers in a routine way (CRP, IL-6, IL-1, PSP, PCT) and no papers have investigated the presence of disturbances in the perception of cold, heat and food texture sensitivity in association with

Table V. *Pearson's linear correlation coefficient in mild patients*

Variables	Pearson Coefficient (r)	95% confidence intervals	P value
IL1 β vs IL6	0.67	0.48 to 0.80	<0.05
IL1 β vs CRP	0.64	0.433 to 0.78	<0.05
IL1 β vs PCT	0.38	0.10 to 0.60	<0.05
IL1 β vs PSP	0.55	0.31 to 0.72	<0.05
IL6 vs CRP	0.735	0.56 to 0.844	<0.05
IL6 vs PCT	0.25	0.03 to 0.50	<0.05
IL6 vs PSP	0.38	0.10 to 0.60	<0.05
CRP vs PCT	0.23	-0.05 to 0.49	> 0.05
CRP vs PSP	0.49	0.24 to 0.68	<0.05
PCT vs PSP	0.27	-0.008 to 0.52	> 0.05

Table VI. *Pearson's linear correlation coefficient in moderate patients*

Variable	Pearson Coefficient (r)	95% confidence intervals	P value
IL1 β vs IL6	0.86	0.73 to 0.93	<0.05
IL1 β vs RCP	0.72	0.48 to 0.86	<0.05
IL1 β vs PCT	0.78	0.58 to 0.89	<0.05
IL1 β vs PSP	0.88	0.72 to 0.94	<0.05
IL6 vs RCP	0.61	0.31 to 0.80	<0.05
IL6 vs PCT	0.68	0.41 to 0.84	<0.05
IL6 vs PSP	0.81	0.63 to 0.91	<0.05
RCP vs PCT	0.52	0.19 to 0.75	<0.05
CRP vs PSP	0.75	0.53 to 0.88	<0.05
PCT vs PSP	0.64	0.36 to 0.82	<0.05

Table VII. *Mann Whitney U test in patients with alterations in the perception of cold, heat and food texture (A.P.C.H.F.T.) vs patients with alterations in the perception of cold, heat and normal perception of food (A.P.C.H.)*

Variable	P value
IL1 β (A.P.C.H.F.T.) vs IL1 (A.P.C.H.)	>0.05
CRP (A.P.C.H.F.T.) vs CRP (A.P.C.H.)	>0.05
IL6 (A.P.C.H.F.T.) vs IL6 (A.P.C.H.)	>0.05
PCT (A.P.C.H.F.T.) vs PCT (A.P.C.H.)	>0.05
PSP (A.P.C.H.F.T) vs PSP(A.P.C.H)	>0.05

taste disturbances and whether the inflammatory process can influence the perception of thermal (hot / cold) and tactile sensitivity.

The results of this study showed that: i) there was a statistically significant difference of the biomarkers considered between mild and moderate patients at admission ($p < 0.05$) with higher values in moderate patients; ii) there was a statistically significant correlation in the matching of biomarkers considered in mild patients ($p < 0.05$) except for CPR vs PCT and PCT vs PSP ($p > 0.05$); iii) there was a statistically significant correlation in the matching of biomarkers considered in moderate patients ($p < 0.05$). Besides, this study showed that: i) there was no statistically significant difference in the parameters considered between mild patients with taste disturbances and mild patients without taste disturbances ($p > 0.05$), ii) there was a statistically significant difference in moderate patients between those without taste alterations and those with taste dysfunction ($p < 0.05$), iii) the presence of alterations in the perception of heat, cold and texture in association with taste disturbances; iv) there were no statistically significant differences in biomarkers levels between patients with alterations in perception of cold, heat and food texture and patients with alterations in perception of cold, heat and without alteration of food texture ($p > 0.05$).

The thermo-receptors (TRP ion channel) and mechanoreceptors (Merkel cell-neurite complexes, encapsulated corpuscles and free nerve endings) are located at the level of the filiform papillae, which are not involved in gustatory sensitivity. In fact the filiform papillae, richly innervated, are considered mechanoreceptors while they do not have taste buds (54). Both thermo-receptors and mechanoreceptors are ion channels. Different researches demonstrated the link between inflammation and ion transport and that ion channels can be influenced by cytokines, chemokines and other inflammatory mediators (55). Inflammatory mediators may cause changes in epithelial ion transport with impaired cell permeability and may influence cell proliferation with the appearance of less differentiated cells with a reduced number of ion channels (55).

Excessive production of inflammatory cytokines can cause cell death and inhibit cell renewal in the

taste buds, which can contribute to the development of various associated taste disorders diseases, also due to the paracrine activity of some inflammatory mediators, especially if sepsis occurs. Instead, the filiform papillae could be prematurely damaged by tissue inflammation with immediate alteration of tactile and thermal sensitivity due to the direct action of the virus through the spike protein.

The SARS-CoV-2 virus targets cells for entry by binding its spike protein to cell-surface angiotensin-converting enzyme 2 (ACE2), located at the level of the filiform papillae (14). Non-gustatory papilla epithelial cells are prime targets for SARS-CoV-2 infection in the tongue; thus, the taste loss in COVID-19 patients is likely not caused by a direct infection of SARS-CoV-2 to the taste buds because ACE2 is not expressed in these cells but is the consequence of a local inflammatory process (14).

Recent studies suggested the possible role of local inflammatory phenomena on the receptors of the olfactory and gustatory cells (4) rather than permanent cellular damage linked to the action of the virus. The dysfunctions might be linked to peripheral action of inflammatory mediators at the level of cells infected by the virus. Taste cells produce, in response to inflammatory stimuli, high levels of various molecules associated with internal defence responses, including multiple inflammatory cytokines. The filiform papillae could be early damaged by tissue inflammation with immediate alteration of tactile and thermal sensitivity for the direct action of the virus through the spike protein. For this reason, the correlation between mild and moderate forms relative to biomarkers (CRP, IL-6, IL -1, PSP, PCT) levels is not significant as it seems that the filiform papillae are damaged early with possible alteration of cold, heat, and food consistency perception (Fig. 3).

Summarizing, the loss of taste can be due to the action of inflammatory mediators on the gustatory buds present in the oral mucosa, while the alteration of cold, heat, and food consistency perception may be due to a direct damage of the filiform papillae with tactile function for the binding of the virus through the receptors for the spike protein. This is the first study that investigates the presence of other chemosensory disorders in COVID-19 patients by adding a step in

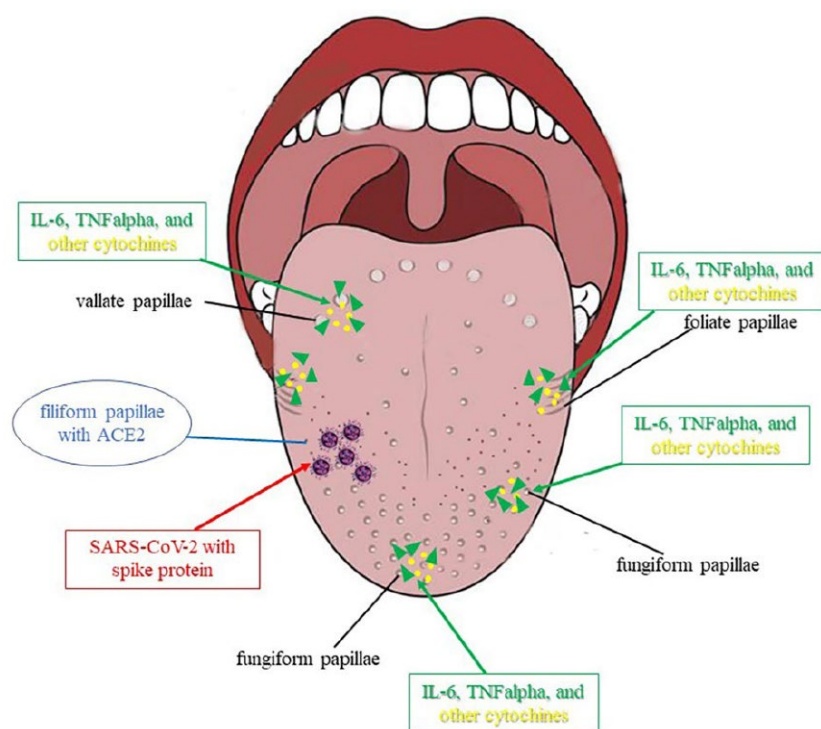


Fig. 3. SARS-CoV-2 seems to directly damage the filiform papillae through the link between the Spike protein and the ACE2 receptors present on the epithelial cells of the filiform papillae while the damage of the fungiform, valley and foliate papillae responsible for the taste alteration is due to the action of IL-6, TNF- α and other cytokines present following the infectious process

the study of the physiology of taste. However, there are limits related to the limited number of patients enrolled and the use of short questions with quick answers (yes / no) for the identification of the disorder. Data on larger case series are needed for confirming this theory.

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Bleaching in vital teeth: a systematic review

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There are mainly three approaches by which teeth whitening treatments can be carried out: in-office, at-home and via over-the-counter (OTC) products. There are conflicting opinions in the literature on which treatments are most effective and stable over time, and on which ones give greater dental sensitivity during the whitening treatment, this being the main adverse effect of the treatment. The objective of this review was to evaluate the efficacy of post-treatment whitening (primary outcome), its stability after several weeks (secondary outcome) and the prevalence of dental sensitivity (tertiary outcome) in patients undergoing whitening treatment, in order to evaluate which is the most effective and safest whitening approach for patients. The following systematic review was conducted on the basis of the indications of the Prisma protocol; 10 studies were identified through literature searches on the PubMed database. The various procedures related to the studies included in this review have shown that they can produce satisfactory post-treatment whitening efficacy and, albeit with less data available, also in the long term; furthermore, dental sensitivity is present in the first days of application, and tends to disappear after a few days, and its intensity is generally mild to moderate for all the whitening techniques tested. For a better evaluation of the stability over time with the different techniques, it could also be useful to check the eating habits of the patients since the diet could be an important factor that influences the extrinsic staining of the teeth; it is necessary to undertake further research into desensitizing protocols that can further improve patient comfort.

Teeth whitening is one of the aesthetic requests made by patients due to the discoloration process that teeth can undergo. The term "dental discoloration" is used to describe any change in the color or translucency of a tooth, and is generally classified as extrinsic and intrinsic (1).

The extrinsic stains are mainly localized in the film and can be generated by the reaction between sugars and amino acids or acquired by the retention of exogenous chromophores in the film(2); are mainly associated with

environmental factors or individual behaviors, such as tobacco use, exposure to metal salts, or consumption of pigmented foods or beverages (3-5).

Intrinsic stains, on the other hand, are integrated into the tooth structure (6); may arise due to systemic conditions, such as genetic diseases affecting the hard tissues of the tooth (e.g., dentinogenesis imperfecta, amelogenesis imperfecta) or local pre-eruptive or post-eruptive factors, such as age or use of tetracyclines in childhood (1,7-9).

Keywords: Vital tooth bleaching; bleaching agents; home bleaching; office bleaching

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Vital teeth were whitened as early as the late 1800s using various oxidizing agents, such as oxalic acid; later hydrogen peroxide was used for whitening in the office with a heating tool or with a light source (5). This technique remained the predominant method for teeth whitening until the introduction of an at home approach called “nightguard vital bleaching” in 1989, which used a vacuum-packed plastic tray containing a carbamide peroxide whitening agent (10).

10% carbamide peroxide was first used in the late 1960s when an orthodontist, instructing his patients to use an “over-the-counter” oral antiseptic containing this molecule for the treatment of gingivitis, found that it not only improved gum health, but also that teeth were whitened (11).

Later an over-the-counter whitening strip was introduced for applying a whitening agent to hydrogen peroxide or low-dose carbamide peroxide (12); this system has become very popular and has been shown to be safe and effective in clinical studies (13). Over-the-counter products also developed whitening toothpastes, which rely mainly on abrasives for mechanical removal of extrinsic surface stains, although some contain low levels of peroxide (14,15). Finally, Power Bleaching is another in-office whitening procedure that uses concentrated solutions of hydrogen peroxide, with or without light activation (16). In-office teeth whitening remains a popular aesthetic procedure and much re-requested by patients because it produces more immediate results, in fewer sessions, than at-home treatment (17), although several clinical studies have demonstrated the efficacy of whitening with both procedures (18-20); even the use of over-the-counter (OTC) products, such as whitening strips, has been shown to have good efficacy (21). Tooth sensitivity is a very common side effect of whitening treatment (22). There are conflicting opinions in the literature on which treatments are most effective and stable over time, and on which ones give greater dental sensitivity during whitening treatment (23).

The objective of this review is to evaluate the effectiveness of post-treatment whitening and its stability after a few weeks in the works that measured the color difference from the baseline with an objective method (spectrophotometer) and expressed as ΔE ,

and to evaluate the prevalence of dental sensitivity in patients undergoing whitening treatment, in order to evaluate which is the most effective and safest whitening approach for patients.

MATERIALS AND METHODS

The following systematic review was conducted based on the indications of the Prisma protocol. The study was built on the PICO questions of population, intervention, control and outcome: population (adult patients who have undergone vital teeth whitening), inter-vention (Vital tooth bleaching), comparison (different whitening protocols) and outcome (efficacy post-treatment whitening and color stability evaluated by spectrophotometer (ΔE), and prevalence of dental sensitivity).

The formulation of the PICO question is as follows: what is the whitening effectiveness of the various vital tooth bleaching protocols (primary outcome)? Other questions were also raised: how stable is the tooth whitening result a few weeks after treatment (secondary outcome) and what is the prevalence of tooth sensitivity in patients (tertiary outcome)? After an initial selection phase of the records identified in the PubMed database, the potential eligible articles are qualitatively evaluated in order to identify the evidence-based differences in terms of dental sensitivity and efficacy between the different whitening protocols.

Eligibility criteria

The papers taken into consideration are clinical studies with parallel, split-mouth and opposing-arch design concerning vital tooth bleaching protocols and published with abstracts in English. The potentially eligible articles were finally subjected to a full-text analysis to verify their use for a qualitative and quantitative analysis. The following criteria were applied in the full-text analysis:

- Inclusion: all those studies that evaluated the various vital tooth bleaching protocols in the adult population, whose color change, expressed as ΔE , was objectively evaluated using a spectrophotometer.
- Exclusion: studies on age groups <18 years, in vitro studies, animal studies, studies on patients with severe dental discolouration (tetracyclines, fluorosis, ...), studies on devitalized or filled teeth, studies written in a language other than ‘English’.

Search strategy

The studies were identified through literature searches on the PubMed database. The search was conducted between 15.12.2021 and 10.01.2022 and the last search for a partial update of the literature was carried out on 14/12/2022. The following search terms were used: “Vital tooth bleaching” (454 records), “Ex-ternal bleaching” (322 records), “tooth discoloration” AND “bleaching agents” (500 records); as a complement to this search, a manual search of the articles included in the bibliographic references of other sources was performed, selecting the citations considered relevant (6 articles), for a total of 1282 articles (Fig. 1).

Screening methodology

Initially, the articles were selected by analyzing the title and abstract according to the research described above and, in doubtful cases, the text was also analyzed to eliminate records not related to the topics of the review. The articles obtained were subject to full-text analysis (67 articles), considered eligible for qualitative analysis for the following three outcomes:

1. Primary outcome, whitening efficacy of the various vital tooth bleaching proto-cols;
2. Secondary outcome, stability of dental whitening a few weeks after treatment;
3. Tertiary outcome, prevalence of dental sensitivity in patients.

RESULTS

After screening the database and manually searching for articles included in refer-ences from other sources, 1282 studies were identified (Fig. 2). After the evaluation of the articles by title and abstract, 67 were selected for the evaluation of the full-text, and of these only 10 were selected for qualitative and quantitative analysis.

Characteristics of the included studies

The characteristics of the 10 selected studies are listed in Table 1. The data was collected by first author, date, journal, study design, application

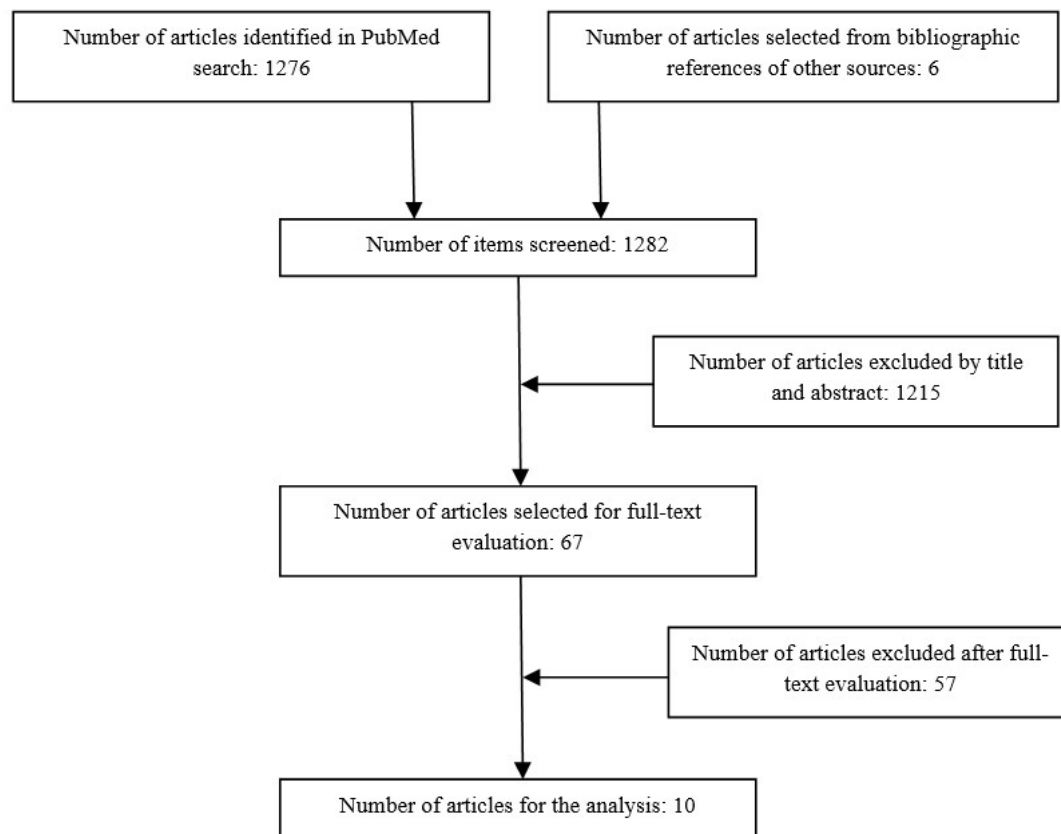


Fig. 1. Flow chart of study identification

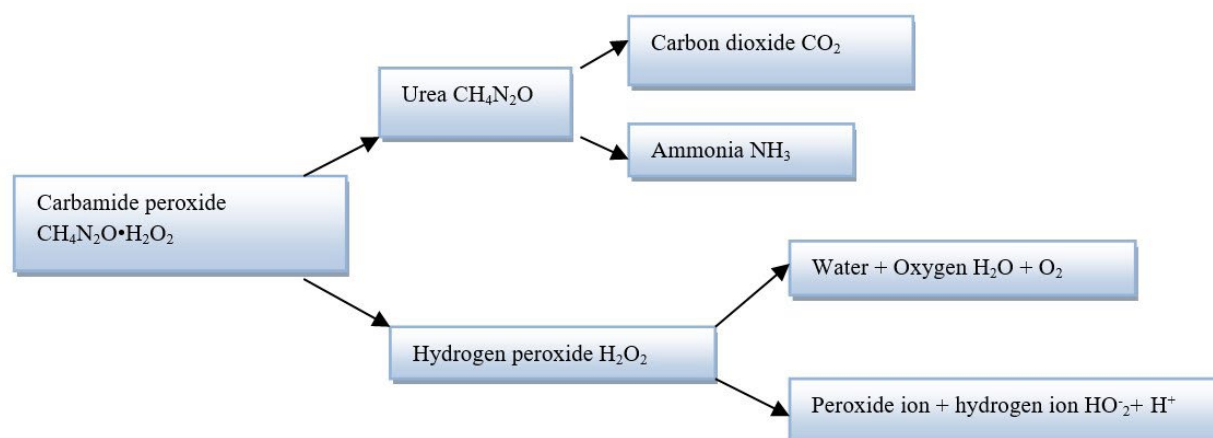


Fig. 2. Formation of final products starting from Carbamide peroxide

Table I. Main features of the included studies

First Author, Date, Journal	Study design	Application Type	No. of subjects (male/female)	Mean subjects' age $\pm$ SD (range) years	Groups/materials	Bleaching protocol
Abouelfotouh IFI, 2018, Stomatological Disease and Science	Parallel	AH; IO; combined	21 (n.r.)	n.r. (18-45)	25% HP with LED irradiation (IO) 9.5% (AH) Combined	IO: 3 x 15-minutes sessions with LED; AH: 30 minutes, twice a day, for 14 day; Combined: 2 x 15-minutes sessions + 30 minutes, twice a day, for another 14 days
V Alonso de la Peña, 2014, Operative Dentistry	Parallel	AH	96 (28/68)	25.9 $\pm$ 5.6 (n.r.)	10% CP 15% CP 7.5% HP 9.5% HP	1 h/day, for 2 weeks
Bernardon JK, 2010, Operative Dentistry	Split-mouth	AH; IO; combined	90 (n.r.)	n.r. (n.r.)	HB/OBL OB/OBL HB/HB+OBL	HB: 8 h/day for 2 weeks OB/OBL: 2 appointment (15-day interval), 3 x 15-minutes applications for each session, without/with light Brushing the teeth with the toothpastes 3 times daily, for 3 minutes for 3 weeks
Khemiss M, 2021, International Journal of Dentistry	Parallel	OTC	38 (12/26)	26.2 $\pm$ 4.2 (18-35)	3% CP activated by 5% Lactoperoxidase; Control (sodium fluoride)	2 h/day for 3 weeks
Meireles SS, 2008, Operative Dentistry; Journal of Dentistry	Parallel	AH	92 (31/61)	25.3 $\pm$ 7.9 (18-55)	10 % CP 16% CP	2 h/day for 3 weeks
Moghadam FV, 2013, European Journal of Dentistry	Split-mouth	AH; IO	20 (8/12)	n.r. (18-55)	AH:15% CP IO: 38% HP with LED	AH: 4 h/day for 2 weeks; IO: 3 x 15-min applications and activated by LED curing system
Ontiveros JC, 2009, Journal of Dentistry	Opposing-arch	IO	20 (n.r.)	n.r. (n.r.)	25% HP with and without light 38% HP	2 separate 45-min exposures
Polydorou O, 2013, Operative Dentistry	Parallel	IO	60 (n.r.)	27.64 $\pm$ 5 (18-70)	38% HP with halogen 38% with laser unit	4 x 15-minutes single visit treatment (halogen for first 8 minutes for each session; laser for the first 30 seconds for each session)
Tsujimoto A, 2021, American Journal of Dentistry	Parallel	IO	50 (17/33)	n.r. (n.r.)	35% HP with/without halogen lamp	3x15-minutes sessions (with 3 minutes of irradiating light); 3x20-minutes sessions (without light)
Zekonis R, 2003, Operative Dentistry	Split-mouth	AH; IO	19 (n.r.)	n.r. (n.r.)	10% CP (AH) 35% HP (IO)	AH: trays for 14 nights; IO: two appointments, each with three 10-minutes applications with 7 days between appointment

AH: At-home; IO: In-office; CP: carbamide peroxide; HP: hydrogen peroxide; HB: at-home with 10% CP; OBL: in-office with 35% HP; with light; OB: IO without light; OTC: over the counter.

type, number of subjects (male/female), mean subjects' age $\pm$ SD (range) in years, groups / materials and bleaching protocol.

The parallel study design was predominantly used in six studies (19, 20, 41-45), considering the two study of Meireless SS as one; three studies used the split-mouth design (18, 46, 47), and only one study used the opposing-arch design (48). From six studies it was possible to derive the prevalence of cases in which patients reported dental sensitivity (19, 20, 41, 43, 44, 46, 47).

The smallest number of patients included among these studies is 19 (47), while the study that included the largest number of patients is 96 patients (19); most of the subjects are female, and the mean subjects' age in the various studies is comparable.

Regarding the type of bleaching agent application, at-home application was used in two studies (19, 20, 43), three studies have used the in-office one (44, 45, 48), two studies evaluated both types of at-home and

in-office applications (46, 47), and two other studies, in addition to these two types of application, also evaluated the combination of at-home and in-office application (18, 41); the use of over-the-counter (OTC) products as bleaching agents was evaluated in a single article (42). The use of a light source as an activation of in-office whitening was reported in six studies (18, 41, 44-46, 48). The at-home protocol was performed in most studies for 14 days, while in one study it was performed for 3 weeks (20, 43); the tray at home use time reported in these studies is 1 hour per day (19, 41), 2 hours per day (20, 43), 4 hours per day (46), 8 hours per day (18), while the number of hours of use of a study is not specified (47).

The in-office approach was performed in 1 (41, 44-46) or 2 appointments (18, 47, 48) after 7 days (47) or 15 days (18) the one from the other; in the study by Ontiveros JC and Paravina RD (48), the interval between the two appointments is not reported; the expo-sure time to the whitening agent in the in-

Table II. *Bleaching effectiveness post-treatment, color stability, prevalence of tooth sensitivity*

First Author, Date, Journal	Bleaching effectiveness ΔE (SD) post-treatment	Color stability ΔE (SD)	Prevalence of tooth sensitivity
Abouelfotouh IFI, 2018, Stomatological Disease and Science	IO: 8.06 (2.76) AH: 8.13 (1.21) Combined: 9.59 (3.95)	6 Months IO: 8.63 (2.38) AH: 7.03 (3.23) Combined: 11.15 (5.25)	IO: 100,0% AH: 57,1% Combined: 57,1%
V Alonso de la Peña, 2014, Operative Dentistry	10% CP: 6.6 (3.5) 15% CP: 6.5 (4.0) 7.5% HP: 7.4 (2.6) 9.5% HP: 7.1 (4.0)	n.r.	10% CP: 54.2%; 15% CP: 54.2%; 7.5% HP: 58.3%; 9.5% HP: 58.3%
Bernardon JK, 2010, Operative Dentistry	HB/OBL: 8.91 (3.42)/ 9.18 (3.76) OB/OBL: 8.41 (3.14)/ 8.76 (3.40) HB/HB+OBL: 10.00 (3.62)/ 10.82 (3.62)	16 Weeks HB/OBL: 8.82 (3.76)/ 8.98 (3.84) OB/OBL: 8.03 (3.08)/ 8.37 (3.08) HB/HB+OBL: 9.70 (3.37)/ 10.32 (3.62)	n.r.
Khemiss M, 2021, International Journal of Dentistry	3%CP: 5.34 (2.31) Control: 4.32 (1.56)	n.r.	n.r.
Meireles SS, 2008, Operative Dentistry; Journal of Dentistry	10% CP: 4.3 (1.9) 16% CP: 4.6 (2.0)	6 Months 10% CP: 3.9 (1.4) 16% CP: 4.5 (1.7)	10% CP: 41,3%; 16% CP: 44.4%
Moghadam FV, 2013, European Journal of Dentistry	IO: 6.9337 (2.59) AH: 7.1244 (3.32)	6 Months IO: 5.6848 (2.34) AH: 6.9507 (3.18)	IO: 40% AH: 30%
Ontiveros JC, 2009, Journal of Dentistry	With light: 6.0 (2.6) Without light: 4.7 (2.2)	n.r.	n.r.
Polydorou O, 2013, Operative Dentistry	38% HP: 4.8 (3.7) 38% HP with halogen: 6.1 (1.9) 38% with laser: 2.15 (2.4)	3 Months 38% HP: 7.05 (2.3) 38% HP with halogen: 5.1 (2.1) 38% with laser: 6.7 (2.8)	38% HP: / 38% HP with halogen: / 38% with laser: 20,0%
Tsujimoto A, 2021, American Journal of Dentistry	With light: 3.40 (1.58) Without light: 3.30 (1.54)	6 Months With light: 3.09 (1.60) Without light: 2.91 (1.12)	n.r.
Zekonis R, 2003, Operative Dentistry	AH: 12.32 (2.89) IO: 5.32 (1.93)	12 Weeks AH: 6.39 (2.39) IO: 3.48 (1.27)	IO: 15,8% AH: 10,5%

office approach in one study was 30 minutes with 3 applications of 10 minutes each (47), in 5 studies of 45 minutes (18, 41, 45, 46, 48) with 3 applications of 15 minutes each, even if of a non the number of applications is specified (48), and in one study the exposure time was 60 minutes with 4 exposures of 15 minutes each (44). In the in-office treatments a higher concentration of bleaching agent was used (25-38% HP), while in the at-home treatments it was mainly 9.5-16% CP, and in one at-home study in addition to the CP the effect of 7.5-9.5% HP was evaluated (19).

Bleaching effectiveness post-treatment, color stability, prevalence of tooth sensitivity

Table 2 shows the data relating to bleaching effectiveness post-treatment, color stability, both expressed as ΔE , and to the prevalence of tooth sensitivity.

In 3 studies, no follow-up was carried out, therefore the data relating to color stability was not reported (37, 42, 48); however, the prevalence of tooth sensitivity data in 4 studies were not reported (36, 42, 45, 48).

DISCUSSION

From the analysis of the literature it emerges that current teeth whitening materials almost exclusively use peroxide compounds as an active ingredient, and in particular carbamide peroxide and hydrogen peroxide are the most commonly used (24).

The whitening action in chemically induced whitening is mainly due to the effects of carbamide peroxide, which releases approximately 33% of its content as hydrogen peroxide (H_2O_2), which can act as a powerful oxidant and which forms free radicals such as hydroxyl radicals and perhydroxyl and superoxide anions (25), reactive oxygen molecules which are unstable and transformed into oxygen and hydrogen peroxide anions (26). Furthermore, carbamide peroxide also releases urea, which is rapidly decomposed into carbon dioxide and ammonia (17, 27) (Figure 2).

Hydrogen peroxide crosses the enamel-dentinal junction and interacts in the underlying dentin with the chromophores, pigments and ions that are recognized to be responsible for tooth staining

(28); it is believed that the whitening process occurs when the reactive oxygen molecules generated by hydrogen peroxide attack the pigmented organic molecules in the spaces between the inorganic salts in the tooth enamel by attacking the double bonds of the chromophore molecules (17, 29); this involves the splitting of the chromophore molecules into smaller and less pigmented constituents, which will result in a change in the absorption spectrum of the chromophore molecules with consequent whitening of the dental tissues (5).

The release of ammonia and carbon dioxide from urea plays an important role in preserving the structure of the dental tissues as it elevates the pH of the whitening agent in the oral cavity to a more basic environment within 15 minutes (30).

There are mainly three approaches by which teeth whitening treatments can be carried out:

- “in-office” or “dentist-supervised in-office whitening”
- “at-home” or “home treatment supervised by the dentist”
- through over-the-counter (OTC) products, which can be used by patients without any supervision by the dentist (21, 31).

The in-office approach involves the use of highly concentrated hydrogen peroxide (greater than 30%) or highly concentrated carbamide peroxide (greater than 37%) in one or three clinical appointments of 30-50 minutes each, at a distance 2-7 days (5, 32); moreover, the peroxide may or may not be activated by heat or light (33).

The at-home treatment, on the other hand, involves the home use of the whitening gel at lower concentrations (10-20% carbamide peroxide) positioned in custom-made masks, and whose daily application time varies depending on the concentration of the product for at least two weeks; this technique has been used for many decades and is probably the most widespread (34).

The association between in-office and at-home procedures has also been suggested to speed up the whitening process (35, 36) as more than one session is usually required. office and some time is needed between consecutive sessions for the reduction of pulp inflammation caused by the high concentrations

of peroxides that delay treatment (37, 38).

Finally, a variety of over-the-counter (OTC) products are available which include strips, paints, mouthwashes, chewing gums, whitening toothpastes, dental floss whiteners (1), which can be easily applied at home by the patient. Whitening toothpaste is the most common over-the-counter product, containing abrasives for stain removal in combination with reduced amounts of whitening agents (39) similarly found in other products (6, 40).

In particular, the analysis of the scientific literature has identified very heterogeneous procedures in the various studies included (which is why summarizing the data in a meta-analysis results in a high risk of bias between the studies), even within the same type of question: example, tray at home use reported in these studies is 1 hour per day (37, 41), 2 hours per day (38, 43), 4 hours per day (46), 8 hours per day (36); another example of heterogeneity is due to the time interval between one session and another of in-office treatment, which in one study was 7 days (47) while in another study it was 15 days (36). The measurement of the color difference following bleaching in the studies of this review was carried out with the CIELAB system (49).

ΔE is the color difference between two objects and can be calculated within the CIELAB system (49). The naked eye is able to distinguish color differences if the ΔE value is greater than 3.3 (50), therefore small color variations could not be perceived; instead, the spectrophotometer is considered the most reliable measurement tool because it is more objective and more precise than observations of the human eye or conventional techniques (51, 52).

The whitening system that uses light (LED, laser, halogen) as a lightening accelerator has been used in most of the studies evaluating in-office treatment (36, 41, 44-46, 48); in the literature it has been stated that the use of a light source accelerates the whitening process (29), although in this study the results obtained are comparable with those without the use of light, as also confirmed from other research projects (53, 54). It has been stated that LED is the most favorable light source as it emits high-energy blue light which stimulates the decomposition of hydrogen peroxide without producing heat (5); in an in vitro study, the

use of LED light did not show a significant increase in the intrapulpary temperature of the teeth when used for the recommended exposure time (55).

The higher concentration of hydrogen peroxide used in in-office treatments gives evident results in a shorter exposure time; however, the short exposure time to a high concentration can be compensated for by a lower concentration of the bleaching agent and longer exposure times (56). The effect of the high concentration could be explained by the dehydration of the teeth that these concentrations cause after whitening (57).

Khemiss et al (42) reported that the ΔE of a whitening toothpaste containing 3% CP and 5% lactoperoxidase was higher than a non-whitening toothpaste, although an improvement in tooth color was also recorded with this type of toothpaste, attributable both to the cleansing properties of normal toothpaste and to the optimal oral hygiene of patients (58, 59). Whitening toothpastes generally rely on abrasives for mechanical re-moval of extrinsic stains, but low levels of peroxide may also be present to help lighten tooth color (15, 34); activating agents, such as chemicals and enzymes, can also be added, which can activate whitening; lactoperoxidase is one of the enzymes that can be used for this purpose (58, 60). One of the side effects of vital teeth whitening is tooth sensitivity (26,61); this finding was also confirmed by the studies considered in this review. Patient-reported sensitivity assessment can be recorded using several methods: "Yes" or "No," (62), scale from 0 (none) to 4 (severe) (38) and scale from 0 to 10 (high hypersensitivity) (63).

The sensitivity of the teeth may be associated with the heating of the whitening agent due to the use of a light source (53, 61); in the study by Polydorou O et al (44), in which three whitening protocols with 38% HP were compared with halogen, laser and without light, only laser whitening resulted in the sensitivity of the teeth during the procedure; this can be explained by the increase in pulp temperature resulting from the use of the laser, even if it is not the only trigger, as the use of a highly concentrated whitening agent is a factor that favors dental sensitivity (29); in fact it has been shown that peroxide diffuses into enamel and dentin and reaches

the pulp, in an amount and with effects correlated to the concentration of the whitening agent (20); despite this, even the low concentrations used in home treatment caused dental hypersensitivity in the patients in the different studies; in fact, in this case, the low concentration is compensated by the longer exposure time with home treatment which leads to sensitivity levels comparable to those resulting from treatment at higher concentrations (64). To reduce dental sensitivity, many whitening agents have potassium and / or sodium nitrate in their composition, associated with lower risk and intensity of tooth sensitivity in both in-office and at-home whitening (65, 66).

In the studies of this review which reported the prevalence of dental hypersensitivity, this is present in the first days of application, and tends to disappear over time, and its intensity is generally mild to moderate for all the bleaching techniques tested.

All these studies showing that the various techniques can produce a satisfactory post-treatment whitening efficacy and, albeit with less data available, even in the long term, even if diet has not been considered, which could be a determining factor in dis-coloration. dental after treatment (67).

Authors should discuss the results and how they can be interpreted from the per-spective of previous studies and of the working hypotheses. The findings and their im-plications should be discussed in the broadest context possible. Future research direc-tions may also be highlighted.

Within the limitations of the present study, the different bleaching techniques tested showed similar clinical efficiency and color stability over time; furthermore, the various whitening techniques tested showed a similar degree of dental hypersensitivity.

For a better evaluation of the stability over time with the different techniques, it could also be useful to check the eating habits of the patients since the diet could be an important factor that influences the extrinsic staining of the teeth. Further research into desensitizing protocols that can further improve patient comfort needs to be addressed.

Conflicts of Interest

The authors declare no conflicts of interest.

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A 10-year experience in preoperative ultrasound imaging for parotid glands' benign neoformations

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Salivary gland neoplasms represent less than 4% of all head and neck lesions, being 80% in the parotid gland and usually benign. Imaging plays a key role in the evaluation of parotid gland masses. Ultrasound is cheap, with an excellent resolution and a safe real time assessment making it an ideal first evaluation option. Conversely, MRI is considered a second-line pre-surgery exam used to determine the location, the extension and the signal features of a parotid lesion. Both US and MRI are poorly reliable for predicting histology, therefore a fine-needle aspiration cytology (FNAC) is usually needed.

In our retrospective study, we examined 263 patients with parotid diseases and a FNAC positive for a benign neoplasm, who underwent surgery between 2010 and 2020, in the departments of Otorhinolaryngology and Maxillofacial surgery in Verona. We compared a group of 126 patients preoperatively evaluated with ultrasound and a control group of 137 patients studied through third level imaging (usually MRI).

In our case series, both third level imaging and US were used in equal measure, despite the lesion size. We found the recurrence rate to be almost the same between the two diagnostic methods and we saw that the patients studied through third level preoperative imaging had a higher complication rate and a worse facial nerve outcome.

In our opinion, for patients with a FNAC positive for benign lesion the exclusive use of ultrasound imaging provides enough information to study the neoplasm while allowing for a faster and cheaper preoperative evaluation.

Salivary gland neoplasms are uncommon, representing less than 4% of all head and neck tumours, with a site distribution of approximately 80% within the parotid gland and 10% within the submandibular and minor salivary glands respectively. Most parotid gland tumors are benign,

while tumors in the submandibular and sublingual glands have a higher risk of being malignant.

Pleomorphic adenomas (PAs) and Warthin tumors (WTs) are the most common benign parotid tumors, making up 75% to 90% of all neoplastic diseases. Even though these tumors are benign, preoperative

Keywords: ultrasound imaging, MRI, parotid glands, fine-needle aspiration cytology, preoperative evaluation

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knowledge of tumor pathology affects the treatment strategy, the surgical procedure, and morbidity (1). PAs are associated with a 2% to 25% risk of malignant transformation over time, and recurrence rates have been shown to be higher in patients who undergo enucleation. Conversely, WTs usually do not recur, and a malignant transformation has not been observed; WTs are multicentric or bilateral in up to 20% of cases (2).

Epithelial tumors account for the majority (95%) of malignant parotid gland neoplastic diseases, but are infrequently encountered, with an overall incidence in the western world of approximately less than 10 cases per million per year (3, 4).

The surgical treatment of malignant tumors includes the removal of the salivary gland, with or without a neck dissection, according to the stage of the disease.

Imaging plays a key role in the evaluation of salivary gland masses, both as a diagnostic tool and for the surgical planning. Ultrasound (US) has several qualities including wide availability, low cost, safety, excellent resolution, real-time assessment and image guidance for needle biopsies, making it an ideal first line technique for parotid gland evaluation (5). Moreover US provides excellent localization of tumors and it allows for a differential diagnosis with cystic masses. Furthermore, through color and spectral Doppler analysis the tumor vascularity pattern can be studied.

PAs typically appear as well-circumscribed, smooth, round, or lobulated hypoechoic masses with a posterior acoustic enhancement. They usually appear as hypo vascular, with a peripheral distribution on power Doppler if compared to WTs and malignant neoplasms (6). WTs are typically well-circumscribed, oval or round, hypoechoic, solid or partially cystic masses with a slightly heterogeneous echo pattern. WTs have a prominent vascularity on power Doppler with a central or mixed distribution.

Primary salivary malignancies' sonographic features are more varied than the ones of benign tumors, partially reflecting the range of histologic grades. High-grade malignancies have irregular or ill-defined margins, while in low grade malignancies smooth margins are more common. Other

malignant features, although less reliable, include a heterogeneous echotexture, a chaotic and increased vascularity, and high resistive vascular indexes on spectral Doppler (7).

In the last decades many US advanced techniques have been developed which may significantly increase US accuracy in differentiating salivary gland pathologies. Microvascular sonography shows micro vessels with a slow flow in small salivary gland tumors that are not generally seen on conventional Doppler sonography. Recent studies have proved that the diagnostic accuracy of microvascular sonography in differentiating between pleomorphic adenomas and Warthin tumors is higher than the one of Doppler sonography (8).

Contrast-enhanced ultrasound (CEUS) uses microbubble agents as acoustic signal enhancers to describe the micro vascularity of the lesion and provide more objective qualitative and quantitative diagnostic data for a clinical diagnosis. Different studies have proved that the score based on combined CEUS and Color Doppler is a useful means to differentiate benign from malignant focal lesions in major salivary glands (9).

Ultrasound elastography (USE) is a non-invasive technique that measures and displays tissue elasticity evaluating the responses recorded by the probe to the mild transient deformations produced by mechanical or acoustic impulses. Many studies about USE in parotid and submandibular neoplastic diseases have been published, most of which suggest that salivary malignancies have higher mean stiffness indexes than benign neoplasms, although there is still marked overlapping (10).

MRI is considered as a second-line exam for the assessment of salivary gland pathologies, and it is usually performed for a pre-operative evaluation to determine the deep or superficial location of a parotid lesion, to describe the tumor extension and signal features and to establish the relationship between the tumor and the facial nerve (11).

Both US and MRI techniques are not precise for predicting the histology, with a considerable overlapping between the various salivary lesions. Therefore, the pre-operative examination of parotid masses usually includes a fine-needle aspiration

cytology (FNAC). FNAC is widely used as a first-line technique for the diagnosis of salivary gland diseases, but many studies have highlighted its limitations, including a high rate of false-negative results and poor accuracy in distinguishing the various types of malignant tumors (12, 13). A recent publication reported a 6% false-negative rate and a 10% false-positive rate (out of 138 cases), a sensitivity for malignancy of 73% and a specificity of 87% (14). A meta-analysis showed that ultrasound-guided core needle biopsy (USCB) has higher levels of accuracy and reduced non-diagnostic rates if compared to FNAC, in addition to good patient tolerability (15). A degree of caution should, however, be exercised because of the potential for tumor seeding.

In our study, we analyzed the role of US in the pre-surgical evaluation of parotid gland tumors in order to understand if it can be considered a sufficient tool, considering surgical complications and recurrence rates.

MATERIALS AND METHODS

In our retrospective study, we examined patients with parotid diseases who underwent surgery between

2010 and 2020. Two departments took part in this study, the department of Otorhinolaryngology and the one of Maxillo-facial surgery of the University of Verona.

The first one examined patients treated between 2014 and 2020 while the second one examined patients who underwent surgery between 2010 and 2020. We created a multi-parameter retrospective database for patient evaluation with a total of 402 patients. We then selected only the ones with a benign pathology for a total of 278 patients, of these 15 were lost during the follow up, thus obtaining a final number of 263 patients actually included in the present study.

Among all the patients in our retrospective database, we selected the ones who had undergone surgery after being evaluated only through preoperative ultrasound imaging for a benign pathology after FNAC (126 altogether). As a control group we used the patients who had undergone surgery for benign pathologies after FNAC, preoperatively studied through third level imaging, more frequently MRI (all in all 137 patients).

5 researchers performed either a partial or a total parotidectomy; 3 of them collected data and devoted to text-processing; 1 of them helped with text-processing and edited the bibliography; 1 of them made the ultrasound and radiological evaluation.

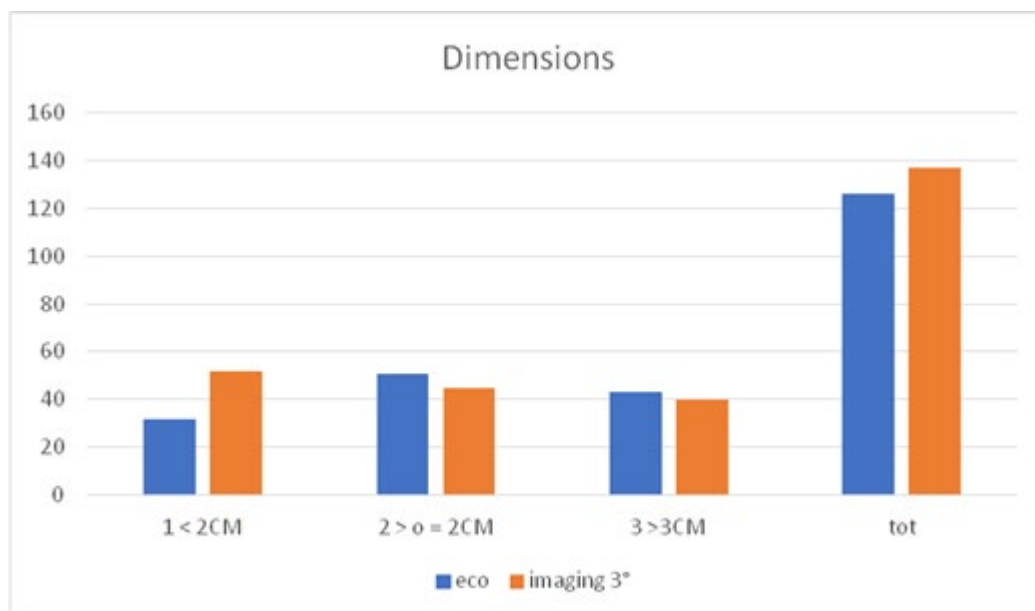


Fig 1. *Dimensions*

RESULTS

We subdivided the total number of patients according to the dimension of their lesion into three groups, below 2 cm of size, between 2 and 3 cm and bigger than 3 cm. The largest group was the one with lesions sized between 2 and 3 cm. For all groups both US and third level imaging were used as diagnostic means. While in the first group the most widely used

diagnostic method turned out to be the third level one (38% vs 25.4% of the US), in the other two dimensional groups US was slightly more frequent (74.6% vs 62%) (Fig. 1).

We then examined the relapse rate of patients studied with ultrasound and those studied with third-level exams. In this case, as can be seen in Fig. 2, the results don't have a clear statistic relevance. In 97,6% of the patients (123) studied with ultrasound there wasn't any kind of recurrence while in the

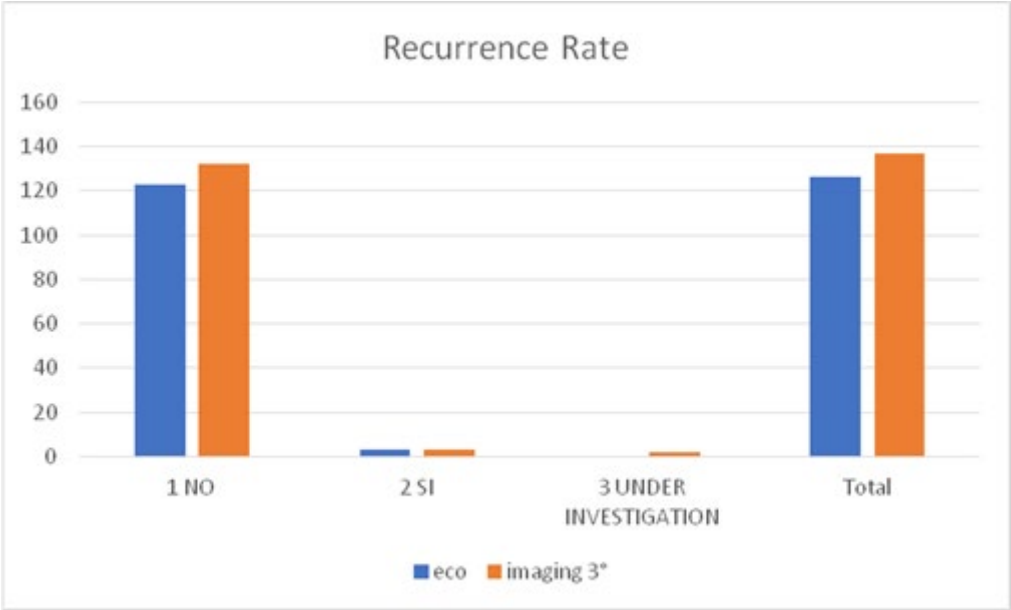


Fig. 2. Recurrence rate

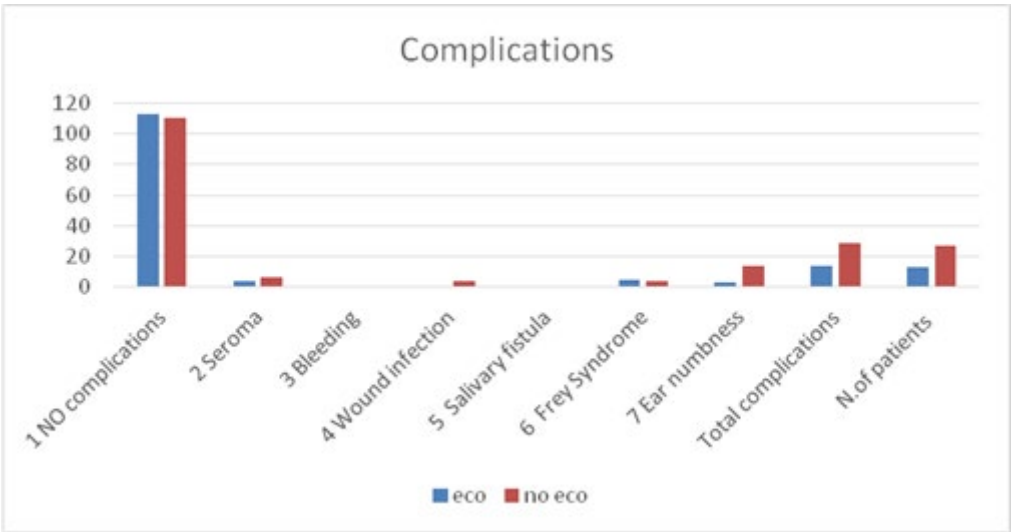


Fig. 3. Complications

remaining 2,4% (3 patients) we had a recurrence. Conversely, while examining the patients who had undergone third-level imaging we found that the rate of patients without recurrence was 96,3% (132); 2,2% patients had a recurrence (3) and in 1,5% of cases investigations were being carried out at the time of writing (2). Therefore, the statistics of the patients studied with the ultrasound technique was better than the one of the patients studied with third-level imaging.

For sure the most interesting evaluation was the one about postoperative complications reported in Fig. 3. In this case the incidence of complications was unexpectedly lower for the patients studied with exclusively preoperative ultrasound imaging (only 10,3%) while the patients with third-level imaging exams had a higher incidence of complications (19,7%).

Last but not least, we took the outcome of the facial nerve into account in Fig. 4. For practical reasons, given the small number of patients, we divided them into two categories, those with a partial impairment and those with a complete one. The patients without any deficits after surgery studied with ultrasound preoperative imaging were 112 out of 126 while the patients studied with third-level exams without deficits were 110 on a total of 137. In the third level

imaging group, the patients with a partial deficit were twice as many as the ones studied with US (25 vs 13). Only 3 patients out of the overall group of 263 who had undergone surgery for a benign lesion had a complete deficit of the facial nerve. So, also in this area there wasn't a relevant statistical difference between the two groups of diagnostic method.

DISCUSSION

Over the years a great debate has arisen among surgeons about the best choice in preoperative exams before major salivary gland surgery. Some schools are in favor of third level imaging while others prefer to combine FNAC with ultrasound and, when malignancy is suspected, MRI or CT scan for a more accurate investigation of the gland and a complete evaluation also of the neck nodes (16).

US is a valuable and useful method for diagnosis of salivary gland tumors, it offers information about the tumor localization and the pattern of vascularization using spectral Doppler and it is able to assess the cystic component of the lesion at hand (17).

MRI, the most commonly used third level diagnostic method in our case series, is normally seen as a second-line diagnostic evaluation for

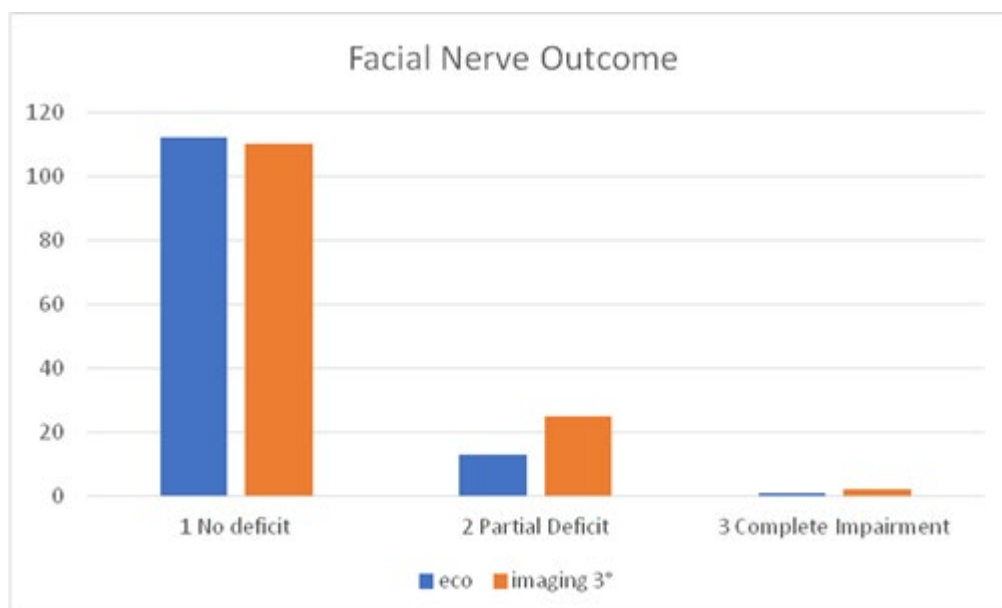


Fig. 4. Facial Nerve Outcome

salivary gland disease and it is usually chosen before surgery is carried out, in order to assess the tumor characteristics, deep or superficial location, signal features and extension. Moreover, MRI has proven to be particularly useful in determining perineural spread and in analyzing the relationship between the tumor and the facial nerve (18).

Considering our 10-year experience from 2010 to 2020 on 263 patients treated for a parotid gland benign neoplastic disease, we might say we obtained some interesting results if compared to literature. As shown above, it is important to point out that we used both diagnostic methods (US and third level) in more or less equal measure, regardless of the dimension of the lesion, proving our results to be relevant for all size groups.

Interestingly, we found the recurrence rate to be almost the same whichever of the two diagnostic method was chosen, leading us to believe that US as the only imaging technique is not a risk factor for recurrence. Moreover, as far as the risk of postoperative complications is concerned, we saw that the patients studied through third level preoperative imaging generally had a worse outcome, even when the facial nerve result was concerned.

We therefore are led to believe that for patients with a parotid gland neoplastic disease with a FNAC positive for a benign lesion, the US as the sole diagnostic method of choice is enough to properly evaluate the lesion and plan the surgical treatment even for neoplasms of big dimensions (>2-3 cm), while allowing for a faster, cheaper and safer preoperative evaluation that may speed up the assessment of the patient and shorten the length of time before surgery.

In keeping with literature, the last ten years of our experience have shown that patients who have to undergo surgery for lesions involving the parotid glands must be tested through FNAC. In our study no difference in the incidence rate, whatever the lesion dimension, was found between ultrasound evaluation and a third level imaging technique, in addition the recurrence rate and the rate of complications were comparable between the two methods analyzed, with lower values in the complication rate for the US.

In the opinion of the current authors, for patients

with a FNAC positive for benign lesion and in patients without clinical sings of neck adenopathies, the exclusive use of ultrasound imaging provides enough information to study the neoplasm and plan the surgical treatment while allowing for a faster preoperative evaluation and a consequent quicker access to the operating room.

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Innovation in oral implantology: the use of surgical guide in the modern implant surgery of the maxillary bones

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Implant surgery was born as freehand surgery, and most protocols are still based on this way of operating today. However, one of the most important trends in the implant field today is represented by guided surgery. There are different types of surgical guides on the market, differing in construction, materials and characteristics. This work aims to evaluate guided surgery using the B&B Dental surgical guide to understand whether it can increase the accuracy and precision of implant insertion. In order to carry out this multicenter study, each operator was assigned 15 implants to be inserted and distributed to different patients. In total, 6 patients were enrolled who in the first phase underwent a pre-operative CBTC (cone beam computed tomography) to then be identified for privacy reasons through a patient ID. In total, 9 B&B Dental implants were placed on a number of 6 enrolled patients. 3 implants were placed in the upper arch and the remaining 6 in the lower arch. On 3 patients a single implant was inserted instead on the remaining 3, during the surgical treatment 2 implants were inserted for specific arch of interest. Analyzing the data published in other works of the literature, it is possible to affirm that the surgical technique with the B&B Dental protocol proposed by us is currently a valid alternative that deserves a particular interest in development and application.

Implant surgery was born as freehand surgery and most protocols are still based on this way of operating today. One of the most important trends in the implant field today is represented by guided surgery. With this definition, dentists encompass at least two broad categories, the first is represented by static guided surgery, based on the use of operating templates, and the dynamic one, namely real-time navigation. The main advantage of guided surgery is probably the greater accuracy of insertion of the fixtures, which results in greater predictability of the intervention as regards the final result. This positively affects the success of the therapy. In fact, at present oral rehabilitation using implants must provide, in addition to a good result in terms of functionality,

also a satisfactory aesthetic achievement. An accurate design is therefore necessary to obtain an optimal positioning of the system and to achieve these goals (functionality and aesthetics) (1).

Around the mid-1990s, guided implant surgery gained popularity; around the mid-1990s, guided implant surgery gained popularity (2). Thanks to these guided methods, the surgeon has a greater quantity of preoperative information at his disposal, thus enjoying important advantages in treatment planning as well as having the possibility of reducing the opening of muco-periosteal flaps, or even eliminating them, causing thus less pain and discomfort for patients in the post-operative period, further avoiding the so-called re-opening (3). However, the evidence to support the

Keywords: Implant surgery; surgical guide; preoperative planning

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hypothesis that there is a real clinical advantage using guided surgery over conventional freehand implant placement is still limited.

The technique under consideration certainly has some advantages for which it is strongly appreciated by patients given the reduced surgical invasiveness. For the operator, the advantages are above all of a biological nature, as it operates in a completely atraumatic and respectful way of the bone physiology, eliminating bacterial contamination and any formations of bacterial micro-environments that cause the release of ROS, in the case of titanium implants, which can prevent proper osseointegration of the implant (4).

A recent review, 19 clinical studies analyzed the clinical results of computer-guided implantology. From this review, it emerged that survival rates, from 1 year to 5 years, for computer-guided implantology are comparable with those in which implant placement was performed freehand in a conventional manner revealing no obvious difference between the two clinical methods. From the clinical studies included in this review, however, were not reported specific complications of computer-guided implantology such as fracture of the template, incorrect implant placement, change of treatment plan, lack of primary stability or the creation of inadequate prostheses (5).

One of the indisputable advantages of guided implant surgery is minimally invasive, as it is possible to reduce the flaps or even avoid them, allowing the maximum preservation of the peri-implant papillae, and the reduction of recessions of the mucous membranes (6). The guided procedure offers better planning and simplicity of procedure, favoring operators who may even be a little less experienced. Intervention planning can also be facilitated by sharing and managing patient data, through a network system that allows clinicians to access records, share work but at the same time ensure their safety and privacy. The anonymous sharing of data related to this type of guided procedure lays the foundations for the development of precision medicine (7).

Obviously, the costs of this guided method are higher, and the patient must be informed of this in advance, evaluating the costs and benefits together with him (8). In an all-Italian study published in

the European Journal of Oral Implantology, he compares the results of guided and classic freehand implantology.

This clinical study enrolled 20 people, divided into two groups: 10 patients saw the insertion of their implants through a computer-guided procedure, the other the standard one. The enrolled subjects needed rehabilitation with a prosthesis and two implants, with 4 mm of bone width and at least 7 mm of height. However, the outcome of both approaches was positive: no prosthesis, in fact, failed. Patients treated with the traditional method after 5 years noticed a slightly higher marginal bone loss, followed by the failure of two of the conventionally inserted implants. Patients in the group undergoing supported surgery, on the other hand, reported slightly less swelling and post-operative pain than those drawn for freehand surgery. All the people involved in the research, however, were satisfied with the final result. The differences between the two techniques are not yet significant from a statistical point of view (9).

Static guided surgery uses customized templates (with dental, bone or mucous support) designed on the computer and printed in 3D, for the guided insertion of implants in position, inclination and depth (10). By surgical guide we mean a personalized medical device that guides the drills and implants in the most suitable area, making the most of the bone availability according to the conformation and anatomical predisposition of the patient.

In order to be able to create a surgical template, the clinician loads the data derived from CBCT in DICOM format (Digital Imaging and Communication in Medicine) in the design software, together with the patient model (derived from scanning the plaster models in the laboratory or from scanning intraoral), in STL format. After aligning the STL file on the bone anatomy, through dedicated operators, it is possible to upload optional files such as the virtual diagnostic wax-up, essential in the case of multiple implants. At this point the clinician can plan the positioning of the implants and, once the project is confirmed, draw the surgical guide, which will be 3D printed (11).

To date, most static guided surgery systems use bushings. Guide bushings are inserted inside the surgical guide. The guide bushings, also called

sleeves, can have two dimensions and are presented as cylinders incorporated in the surgical templates. They have the main function of guiding the surgical instruments during the preparation of the implant site by guiding the position and inclination of the drills. The use of guided surgery through the templates is very frequent today. There are different types of templates on the market, differing in construction material and characteristics. The purpose of this work is to evaluate guided surgery using the B&B Dental template, to understand whether it is able to increase the accuracy and precision of implant insertion.

MATERIALS AND METHODS

The primary objective is the evaluation of implant accuracy in terms of implant position with respect to the expected result, contained in the planning file performed on the computer and obtained through scientific literature.

To carry out this multicenter study, each operator was assigned 15 implants to be inserted and distributed to different patients. Specifically, in the case of patients they had after digital scanning, the operator was limited in the insertion of only 3 implants. Patients to be enrolled had to have the following criteria: at least 18 years of age and the ability to undergo surgical and rehabilitation procedures. On the contrary, patients with general contraindications to implant treatment and / or problems related to head and neck irradiation were excluded. In total, 6 patients were enrolled who in the first phase underwent a pre-operative CBTC (cone beam computed tomography) to then be identified for privacy reasons through a patient ID.

All patients signed informed consent to participate in the study and undergo surgery. The evaluation is carried

out with the 3D image processing platform through the superimposition of the images (STL file) of the design and the images (DICOM) of the post-operative CT control. The primary objective was to evaluate, for each single implant inserted, the following parameters:

- deviation apex (mm);
- deviation hex (mm);
- deviation angle ($^{\circ}$);
- deviation depth (mm);
- coordinates depth pre- op e op (mm).

The listed parameters made it possible to study the validity of the system in terms of accuracy and are represented in Fig.1.

Each of the points treated will give rise to a linear measurement in mm which will be decomposed into the three coordinates of the space x, y, z. The degree measurement obtained will be broken down into the three planes of space.

As an evaluation regarding the accuracy of the method, our results were compared with the data in the literature in traditional guided implantology. The comparison was made with a 2009 article by Schneider D. et al., In which the results of different guided surgery techniques were summarized (12).

Regarding the identification of factors that increase the probability of error, an average value will be extracted from the results for each point described. Subsequently, the average value obtained will be compared with the results obtained.

RESULTS

In total, 9 B&B Dental implants were placed on a number of 6 enrolled patients. 3 implants were placed

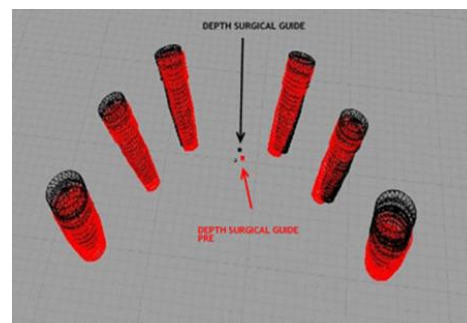
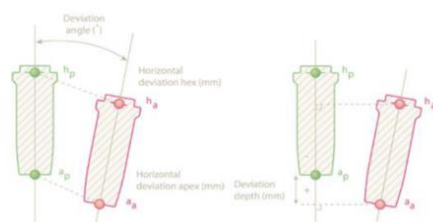


Fig. 1. Graphic visual representation of the individual parameters.

in the upper arch and the remaining 6 in the lower arch. On 3 patients a single implant was inserted instead on the remaining 3, specifically ANT GUG, BARONI and ROSSI during the surgical treatment 2 implants were inserted for specific arch of interest. The accuracy values are shown in Figure 2 and 3.

None of the 6 patients has an average of values higher than those defined as acceptable in the literature in guided implantology according to the chosen work. The mean values found in the measurements of all 9 implants placed were lower than the data expressed in the literature as acceptable:

- average linear distance of the implant head: 0.90 mm
- average linear distance of the implant apex: 1.15 mm
- mean angular deviation of the implant axis: 3.15°.

As regards the evaluation of the deviance depth calculated before and after the intervention, with the aid of templates, values ranging from 0.30 to 2.27 mm were found.

DISCUSSION

The discussion of the results of this work translates into reliability results of the surgical technique with B&B Dental protocol in terms of accuracy and,

subsequently, in terms of clinical results. With regard to the accuracy results, we talk about how the use of guided surgery techniques should favor an improvement in the therapeutic process. Numerous publications, in fact, define criteria according to which guided surgery should be predefined, minimally invasive, rapid, accurate and repeatable.

The preoperative planning of the implant plays, in fact, a key role in implant-prosthetic rehabilitation, because not only is the surgical procedure suitable for the patient's problem chosen, but in the last period numerous studies have also been carried out on the choice of implant material.

Titanium is the leading material in implant-prosthetic treatments, however, horizons are also expanding on the use of titanium implants appropriately coated with allotropic materials such as phosphorene and / or borophene which have shown interesting antibacterial characteristics but also broad biocompatibility and biodegradability (13-15). All this is also possible thanks to the supply of a B&B Dental guided surgical kit made of burs that adapt perfectly to the narrow spaces of the oral cavity, without the need to adapt with instruments taken from different kits. Also for the optimization of an implant in aesthetically sensitive cases, a pre-implant diagnosis and the implementation of planning with computer

IMPLANT BRAND	OPERATOR	PATIENT	ARCH	IMPLANT	DEVIATION APEX [mm]				DEVIATION HEX [mm]				DEVIATION ANGLE °
					Xv	Yv	Zv	V	Xv	Yv	Zv	V	
B&B	ND	FA_CAR_GUA	superior/ dental support	25	-1,723	-1,508	0,838	2,44	-0,646	-0,585	0,872	1,23	6,81
B&B	ND	ANT GUG	inferior/ dental support	34	0,392	0,102	-0,102	0,42	-0,173	-0,098	0,071	0,21	1,27
				36	-0,237	-0,436	-0,003	0,50	-0,253	-0,251	0,049	0,36	1,266
B&B	ND	BIAN ELIS	superior/ dental support	14	-1,516	-0,561	0,966	1,88	-0,734	-0,071	0,619	0,96	4,73
B&B	ND	FA ROST RA	superior/ dental support	25	-1,671	-0,414	1,407	2,22	0,943	0,443	-1,463	1,80	5,27
B&B	ND	Baroni	inferior/ dental support	46	0,42	0,41	-1,96	2,05	0,017	-0,053	-1,993	1,99	3,50
				47	-0,639	-0,587	-2,575	2,72	-0,373	-0,137	-2,511	2,54	3,77
B&B	ND	Rossi	inferior/ dental support	32	0,347	0,3	-1,266	1,35	0,126	0,183	-1,279	1,30	1,20
				42	0,012	0,198	-1,346	1,36	0,115	0,250	-1,338	1,37	0,55

Average	1,15	0,90	3,15
Media references scientific literature *	1.63 mm	1.07 mm	5.26°

Fig. 2. Values of study parameters.

COORDINATES DEPTH SURGICAL GUIDE pre-op [mm]			COORDINATES DEPTH SURGICAL GUIDE op [mm]			DEVIANCE DEPTH
X	Y	Z	X	Y	Z	
66,39	42,48	55,42	67,09	43,11	54,55	1,29
11,60	11,60	-3,66	11,82	-13,84	-3,72	0,30
-6,93	-17,80	-6,94	-6,15	-17,70	-7,58	1,01
72,15	38,87	49,93	73,19	39,31	48,47	1,84
-33,05	-15,29	15,19	-32,90	-15,20	17,45	2,27
2,49	-24,12	-23,50	2,34	24,35	-22,19	1,34

Fig. 3. Values of study parameters.

assisted methods are recommended (16-19). The simplicity of the treatment decreases the biological cost of the intervention, the postoperative morbidity and the healing time, when compared to major pre-prosthetic reconstructive interventions.

Analyzing the data published in other works of the literature, it is possible to affirm that the surgical technique with the B&B Dental protocol proposed by us is currently a valid alternative that deserves a particular interest in development and application. In general, the study we carried out on survival, success rate and complications confirms what has already been argued in the literature, namely that prosthetic rehabilitation is safe and reliable in the medium and long term and guarantees an effective and immediate result, both aesthetic how functional. It is therefore possible to conclude, in accordance with the scientific literature, that guided implantology represents a real and valid alternative to bone reconstruction techniques in the treatment of atrophies. It is essential to apply the correct indications and the rigorous guided implant surgical technique proposed by the kit, which contains the useful and personal tools for the operation. If

well studied, this technique can introduce enormous progress in the realization of prosthetic projects that are increasingly performing from an aesthetic and functional point of view, optimizing times and avoiding numerous finishing operations on the prosthetic components.

Conflicts of interest:

The authors declare no conflict of interest.

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When maxillofacial surgeons meet ophthalmologists: application of piezosurgery in dacryocystorhinostomies

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Background: Chronic obstruction of the nasolacrimal duct leads to inflammation or infection of the lacrimal sac (dacryocystitis). The aim of this study was to evaluate the clinical outcomes of piezosurgery device vs high-speed electric drill with a diamond burr for dacryocystorhinostomies (DCR) in patients with external dacryocystitis.

Patients and Methods: Two patient with nasolacrimal duct obstruction was recruited for the study. All procedures were performed by a maxillo-facial surgeon and an ophthalmologist. The follow-up length was 12 months.

Results: Two patients, with average age of 53.2 years old, underwent to piezosurgery device vs high speed bur for DCR. After one year from surgery, resolution of symptoms was observed. Surgical outcomes showed for both patients, complete resolution of the disease.

Conclusions: The authors' results, in accordance with the literature data, indicate that piezosurgery dacryocystorhinostomy is a promising surgical technique, both in terms of results and postoperative patient's quality life.

It is well known that, because of the very close relationships between the course of the nasolacrimal duct and the nasal structures, each pathology affecting the lower and anterior part of the nasal cavities, can cause important repercussions on the lacrimal canal, and in particular can cause stenosis or occlusion with chronic stagnation of tears in the lacrimal sac and consequent dacryocystitis (1). In fact, dacryocystitis is inflammation of the lacrimal sac, often caused by a bacterial infection, usually resulting from an

obstruction of the nasolacrimal duct (1). During acute dacryocystitis, the patient presents lacrimal sac pain, hyperemia and edema. Diagnosis is suspected based on symptoms and clinical signs and when lacrimal sac acupressure causes mucoid discharge from the lacrimal punctures. Treatment initially involves the application of warm compresses and the use of antibiotics (2).

Generally, a 1st generation cephalosporin or synthetic penicillin resistant to penicillinase is used.

Keywords: dacryocystorhinostomy, nasolacrimal duct obstruction, epiphora, dacryocystitis, piezosurgery device

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If the infection is unresponsive to initial treatment, methicillin-resistant *Staphylococcus aureus* should be suspected, and antibiotic therapy should therefore be prescribed accordingly (3). Other potential pathogens involved in the disease were, beta-hemolytic streptococci, pneumococci, and *Haemophilus influenzae*. If the initial antibiotic therapy proves ineffective, surgical drainage of the abscess can be proceeded and antibiotic therapy based on the results of the microbiological culture examination (3,4). The differential diagnosis includes acute ethmoid sinusitis, lacrimal sac or sinonasal tumor, and infected sebaceous cyst (5).

Subjects affected from chronic dacryocystitis usually presents a swelling inferior to the medial canthal tendon and chronic conjunctivitis. The definitive treatment of acute dacryocystitis or chronic conjunctivitis is generally surgical and consists in dacryocystorhinostomy (DCR), the creation of direct communication between the lacrimal sac and the nasal cavity (6).

Piezosurgery is an advanced surgical technique that works on the principle of ultrasonic micro vibrations for sectioning the hard tissues sparing the adjacent soft tissues (7, 8). Given these potential advantages and the relative lack of current literature, we aimed to investigate the rate of piezosurgical devices versus high-speed electric drill with a diamond burr, in external DCR.

Case reports

Two female patients, with average age of 53.2 years old, underwent to piezosurgery device vs high-speed electric drill with a diamond burr for dacryocystorhinostomies.

This study was carried out according to the Helsinki declaration and informed written consent was obtained from all patients included in the study. In the present manuscript, data regarding medical history and clinical-instrumental work-up were assessed for each patient. All procedures were performed by a maxillo-facial surgeon and an ophthalmologist (MDC and GS). After general hypotensive anesthesia (A.M.), the direct incision to the nose side was made vertically, anterior to the angular vein, initially through the skin only.

The incision was placed at 1 cm from the medial canthal angle and extends approximately 2 mm above and 15 mm below the horizontal intercanthal line. For the first patient, osteotomy was performed using piezosurgery medical handpiece tip (Mectron, Italy) to incise the bone of the anterior lacrimal crest and sac fossa. The free bone fragment was removed with a freer elevator and/or forceps to create a rectangular bone window (Fig. 1).

For the second patient, osteotomy was performed using high-speed electric drill with a diamond burr, removing part of the anterior lacrimal crest and a spine of bone between the nasal mucosa and the nasolacrimal duct (Fig. 2).

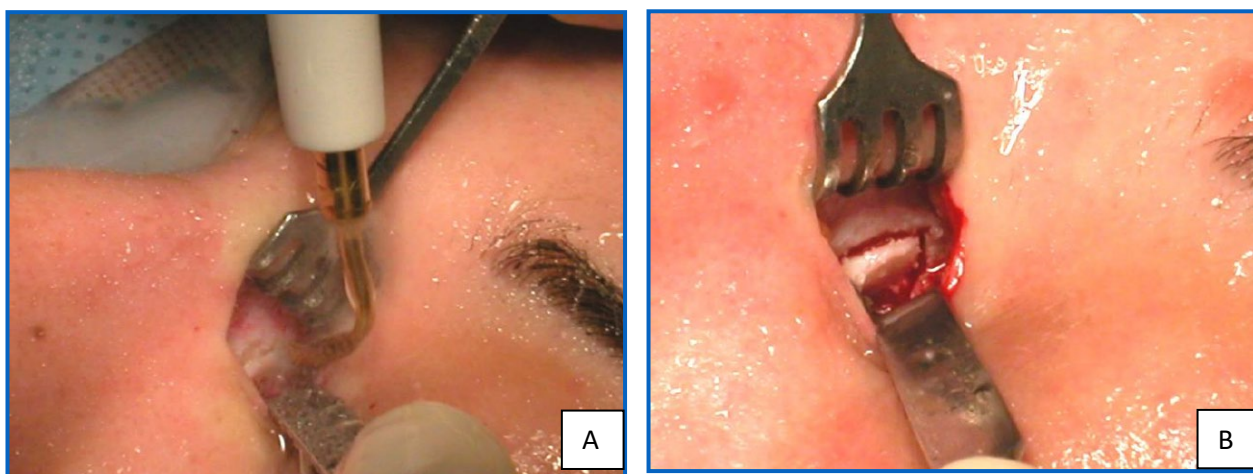


Fig. 1. Osteotomy with piezoelectric device. A-) A finalized bony ostium through the left lacrimal fossa performed with the ultrasonic bone aspirator. B-) The nasal mucosa remains intact given the ability of the device to cut bone while sparing underlying soft tissue.

RESULTS

Postoperative treatment included oral antibiotics and analgesics, steroid-antibiotic combination (tobramycin + fluorometholone) eyedrops for 4 weeks in tapering dose, and nasal decongestant (oxymetazoline) for 2 weeks. Tube removal was performed at 4 weeks postsurgery. There were only one cases of postoperative bleeding, in the external DCR treated with high-speed electric drill with a diamond burr (Fig. 3).

We judged this evidence on complications to be very low-certainty, downgrading one level for risk of bias due to the very low number of cases. In addition, the major advantage for the surgeon when use a piezosurgery medical handpiece, is protection of the soft tissues, which are vital for the outcome and, also in our case, for the patient's quality of life compared to high-speed electric drill with a diamond burr surgical procedure. Besides, after from surgery 12 months, resolution of symptoms was observed. Surgical outcomes showed for both patients, complete resolution of disease without relapse.

DISCUSSION

External DCR remains the gold standard in terms of functional outcome in the treatment of nasolacrimal duct obstruction (9, 10). The advantages

of external DCR comprise high predictability and the direct visualization of anatomy, also helping accurate anastomosis between the lacrimal sac and nasal mucosa (11).

Nevertheless, external DCR presents some disadvantages, including facial scarring, lacrimal pump dysfunction resulting from the interruption of medial canthal anatomy and the orbicularis oculi muscles, and limitations in acute dacryocystitis patients with abscess formation (12). However, endoscopic DCR has some advantages over external DCR such as limited invasiveness, shorter operative time, preservation of pump function, less bleeding, and absence of skin trauma that can lead to an external scar (13). This silicone device may lead to correct healing, but can



Fig. 3. *Postoperative bleeding management.*

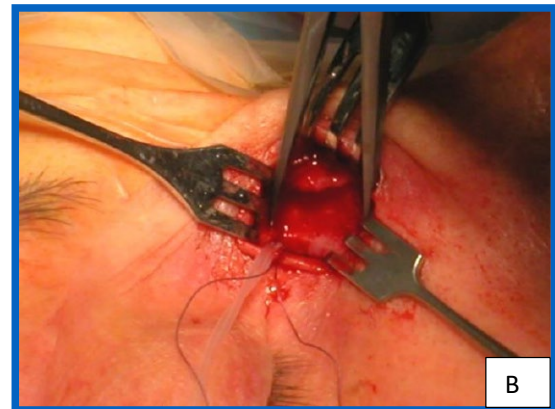
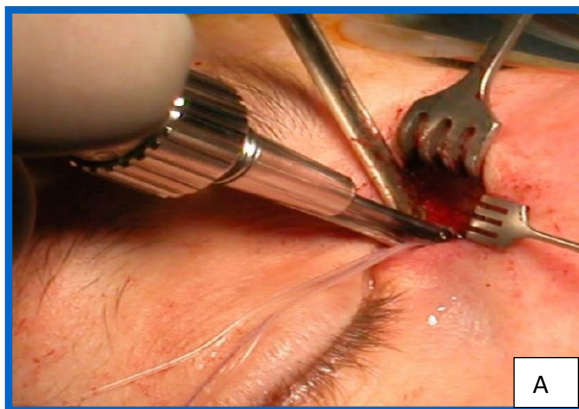


Fig. 2. *A): Osteotomy through the right lacrimal fossa performed with the high-speed electric drill with a diamond burr. B): The nasal mucosa demonstrates a small tear, an uncommon but potential complication of high-speed drilling. Silicon tube removal was performed at 4 weeks post-surgery.*

cause formation of granulation tissue, infection, and ulceration of the lacrimal pathway. In addition to this, it can dislocate and cause patient discomfort, leading to mandatory stent re-positioning (14).

Piezosurgical devices offer potential advantages during external DCR, through selectively bone cutting, as well minimizing collateral damage to contiguous soft tissue and mucosa (7, 8). Even though it is a time-consuming technique with a large learning curve, its clinical advantages overrule its drawbacks. Recently it was emerging as a promising surgical modality with a wide range of clinical applications throughout the whole field of surgery.

The purpose of this study was to directly compare DCR outcomes using a single piezoelectric device versus a high-speed electric drill with diamond burr. Definitions for surgical success vary throughout the literature, leading to heterogeneity in success rates. The authors attempted to choose a definition of surgical success similar to the majority of other authors, though we recognize that objective data, such as Jones testing, fluorescein dye disappearance testing or validated patient symptom questionnaires were not used in the current study (13-16).

Finally, we can speculate that the reports of this manuscript, could help formulate a structured curriculum for ophthalmic and maxillofacial surgeons fellowship programs, especially in view of the increasing use of piezosurgery device in ophthalmology.

CONCLUSIONS

The piezosurgery device offers comparable outcomes and complication rates to more conventional surgical tools for external DCR. Through reducing operative time and preserving delicate mucosa, this device is an appealing option for both novice and experienced surgeons. Different techniques of external DCR should also be assessed, as the choice of a technique in particular, can influence the outcome. Future larger RCTs are required to further assess the success and complication rates of external DCR treated by piezosurgery device. Strict outcome criteria should be adopted to assess functional and anatomical outcomes with a minimal follow-up of six months.

Conflicts of interest: "The authors declare no conflict of interest."

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The influence of abnormal head posture on facial asymmetry

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Aims: The aim of this study was to evaluate the association between the facial asymmetry and the Altered Head Position (AHP), in four patients affected by torticollis (TC).

Methods and results: Three patients with diagnosis of ocular TC (OTC) and one patient with diagnosis of congenital muscular TC (MTC), aged between 6 and 15 years, were referred to University of Foggia. All patients underwent a detailed diagnostic check-up based on the collection of the following diagnostic records: anamnestic data; extra-oral and intra-oral clinical examination; panoramic radiograph, latero-lateral and postero-anterior teleradiographs with their cephalograms; posture-stabilometric examination; electromyographic screening. Clinically, each patient showed facial asymmetry, although in the OTC patients the head resulted deviated to the contralateral side of the affected eye, while in the MTC patient it was deviated to the ipsilateral side of the affected muscle. Moreover, a decreased growth of the hemimandible on the ipsilateral side to the head deviation was found in all patients, with the prevalent involvement of the mandibular body. Functionally, an asymmetric jaw muscular activation was also found in all patients, both at rest and during function, as confirmed by electromyographic results.

Conclusion: The clinical, radiographic and electromyographic findings of the present paper confirmed the influence of the AHP on the development of facial asymmetry, in patients with TC.

Facial asymmetry is a condition in which the two sides of the face are not similar (1). Although a certain degree of asymmetry can be observed in the normal population, in severe cases this condition negatively affects the aesthetics and the function of the entire cranio-facial district, involving dental, skeletal, or muscular structures (2, 3). In literature, several causal factors have been proposed in the etiology of facial asymmetries, including genetic factors, such as muscular palsy, palatal/lip clefts and

hemifacial microsomia, or environmental factors, such as trauma, infection, tumors and condylar hyper/hypoplasia (2-5).

Among the casual factors, it has been largely suggested (6) that an Abnormal Head Posture (AHP) can also led to facial asymmetry (1), because an altered posture over time during the development stages of children could induce an anomalous growth of the facial bones (6). An AHP occurs when the head is deflected from its normal

Keywords: head posture, facial asymmetry, torticollis (TC), congenital muscular TC

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upright position, due to anomalous or compensatory conditions, as in the case of Torticollis (TC) (1). TC is a postural deformity evident shortly after birth, that clinically appears as a twisting of the head and neck (7). This AHP is caused by congenital or postnatally acquired factors (8). The congenital muscular torticollis (MTC) is the most common cause of facial asymmetry in children with a prevalence of 0.3-2 %, and represents the third most frequent pediatric orthopedic diagnosis in childhood (9), affecting 3.9% to 16% of infants (10). It is developed following a trauma to one of the sternocleidomastoid muscles (SCM) (11).

The SCM is a large, paired muscle located at the anterior side of the neck: it is attached to the sternum at one end and to the mastoid process at the other, without attachment to the facial muscles (11). Neck trauma during labor is the most common cause of SCM abnormality (of varying degrees of severity) with a prevalence of 1 in 300 children (11). Although the etiology is still unclear, MTC is due to unilateral shortening sternocleidomastoid muscle, that induces a cervical lateral flexion to the side of the shortened muscle and a contralateral cervical rotation in the opposite side, with or without a palpable sternocleidomastoid mass (10). Clinically, the child with MTC appears with the head tilted to the side of the involved and damaged muscle and with the chin pointing in the opposite direction (11). MTC increases the risk of facial, ear and mandibular asymmetry: in literature, it has been reported that up to 90% of children with MTC presents cranio-facial anomalies (10), because there isn't a spontaneous resolution of this disease and the patients that are untreated or treated after early infancy patients will develop dento-skeletal deformities of different severity during growth (10).

The ocular torticollis (OTC) is a frequent sign in pediatric patients, occurring with an incidence of 3.19% (12). OTC is often accompanied by ocular disorders (such as diplopia or nystagmus) because it is caused by ocular motor dysfunctions due to a wide range of congenital or acquired ocular conditions, commonly represented by sixth nerve palsy, strabismus, palpebral ptosis, nystagmus or refractive errors (12). The most frequent clinical

sign is an abnormal twist or turn of the neck that represents a compensatory head posture adopted to improve vision, maintaining single binocular vision and centering residual visual field with the body (12). Clinically, there may be associated head tilt, face turn, chin elevation, chin depression or a combination of these postures (13). Many studies suggested that the compensatory chronic posture of head and body in OTC patients may influence the bone growth, inducing facial and bodily asymmetries (such as scoliosis) or other musculoskeletal diseases (13). An early surgery of the ocular defects was associated with a better outcome in the treatment of OTC, but, although the surgical correction, several authors reported a persistence of torticollis, probably due to the tightness of the neck muscles, continuously maintained in an improper posture for a long period of time (14). Despite the different origin, both MTC and OTC are considered as important causes in the development of facial asymmetry and their clinical signs are reported to be the same (11): the unilateral contractions of the SCM led to the rotation of the head while its bilateral contractions result in the flexion of the head and neck, and its different muscular activity influences the extent of head tilt or turn (15, 16).

Although the association between AHP and asymmetries, in literature there were only few studies that assessed the role of the AHP due to TC in the development of dento-facial asymmetries (11, 17-20).

The aim of the present study was to evaluate the association between AHP and facial asymmetries, in patients with TC.

Case reports

Three patients with diagnosis of OTC and one patient with diagnosis of MTC were referred at the School of Dentistry of the University of Foggia, Italy. This clinical study was conducted in accordance with the provisions of the Declaration of Helsinki declaration; the parents of all subjects signed an informed consent.

All patients underwent a detailed diagnostic check-up based on the collection of the following diagnostic records:

- anamnestic data.
- extra-oral clinical examination.
- intra-oral clinical examination.
- examination of Temporo-Mandibular Joint (TMJ).
- OPT with its mandibulogram.
- Latero-lateral (L-L) teleradiograph with its cephalogram according to Gianni's method (21).
- postero-anterior (P-A) teleradiograph with its cephalogram according to Gianni's method (21).
- postural and stabilometric examination (through a scoliosometer and a posture-stabilization platform).
- Electromyographic screening (SCAN 9 at rest on: right and left anterior temporalis, R-AT/L-AT; right and left masseter muscles R-MM/L-MM; right and left posterior temporalis R-PT/L-PT; right and left anterior digastric R-AD/L-AD; SCAN 11 during clenching on teeth or on cotton rolls on: R-AT and L-AT, R-MM and L-MM).
- ophthalmic examination.

Patient no. 1

V.L., aged 15, reported a previous OTC due to a deficit of the superior oblique muscle of the left eye, leading to rotation and tilting of the head to the right. The medical history showed that the patient hadn't undergone surgery to correct her eye defect. Moreover, the patient complained of muscular and articular disorders.

The extra-oral examination showed an altered posture of the head and body, and a slight facial asymmetry: the analysis of the inter-pupillary and inter-comissural lines showed a convergence of this line on the ipsilateral side to the inclination of the head, confirming an altered growth of the facial bones. At the intra-oral examination, the lower inter-incisal line was deviated to the right by 3.5 mm in relation to the upper inter-incisal line, which was centered on the facial midline and on the upper lip filter. The cephalometric analysis showed a skeletal Class I ($ANB=3^\circ$) with maxillary and mandibular biretrusion ($SNA=76^\circ$; $SNB=73^\circ$), an hyperdivergent growth pattern ($S-N/GO-GN=37^\circ$) and a prediction of growth in post-rotation

($N^{\wedge}S^{\wedge}PC^{\wedge}Go^{\wedge}Gn=394^\circ$) (Table I).

The mandibulogram performed on the OPT showed differences in the length of mandibular bodies and in the gonial angles, but not in mandibular *rami* (Table II). From the mandibulogram obtained from the P-A cephalogram, asymmetries of the mandibular bodies (GO-ME distance) were found among the left and the right sides.

The analysis of the right and left *ramus* (AR-GO distance) showed similar results (Table III). The aesthetic analysis of the face revealed an asymmetry between the aesthetic line of the face and the chin (Table IV). The electromyography at rest showed an asymmetric pattern of MM and AT, with prevailing of L-MM and R-AT that showed a hyper-tone compared to normal values. This increased activity was indicative of a frontal plane torsion of the mandible which forces the L-MM and R-AT to contract even at rest.

A crossed muscle activity was also shown by the slight increase of L-AD and R-PT activity at rest. The electromyography during clenching on tooth or on cotton rolls (scan 11) showed a muscular asymmetry between the right and left sides, with a prevalence of the left one (L-AT and L-MM). However, the recorded values during function were very low compared to normal values, indicating a muscular fatigue which decreased the contractile activity of the considered muscles. Therefore, the electromyographic results reported a crossed activity of the masticatory muscles at rest (R-AT and L-MM), that confirmed a mandibular torsion on the frontal plane with muscular fatigue; during clenching, the left side was prevalent.

D.N., aged 14, had OTC due to a deficit of the superior oblique muscle of the right eye. From the medical history, it appeared that the patient hadn't undergone surgery for the correction of the defect. The postural examination on a scoliosometer revealed altered head and body posture: the patient has a head tilt to the left and a different vertical height between the right and left shoulder. In addition, the analysis of the inter-pupillary and labial lines showed a convergence to the left. At intra-oral examination there was a deviation of both inter-incisal lines to the left relative to the midline

of the face, due to two different etiological causes.

The upper inter-incisal line was deviated by 5 mm due to the presence of a supernumerary tooth in the 1.2-1.3 area, and to the concomitant agenesis

of 22. The deviation of the lower mid-line was approximately 3-4 mm, due to both the adaptive response to the maxillary position and the abnormal position of the head related to the ocular deficit.

Table I. Cephalometric analysis of the L-L radiographs.

		Patient 1	Patient 2	Patient 3	Patient 4
Sagittal (°)	<i>Normal value</i>				
S [^] N [^] A (°)	82+/-2	76	84	82	83
S [^] N [^] B (°)	80+/-2	73	77	77	80
A [^] N [^] B (°)	2+/-2	3	7	5	3
Sagittal (mm)					
S-N (mm)		65	72.5	68	69
PNS-A (mm)		45.5	53	48	49
GO-ME (mm)		61.5	74	59	71
Vertical (°)					
ANS-PNS/GO-ME	20+/-5	25	21	19	37
OCLP-OCLA/ANS-PNS	8+/-2	9	6.5	6	22
OCLP-OCLA /GO-GN	12+/-3	16	14	13	13
S-N/ANS-PNS	10+/-3	12	10	9	9
S-N/O OCLP-OCLA	14+/-3	21	17	15	21
S-N/GO-GN	32+/-5	37	30	29	42
S [^] N [^] D	76+/-3	71	75	73	77
Vertical (mm)					
SOR-ME		114	122,5	113	131
SOR-ANS		55.5	63	51	61
ANS-ME		60	68	55	74
IST-GO		62	72	64.5	64
IST-PNS		36	44	40	42.5
PNS-GO		41.5	49.5	39.5	36.5
ant VD/post VD (%)	62	54.38	58.77	57.08	48.85
Growth prediction (°)					
PC [^] Go [^] Gn	120+/-5	124	117	127	141
PC [^] GO [^] N	50+/-2	52	50	60	52
N [^] GO [^] GN	70+/-3	72	67	67	83
N [^] S [^] PC	122+/-5	136	127	125	122
S [^] PC [^] GO	143+/-6	134	145	137	141
N [^] S [^] PC [^] Go [^] Gn	396+/-2	394	389	389	404
N [^] S [^] BA	129+/-5	140	141	132	132

S=Sella; N=Nasion; A=point A; B=point B; ANS=Anterior Nasal Spine; PNS=Posterior Nasal Spine; GO=Gonion; ME=Menton; OCLA=Anterior Occlusal Point; OCLP=Posterior Occlusal Point; SOR= Supraorbital Point; IST=inferior point of the sella turcica; D=center of the chin symphysis; PC=condylar point; BA=Basion; ant VD=Anterior Vertical Dimension; post DV=Posterior Vertical Dimension; OCLA-OCLP=occlusal plane; PC[^]GO[^]GN= total gonial angle; PC[^]GO[^]N=superior gonial angle; N[^]GO[^]GN=inferior gonial angle; N[^]S[^]PC=sellar angle; S[^]PC[^]GO=articular angle; S-N=length of cranial base; PNS-A=maxillary length; GO-ME=mandibular plane; ANS-PNS=palatal plane; OCLA-OCLP=Occlusal plane; S-N=cranial plane; S[^]N[^]D=cranial-symphysis angle; N[^]S[^]PC[^]Go[^]Gn=sum of N[^]S[^]PC + S[^]PC[^]GO + PC[^]GO[^]GN angles ; N[^]S[^]BA =posterior cranial base angle.

The cephalometric analysis of the L-L cephalogram showed a skeletal class II ($ANB=7^\circ$), a mandibular retrusion ($SNB=77^\circ$), a skeletal normo-bite ($S-N/GO-GN=30^\circ$) and an eugnathic prediction of cranio-facial growth ($N^{\wedge}S^{\wedge}PC^{\wedge}Go^{\wedge}Gn=389^\circ$) (Table I). From the OPT mandibulogram, the height of the right and left mandibular *ramus* (CON-GO distance) was similar, with a physiological difference of 1 mm. The length of right and left mandibular bodies (GO-ME distance), such as the angular values of the gonial angles ($CO^{\wedge}GO^{\wedge}ME$ angle), weren't similar (Table II). From the mandibulogram obtained from the P-A cephalogram, an asymmetry among the left and the right sides was found in the mandibular bodies (GO-ME distance) but not in the mandibular *ramus* (AR-GO distance) (Table III). In the aesthetic evaluation, there was a discrepancy of the aesthetic line of the face and the chin, indicating a facial asymmetry (Table IV). On scan 9 of the AT and MM, an asymmetrical activation at rest was shown, with a prevalence of the L-MM and R-AT activity. The prevalence of the left side over the right side was also confirmed by the greater activation of the L-AD and L-PT during scan 9. During scan 11, a higher activation of L-AT and L-MM was recorded during clenching both on tooth and on cotton rolls. A mild R-MM fatigue during the function was also found, due to the presence of lower-than-normal values. Therefore, these electromyographic findings recorded a crossed muscle activity at rest (L-MM and R-AT) indicating a horizontal mandibular torsion, while during the function the left side was prevalent.

Patient no. 3

R.V., a 6-year-old female, was referred with diagnosis of OTC due to deficit of the superior oblique muscle of the right eye. At the time of the examination, the patient had not undergone any surgical treatment to correct the OTC. At extra-oral examination, there was an abnormal posture of the head and body: the head was inclined to the left with the ipsilateral shoulder higher than the right one, and the inter-pupillary and labial lines converged on the side of the TC, confirming the presence of a facial asymmetry.

At intra-oral examination the patient was in mixed dentition, with a deviation of the lower interincisal midline 2 mm less than the upper one. The cephalometric analysis of the L-L cephalogram showed a skeletal Class II ($ANB=5^\circ$) from mandibular retrusion ($SNB=77^\circ$), a normodivergent growth pattern ($S-N/GO-GN=29^\circ$) and a prediction of eugnathic craniofacial growth ($N^{\wedge}S^{\wedge}PC^{\wedge}Go^{\wedge}Gn=385^\circ$) (Table I).

The mandibulogram obtained from the OPT showed asymmetries of the mandibular bodies (CON-GO distance) and of the gonial angles ($CO^{\wedge}GO^{\wedge}ME$ angle) between the right and the left sides, while the values of both *rami* (CON-GO distance) were similar (Table II). From the mandibulogram obtained from the P-A cephalogram, asymmetries of the mandibular bodies (GO-ME distance) were found among the left and the right sides. The analysis of the right and left *ramus* showed similar results (AR-GO distance).

The facial aesthetic analysis revealed an

Table II. Cephalometric analysis of OPT.

	Patient 1		Patient 2		Patient 3		Patient 4	
Mandibulogram	R	L	R	L	R	L	R	L
CON-GO (mm)	68	69	67	66	54	55	65	65
CON-ME (mm)	138	132	135	133	125	120	137	144
GO-ME (mm)	98	92	96	91	89	84	86.5	91
$CO^{\wedge}GO^{\wedge}ME$ ($^\circ$)	125	118	111	115	113	118	130	134

R=right side; L=left side; CON=Condylion; GO=Gonion; ME=Menton; n/a=not reported.

asymmetry between the aesthetic line of the face (a vertical line passing through the glabella and the upper nasolabial filter) and the chin (Table IV).

The electromyographic exam showed an

asymmetrical activation at rest: in the scan 9 of MM and AT, hyperactivity of the R-AT was found compared to both the right side and normal values, while a greater activation of L-MM on the left side

Table III. Cephalometric analysis of the P-A radiographs.

	Patient 1		Patient 2		Patient 3		Patient 4	
Latero-posterior vertigram	R	L	R	L	R	L	R	L
PAS-GO	83	76	99	101.5	59.5	60	81	81
PAS-CON	71.5	67	74.5	74	55.5	56	74	74
CON-GO	26.5	29.5	47.5	43	33.5	31	41	38
Anterior vertigram								
X-SNAC (mm)	49.5				49.5		55	
SNAC-ME	49				49		58	
Anterior cranial fossa								
PASr-PASl/symmetry axis	+5.5				+5.5		+1	
FAR-FAI/ symmetry axis	+3.5				+3.5		+1	
Craniogram								
AR-EA (mm)	12	12	18.5	18.5			20.5	21
AR-0 (mm)	52	49.5	67	63	50	48	54	57
EA-0 (mm)	42	42.5	57	52.5			44	41.5
Maxillogram								
MX-SNAC	26.5	29.5	29	32.5	32	32	30	29
MX-0	57	59	70	71	54	54	63.5	61.5
MXr-MXl	53				53		57.5	
Mandibologram								
AR-GO	57	55.5	56	57	46.5	46.5	51	52
AR-ME	97	92.5	88	77	100	96	98	108
GO-ME	50	45	56	38	60	55	56	65
AR-0	52	49.5	67	62	50	48	54	57
ARr-ARl	90				90		94.5	
Dental								
PAS-MX-CVM	Endo	Endo	Endo	Endo	Endo	Endo	Endo	Normo
Growth prediction								
AR^GO^ME	131	132	104	105	140	145	133	132
AR^GO^0	34	31	29	25	42	42	28	34
0^GO^ME	97	101	75	80	96	103	105	98

PAS=cephalometric orbito-sphenoidal point (r=right; l=left); GO=Gonion; CON= cephalometric point of coincidence between occipital condyle and large occipital hole (r=right; l=left); X=point defined at the intersection of the perpendicular lamina of the ethmoid and the projection of the floor of the anterior cranial fossa; SNAC= cephalometric anterior nasal spine; ME=menton; FA=the highest point of the orbital cavity (r=right; l=left); EA=the highest point of the arcuate eminence of the petrous rock (r=right; l=left); AR=articular point of the mandibular condyle (r=right; l=left); 0=point zero, point of intersection between the spheno-orbital line (PASr-PASl) and the axis of symmetry; MX= maxillary point (r=right; l=left); CVM=superior molar point (r=right; l=left); AR-GO-ME=total gonial angle; AR^GO^0=superior gonial angle; 0^GO^ME=inferior gonial angle; symm axis=axis of symmetry coinciding with the median sagittal plane; endo=endodontia; normo=normodontia.

was showed compared to the right one. The scan 9 of the PT and AD muscles showed a basal hypertone of the AD bilaterally, with a prevalence of the left side (L-AD), while R-PT resulted slightly increased compared to L-PT. The scan 11 during clenching on tooth showed an asymmetric function with prevalence of the L-AT and of the L-MM.

Lower than normal values were found in the R-AT findings during function, indicating a muscular fatigue, while a fatigue of R-MM was found only during clenching on tooth and not on cotton rolls. Therefore, the electromyographic findings detected muscular asymmetry with

horizontal torsion, due to the presence of crossed muscle activity at rest between the right and left side (L-MM and R-AT; L-AD and R-PT). Instead during function, the muscular activity of the left side was more prevalent compared to the right one.

Patient no. 4

S.C., an 11-year-old female, was referred with diagnosis of MTC due to fibrous retraction of the left SCM muscle: the patient had never undergone any treatment for MTC correction. The extra-oral examination showed an altered head and body posture with a marked inclination of the head

Table IV. *Aesthetic assessment: evaluation of the chin deviation from the aesthetic line.*

	Patient 1		Patient 2		Patient 3		Patient 4	
	R	L	R	L	R	L	R	L
Chin deviation		5		2		2.5	3	

R=right side; L=left side.

Table V. *Electromyographic findings, expressed in milli-Volt (mV).*

SCAN 9 <i>at rest</i>	Patient 1	Patient 2	Patient 3	Patient 4		<i>Normal value (mV)</i>
L-AT	2.5	1.2	2.2	1.7		2.0-2.5
L-MM	5.7	2.1	2.2	0.9		1.5-2.0
R-MM	1.9	1.5	1.9	1.4		1.5-2.0
R-AT	3.5	4.0	4.5	2.1		2.0-2.5
L-PT	2.3	1.4	2.5	2.2		2.0-2.5
L-AD	1.8	2.5	8.5	1.2		1.5-2.0
R-AD	1.6	0.8	7.0	1.3		1.5-2.0
R-PT	2.4	1.6	2.6	2.4		2.0-2.5
SCAN 11 <i>during clenching</i>						
L-AT	99	152	130	102		100-300
L-MM	20	170	99	69		100-300
R-MM	15	83	73	32		100-300
R-AT	50	145	60	15		100-300
SCAN 11 <i>on cotton rolls</i>						
L-AT	92	178	120	89		100-300
L-MM	75	203	120	47		100-300
R-MM	58	98	102	55		100-300
R-AT	68	169	68	96		100-300

R=right side; L=left side; AT=anterior temporalis; MM=masseter muscles; PT=posterior temporalis; AD=anterior digastric.

to the left and a different height in vertical plane between the right and left shoulders. In the intra-oral analysis, a 3 mm deviation to the left of the lower inter-incisal line was recorded. The patient also had a hypoplasia of the palate with bilateral posterior crossbite, with a canted occlusal plane. The cephalometric analysis of the L-L cephalogram showed a skeletal Class I ($ANB=3^\circ$), skeletal open-bite ($S-N/GO-GN=42^\circ$), growth prediction in post-rotation ($N^{\wedge}S^{\wedge}PC^{\wedge}Go^{\wedge}Gn=404^\circ$) (Table I). From the OPT mandibulogram, the *ramus* of the right hemimandible had the same height of the left one, while different outcomes were found for mandibular bodies and gonial angles, indicating a mandibular asymmetry (Table II).

In the mandibulogram obtained from the P-A cephalogram an asymmetry among the left and the right sides was found in the mandibular bodies and in the gonial angles, and not in the mandibular *ramus* (Table III). At scan 9, a right unilateral prevalence of muscular activities (R-MM, R-AT, R-AD, R-PT) was recorded, indicating the presence of vertical mandibular torsion. The records of scan 11 showed a prevalence of the left side during clenching on teeth, while the records of the right side showed a muscular fatigue at the level of R-MM and R-AT. An opposite situation was recorded during clenching on cotton rolls, in which there was an increased activity of the right side. However, all the findings confirmed the presence of an asymmetry at muscular level.

DISCUSSION

In the objective diagnosis of facial asymmetry due to AHP, patient history, clinical examination and medical imaging were necessary to determine the involvement of the skeletal, dental, and functional structures (3, 11, 22). A detailed history was crucial in the initial assessment of the facial disharmony to understand its etiology (23, 24).

As in the case of the four patients considered in the present study, a positive history of labor trauma to the neck muscles or of congenital syndrome helped the clinicians to understand the nature of TC and whether it was due to a congenital or acquired factors.

Clinical examination was another important diagnostic tool in the assessment of AHP and facial asymmetry (25). The extra-oral clinical analysis was based on the visual assessment of the facial morphology in sagittal, coronal, and vertical dimensions, focusing on the inclination of the head and on position of the chin while the patients were upright and looking forward in normal occlusion (2).

According to literature (1, 26), the present outcomes showed that the position of the head in MTC child was deviated ipsilateral to the affected side, while in OTC patients the head was deviated contralateral to the affected eye. In fact, in case of MTC, the mechanical limitation caused by the shorter size of the affected SCM prevented the child from turning its head on the contralateral side, preferring the side of TC (11). At the contrary, the patients with OTC didn't report limitations in neck movements, because the tone of SCM on both sides was similar (1, 18). As in these examined cases, the deficit in the activation of the superior oblique muscle in one eye induced the OTC patients to deviate the head in the contralateral side of the affected muscle to prevent diplopia (19) and this AHP altered the basal tone of the facial and neck muscles, leading to tilting and turning of the head in the opposite direction to the affected eye, with a possible downward movement of the head (1, 26).

The qualitative evaluation of the facial asymmetry was also supplemented with extra-oral photographs of the examined patients (11). In addition to a three-dimensional assessment based on direct clinical observation of the asymmetry in the two sides of the face, the facial analysis made use of a bi-dimensional method based on facial lines drawn on frontal facial photographs, using soft tissue landmarks as reference. Each patient was investigated through the photographic analysis of three lines that connected the center of the eyes (inter-pupillary line), the corners of the mouth (labial line) and the mid-line of the face, corresponding to a line perpendicular to the ground, passing through the glabella (2). All patients considered in this study showed an hemifacial asymmetry on the vertical plane, due to dissimilarity of the left and right side of the face, and a convergence of inter-pupillary

and labial lines on the ipsilateral side to the head inclination, indicating an AHP on transversal plane.

In addition to this qualitative assessment, a quantitative radiographic method was also used for assessing the facial size of the sides of the face (3). Among radiographic exams, lateral cephalograms provided only limited information on asymmetry, due to the radiographic overlap between the right and left side (2). Instead, panoramic radiographs and postero-anterior cephalograms provided a comparison of bilateral differences of the dento-skeletal structures (2), focusing on the extent of the existing asymmetry (3). In the present study, the radiographic imaging and the cephalometric analysis have confirmed the clinical mandibular asymmetry of patients both with MTC and OTC. However, the analysis of the mandibulograms showed that the mandibular asymmetry affected only the shape of the gonial angles and the dimension of the mandibular bodies, as the *rami* were almost the same size on the right and left sides.

The mechanisms by which tilt and rotation of the head due to TC may influence facial and mandibular shape are not yet clearly understood, although continuous muscle pressure or changes in muscle innervation appear to be relevant, as previously reported by the functional matrix hypothesis introduced by Moss (27-29). The SCM is the muscle most responsible for the tilting and rotating movements of the head and, although it is not directly attached to the mandible or to the face, it is involved in the deviation of the head. In fact, several authors have suggested that the facial asymmetry following long-term TC, causes a visible alteration of the face, mandible, cheeks, nasal septum, and forehead in both sides, due to an AHP (1).

Over time, this altered head and mandibular position induces an abnormal relationship between maxillary and mandibular jaws, leading to the development of a dento-skeletal malocclusion (30). Moreover, the abnormal posture of the mandible and head can lead to an alterations in the functional mandibular dynamics, resulting in an altered activation of the masticatory muscles (31). In literature, the facial electromyography has always been reported as the standard diagnostic tool to

evaluate the muscular function during physiological and pathological conditions (32).

In the present paper, the evaluation of muscular activity using electromyography has been used to evaluate changes in the masticatory system due to TC under different conditions, such as at rest, during clenching on tooth (isometric contraction) and on cotton rolls (isotonic contraction) (33). The electromyographic findings of the SCAN 9 (electrical activity at rest) and the SCAN 11 (muscle activity during function) demonstrated an asymmetric muscular activation both at rest and during function, in patients with MTC and OTC.

In particular, all the patients with OTC reported a cross muscle activity at rest, with an activation of the MM and AD ipsilateral to TC side (and contralateral to the affected eye), and an activation of AT and PT contralateral to the TC side (and ipsilateral to the affected eye). Moreover, all these OTC patients showed a higher muscular activation during function by the same side of TC (and opposite to the affected eye).

In the patient with MTC, an increased activation of the muscular activities was recorded on the side of TC (the same of the affected SCM), while during function a muscular fatigue was shown on the ipsilateral side of TC.

Therefore, as reported by previous studies in which facial asymmetry is associated with a more asymmetric EMG patterns during jaw movements than in healthy subjects (34), in the present paper an abnormal jaw muscle activity was recorded in each TC patient: this asymmetric activity was most probably due to postural factors related to an AHP, in order to maintain a stable mandibular position relative to the maxilla during statics and movements (34, 35).

CONCLUSIONS

The findings of the present paper suggested the strong correlation between AHP and facial asymmetry, in patients with TC. Specifically:

In the OTC patient the head is deviated to the contralateral side of the affected eye, in the MTC patient the head is deviated to the ipsilateral side of the affected muscle.

Clinically, both MTC and OTC are associated with facial asymmetry, as confirmed by clinical and radiographic exams: a decreased growth of the hemimandible on the ipsilateral side to the deviation was found in these patients, with prevalent involvement of the mandibular body.

Functionally, an asymmetric muscular activation was found in all patients, both at rest and during function, probably due to altered mandibular dynamic related to the AHP.

Conflicts of Interest: "The authors declare no conflict of interest."

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Mastication and its connection with brain cortex

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Mastication is the first stage of digestion in most mammals. It is an intermittent rhythmic act in which the tongue, facial, and jaw muscles act in coordination to position the food between the teeth, cut it up, and then prepare it for swallowing. Epidemiological studies suggest that chronic periodontitis is closely associated with the incidence and progression of cognitive impairment. The periodontal tactile input does not uniquely increase prefrontal cortex activity. Further research is needed in the next future.

Mastication is the first stage of digestion in most mammals. It is an intermittent rhythmic act in which the tongue, facial, and jaw muscles act in coordination to position the food between the teeth, cut it up, and then prepare it for swallowing (1-20). The production of the rhythm and of the opener and closer motoneuron bursts are independent processes that are carried out by different groups of cells (1).

Very little is known about the properties of temporomandibular joint (TMJ) receptors and even less about their activity during mastication (1). Sensory or afferent nerve receptors can be described

from either a functional or a structural point of view (21). Functionally, the sensory receptors are part of the peripheral nervous system, relaying sensory information back to the central nervous system (21-28). Proprioception, also called kinesthesia, is described as usually unconscious sense that provides an individual with the knowledge of position and physiologic state of muscles and joints (21, 29-34).

Epidemiological studies suggest that chronic periodontitis is closely associated with the incidence and progression of cognitive impairment (35-47). Xue et al. (35) investigated the causal relationship between chronic periodontitis and cognitive decline and the underlying mechanism in mice, observing cerebral neuronal and synaptic injury and glial activation in this mouse model of chronic periodontitis. Goto et al. (48) examined whether periodontal tactile input could increase cerebral blood flow in the prefrontal cortex against elderly patients with dental implants lacking periodontal tactile (implant group), elderly individuals with natural teeth (elderly group) and young individuals with natural teeth (young group),

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reporting that there were no significant differences between the elderly and implant groups. Regarding the mean occlusal force value, compared with the young group and the elderly group, the implant group had a numerically, but not significantly, larger occlusal force exceeding the directed range. The periodontal tactile input does not uniquely increase prefrontal cortex activity (48-58).

It is also true that continuous observation with daily clinical practice by physicians and surgeons, continuous scientific research and further discoveries, the use of 3-dimensional virtual reality and modern surgical technologies will provide new solutions in the next future (59-121). Epidemiological studies have shown that chronic periodontitis is closely related to ischemic stroke. However, it remains unknown whether periodontitis plays a direct role in the injury of cerebral ischemia. Chi et al. (122), to explore the role of chronic periodontitis in the development process of ischemic stroke, combined two mouse models: experimental periodontitis induced by a periodontal injection of lipopolysaccharide and ischemic stroke induced by the photothrombotic method. Alveolar bone loss and inflammatory infiltration of the periodontal tissue were found in the mice with experimental periodontitis (122-135). Periodontitis significantly increased the infarction volume and numbers of activated microglia and astrocytes (136-163).

Clinically, declined masticatory performance is related to worsening peripheral conditions, such as fewer teeth, decreased saliva flow rate, or the reduction in biting force or masticatory muscle volume (164-177). Our findings highlighted that, in addition to these peripheral factors, individual differences in the brain signatures may contribute to the age-related decline in masticatory performance (164-183). Such a widespread engagement of multiple brain regions associated with the masticatory performance index may reflect an increased demand in sensorimotor integration, attentional control and monitoring for older adults to maintain good mastication. Further research is needed in the next future.

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The relationship between volumetric assessment of cleft lip and palate defects with age using cone beam computed tomography

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Aim: The aim of this study was to evaluate the Relationship between volumetric assessment of unilateral cleft lip and palate (UCLP) with age in subjects using computed tomography.

Materials and methods: This retrospective study consisted of CBCT scans of 96 non-syndromic UCLP patients 52 boys and 44 girls between 7 to 15 years old. The patients with the following criteria were excluded from the study: previous orthodontic treatment, alveolar grafting, orthognathic surgery, trauma, syndromes, history of tonsillectomy, and adenoidectomy. Patients were classified into 4 groups according to their age with approximately equal samples. Materialize Mimics innovation suite 20 software (Leuven, Belgium) was used to measure the maximum diameter of defect in the axial, coronal, sagittal plane in mm, bone defect volume in mm³, and also nasal floor deficiency area, alveolar deficiency area in mm². Kruskal Wallis test was used to analyze the data.

Results: The Maximum diameter of cleft in the sagittal aspect was 39.2±24.6 mm in the 7 till 8 age group and 26.1±10.9 mm in the 13 till 15 years old age group in both genders. There was a reverse significant relationship between age and the maximum diameter of cleft P<0001. There was not any significant relation between defect volume and age.

Conclusions: There was not any significant relation between defect volume and age. However, CBCT imaging can be used to assess the volume of the clefts and thus evaluate the amount of bone necessary to repair the cleft area for each age.

Cleft lip with or without cleft palate (CL/P) is the most common congenital deformity and it affects one to eight out of 1000 (1-20) precise assessment of cleft size by two-dimensional (2-D) imaging is very difficult

because of distortion, overlapping of structures, identifiable landmarks, and no volumetric data (21-40). Cone beam computed tomography (CBCT) has become a broadly device for diagnosis and treatment

Keywords: unilateral cleft lip and palate (UCLP), age, gender

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planning in oromaxillofacial deformity especially in cleft lip and palate (CLP) patients (41-60).

Three-dimensional (3D) analysis of the defect plays an essential role to evaluate the accurate size of defect, and to assess outcome of alveolar bone grafting and can allow the surgeon to better plan the surgical procedure and hence to minimize any unnecessary excess to the defect. Therefore, patients will benefit treatment outcome and in turn, the costs and total operative time will decrease (61-80). It is essential to acquire an accurate approximation of the alveolar cleft volume and its characteristics to regulate the quantity of bone. CBCT permits high-definition visualization of 2D slices in the axial, coronal, and sagittal planes without the problems associated with traditional 2D digital radiography (14). Moreover, CBCT have many benefits such as emitting rather lower radiation, low cost, and easy use. With the increased presence of CBCT in dental practice, more patients with CLP are undergoing CBCT scanning prior to alveolar bone grafting procedures. Visualization of anatomic structures in all three planes allows a better appreciation of 3-dimensional anatomy of affected areas of CLP patients (81-100).

To our knowledge, it is still unclear whether there is any relationship between the amount of alveolar cleft size and the age of the cleft patients. The aim of this study was to determine the volumetric size of the alveolar bone defect in nonsyndromic unilateral cleft lip and palate (UCLP) patients, prior to secondary bone grafting and to compare the cleft volume between different ages.

MATERIALS AND METHODS

In this cross-sectional study, CBCT scans of 96 non-syndromic UCLP patients 52 boys and 44 girls between 7 to 15 years old were thoroughly selected. The research was approved by the ethics committee of the craniofacial research center, (1395, 41).

All the patients had undergone similar surgical procedures by the same surgeon for lip closure between 3-5 months and palate closure between 8-14 months without any infant orthopedics. The exclusion criteria were history of previous orthodontic treatment, alveolar grafting, orthognathic surgery, trauma, syndromes, history of

tonsillectomy, and adenoidectomy. Patients were classified into 4 groups with approximately equal samples.

All CBCT scans had been attained in standard format at maximum intercuspation and in upright position by NewTom 5G CBCT scanner (QR, Verona, Italy). The scanning time was 14 to 18 s, the exposure time was 3.4 s, and the voxel size was 0.3 mm. 3D images were reconstructed with 0.25 mm slice thickness in DICOM format and exported to Materialise Mimics innovation suite 20 software (Leuven, Belgium).

Specialized imaging software of Materialise Mimics innovation suite 20 software (Leuven, Belgium) was used to render volumetric measurements from the cone-beam computed tomography images in the horizontal, sagittal, and coronal planes. Using anatomic landmarks, 6 following measurements were collected from the CBCT image for each patient: Maximum diameter of defect in axial plane in mm, maximum diameter of defect in the coronal plane in mm, maximum diameter of defect in the sagittal plane in mm, Bone defect volume in mm³, nasal floor deficiency area in mm², alveolar deficiency area in mm². Statistical analysis, including means, and standard deviation was used to calculate the relationship between each landmark and different age groups.

To measure the cleft defects, the files with the PRJ suffix are clicked. In this study, most measurements are in axial, panoramic, and 3D. To measure the cleft area in each view, tool options are chosen from toolbars then area and cure pen are selected. A cure pen gives us the ability to select the cleft region. All measurements were made by one calibrated engineer expert in medical engineering software. To assess the reliability of the measurements, 12 images were randomly selected and measured again by the same examiner after 3 weeks; test-retest reliability assessment showed that the intra-examiner reliability was found to be over 0.8. Thus, the results had optimal reliability. To evaluate the data distribution kalmagroph Smirnoff test was used and the Kruskal Wallis test was applied to analyze the data. The level of significance was set at 0.05.

RESULTS

The Maximum diameter of cleft in the sagittal aspect was 39.2±24.6 mm in 7 till 8 age group and 26.1±10.9 mm in 13 till 15 years old age group in both genders table1. Kruskal wallis test showed that the correlation between age

and maximum diameter in sagittal plane was significant ($p<0.001$). There was a reverse significant relationship between age and the maximum diameter of the cleft. This test also revealed that this correlation between age and maximum diameter in the sagittal plane was significant in girls $p<0.05$ but not in boys $p<0.8$. Kruskal Wallis test showed that there were no significant changes between age and cleft defect size in axial and coronal aspects neither in

girls nor boys. The same test also revealed that there were not any significant changes between bone defect volume, nasal floor deficiency area, and alveolar deficiency area in different age groups.

The Maximum Bone defect volume was 671.8 ± 212.2 mm³ which was in the 7 to 8 age group. Tables I, II, and III show the comparison of the maxillary cleft size at different ages in both gender, boys and girls respectively.

Table I. Comparison of the maxillary cleft size at different ages in both genders.

		Max.diameter axial mm	Max.diameter coronal mm	Max.diameter sagittal mm	Bone defect volume mm ³	Nose floor deficiency area mm ²	Alveolar deficiency area mm ²
Age	N	Mean±std	Mean±std	Mean±std	Mean±std	Mean±std	Mean±std
7-8	24	47.8±32.6	25±18.5	39.2±24.6	671.8±212.2	56.2±28.1	63.1±35.4
9-10	27	30.4±24.7	25.2±27.1	31.3±13.5	608.4±183.2	69.7±51.9	51.1±29.2
11-12	21	36.2±26.2	18.4±16.3	27.9±5.5	618.6±219.2	51.5±28	50±29.4
13-15	24	44.3±28.6	28.9±21	26.1±10.9	577.1±123.6	44.3±22.9	45±24.3
<i>p-value</i>		0.49	0.74	0.001	0.21	0.42	0.1

Table II. Comparison of the maxillary cleft size at different ages in boys.

		Max.diameter axial mm	Max.diameter coronal mm	Max.diameter sagittal mm	Bone defect volume mm ³	Nose floor deficiency area mm ²	Alveolar deficiency area mm ²
Age	N	Mean±std	Mean±std	Mean±std	Mean±std	Mean±std	Mean±std
7-8	12	50±18.7	44.2±16.7	21.6±16.2	685.8±256.7	54.8±27.5	69.5±37.6
9-10	18	35.5±34.4	30.4±30.5	31.1±31	586.9±195.4	54.3±55.8	52.3±26.9
11-12	10	30.3±23.6	27.9±13.1	17.6±17.8	539.7±199	48.1±46.6	38.1±38.1
13-15	12	51.4±25.13	30.6±31.6	30.1±30.9	613.4±92.6	39.6±19.5	47.7±21.1
<i>p-value</i>		0.88	0.93	0.86	0.25	0.22	0.08

Table III. Comparison of the maxillary cleft size at different ages in girls.

		Max.diameter axial mm	Max.diameter coronal mm	Max.diameter sagittal mm	Bone defect volume mm ³	Nose floor deficiency area mm ²	Alveolar deficiency area mm ²
Age	N	Mean±std	Mean±std	Mean±std	Mean±std	Mean±std	Mean±std
7-8	12	45.6±14.2	28.4±16.1	34.1±16.4	657.8±160.1	57.6±19.8	56.8±27.3
9-10	9	20.2±11.6	13.4±14.2	33.2±13.2	651.4±152.7	100.4±101.7	48.7±48.1
11-12	11	41.5±28.3	19.2±16.4	27.9±19.6	690.3±219.7	54.7±54.1	60.9±61.5
13-15	12	37.3±27.6	27.7±18.8	25.6±28.4	540.9±111.6	49.9±50.7	42.3±41.4
<i>p-value</i>		0.11	0.72	0.05	0.39	0.81	0.77

DISCUSSION

This study showed that there were not any significant changes between defect size and age. However, the size of cleft in sagittal plane was decreased by age just in girls. In the current study, all samples had no previous orthodontic and orthopedic procedures when CBCT were taken. Thus, all the inventions were eliminated such as maxillary expansion and orthopedic protraction.

The popularity of CBCT has been increasing in the recent years. CBCT permits clinicians to achieve better treatment planning because of its precise assessments of shape, quality, height, and thickness of the bone, high-definition imagining of anatomic structures through slices completed in the sagittal, axial, or horizontal planes (101-120). CBCT imaging will allow clinicians to have more data about the size of cleft and how much bone should be taken and obtaining more information results in a better outcome of surgery. Despite the variation in field of view and voxel size, CBCT is applicable and accurate means for measurement of volumetric cleft (121-140).

Volumetric assessment of cleft could be used to evaluate the different cleft grafting materials or quantify operation techniques (18,19, 141-144). Bone graft placement is an important phase in the treatment of CLP patients to permit the proper eruption of teeth, attain upper arch continuity, maximize bone support for dentition and creating alveolar structure (20). Having knowledge of the volume of defect is very beneficial in determining the site of autogenous bone harvest and thus preventing redundant overharvesting of bone, warning the incision size of the donor site, and leading to a reduction in postoperative morbidity. Finding more information about the morphology of the defect size will eventually help in a better overall result of surgery in complex cases of CLP patients (21).

3D imaging will allow clinicians to have more data on the alveolar cleft and a better information of where the ideal site would be for harvesting and how much bone should be occupied. Conventional 2-Dimensional cephalometric do not illustrate depth or bone volume in cleft sites. Lee et al. (7) reported that CBCT could be a suitable method in diagnosis and treatment plan in

CLP patients, moreover this technique is also reliable, reproducible process of volumetric assessment of the cleft site to estimate defect size (7). Oberoi et al. (10) used three measurements including: facial width, facial height, and facial-palatal length for evaluating the volume of the cleft prior to secondary repair of the alveolar cleft. In this study, the volumetric reconstruction was based on manually detecting the outline of the cleft, which enhance the accurateness of volumetric measurement. If the exact volume for bone is recognized, an adequate quantity of bone can be attained (23). Oberoi et al. (10) selected CBCT before grafting, along with at least one year after grafting to assess the residual defect. It must be mentioned that the new bone would be difficult to distinguish from adjacent bone. Similarly, de Rezende Barbosa et al. (142) reported that the amount of volumetric size of cleft can be different from 760.70 mm³ till 1582.80 mm³ with average of 1242.6 $\pm$ 428.99 mm³. The average amount of cleft in their study was different from our study.

This difference is related to different methodology and the software selected for volume assessment. In a similar study Kasiri et al. (143) found that the mean volume size of cleft was 628.66 $\pm$ 172.84 mm³. She also found that a significant negative correlation was occurred between cleft volume and fenestration and a significant positive correlation was existed between cleft volume and dehiscence. Recently in a systematic review Chetpakdeecheit et al. (144-153) reported that there is a lack of a standard definition of cleft size. They also pointed out a meta-analysis could not be completed due to the heterogeneity, however in their study they showed the mean volume of cleft was 0.89 $\pm$ 0.33 cm³.

CONCLUSION

There was not any significant relation between defect volume and age. However, CBCT imaging can be used to assess the volume of the clefts and thus evaluate the amount of bone necessary to repair the cleft area for each age.

Ethical Approval and Consent to participate: The study protocol was approved by the Ethics Committee of craniofacial research center, (1395, 41). All

participants gave written informed consent prior to the use of their data and this study.

Consent for publication: Not applicable

Availability of supporting data: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request

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Author contributions:

Study concept and design and drafting of the manuscript: AJ

Analysis and interpretation of data: HD and DF

Literature review: SE

Acquisition of data, Material support: SH and AP

Statistical analysis: AD

Administrative, Critical revision of the manuscript for important intellectual content: BS

Study supervision and corresponding: AJ

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Elastodontic therapy in adult patient improving the mucogingival status: a case report

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Elastodontics is a specific orthodontic treatment that uses removable elastomeric appliances. They are functional appliances that produce neuromuscular, orthopedic, and dental effects. Thus, these devices are useful in the developmental age, when skeletal structures are characterized by important plasticity and adaptation capacity, allowing to remove factors responsible for malocclusions. Elastomeric devices are generally well tolerated by patients requiring simple collaboration and management. Neuromuscular and dental effects can perhaps be obtained, with these devices, even in adults. The authors present a case report of elastodontic myofunctional treatment in an adult case. The patient improved functionally and even aesthetically, solving the mostly recessions too, with a significant improvement of the aesthetic outcomes.

Elastodontic therapy is nowadays increasingly used in orthodontic interceptive treatment (1-3). It uses removable elastomeric functional appliances that produce neuromuscular, orthopedic and dental effects (4).

Thus, these devices are useful in the developmental age, when skeletal structures are characterized by important plasticity and adaptation capacity, allowing to remove factors responsible for malocclusions (5). Elastodontic appliances not only improve orthodontic parameters such as Overjet (OVJ) and Overbite (OVB) but also eliminate functional disorders of the stomatognathic system and act in a three-dimensional way within the oral cavity, improving breathing, swallowing, and postural problems, especially if associated with targeted functional exercises (6-7).

These devices act as rehabilitative therapy for altered muscular functions. The presence of a lingual

ramp and a button for the tongue, in addition, allows the restoration of a correct posture and lingual function (1). Furthermore, elastomeric devices are generally well tolerated by patients requiring simple collaboration and management, they are both simple to use and comfortable (5-6, 8-10). Not only in young but also in adult patients we could have an effect of oral muscles re-education with the aim of starting the modification and correction of the oral functions of swallowing, breathing, and chewing; thanks to an elastic myofunctional trainer it is possible to modify, if necessary and at any age, the previous motor engram.

Furthermore, the dentoalveolar process of the maxillaries is subject to a continuous alteration even during adulthood; this can allow a shaping of the dental arch and a modification of the root crown torque at any age following an adequate stimulation such as that provided by the elastodontic device. Due

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to their good points, these appliances may be used, in our opinion, even in adults to obtain neuromuscular and dental effects, especially in patients affected by occlusal disharmony, parafunctional habits and temporomandibular disorders (TMD) (11).

TMD affect approximately 5% to 12% of the population and it's the second most common musculoskeletal condition (after chronic low back pain) resulting in pain and disability (12). TMD has a complex multifactorial etiology and parafunctions, like bruxism and clenching, and psychological factors have been widely recognized much more as important risk factors than the occlusion (13).

According to actual evidence, pain-related TMD has to be treated with reversible approaches. The reversible therapies commonly used for the management of TMD include physiotherapy, pharmacotherapy, psychological therapy (cognitive behavioural therapy) and occlusal therapy (occlusal appliances) (14-15). These modalities can be offered together or as single management strategy. Counselling is always a first approach (16).

In this case report the authors describe the use of a novel minimally invasive approach for the treatment of TMD and sleep bruxism by an elastodontic appliance used as myofunctional trainer. Going beyond the orthodontic interceptive treatment, the authors exploited the abovementioned neuromuscular and dental effect of these kind of appliances even in this adult case, achieving not only a functional and occlusal improvement but also a reduction of the gingival recessions exhibited by

the patient, with a significant improvement of the aesthetic outcomes.

The aim of the authors was to take advantage of a single therapeutic approach to deal with both the alteration of the correct occlusal scheme (deep bite and occlusion trauma) and the “dysfunctional” problems (bruxism and myofascial pain); these ones representing a reason for daily patient's discomfort (muscle tension upon awakening and frequent headaches). This combined approach has a double rationale. The first one is the simplification of the treatment and the greater compliance of the patient respect to other differential, multiple, in more times and more expensive treatments. The second one is the clinical experience of the authors who consider the above-mentioned problems interconnected and potentially connected to the contextual problems of the marginal periodontium.

MATERIALS AND METHODS

This elastodontic device is not a common nocturnal occlusal splint but it is a “three-dimensional bite” made in thermoplastic material (Fig. 1). The myofunctional trainer used consists in a double-track, one for the upper arch and the other one for the lower arch, and it is one-piece device wrapping both the arches. A horizontal plane, more rigid, on which the arches lay down, is made to levelling the dental arches according to a predetermined anatomical plan. Two softer vertical flanges, one internal and one external, are able to wrap both the arches, in order to neutralize abnormal centripetal and/or centrifugal



Fig. 1. Comparison of initial and final clinical examination after 12 months.

muscle forces that may insist on the arches, to obtain a harmonious shaping. The occlusal horizontal plane could have differentiated thicknesses; in this case the author used a device thicker in the anterior part to give the intrusive information on the frontal teeth, in order to obtain the correction of the deep bite.

The device, in general, follows the antero-posterior relationship of the arches themselves (1, 2, 3 class), the vertical relationship and the shape and diameter of the arches.

To select the desired size, you must measure the intermolar diameter (DIM), that is the distance between the external sides of the distobuccal cusps of the upper first molars in millimeters (mm). The patient's maxillary DIM was 60 mm. As mentioned before, the appliance has a conformation based on the specific shape of the arches and on the intermolar diameter of the upper arch, so it was deliberately chosen to use a device size of 65 mm DIM to allow arch reconfiguration with slight dento-alveolar expansive effect.

The appliance was initially worn 30 minutes during the day (for the first 30 days), by practicing some myofunctional exercises explained to the patient, with the aim of start to correct the functions of swallowing, breathing, and chewing by acting on the internal and external oral. Immediately afterwards, nocturnal use for 12 months was introduced and allowed these new, more correct motor engrams to become automatic. The patient was observed monthly.

Case report presentation

A 45-year-old man presented to our private practice with the complaint of "poor aesthetics due to abfractions and wear facets, dental sensibility, facial pain and tenderness, headache especially upon awakening and progressive gingival recessions".

The anamnesis resulted a patient with insulin dependent diabetes pharmacologically compensated, absence of others systemic pathologies, no allergy, no trauma in the orofacial area, no familiarity with periodontitis. Patient reported intermittent episodes of pain, tooth sensibility and bleeding gum associated to gingivitis, with tenderness and pain in masseterin region and he was generally unhappy with appearance of his front teeth and smile because of his receding gums.

Clinical examination revealed bilateral masseter pain-induced palpation, no TMJ sounds or deviations in

mandibular opening, besides based on muscle examination and reported medical history the several headaches reported by the patient can be classified as "muscle tension type headache" caused by TMD. Intraoral examination revealed a sufficient oral hygiene with mild gingivitis and uneven anterior occlusal plane with a deep bite.

The patient reported using medium bristle toothbrushes and correct brushing techniques, however presence of multiple V- shaped gingival recessions associated with abfractions and wear facets; in addition, the presence of nocturnal parafunctions, and the anamnesis made, led us to diagnose sleep bruxism.

Furthermore grade 2 superior premolars mobility associated with the widening of the periodontal space, other signs, and symptoms present, denote a primary occlusal trauma. The parafunctions had also caused severe wear of the lower incisal margins with loss of correct anatomy. The resulted data from the anamnesis and from the clinical examination are summarized below:

- Gingivitis
- Miller Class I V-shaped gingival recession #16,15,13,12,11,21,22,23,24,25,34,32,31,41,42,44,45
- Abfractions #15,11,21,22,23,24,34,32,31,41,42,44,45
- Deep bite
- Trauma of occlusion and Bruxism
- Myofascial pain and headache attributed to TMD
- Wear of lower incisors

Therapeutic interventions

Based on data found, the treatment goals for this patient were:

1. to eliminate gingivitis by etiologic periodontal therapy followed by maintenance therapy by reinforcing meticulous oral hygiene.
2. to manage the TMD with counseling by educating the patient to avoid overloading of the masticatory system.
3. To process the "extra periodontal" problems already listed (TMD, bruxism, covered bite) which were certainly responsible for part of the patient's symptoms but also represented dangerous "mechanical" risk factors for periodontal tissues already in recession and for the already deep erosions.

Afterwards the case would be re-evaluated for the possible correction of gingival recessions and erosions through mucogingival surgery.

RESULTS

On clinical level, the consequences of this “integrated” therapeutic approach have been early and multiple. After 1 month: remission of algic-dysfunctional symptoms was obtained already with the disappearance of tension on awakening, of face and neck muscles stiffness and of recurrent tensive headaches.

After 6 months (Fig. 2) there were a complete remission of algic-dysfunctional symptoms and clear signs of improvement in the shape of the arches and an improvement of the marginal periodontal tissues; absence of inflammation and of further erosive manifestations at the level of the amelo-cement junction; remission of any symptom (hypersensitivity) previously reported in correspondence of the elements with the greatest degree of root coverage.

There were moreover (and above all) an initial but significant recovery of the gingival recession#16,15,13,12,11,21,22,23,24,25,34,32,31,41,42,44,45, especially on the frontal elements of the upper arch.

After 12 months (Fig. 3) an almost complete root coverage on the elements occurred, with an average recovery value of (0,85 mm) and a maximum value of 1,3 mm. (Table I).

Recessions of the upper arch have recorded average gain of 1,1 mm compared to those of the lower arch (average gain 0,63mm) (Table IA).

An even better definition of the shape of the dento-

alveolar process of the arches occurred, that has its most evident expression in the improvement of the vertical parameters of OVB (-3mm) and of the DIM +2mm. Table II shows OVB, DIM measurements post 12 months of treatment and the difference found with baseline values.

The previously achieved improvements of the functions and their effects on the motor engrams were consolidated and a very satisfactory aesthetic appearance of the smile was obtained, fully in line with the best expectations of the patient and able to improve his self-esteem and social life.

DISCUSSION

Moawia M Kassab *et al.* (17) in a review on the etiology and prevalence of gingival recession, concluded that recession is multifactorial, with one type being associated with anatomical factors and another type with physiological or pathological factors and that it has been found more frequently on buccal surfaces than on other aspects of the teeth (18-19). Several factors connected to the onset of gingival recessions subsist like:

- Tooth position;
- Plaque presence;
- Mechanical trauma caused by improper tooth brushing habits;
- Periodontal Biotype;
- The impact of cervical restorative margins (20-21);
- The impact of orthodontics.



Fig. 2. Patient with removable elastomeric functional appliance.

There is a group of conditions, frequently reported by clinicians that could contribute to the development of gingival recessions (22); these include persistent gingival inflammation (e.g. bleeding on probing, swelling, edema, redness and/or tenderness) despite appropriate therapeutic interventions and association of the inflammation with shallow vestibular depth that restricts access for effective oral hygiene, frenum position that compromises effective oral hygiene and/or tissue deformities (e.g. clefts or fissures). Future studies and documentation focusing on these conditions should be done (23).

For many years and in most of the available clinical studies, gingival recession has been classified according to Miller (24). In general, this classification proved to be very useful but also revealed some limitations over time. Miller's classification system depends on the mucogingival junction (MGJ), the presence or absence of keratinized tissue (KT), and the interdental bone/soft tissue loss. Recently, a novel treatment-oriented classification has been proposed, which is based on the assessment of the gingival phenotype, the severity of the recession, and the presence of associated cervical lesions (23).



Fig. 3. *Clinical results after 12 months.*

In a first step, the gingiva should be categorized into different phenotypes/biotypes. In general, three different categories can be distinguished (25). Thin scalloped phenotypes show a higher association with a slender triangular-shaped crown, subtle cervical convexity, interproximal contacts close to the incisal edge and a narrow zone of KT, clear thin delicate gingiva, and a relatively thin alveolar bone. Thick flat phenotypes exhibit more square-shaped tooth crowns, pronounced cervical convexity, large interproximal contact points located more apically, a broad zone of KT, clear thick, fibrotic gingiva and a comparatively thick alveolar bone. Thick scalloped phenotypes show a clear thick fibrotic gingiva, slender teeth, narrow zone of KT and a high gingival scallop. Nevertheless, there are overlaps in definitions and the gingival phenotype can vary within the same individual and among different individuals.

Furthermore, the influence of tooth position in

Table I. Clinical measurements (MM) of recession at baseline and after 12 months treatment.

CLINICAL MEASUREMENTS (MM) OF RECESSION AT BASELINE AND AFTER 12 MONTHS TREATMENT			
TOOTH	BASELINE	FOLLOW UP 12 MONTHS	GAIN
11	1,5	0,3	1,2
21	1,7	0,5	1,2
22	1,6	0,4	1,2
12	0,7	0,0	0,7
23	0,9	0,2	0,7
13	0,9	0,0	0,9
24	1	0,0	1
25	1,2	0,0	1,2
15	0,7	0,1	0,6
16	1,5	0,2	1,3
TOOTH	BASELINE	FOLLOW UP 12 MONTHS	GAIN
42	1,5	0,7	0,8
41	1,4	1	0,4
31	2,8	1,8	1
32	1,7	0,7	1
34	2,4	1,7	0,7
44	2,3	1,9	0,4
45	2,1	2,0	0,1

Table IA. Upper and lower arch mm gain.

	GAIN
Upper arch average	1,1mm
Lower arch average	0,63mm
	GAIN
Total average	0,85mm

Table II. Overbite and dimension before and after 6 and 12 months.

	BASELINE	12 MONTHS	GAIN
OVB	6	3	-3
DIM	60	62	+2

the alveolar process is important. The bucco-lingual position of teeth shows increased variability in GT, i.e., buccal position of teeth is frequently associated with thin gingival (26) and thin labial bone plate (27).

Historically, it has been suggested that excessive occlusal force might be a causative factor in gingival recession.

Many authors, in the scientific literature supported the concept that recession was caused by trauma to the periodontium because of occlusal interferences (28). They had noted that, teeth which exhibited gingival recession commonly had signs and symptoms of traumatic occlusion, such as wear facets, heavy occlusal contacts, etc. Jati *et. Al.* confirmed this relationship however there is much disagreement on whether occlusal trauma contributes to or causes gingival recession (29). Harrel and Nunn reported that more than 70% of teeth with functional disturbances were associated with gingival recession. Gorman who evaluated 164 patients with gingival recession, however, could not relate the presence of recession to occlusal trauma. Bernimoulin and Curilovie evaluated 107 teeth with mobility and gingival recession but found no correlation between the two. Hence, insufficient evidence in this area

prompted us to further investigate the possibility of an association between the presence of signs of trauma from occlusion and the development of gingival recession. (30-31). The Word Workshop of classification of periodontal (2017) reports absence of evidence (32).

In this clinical case the authors observed improvement of the mucogingival status after elastodontic myofunctional therapy. After etiological therapy of gingivitis, it has been decided to implement an innovative myofunctional trainer. The intrusive effect of the elastodontic appliance, due to its greater thickness of the anterior side of horizontal occlusal plane, allowed the correction of the deep bite and this effect may have played a role in recession's improvement. In this regard, the scientific literature already has clear evidence.

Zimmer et al. in their research on changes in gingival recession related to orthodontic treatment of traumatic deep bites in adults, observed 41 incisors sites with trauma -related recession and found that the clinical crown lengths (mean: -1.13 ± 0.97 mm) and recession depths (mean: -2.05 ± 0.93 mm) decreased significantly ($p < 0.001$) in the trauma group. They also observed significant shortening ($p < 0.05$) of clinical crown lengths in the buccal sites of upper incisors (U-buc) (mean: -0.16 ± 0.46 mm). The Authors concluded that Orthodontic treatment of traumatic deep bites involving removal of gingival

trauma and intrusion of incisor teeth shows great potential in reducing the length of clinical crowns and depth of gingival recessions (33-64). Therefore, the treatment plan was oriented on the control of the nocturnal parafunction with the same appliance in the same time.

The myofunctional trainer applied has provided an effect of oral muscles re-education through a series of myofunctional exercises with the aim of starting the modification and correction of the functions of swallowing, breathing and chewing acting and it allowed the muscular reprogramming and the modification of the previous motor engram (Fig. 4).

The appliance showed both its arch reconfiguration and intrusive effect. Patient's baseline intermolar diameter (DIM) was of 60 mm with high negative torque of the upper posterior teeth especially the premolars and contraction of the upper arch and the baseline OVB was 6mm.

After 12 months of treatment OVB decreased of 3 mm and DIM increased of 2 mm, settling at 62 mm. The improvement of the deep bite may be attributed to the increased thickness of the occlusal plane in the anterior sector, which resulted in control/intrusion of the anterior group and extrusion of the posterior group, acting as a bite plane. The improvement in DIM may be attributed to the dentoalveolar arch reconfiguration with normalization of the negative

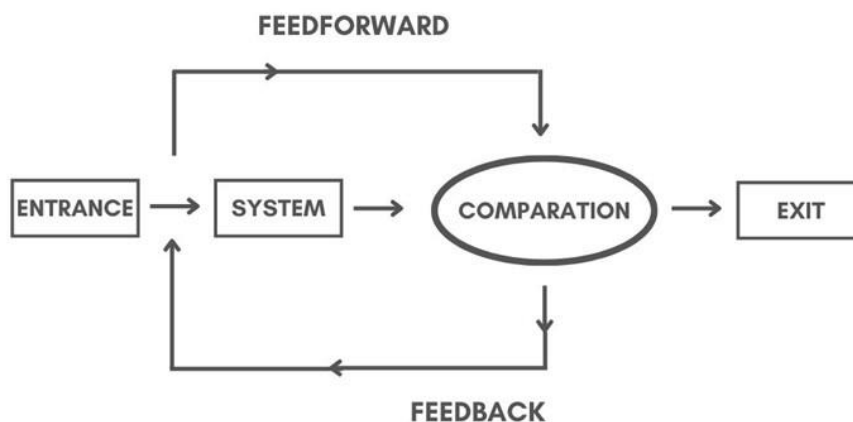


Fig. 4. Diagram of reprogramming and the modification of the previous motor engram.

torque of the posterior sector, which occurred due to the action of the high vestibular flanges of the used device with increased transverse diameter. These flanges cancelled the centripetal action of the external musculature and increased the centrifugal ones of the tongue. In fact, the device presented a reference point for the tongue muscles to allow, during daily myofunctional exercises, but even at rest, a correct positioning up and behind the upper incisors. The whole treatment took around 12 months for completion. Each measure was made with DeltaDent® software on the photographs, using maximum width of one tooth clinical crown as the reference value. It was not necessary to resort to surgical therapy for the root covering of any of the recessions. Most of them, in fact, completely re-entered, especially in the upper arch, where, a very rare event, the covering was also obtained on elements 16 and 25, which had a prosthetic margin inside the gingival sulcus.

To complete the treatment, the prosthetic restoration of three of the four lower incisors was necessary; they were severely worn both at the cervical and incisal level so as not to allow a conservative restoration (Fig. 5).

The elastic myofunctional trainer has restored a correct “neutral corridor” of the arches allowing the most correct positioning of the teeth in a three-dimensional position able to not receive oblique and deflecting forces. This result, obtained thanks to the elastodontic action of the device, was in our opinion

due to the combined effect of the intrusive action by the device on the superior frontal group (the inferior one, which was particularly under-leveled because of the serious wear of the incisal margins, did not have a similar intrusive effect) and the harmonizing action on the posteriorly contracted arch (with vestibular tipping movement that normalized the excessively negative torque present at the level of the premolars).

The unblocking of the upper arch (which started out contracted and in a “stressogenic” relationship with the antagonist), in particular, is clearly visible in the comparison between the final images and the starting ones. This is, probably, the reason why the recessions of the upper arch have better recovery (average gain 1,1 mm), compared to those of the lower arch (average gain 0,63mm).

The clinical impression is, in fact, that the greater amplitude of the maxillary arch obtained thanks to the action of the myofunctional trainer, has allowed the elimination (or the reduction) of oblique and deflecting forces having their greater stressogenic action at the level of the amelo-cement junction of the upper diatonic sectors. The control of sleep bruxism has also reduced the entity of these same forces from a quantitative point of view. It is conceivable that for this reason the generalized abfractions present at the beginning of therapy have completely disappeared with the exception of elements 4.5,4.1,3.1.

The most relevant result has been achieved on the frontal sector of the upper arch where the complete



Fig. 5. Comparison of initial and final clinical examination after 12 months with open mouth.

root coverage has been reached also thanks to the decisive contribution of the intrusion of the clinical crowns that appear, from the pre/post comparison, visibly reduced; this has allowed an improvement of the smile design with a very satisfactory aesthetic effect.

We would like to point out that this therapeutic approach has undoubted advantages over other options (traditional orthodontic and/or surgical for example) that may be just as effective; first of all, the mini-invasiveness that, from the periodontal point of view, also appears in the absence of any impact on the daily hygienic procedures.

As for all medical acts (never 100% predictable) a value is also that of the reversibility of the treatment. Especially in a case like the one presented, characterized by important dysfunctional symptoms, the action through traditional fixed orthodontic procedures, e.g., aimed at the appropriate correction of the deep bite and at the harmonization of the occlusal scheme, would certainly be less easily “reversible” in case of unexpected problems and / or worsening of symptoms than the removable device used at night. From the point of view of the cost-benefit ratio, which should always be taken into account in the ethics of our therapeutic choices, the “integrated” approach here used is certainly brilliant.

Because of all the previous considerations, the Authors want to focus the attention on the use of these new devices in cases where there is a possible traumatic and/or parafunctional component to support mucogingival lesions, before proposing invasive therapies such as surgical root covering. They believe that further studies are needed to better investigate these innovative therapeutic procedures and their clinical results.

CONCLUSION

The use of elastodontics in the treatment of adult patients and can be effective not only for the management of neuromuscular problems but also for restoring occlusal harmony; the effects of these devices on periodontal soft tissues could be a further advantage deriving from their correct use.

In this clinical case, the patient achieved, in just

one time, the return of his dysfunctional problems and a significant aesthetic improvement. Showing excellent compliance and declaring full satisfaction The patient was very pleased with the overall outcome of the innovative treatment: he feels a great improvement of his stomatological functions and of his dental aesthetic. The patient provided his written informed consent.

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Conflict of Interest: Since the present manuscript is a case report that does not require an IRB certificate

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Orthodontic emergencies and patients' perceptions of orthodontic patients during the COVID-19 pandemic

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Aim: This retrospective research was aimed to evaluate the impact of coronavirus disease 2019 (COVID-19) on orthodontic emergencies and Patients' perceptions of orthodontic patients.

Material and Methods: A total of 204 patients were gathered who were not seen for nearly 5 months from the first of March 2020 to the end of July 2020 due to dental clinic closure. The mean age of the samples was 20.2 (SD = 12.5) years consisting of 134 females (66%) and 70 males (34%). All patients had undergone active orthodontic treatment with fixed and removable appliances before the pandemic. The survey included demographics, types of orthodontic emergencies, and Patients' perceptions of orthodontic treatment during the closure of the dental clinic. Continuous variables were analyzed by mean and standard deviation, while categorical variables were analyzed by frequency and percentage.

Results: In general, 46.5% of the patients suffered from various emergencies. The incidence of emergencies was approximately 3 times higher than that of the normal appointment times. Debonding and poking wire had the most frequently reported classification respectively (14.2%) (7.9%). 30.4% of patients stated that pandemic had a significant impact on the efficacy of orthodontic treatment.

Conclusions: This study showed that the COVID-19 pandemic had a negative impact on patient care

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due to a higher number of emergencies and in turns, it delayed the therapeutic progress of patients. 16% of patients with active orthodontic appliances did not continue their treatment due to pandemics. More than half of the patients were willing to be seen every 8 weeks.

Keywords: orthodontic; emergencies; perception; COVID-19; pandemic

The coronavirus disease which has been characterized as a pandemic by the World Health Organization (WHO) has disrupted every aspect of our society, due to the high transmissibility rate, large quantities of droplets and aerosols could be generated during dental and orthodontic cares (1-10). Strict procedure of infection control was recommended to control transmission of this highly infectious disease. Social distancing measures, personal protective equipment, including aspirator mask, eye and face protection, aspirator mask, and reduction of aerosol-producing procedures were also instructed (11-23). A significant amount of aerosol can be produced during bonding, deboning, scaling, and adjustment of orthodontic appliances, furthermore, impression taking could provoke, gag reflex, coughing or vomiting, which could spread infection. Treatment of orthodontic needs regular visits for adjustment every month according to type of malocclusion in a period of nearly 24 months or longer. Therefore, the closure of dental clinics makes great challenge to both orthodontists and their patients (24-28).

Due to the quarantine policies, most of the patients had to suspend their routine visits and they encountered various dental and orthodontic emergencies (29-40). The main dental emergencies were dental trauma, abscess, Pulpitis, abscess, infection, swelling during the pandemic (41-60). Orthodontic emergencies such as bracket deboning, broken wire, attachment falling off, trauma or injury to orthodontic wires, pain, discomfort, irritation, appliance breakage, bleeding of the gums and mouth contributes to a prolonged orthodontic treatment. These adverse events require quick action to assure the patient and alleviate discomfort (61-80).

As a result of quarantine policy and closure of dental clinics during the COVID-19 crisis, access to orthodontic services to active patients were restricted.

Besides, some researchers and patients might be concerned about the impact of the COVID-19 crisis on the course and effectiveness of orthodontic treatment. Therefore, the aim of this study was to assess the impact of the COVID-19 pandemic on the orthodontic appointment of patients with different orthodontic appliance, types of emergencies, the incidence of emergencies, and Patients' perceptions on active removable and fixed orthodontic patients.

MATERIAL AND METHODS

The survey was conducted according to the guidelines of the Declaration of Helsinki. No animals were used in this research. All human research was conducted in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013. All subjects who participated in the survey signed informed consent. For cases below 18 years of age, informed consent was obtained from their guardians. All dental hospitals and clinics have been closed nationwide for nearly 5 months from the first of March 2020 to the end of July 2020.

All patients were called by phone at the end of July. After opening dental hospitals, the questionnaires were distributed to each patient in an orthodontic dental clinic before starting the treatment procedure. The instruction for emergencies was given by WhatsApp or throughout the website during the closure of the dental clinic. The inclusion criteria were as follows: All patients had undergone actively fixed or removable orthodontic treatment before the pandemic. Each questionnaire was given just one time to each patient. It was insisted on each patient to answer all questions completely. There was not any personal information in each questionnaire. Patients undergoing clear aligner, subjects with retention, and cases with craniofacial disorders, syndromes, and mental health problems were excluded. It was obviously itemized

that participation was voluntary. Characteristics of the study population included sex, age, Angle's classification, extraction or no extraction procedure, type of orthodontic appliance before the outbreak of COVID19 were recorded.

Basic information, the type of orthodontic emergencies, patients' self-assessment about the influence of the effect of COVID-19 on their orthodontic treatment were also evaluated. The impact of a pandemic on the efficacy of orthodontic treatment was divided into 5 categories as follows: Category 1= not at all, 2= a little, 3= moderately, 4= much, 5= very much. By considering a power study of 0.8, an alpha error of 0.05, a minimum of 190 samples were selected. By considering the dropout of samples, 250 patients were selected. All data were evaluated by one examiner. Continuous variables were analyzed by mean and standard deviation, while categorical variables were analyzed by frequency and percentage. SPSS Statistics version 26 (IBM Corp, Armonk, NY) was applied to evaluate the data.

RESULTS

A total of 250 fixed and removable orthodontic

patients were selected. Some of the samples were excluded because of incomplete answers or no answers, therefore the final samples which were gathered by the survey were composed of 204 patients. The mean age of the samples was 20.2 (SD = 12.5) years consisting of 134 females (66%) and 70 males (34%). Table I shows the detailed information about sex, age, Angle's classification, extraction protocol, type of orthodontic appliance before the COVID-19 outbreak; 167 of patients had fixed orthodontic appliances (81.9%) followed by 37 subjects with removable appliances (18.1%). Table II shows the basic information about samples. It reveals the percentage of patients who have been in orthodontic treatment before the pandemic.

It shows that 33 patients (16.1%) did not want to continue their orthodontic treatment and they wanted to be debonded due to pandemic after opening the dental office. The type of orthodontic emergencies as reported by patients is shown in Table III.

Debonded bracket (14.2%), was the most common orthodontic emergency. This was followed by poking wire (7.9%). One of the most common problems

Table I. *Characteristics of the study population.*

Variables	Frequency (n)	Percentage (%)
Male	70	34
Female	134	66
Class I Malocclusion	62	30.4
Class II Malocclusion	113	55.4
Class III Malocclusion	29	14.2
Extraction	80	39
Nonextraction	124	61
Removable Appliance	37	18.1
Fixed Appliance	167	81.9

Table I. *Characteristics of the study population.*

Questions	Response	Frequency (n)	Percentage (%)
How long you have been in orthodontic treatment?	> 3 years	43	21.1
	2-3 years	55	27
	1-2 years	70	34.3
	1-12 months	36	17.6
How many patients do not want to continue orthodontic treatment		33	16.1

which was reported by removable appliances during the pandemic is that the appliances were easy to become loose (4.4%). Three patients had the surgical procedures before closing the clinic and they were not visited for 5 months. Two of these patients had class 3 malocclusion and had a mandibular setback. The

malocclusion of class 3 was relapsed in one patient and root resorption in the lower anterior was seen in another one. The third patient had class 2 malocclusion and had gone under mandibular advancement procedure and did not have any serious problem. The influence of the pandemic on their orthodontic

Table III. *Orthodontic emergencies.*

Variable	Frequency (n)	Percentage (%)
Debonding	29	14.2
Debanding	6	3
Poking distal wire	16	7.9
Arch wire fracture	4	1.9
Periodontal Problems	13	6.4
Loose retention of removable	9	4.4
Lost Removable Appliance	4	1.9
Power chain/coil spring loss	11	5.3
Loss of the first time after orthognathic surgery	3	1.5
Total	95	46.5

Table IV. *Patients' self-assessment of the impact of pandemic on orthodontic treatment.*

Variables	Category	Frequency (n)	Percentage (%)
Efficacy	1	25	12.3
	2	29	14.2
	3	37	18.1
	4	51	25
	5	62	30.4

Table V. *Patient/orthodontist follow-up during the pandemic.*

Questions		Frequency (n)	Percentage (%)
My orthodontic treatment will be delayed because of the pandemic	Strongly agree	89	43.6
	Agree	58	28.5
	Disagree	35	17.1
	Strongly disagree	22	10.8
If you had any emergency, how do you classify your orthodontic emergency?	Severe	99	48.6
	Moderate	76	37.2
	Minor	29	14.2
How urgent you felt the need to be seen by an orthodontist for your emergency during the pandemic?	Extremely	51	25
	Necessarily	39	19.1
	Neutral	43	21.1
	Unnecessary	71	34.8
Do you think that an emergency issue can be solved via tele-dentistry?	Strongly agree	84	41.2
	Agree	56	27.5
	Neutral	29	14.2
	Disagree	18	8.8
	Strongly disagree	17	8.3
How often would you like to be seen for regular checkups during the pandemic?	Every 12 weeks	8	4
	Every 10 weeks	19	9.3
	Every 8weeks	110	53.9
	Every 6 weeks	38	18.6
	Every 4 weeks	29	14.2

treatment can be seen in Table IV, showing that 30.4% of patients stated that the pandemic had an impact on the efficacy of orthodontic treatment in 2020.

Table 5 shows the Patients' perceptions during the pandemic and reveals that 43.6% of patients believed that their treatment has been delayed because of the pandemic. 53.9 % of samples stated that it would be better to be visited every 8 weeks during the pandemic.

DISCUSSION

COVID-19 pandemic has caused huge limitations to dental offices, especially to orthodontic clinics, which orthodontic treatment requires regular follow-up visits. As a consequence, the appointments for patients were delayed due to COVID-19 pandemic. Our study indicates that the pandemic does have some negative impacts on orthodontic patients. Loosening of removable appliance was the most common problem which was reported during the pandemic (4.4%).

Another common problem reported by patients with fixed orthodontic appliances were debonding (14.2%) and poking distal wire (7.9%). 16.1% of patients decided to stop their treatment due to the pandemic crisis. Unfortunately, 3 patients had surgical procedure before closing the clinic and they were not seen for more than 5 months. Unfortunately, 2 of them were encountered serious problems due to broken wires and brackets, excessive use of elastic. One of the patients was told to use Class 3 elastic during a phone call when the office was closed. Due to the excessive use of class 3 malocclusion, some mobility and root resorption was seen in the lower anterior teeth of one patient, and for the other patient, due to the fact that he had not contacted at all and had not seen for 5 months, the mandibular pragmatism was relapsed, and the case was finished by edge-to-edge malocclusion. The third patient who had gone under mandibular advancement did not show any serious problem.

This study asserted that it is very important to visit patients after orthognathic surgery. This feature highlights how important it is for orthodontists to be accessible especially after surgical procedure. The other emergencies were not a serious problem. We encountered a high percentage of emergency in fixed and removable appliances during the lockdown.

Before pandemic the patients were visited every 4 weeks in dental clinic, however, this study showed that the patients can be seen every 8 weeks in orthodontic clinic without any serious problem except the patients who have gone under orthognathic surgery.

In comparison with removable and fixed appliances, fixed appliances caused more emergencies during treatment, which indicates that removable appliances have advantages for patients who live far from dental clinics or have to schedule the follow-up visit in a long period for some reasons. Loosening or dislocation of appliances were the main problem of removable appliances. Removable appliances were used in growing young patients. Growth of alveolar bones and Jaws (81-100), incorrect use of the removable appliances during the pandemic and not seen the patient for a long term, resulted in problems in settlement of removable appliances. However proper design of removable appliances is the useful method to increase the stability of them (101-120).

The success of treatment highly depends on the communication between doctor and patient (121-140). It seems very important for orthodontists to improve this communication and consider many precautions to avoid spreading COVID-19. Besides, the strict anti-infection guidelines of dentists, wearing personal protective equipment encouraged patients to undergo orthodontic treatment. To enhance patients' trust, it is essential to describe all the precautions considered by the doctors to avoid COVID-19 infections (141-165). Similarly, to this study, Xiang *et al.* (32) showed that debanding was the most common problem (24.1%) and followed by poking wire. On the contrary Turkistani (2) reported that the most common orthodontic emergency was poking wire 30% and it was followed by debonded bracket (27.3%). Almosa *et al.* (34) in a systematic review pointed out that the incidence of debonding were 0.6% to 9.6% in most studies. A higher incidence of brackets failure in the studies during the pandemic in comparison with the non-pandemic era was due to long no follow-up visits period caused by the pandemic. In this study 6.4% of patients had Periodontal Problems, similarly Turkistani (2, 18) showed 9.3% of patients had inflammation and bleeding. In general, 46.5% of the patients (N= 95) of this study suffered from different

kinds of emergencies. Xiang *et al.* (32), reported that 16.0% of the patients bothered from emergencies during an appointment interval of normal times.

This study showed that the incidence of emergencies increased 3-fold during the pandemic. This high rate of emergencies had a negative impact on orthodontic treatment. Motevasel *et al.* (97), found that COVID-19 pandemic has made a major and significant impact on the patient care and financial aspects of U.S. orthodontic practices. On the other hand, Quan *et al.* (98), reported that pandemic had moderate to little impacts on orthodontic patients. This study showed that the pandemic had a broad and significant impact on efficacy of orthodontic treatment in 2020 (Table 4). More than 50% of samples in this study believed that it would be better to be seen every 8 weeks during the pandemic. On the contrary Arqub *et al.* (99), reported that 73.4% of patients were willing to be seen each 4 weeks. As mentioned before all patients in this study had not been visited by their orthodontist for more than 5 months. Orthodontic emergencies caused discomfort for patients. Moreover, patients could lose their motivation and trust, and stop wearing their elastics or appliances.

Furthermore, they could also experience some extent of anxiety, fear. For this, using virtual assistance by tele orthodontics, showing how to treat emergencies on the website by some useful video in this regard, and maintaining appropriate communication channels were set up for all patients. One limitation in this study was that the socioeconomic status of the patients was not evaluated, which surely, affects their behavioral reaction to the crisis during pandemic.

CONCLUSIONS

This study suggests that the COVID-19 pandemic has delayed the appointment of fixed and removable orthodontic patients and in turn, it delayed the therapeutic progress of patients. In general, the pandemic had a broad and significant impact on the efficacy of orthodontic treatment. In comparison with normal appointment times, the incidence of emergencies enhanced approximately 3 folds. Debonding was the most emergency followed by poking distal wire during the closure

of orthodontic closure. 16.1% of patients with active fixed and removable orthodontic appliances did not want to continue their orthodontic treatment due to the pandemic crisis. Patients who had orthognathic surgery, must be visited just one month after the surgical procedure. While the other patients with removable or fixed appliances can be seen every 8 weeks.

Ethical Approval and Consent to participate: The study protocol was approved by the Ethics Committee of the university (IRB: 2020, 312). All participants gave written informed consent prior to the use of their data and this study.

Consent for publication: All patient signed informed consent.

Availability of supporting data: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Toothache and brain: any connections?

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Orofacial pain is a universal predicament, afflicting millions of individuals worldwide. Research on the molecular mechanisms of orofacial pain has predominately focused on the role of neurons underlying nociception. Orofacial pain can arise from different regions and etiologies. Temporomandibular disorders are the most prevalent orofacial pain conditions for which patients seek treatment. Pain on weak tactile stimulation is expected if dentinal terminate synaptically on trigeminal brainstem neurons that deliver a pain message to higher brain centers. Further studies are needed.

Orofacial pain is a universal predicament, afflicting millions of individuals worldwide. Research on the molecular mechanisms of orofacial pain has predominately focused on the role of neurons underlying nociception (1-10). However, aside from neural mechanisms, non-neuronal cells, such as Schwann cells and satellite ganglion cells in the peripheral nervous system, and microglia and astrocytes in the central nervous system, are important players in both peripheral and central processing of pain in the orofacial region (1, 11-27). Headaches,

toothaches, temporomandibular joint dysfunction/inflammation and head neck cancer pain are a few common orofacial pain conditions that can drastically impact the patient's quality of life (28-40).

Some of the most prevalent and debilitating pain conditions arise from the structures innervated by the trigeminal system (head, face, masticatory musculature, temporomandibular joint and associated structures). Orofacial pain can arise from different regions and etiologies (28). Temporomandibular disorders are the most prevalent orofacial pain conditions for which patients seek treatment (28). Pain on weak tactile stimulation is expected if dentinal terminate synaptically on trigeminal brainstem neurons that deliver a pain message to higher brain centers (41-45). Many mechanisms have been proposed to account for A β pain in the context of inflammation and neuropathy (46). Some involve sensitizing changes in spinal and trigeminal brainstem neurons due to the release of pro-inflammatory cytokines and other mediators from neurons, resident glia or invasive immune cells. Others involve changes in network parameters such

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as the activation of synaptic NMDA receptors or shifts in excitatory-inhibitory balance due to the loss of inhibitory interneurons or altered descending control (41,46-49). Therefore, continuous observation with daily clinical practice by physicians and surgeons, continuous scientific research and further discoveries, the use of 3-dimensional virtual reality and modern technologies will provide new solutions (50-110). Those innervating the tooth pulp (tooth pulp cells) had the Nissl pattern characteristic of large light cells of the A type, while those innervating the cornea were small dark cells of the B type (111).

Thirty percent of the tooth pulp cells exhibited histochemically demonstrable carbonic anhydrase activity. The transganglionic transport of HRP-WGA indicated marked concentration of central terminals of the tooth pulp primaries in the rostral subdivisions of the brain stem sensory trigeminal nuclear complex. In contrast, central terminals of the corneal primaries were concentrated in the medullary dorsal horn (111). Jung et al. (112) showed that tooth pulpal noxious signals transmit to the trigeminal subnucleus caudalis and transitional region between the subnucleus caudalis and the subnucleus interpolaris and the 2nd afferent neuron synapse in the thalamic ventral posteromedial nucleus and centrolateral nucleus. Similarly, Rydenhag et al. (113) reported that lesions were made in the thalamus and their effects were checked on the cortical responses to tooth pulp stimulation. If the lesion included the region of basal ventromedial nucleus of thalamus (VMB) bordering to arcuate nucleus of the ventrobasal complex (VBA) the cortical responses decreased in amplitude. I

t is concluded that VMB and the borderzone between VMB and VBA are important relays between the nociceptors of the tooth pulp and the sensory cortex. Patients' sensory-discriminative and emotional-cognitive cortical regions were studied through the transition of a neutral to a painful stimulation. In the putative somatosensory cortex contralateral to the stimulus, 2 well-defined hemodynamic peaks were detected in the homuncular orofacial region: the first peak during the nonpainful phase and a second peak after the pain threshold was reached (114-121). Hu et al. (122), by using an emerging brain imaging technique, functional

near-infrared spectroscopy, investigated the possible chain of brain mechanisms that modulate the patients specific ongoing dental pain experience in a clinical setting and found that patients' pain experience can be predicted concomitantly by their baseline functional connectivity between cognitive emotional and sensory-discriminative cortical areas and their well-defined sequence of hemodynamic responses—from expectation to dental suffering. Identification of brain regions that differentially respond to pain intensity may improve our understanding of trigeminally mediated nociception (123-129). Additionally, most clinical patients experience ongoing pain dentistry as opposed to that experienced in the study paradigm, where a short 1 msec provocative stimulus was required to evoke the pain sensation (123-179). Further studies are needed.

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Is dental prophylaxis required following neurosurgical and maxillofacial surgeries?

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There is a significant paucity of literature regarding dental prophylaxis in spine surgery patients. A point of controversy has remained the question of antimicrobial prophylaxis for patients with a history of neurosurgical procedures and spinal instrumentation undergoing invasive procedures on an outpatient basis. Invasive dental procedure does not increase the risk of postoperative spinal infection and antibiotic prophylaxis before dental procedure was not effective in preventing spinal infection.

There is a significant paucity of literature regarding dental prophylaxis in spine surgery patients. A point of controversy has remained the question of antimicrobial prophylaxis for patients with a history of neurosurgical procedures and spinal instrumentation undergoing invasive procedures on an outpatient basis. These procedures, such as routine dental work, carry a risk of introducing transient bacteremia (1-15).

Controversy exists regarding the need for antimicrobial prophylaxis prior to dental procedures following spinal fusion (16-25). Martin et al. (1) synthesized in their review the published literature to provide recommendations on the use of antimicrobial prophylaxis before dental procedures in patients with a history of spinal fusion.

Although dental work carries the risk of

introducing transient bacteremia, so do normal daily activities including mastication and teeth cleaning. In fact, the cumulative exposure introduced by normal daily activities is almost certainly higher than the risk associated with invasive dental procedures (26-31). Rather than concerning ourselves with the one-time exposure of dental care, we may be better served by encouraging patients to maintain good oral hygiene (1, 32-51). Whereas it is standard practice to utilize perioperative antibiotics to protect against infections acquired during spinal fusion surgery and neurosurgical procedures itself (52-91), yet there remains no consensus on their prophylactic use in patients with a history of prosthetic installations undergoing maintenance healthcare procedures with a risk of introducing bacteremia (1,52,53,92,93). Patients with a history of neurosurgical procedures

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who ask their healthcare or dental providers for guidance are likely to receive contradictory recommendations.

Chaichana et al. (94) study identified that several factors (older age, diabetes, obesity, prior spine surgery and length of hospital stay) which were each independently associated with an increased risk of developing infection among patients undergoing instrumented lumbar fusion for degenerative spine disease. Therefore, continuous observation with daily clinical practice by physicians and surgeons, continuous scientific research and further discoveries, the use of 3-dimensional virtual reality and modern technologies will provide new solutions (95-107).

Spinal infections are mostly caused by hematogenous spread (108). In patients who have undergone spinal fusion surgery, the implant is usually not removed after complete fusion, except in certain circumstances such as infection and the occurrence of implant-related pain (109-120). Although invasive dental procedures that manipulate gingival tissue cause temporary bacteremia and are known as risk factors for infective endocarditis (121-161), invasive dental procedure does not increase the risk of postoperative spinal infection and antibiotic prophylaxis before dental procedure was not effective in preventing spinal infection (92, 162-179).

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The effects of physical exercise on the brain and oral health

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There has long been discussion regarding the positive effects of physical exercise on brain activity. Exercising is used as a non-pharmacological treatment in many chronic diseases. Exercise has been shown to have beneficial effects on brain functions in humans and animals and, therefore, exercise is very important for brain rehabilitation and remodeling. Several studies have shown the beneficial effects of aerobic and resistance exercises in adult and geriatric populations. In addition, physical activity may improve self-esteem and feelings of self-worth in young adults.

Exercising is used as a non-pharmacological treatment in many chronic diseases (1-8). Exercise has been shown to have beneficial effects on brain functions in humans and animals and, therefore, exercise is particularly important for brain rehabilitation and remodeling (9-20).

In patients with Alzheimer's disease, moderate aerobic exercise improved cardiorespiratory fitness, associated with functional capacity and memory performance benefits (21). Physical exercise can promote molecular changes that swerve a chronic

pro-inflammatory state to an anti-inflammatory state in both periphery and central nervous system (22), as exercise can improve memory and learning in age-related neurodegenerative diseases (10, 23-31). In animal models, physical exercise regulates epigenetics, promotes synaptic plasticity and hippocampal neurogenesis, regulates the expression levels of neurotrophic factors, and improves cognitive function (10). Thus, compared with these expensive treatments, physical exercise can play a critical role in improving the brain functions on multiple levels

Key words: physical exercise, neurosurgery, spine, teeth, cancer-related fatigue

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(32). In patients with traumatic brain injury, physical exercise appears to improve the post-concussion symptom scale (PCSS) score and symptoms in patients with a concussion (33). There has long been discussion regarding the positive effects of physical exercise on brain activity. However, physical exercise has only recently begun to receive the attention of the scientific community, with major interest in its effects on the cognitive functions, spatial learning and memory, as a non-drug method of maintaining brain health and treating neurodegenerative and psychiatric conditions (34-48). Cancer-related fatigue (CRF) is a challenging symptom, often compromising quality of life (QOL) and hindering physical activity among patients with cancer (49). Spencer and Staffileno (49) reported that that exercise favorably affects clinical outcomes and is feasible among patients with high-grade glioma. Dulfikar et al. (50) suggested that glioma patient's aerobic endurance and lower limb strength are below criterion cutoffs recommended to maintain independent living. There remain debates on neuroprotection and rehabilitation techniques for acute ischemic stroke patients. Therapeutic physical exercise following stroke has shown promise but is challenging to apply clinically (51). Cranial surgery can be applied to treat different intracranial diseases such as tumors, blood clots, brain abscesses, repair broken cranial bones or clip blood vessels in patients with cerebrovascular aneurysms (52-90). The physical exercise program of patients after cranial surgery including body exercise, muscle relaxing massage, knowledge sharing and management of symptoms affecting postoperative recovery improved the patients' physical mobility (52, 91-112).

Recent studies in humans reported that exercise can be beneficial for the intervertebral discs and provide support for the notion that specific exercise protocols may improve intervertebral discs material properties in the spine (113). In humans, some studies have shown the beneficial effects of aerobic and resistance exercises in adult and geriatric populations (34, 114-119). More recently, studies employing animal models have attempted to elucidate the mechanisms underlying neuroplasticity related to physical exercise-induced spatial learning and memory improvement, even under neurodegenerative

conditions (34). Therefore, continuous observation with daily clinical practice by physicians and surgeons, continuous scientific research and further discoveries, the use of 3-dimensional virtual reality and modern technologies will provide new solutions (120-138). To clarify these issues, the role of physical exercise in the improvement of spatial learning and memory and the cellular and molecular mechanisms involved in neuroplasticity is under discussion (139). Recent advances on the association between serotonin, dopamine and fatigue were reported (139). Physical training protocols induce neuroplasticity, thus modulating the action of these neurotransmitters to improve physical performance (139-152). Oral health problems may have several effects on general health, including physical fitness and performance. In a recent review (153), it was assessed the effect of oral health on general physical fitness, showing that there is a negative effect of poor oral health on physical fitness. The oral conditions that strongly affect the physical strength were malocclusion and periodontal disease, whereas endodontic disease alone was reported not associated with poor physical performance (153-169). Exercise is an effective therapy for depression in young adults and is beneficial in reducing the symptoms of fatigue in certain patient populations, such as those with cancer-related fatigue (170-186). In addition, physical activity may improve self-esteem and feelings of self-worth in young adults (170). These studies suggest that individuals engaging in routine physical activity may benefit from improved self-esteem, decreased depressive symptoms, reduced fatigue and better-quality sleep (170-190).

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Hard and soft tissue changes after Lefort1 osteotomy and mandibular autorotation

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OBJECTIVES: Prediction of soft tissue changes following orthogenetic surgery has always been challenging for orthodontists and surgeons. There is a plethora of literature on the subject of soft tissue changes associated with orthogenetic surgery, but it has remained as a matter of controversial. The aim of this study was to evaluate soft and hard tissue changes in vertical and anterior posterior dimension following Lefort I surgery.

METHODS AND MATERIALS: 15 patients (12 females and 3 males) having CI II Div 1 malocclusion with open bite more than 4 mm were selected. Following the arch coordination and arch decompensation, patients underwent Lefort 1 surgery. Preoperatively, the study casts, panoramic view, and lateral cephalometry were prepared.

RESULTS: The angle of Go.GN/S.N and Y axis followed a significant reduction trend after the surgery from $41/4 \pm 7/3^\circ$ to $34/4 \pm 7/8^\circ$ ($P<0/001$) and from $69/4 \pm 3/8^\circ$ to $66/1 \pm 4/6^\circ$ ($P<0/009$), respectively. In the vertical dimension (related to the Y axis), the following parameters reduced significantly after the orthognathic surgery: L1, B, Pog, Me, PNS. Whereas, in the anterior – posterior dimension (related to the X axis), only the interval of the tip of the mesiobuccal cusp of the maxillary first molar in relative of the X axis modified in significant way ($P<0/01$).

CONCLUSION: In posterior impaction of maxilla, the anterior facial height was significantly reduced and hard and soft tissue cephalometric landmarks of the mandible reduced in the vertical dimension. Lower lip length significantly reduced. Upper lip length and protrusion changed postoperatively but it was not statistically significant.

In recent years, orthognathic surgery has been widely used as a method to correct moderate to severe facial deformities. Improving the aesthetic of the facial profile has a strong effect on the patient's mental and social health. Therefore, predicting the soft tissue profile after surgery has an effective role in patient motivation and treatment planning (1-26). Identifying factors related to esthetics as well as predicting the

final profile, plays an important role in treatment planning (27). Although most patients benefit from these treatments, research has shown that about 22% of them are dissatisfied with the aesthetic results obtained (28). Different methods were described to treat the malocclusion (29-40). However, sometimes the orthognathic surgeries are necessary to return the normal function and esthetic. Numerous studies

Keywords: Lefort I osteotomy; posterior impaction of maxilla; profile changes; autorotation of mandible; soft tissue; hard tissue.

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have been performed to evaluate the effects of hard tissue surgery on the underlying soft tissue and to evaluate their relationship (41-60). Although various diagnostic methods, including three-dimensional imaging techniques have evolved to determine the relationship between hard tissue movements and its effects on soft tissue (61-80), but the details of this relationship, especially in the vertical dimension, are varied and not precisely defined (81-85). One of the most challenging treatments in orthodontics is the treatment of patients with anterior open bite. In adult patients, there are two treatments to eliminate it: camouflage or orthognathic surgery (86-90). Posterior maxillary impaction surgery with or without mandibular surgery is the treatment of choice in adult patients for the treatment of this malocclusion (91-100). There is a plethora of literature on the subject of soft tissue changes associated with Lefort I surgery and mandibular autorotation subsequently, but it has still remained as a matter of controversial, therefore, the aim of this study was to investigate changes in facial soft tissue profiles and related factors following Lefort I Osteotomy in adult patients.

MATERIALS AND METHODS

The study was conducted according to the guidelines of the Declaration of Helsinki. No animals were used in this research. All human's research was conducted in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013. The approval code of the present cross-sectional study was obtained from both the local ethics committee (dental school 17028). The approved written consent including the aims of the study was signed by all the participants, as well.

Evaluating the soft and hard tissue modifications in patients with lefort I osteotomy

15 patients (12 females and 3 males) referred to orthodontic department were selected according to the following inclusion criteria:

- Having Cl 2 Div 1 malocclusion with open bite more than 4 mm.
- No history of previous orthodontic treatment
- No presence of any syndrome

Among the patients, 3 patients underwent the extraction of the maxillary and mandibular second premolars while this procedure was not performed for others. Then, the leveling and aligning were planned with 018 Edgewise Appliance. Following the arch coordination and arch decompensation, patients were ready to undergo Lefort I osteotomy (101-105). Preoperatively, the study casts, panoramic view, and lateral cephalograms were prepared. The Lefort I osteotomy was conducted for posterior impaction of the maxilla. All of patients had rigid fixation and, the panoramic and lateral cephalograms were provided after 6 months.

To evaluate the vertical changes of the face, the S.N line was determined and 7 degrees relative to that, a line was drawn from N point as the horizontal axis (X axis) in preoperative and postoperative lateral cephalometries. Then, at the S point, a line perpendicular to the X axis was drawn as the vertical axis (Y axis). So that, the anterior-posterior and vertical changes were assessed according to the Y axis and X axis subsequently.

The following indicators were measured in relative to X and Y axes:

1. Sn, Sls, Li, Ls, Mlf, Pog', Me', Stm.s, and Stm.i in soft tissue
2. A, B, Pog, Me, ANS, PNS, L1, U1, and the tip of the mesiobuccal cusp of the maxillary first molar in hard tissue
3. The angles of SNA, SNB, ANB, Y axis, Go.GN/S.N, Occ/S.N, and Pal/S.N
4. Soft tissue thickness; Mlf.d, Ls.EL, Li.EL, U.L.P, L.L.P, U.L.L, L.L.L, the chin thickness, the upper and lower lip thickness, Sk.A.F.H, and P.F.H. (Table I)

Statistical analysis

All measurements were made by two calibrated examiners. Ten cephalograms were randomly measured again by the same examiners after one month in order to analyze the reliability of the measurements. Pearson's correlation coefficient was used to assess the intra-examiner reliability. Intra-examiner reliability scores were found to be over 0.7 by test-retest reliability assessment. Thus, the results had substantial agreement. The collected data were analyzed by T-test, Paired T-test, and Wilcoxon test. SPSS Statistics version 26 (IBM Corp, Armonk, NY) was used to evaluate the data. P-value of less than 0.05 was considered significant.

RESULTS

15 patients with the mean age of 24.2 years old were selected (12 females and 3 males) which suffered from malocclusion CI II Div1 malocclusion.

Soft tissue modifications in patients with Lefort I osteotomy

In the vertical dimension (related to the Y axis), the interval of the Li, Mlf, Pog', and Me' reduced after the surgery, significantly ($P<0/004$, $P<0/003$, $P<0/01$, and $P<0/005$ orderly). Meanwhile, the other parameters didn't change significantly (Table II). Also, in the anterior – posterior dimension (related to the X axis), no significant modification was observed (Table III).

Hard tissue modifications in patients with Lefort I osteotomy

In the vertical dimension (related to the Y axis), the following parameters reduced significantly after the orthognathic surgery: L1, B, Pog, Me, PNS, and the tip of the mesiobuccal cusp of the maxillary first molar ($P<0/001$, $P<0/001$, $P<0/008$, $P<0/01$, $P<0/006$, and $P<0/01$ respectively) (Table IV).

Whereas, in the anterior – posterior dimension (related to the X axis), only the interval of the tip of the mesiobuccal cusp of the maxillary first molar in relative of the X axis modified in significant way ($P<0/01$). The other indicators' changes were not significant statistically. However, among them, the U1 and L1 parameters faced decreasing trends and the

Table I. The definition of the cephalometric parameters (Alphabetic order)

A	The deepest midline point on the maxillary alveolus between ANS and the maxillary alveolar crest	Occ/S.N	The angle formed between occlusal and sella–nasion planes
ANB	Measures the relative position of the maxilla to mandible = SNA – SNB	Pal/S.N	The angle formed between the sella-nasion plane and palatal plane
ANS	The angle formed between sella, nasion and point A	P.F.H.	Posterior facial height: the distance in millimeters from point Ar to the mandibular plane
B	The deepest midline point between the mandibular alveolar crest and the gnathion	PNS	Posterior nasal spine: tip of the posterior spine of the palatine bone of the hard palate
Go-Gn	The mandible length	Pog	The most superior point of the center of the symphysis in the sagittal view
Go.GN/S.N	The angle formed between mandibular and sella-nasion planes	Pog'	The most superior point of the center of the symphysis in the sagittal view on soft tissue.
L1-NB	The angle between long axis of the mandibular central incisor and nasion–point B line. The distance from the incisal edge of the mandibular central incisor to nasion– point B line	Sk.A.F.H	Skeletal anterior face height:
Li	Labrale inferius: A point where the boundary of the vermillion border of the lower lip and the skin is intersected by the median sagittal plane	SlS	Superior labial sulcus
Li.EL	Labrale inferius to esthetic plane E-line	Sn	Sella–nasion plane
L.L.L	Lower Lip Length: the distance between the menton' to the most inferior point at the center of the lower lip	SNA	Sagittal position of the maxilla relative to the anterior part of the cranial base
Ls	Labrale superius: The point on the upper lip lying in the median sagittal plane on a line drawn across the boundary of the vermillion border and skin.	SNB	Sagittal position of the mandible relative to the anterior part of the cranial base
Ls.EL	Labrale superius to esthetic plane E-line	S.N-PT	The lower third of the facial height
Me	The most inferior point of the center of the symphysis in the frontal view	Stm.i	Stomion inferius: The most inferior point of the lower lip
Me'	The most inferior point of the center of the symphysis in the frontal view on soft tissue.	Stm.s	Stomion superius: The most inferior point of the upper lip
Mlf	Mento Labial Fold: The deepest point of the mentolabial fold	U1-NA	The angle between long axis of the maxillary central incisor and nasion–point A line. The distance from the incisal edge of the maxillary central incisor to Nasion– point A line
U.L.P	Upper lip protrusion	U.L.L	Upper Lip Length: the distance between the base of the nose to the most inferior point at the center of the upper lip
Y axis	SN to S-gnathion		

Table II. *Soft tissue changes in vertical dimension (related to horizontal axis) pre and post operatively (in mm) in patients with Lefort I osteotomy*

	Stm.S Mean ± SD	Stm.I Mean ± SD	Me' Mean ± SD	Pog' Mean ± SD	MLf= Iis Mean ± SD	Ls Mean ± SD	Li Mean ± SD	Sls Mean ± SD	Sn Mean ± SD
Pre-operatively(mm)	92/4 ± 11/5	93/8 ± 11/8	141/4 ± 19/3	140/1 ± 19/9	121 ± 15/7	87/6 ± 13/4	106 ± 14/3	73/3 ± 11/1	64/6 ± 9/2
Post-operatively(mm)	93/6 ± 12/4	96/2 ± 12/5	140/3 ± 19/9	135/4 ± 18/5	115/6 ± 14/1	86/2 ± 10/9	102 ± 13/5	76/2 ± 11/2	66/2 ± 9/6
Difference (%)	1/3%	2/56%	0/78%	3/35%	4/46%	1/6%	3/77%	3/81%	2/48%
P-value	0/4	0/09	0/005	0/01	0/003	0/3	0/004	0/01	0/1

Table III. *Soft tissue changes in anterior-posterior dimension (related to vertical axis) pre and post operatively (in mm) in patients with Lefort I surgery*

	Stm.S Mean ± SD	Stm.I Mean ± SD	Me' Mean ± SD	Pog' Mean ± SD	MLf= Iis Mean ± SD	Ls Mean ± SD	Li Mean ± SD	Sls Mean ± SD	Sn Mean ± SD
Pre-operatively(mm)	85/8 ± 14/5	84/6 ± 15/8	56 ± 19/9	64/4 ± 20/1	80 ± 18	95 ± 16/6	92/6 ± 17/6	92/8 ± 15/8	94/3 ± 15/6
Post-operatively(mm)	85/8 ± 15/4	85/2 ± 14/7	60 ± 19/9	67 ± 17/9	80 ± 16/6	96 ± 16/9	92/1 ± 15/9	93/5 ± 14/9	94/7 ± 16
Difference (%)	0%	0/71%	7/14%	3/72%	0%	1/05%	0/54%	0/75%	0/43%
P-value	0/3	0/4	0/2	0/1	0/5	0/4	0/7	0/2	0/4

Table IV. *Hard tissue changes in vertical dimension (related to horizontal axis) pre and post operatively (in mm) in patients with Lefort I osteotomy*

	mesiobuccal cusp Mean ± SD	PNS Mean ± SD	ANS Mean ± SD	Me Mean ± SD	Pog Mean ± SD	B Mean ± SD	A Mean ± SD	L1 Mean ± SD	U1 Mean ± SD
Pre-operatively(mm)	88/8 ± 11/4	58/9 ±8/2	58/3 ±8/3	154/27 ±21/3	137/7 ±18/4	122/6 ±16/1	69 ±0/3	100 ±13/8	93 ±12/4
Post-operatively(mm)	84/6 ±10/8	55/5 ±6/7	57/5 ±8/8	149/6 ±21/3	132/9 ±16/9	116/2 ±16/3	68/2 ±10	91/4 ±14/1	97/8 ±16/6
Difference (%)	4/73%	5/77%	1/37%	3/03%	3/49%	5/22%	1/16%	8/6%	5/16%
P-value	0/01	0/006	0/3	0/01	0/008	0/001	0/8	0/001	0/1

others had increased postoperatively. Note that the PNS didn't change at all under the surgical influence (Table V).

Angles' modifications in patients with Lefort I osteotomy

The angles modification showed that the angle of Go.GN/S.N and Y axis followed a significant reduction trend after the surgery from $41/4 \pm 7/3$ degrees to $34/4 \pm 7/8$ degrees ($P=0/001$) and from $69/4 \pm 3/8$ degrees to $66/1 \pm 4/6$ degrees ($P<0/009$), respectively. Pal/S.N and Occ/S.N also had significant changes. (Table VI).

Soft tissue thickness modifications in patients with Lefort I osteotomy

Eventually, the changes of L.L.P, L.L.L, and Sk.A.F.H were decreasing 1/6, 3/2, and 5/9 mm with the P-value of $<0/02$, $<0/003$, and $<0/001$ respectively (Table VII).

DISCUSSION

Considering diminished stability and aesthetic of orthodontic treatment of patients with open bite malocclusion, superior repositioning of maxilla by lefort I osteotomy has been considered as a treatment option for decades (106-100). Several studies were performed to evaluate soft and hard tissue changes following Lefort I (101-120). In this study, all samples had skeletal high angle Class II discrepancy and they were treated just by Le Fort I maxillary impaction. To evaluate craniofacial complex, a reference plane is needed. The S-N plane has been used traditionally in literature (121-130). However, Legan *et al* suggested an alternative reference line (2). They used a line drawn through nasion at an angle of 7° to the S-N line called a constructed horizontal, which tends to be parallel to true horizontal. We used the same reference line. Evaluating the parameters of the soft tissue

Table V. Hard tissue changes in anterior-posterior dimension (related to vertical axis) pre and post operatively (in mm) in patients with Lefort I osteotomy

	Mesiobuccal cusp Mean $\pm$ SD	PNS Mean $\pm$ SD	ANS Mean $\pm$ SD	Me Mean $\pm$ SD	Pog Mean $\pm$ SD	B Mean $\pm$ SD	A Mean $\pm$ SD	L1 Mean $\pm$ SD	U1 Mean $\pm$ SD
Pre-operatively(mm)	47/6 $\pm$ 9/7	21/8 $\pm$ 5/4	81/8 $\pm$ 13/9	56/8 $\pm$ 21/5	79/7 $\pm$ 20/5	65/5 $\pm$ 17/9	76/7 $\pm$ 13/8	76 $\pm$ 15/4	79/9 $\pm$ 14/7
Post-operatively(mm)	43/9 $\pm$ 9/5	21/5 $\pm$ 6/1	82/7 $\pm$ 13	58/2 $\pm$ 19	80 $\pm$ 18/8	66/5 $\pm$ 17/1	76/8 $\pm$ 11/9	75/5 $\pm$ 14/8	78/7 $\pm$ 14/3
Difference (%)	8/43%	0%	1/1%	2/46%	0/38%	0/92%	0/13%	0/66%	1/5%
P-value	0.01	0/9	0/5	0/3	0/5	0/9	0/7	0/8	0/2

Table VI. The angles' changes pre and post operatively (in degrees) in patients with Lefort I osteotomy

	Pal/S.N Mean $\pm$ SD	Occ/S.N Mean $\pm$ SD	Y axis Mean $\pm$ SD	Go-Gn/S.N Mean $\pm$ SD	N.A Mean $\pm$ SD	ANB Mean $\pm$ SD	SNB Mean $\pm$ SD	SNA Mean $\pm$ SD
Pre-operatively(degree)	11/1 $\pm$ 4/1	20 $\pm$ 2	69/4 $\pm$ 3/8	41/4 $\pm$ 7/3	106/6 $\pm$ 11/2	5/7 $\pm$ 3	77/7 $\pm$ 4/4	83/2 $\pm$ 4/8
Post-operatively(degree)	7/5 $\pm$ 1/9	16/7 $\pm$ 3/5	66/1 $\pm$ 4/6	34/4 $\pm$ 7/8	105/2 $\pm$ 11/9	3/6 $\pm$ 1/6	79/1 $\pm$ 5/1	83/7 $\pm$ 4
The difference (%)	4/67%	4/65 %	5/46%	8/08%	1/31%	2/78%	1/51%	0/36%
P-value	0/01	0/01	0/009	0/001	0/8	0/9	0/6	0/6

modification in the vertical dimension (in relation to the horizontal axis), the distance of Li, Mlf, Pog, and Me reduced significantly which is understandable as the surgery was performed on maxilla so the posterior impaction of the maxilla caused mandible autorotation. Also, it should be noted that the maxillary indices related to this axis didn't change, which is consistent with the results of Möhlhenrich (65). On the other hand, the evaluation of the soft tissue modification in the horizontal dimension (in relation to the vertical axis) showed no significant data. The reason may be discussed as the maxillary impaction and the following anterior – posterior autorotation of the mandible were not prominent and the bases of the jaws didn't change much in this dimension (131-140). The hard tissue changes in the vertical dimension (in relation with the horizontal axis) revealed that the distance of L1, B, Pog, Me, PNS, and the tip of the mesiobuccal cusp of the maxillary first molar from horizontal axis decreased significantly. As the posterior impaction of the maxilla can affect the posterior changes of the maxilla the results seem acceptable. While the changes of the anterior indices weren't significant (141-160). The reduction of the tip of the mesiobuccal cusp of the maxillary first molar was the only significant data in the horizontal dimension (in relation with the vertical axis) which is explained by the geometrical changes (71). Due to autorotation of mandible, lower incisors move forward but less than the chin, which lead to the better profile (33). Also, the same modification happens for soft tissue as it obeys the changes of the hard tissue (28,32). It is obvious that the Go.Gn/Sn angle's reduction was due to the

reduction of the facial height. As well, the reduction of the Y axis angle was a result of the mandibular rotation. The SNA didn't change as the treatment plan didn't involve any maxillary advancement. However, the mandibular autorotation led to increasing of the SNB. As a result, the ANB angle decreased (34). The soft tissue analysis presented that the L.L.P reduced significantly which has been confirmed by Bailey *et al.* (58). This can be explained by the moving up of the Pog. However, the increscent of the upper lip length was not considerable unlike previous studies (26,34,35). The difference may be from the variation of the surgical technique (26). The Lefort I osteotomy for patients with the malocclusion CI II and anterior open bite is an acceptable procedure and the impaction of the maxilla is one of the most stable orthognathic surgeries. Although the mandible surgery is the other therapeutic option, the relapse is undeniable, because of the pterygomasseteric sling (36-39). In this study, direct formulations and soft to hard tissue ratios from lateral cephalograms were developed. However, in 3D prediction methods, it is not possible to predict soft tissue changes following skeletal tissue by mathematical formulation or continuous equations and soft to hard tissue ratios like 2D prediction methods due to various geometric complexities (40).

Maxillary posterior impaction surgery reduces the vertical height of the patient's face and causes the mandible to rotate upward and anteriorly. The upward movement of the mandible is greater than the forward movement following maxillary surgery and these changes occur in both hard and soft tissues. Posterior maxillary repositioning does not seem to have

Table VII. The changes of the soft tissue thickness pre and post operatively (in mm) in patients with Lefort I osteotomy

	P.F.H Mean ±SD	SK.A. F.H Mean ±SD	L.L Thick- ness Mean ±SD	U.L Thick- ness Mean ±SD	Chin Thick- ness Mean ±SD	L.L.L Mean ±SD	U.L.L Mean ±SD	L.L.P Mean ±SD	U.L.P Mean ±SD	LS.El Mean ±SD	Li.El Mean ±SD	Mlf.d Mean ±SD
Pre-op (mm)	87/4 ±12/4	149 ±20/8	16/4 ±2/1	16/7 ±2/9	15/6 ±4	26/9 ±2/9	29 ±4/6	5/9 ±3/1	5/8 ±2/4	4 ±3/8	3 ±0/33	6/1 ±1/8
Post-op (mm)	85/5 ±11/6	142/1 ±19/4	16/4 ±2/9	17/1 ±3/4	14/1 ±2/9	23/7 ±4	29/4 ±2/6	4/3 ±2/6	4/6 ±2/8	2/8 ±2/6	2/8 ±0/6	6/6 ±1/7
Diff (%)	1/95	3/96	0	2/4	9/62	11/9	1/3	27/12	20/69	30	8/82	8/2
P-value	0/2	0/001	0/8	0/7	0/1	0/03	0/3	0/02	0/2	0/1	0/8	0/4

much effect on N.A angle and the soft tissue of the middle part of the profile in general. Also, maxillary landmarks, especially anterior points, do not undergo significant changes after maxillary posterior impaction surgery. But the length and protrusion of the lower lip are reduced.

Ethical approval and consent to participate

The study protocol was approved by the Ethics Committee of dental school, (1395, 41). All participants gave written informed consent prior to the use of their data and this study.

Availability of supporting data

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests and funding

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History and advances in neurosurgery and maxillofacial surgery

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Technological advances in neurosurgery and maxillofacial surgery, aided by improvements in anesthesia have resulted in surgery that is faster, simpler and safer with excellent perioperative recovery. As a result of improved outcomes, several centers are performing certain neurosurgical procedures on an outpatient basis; where patients arrive at the hospital the morning of their procedure and leave the hospital the same evening, thus avoiding an overnight stay in the hospital. Future efforts to encourage efficient cost savings should focus on practice patterns/pathways for similar conditions rather than limiting the use of certain implants.

Although there is evidence of applications of cranial surgery in ancient times, it is commonly accepted that modern surgery started in the late 19th century (1). The advancements in anesthesiology and aseptic techniques were the main factors contributing to this process. Surgery of the nervous system, however, has a relatively shorter history than surgery of other systems (1-13). Technological advances in neurosurgery and maxillofacial surgery, aided by improvements in anesthesia have resulted in surgery that is faster,

simpler and safer with excellent perioperative recovery (14-25). As a result of improved outcomes, several centers are performing certain neurosurgical procedures on an outpatient basis; where patients arrive at the hospital the morning of their procedure and leave the hospital the same evening, thus avoiding an overnight stay in the hospital (14, 26-48). The field of spine surgery has undergone one of the greatest transformations in medicine over the past 100 years. In that period, the most significant advancement has

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come with the evolution of spinal instrumentation and fusion in the past 3 decades (49-64). Robotic surgery has been the forte of minimally invasive stereotactic procedures for some decades now. Ongoing advancements and evolutionary developments require substantial evidence to build the consensus about its efficacy in the field of neurosurgery (65-69).

Reconstructive neurovascular surgery has become a routine procedure. Extra-intracranial bypass or intraintracranial bypass procedures are now well established and integral parts of surgery for giant aneurysms, arteriovenous malformations, skull base tumors and reconstruction of the venous sinuses (70-86). Also in maxillofacial surgery, there has been a tremendous progress in this field because of significant advances in biotechnology that provided innovative biomaterials to efficiently reconstruct the maxillofacial injured region in the past years (87). Among them, there is a distinction between naturally occurring or synthetic biomaterials (87-93). All these advancements impacted the development and establishment of the field of neurological surgery and maxillofacial surgery by minimizing surgical risk through aseptic techniques and promoting surgical benefit via improved neurological localization and surgical technique. Infections were significant contributors to morbidity and mortality for all surgical patients, and historically almost half of patients lost their lives as a consequence of perioperative wound contamination (70,94-98). Both neurosurgical and maxillofacial contributions have been tremendous, with continued daily innovation, particularly in the areas of navigation, robotics, materials science, and spinal biomechanics (99-110). These contributions have allowed for safer, more efficacious, and more efficient methods of treatment, improving outcomes and quality of life for patients. Looking at the history of spine surgery and its incredible recent journey provides excitement for continued progress in the future (49, 111-120).

Acceptance of the robotic medical manipulation will allow neurosurgeries to move past its challenges and enter a new sphere of development where robots will supplement not supplant surgeons and together, they can perform better than either can individually (65, 121-130). Therefore, continuous observation with

daily clinical practice by physicians and surgeons, continuous scientific research and further discoveries, the use of 3-dimensional virtual reality and new technologies will provide new solutions (131-142).

All these led to increase the patients' quality of life and the impact on the economic burden on currently rising healthcare costs (14, 143-162). Future efforts to encourage efficient cost savings should focus on practice patterns/pathways for similar conditions rather than limiting the use of certain implants (163). The advent of evidence-based medicine has framed the surgical decision-making process into guidelines based on the results of high-quality data, and of randomized controlled clinical trials—not devoid of several flaws in design themselves (164). This approach, despite remaining the gold standard, is limited by the oversimplification of patients' individual characteristics that often do not allow patient-specific analytics. With the exponential growth of data in the era of big data, it is increasingly important to provide clinicians with tools for integrating this individual patient data into reliable prediction models (165-182).

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