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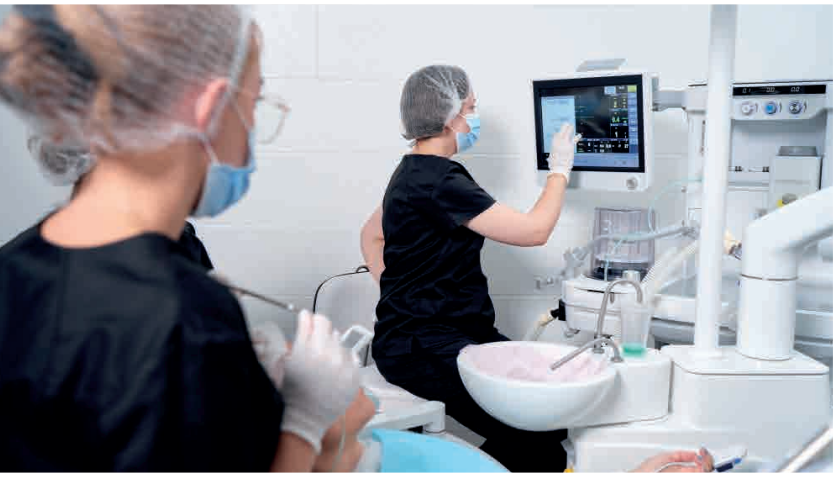

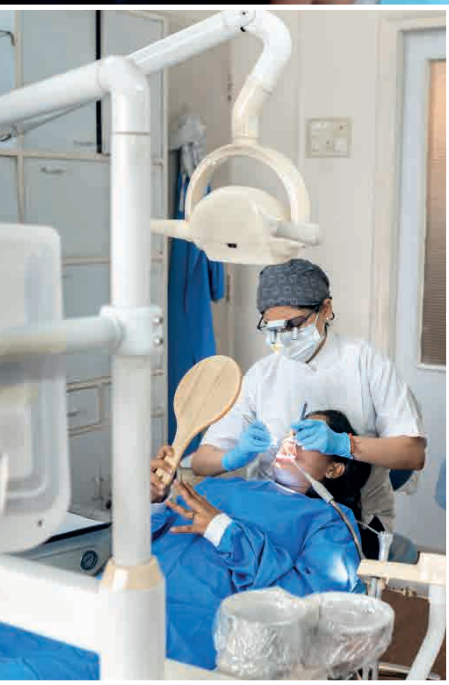

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Ilustre Colegio Oficial de Odontólogos y Estomatólogos de la Iª Región

SPECIAL SUPPLEMENT 2024
volume 21

contents

editorial

Dra. Mª Isabel Leco Berrocal
Director *Científica Dental*

Dra. Mª Victoria Mateos Moreno
Assistant Director
Científica Dental

Dear colleagues and readers of the journal *Científica Dental*,

At *Científica Dental*, we are proud to publish this issue in English, dedicated to our 2024 annual awards, which aim to recognize and highlight the research excellence, clinical quality, and commitment to scientific dissemination of the professionals who share their clinical work and experiences with us.

This issue includes the best papers published in 2024, in the categories of best scientific article, clinical case, and best publication by a new author. A total of six papers are presented, which are the finalists of the previous categories.

In the Best Scientific Article category, the first prize was awarded to the work titled "Correlation between the presence of sleep apnea and prosthetic and implant fractures", authored by E. Anitua. This publication represents a valuable contribution to the identification of clinical risk factors and their management through mandibular advancement devices. The second prize went to the study "From mild COVID to persistent syndrome: comprehensive evaluation of oral health", developed by Sánchez Fernández S. et al., rigorously addressing the oral effects of persistent COVID from a multidisciplinary perspective.

Regarding the Best Clinical Case, the first prize was awarded to the work of Beca Campoy T. and his team, who document the use of the autologous tooth as biomaterial in a lateral access maxillary sinus lift, with a clinical, radiographic and histomorphometric follow-up at six months post-loading. The second prize went to Quispe López N. et al. for the presentation of a complex clinical case with a surgical and restorative approach in the aesthetic area, evaluated by volumetric analysis after de-epithelialized connective tissue graft.

Finally, in the Best First Publication category, the first prize went to Jiménez Pascual S. et al. for their review on pulp regeneration and revitalization in immature permanent teeth. The second prize went to Ouazzani Touhami M. and his work group for their review on osteonecrosis in the jaw and/or maxilla in patients treated with monoclonal antibodies.

From the management and editorial committee, we would like to extend our sincerest congratulations to the authors who have been awarded prizes, as well as to all participants. The quality of the papers presented this year reaffirms our authors' commitment to research and professional excellence.

Hoping you enjoy your long-awaited vacation. We wish you a happy summer.

ORIGINAL ARTICLE

Correlation between the presence of sleep apnea and prosthetic and implant fractures. Series of clinical cases with identification of the process and treatment with mandibular advancement device

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ABSTRACT

Introduction. The presence of dental signs and symptoms in patients with sleep apnea (OSA) that are recognizable to the dentist places us in the first line of diagnosis and subsequent treatment for patients suffering from this pathology. From problems such as wear and tear and fractures, we can reach a diagnosis of a pathology with great repercussions for the patient and address a crucial part of the treatment, such as recovering the vertical dimension and the use of mandibular advancement devices.

Methods. We retrospectively recruited patients who attended our dental clinic with problems in different implant rehabilitations of an eminently mechanical nature (fracture of ceramics, prostheses, or components as well as implants) who underwent respiratory polygraphy to reveal the possible presence of OSA. In those cases where this disorder was found to be present, we selected patients with moderate-severe OSA (apnea- hypopnea index (AHI) ≥ 20) to analyze the different adverse events that occurred according to the severity of the sleep disorder recorded.

Results. Twenty-two patients who met the previously established inclusion criteria were recruited. Adverse events were identified in all patients in their implant restorations, these complications being: fracture of the prosthesis ceramic (63.6%), structural fracture of the prosthesis in 18.2% of the cases (structure itself or resin coating in hybrids) and fractures or cracks in the implants in 18.2% of the cases. The mean AHI (apnea-hypopnea index) of all patients was

33.29 (+/- 18.90; range 20-110). If we analyze the presence of adverse events in the prostheses according to the AHI, we find that most adverse events are concentrated in the higher AHI ranges. A therapeutic approach with CPAP (continuous pressurized airway oxygen delivery device) combined with a mandibular advancement device (DIA) was used in two patients, the rest only DIA. With treatment completed, patients went from a mean AHI of 33.29 (+/- 18.90) to a mean of 17.38 (+-10.37), these differences being.

Conclusions. Bruxism and OSA are closely related, as are the dental signs of both processes, such as wear and fracture of teeth, implants or rehabilitations. Dentists can be a fundamental pillar in the treatment of these patients, including the first step in the diagnosis of undiagnosed cases of OSA, which can.

KEY WORDS

Fracture; Bruxism; Obstructive sleep apnoea.

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INTRODUCTION

Obstructive sleep apnoea (OSA) is defined, according to the Spanish Consensus Document, as "a condition characterised by excessive sleepiness, cognitive-behavioural, respiratory, cardiac, metabolic or inflammatory disorders secondary to repeated episodes of upper airway obstruction during sleep"[1]. At present, it is a major public health issue which, in its most severe forms, affects 3–6% of men, 2–5% of women, and 1–3% of children, causing arterial hypertension and an increased risk of cardiovascular disease in those affected, as well as a consequent deterioration in quality of life, accidents, and excess mortality[1,2]. Early diagnosis is therefore of vital importance, as with appropriate treatment we can reduce patients' symptoms and long-term side effects, substantially improving their quality of life as well as reducing cardiovascular events, which may have a fatal outcome[1-2]. At present, the correlation between sleep disorders such as OSA and oral pathology, for example bruxism or fractures, of various rehabilitations, both on teeth and on implants, is widely documented today. This association has been demonstrated in several epidemiological studies over the years[3-7], with our research group highlighting that the presence of dental wear in patients should prompt a thorough sleep analysis, as the degree of dental wear is directly related to OSA via the AHI (apnoea-hypopnoea index)[9-11]. This relationship is directly proportional, and it is confirmed that patients with more severe wear also exhibit a higher AHI, which is likewise associated with an increased incidence of fractures in enamel, dental roots, and prostheses. Mechanical events may, in some cases, also affect implants, resulting in bone defects due to overload, and in extreme cases, leading to fracture of the implant itself.[12-14]. In the following clinical case series, we sought to retrospectively collect a group of patients who experienced adverse events in implant-supported prostheses associated with mechanical overload (fractures, loosening), to whom a subsequent polygraphic sleep study was performed, identifying those in whom these events could be related to the presence of OSA. The most severe cases identified (AHI ≥ 20) were analysed to obtain data correlating both events (OSA and mechanical complications).

MATERIALS AND METHODS

Patients who attended our dental clinic retrospectively with problems in various implant-supported rehabilitations of a predominantly mechanical nature (fracture of ceramic, prosthesis or components, as well as implants) were recruited, and respiratory polygraphy was performed to determine the possible presence of OSA. In cases where this disorder was confirmed, we selected patients with moderate to severe OSA (AHI ≥ 20), in order to analyse the different adverse events that occurred according to the severity of the recorded sleep disorder, during the period between January 2014 and December 2015. The primary variable of the study is the presence of prosthetic adverse events in relation to a moderate to severe OSA condition, analysing the type of prosthetic adverse event that occurred and its potential relationship with the AHI. As secondary variables, an analysis was conducted of the approach taken for the treatment of OSA and the impact of this treatment both on the values associated with the AHI and on the occurrence of new adverse events once the treatment had been instituted.

A Shapiro-Wilk test was conducted on the data obtained to confirm the normal distribution of the sample.

Qualitative variables were described by means of frequency analysis. Quantitative variables were described using the mean and standard deviation. The association between the severity of OSA (AHI) and the occurrence of adverse events in the prosthesis was analysed using Pearson correlation analysis. Data were analysed using SPSS v15.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Twenty-two patients who met the previously established inclusion criteria were recruited. Of the patients, 54.5% were male, with a mean age of 64.55 years (± 8.06; range 46–84 years). Adverse events were identified in all patients in their rehabilitations with implants, with the complications being as follows: fracture of the prosthesis ceramic in 63.6% of cases, structural fractu-

re of the prosthesis in 18.2% of cases (either the structure itself or the resin coating in hybrid prostheses),

and fractures or fissures in the implants in 18.2% of cases. Fractures of the prosthesis and of the implants were observed equally among men and women, with ceramic fractures being slightly more frequent in the male group (Figure 1).

The location of the adverse event was predominantly in implants placed in position 26 (18.2%), followed by position 16 (13.6%), with the first maxillary molars thus representing 34.5% of all recorded events. The other locations where mechanical incidents were recorded are shown in Figure 2. When grouping the events by maxilla or mandible, a higher incidence was observed in the maxilla, accounting for 68% of cases.

With regard to the type of prosthesis affected by complications, two-unit bridges accounted for 50%, followed by single crowns at 36.4%, and bridges of more than two units at the remaining 13.6%. Of the prostheses that experienced complications, 77.3% were cemented and the remaining 22.7% were screw-retained, with complications being more frequent in cemented crowns and bridges than in complete prostheses, as shown in Figure 3.

The mean AHI for all patients was 33.29 (+/- 18.90);

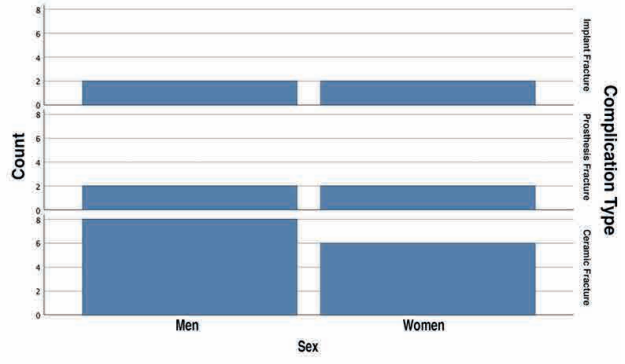


Figure 1. Distribution of prosthetic events according to patient sex.

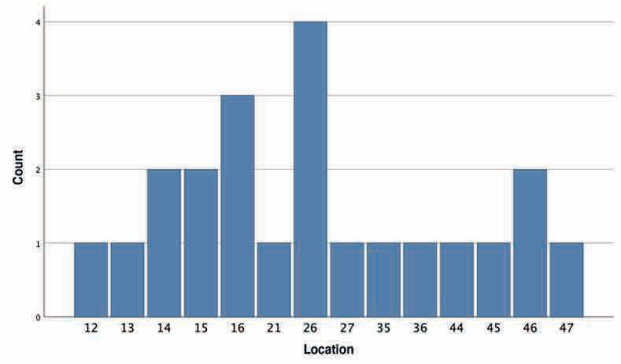


Figure 2. Location of adverse events occurring in the prosthesis.

range 20–110). If the presence of adverse events in the prosthesis is analysed according to AHI, it is observed that the majority of adverse events are concentrated in the higher AHI ranges, as shown in Figure 4, although no positive correlation was found between increasing AHI and the type of complication observed (p=0.432).

Once the respiratory disorder was identified in the patients, the issue was addressed and treatment for OSA was undertaken using intraoral mandibular advancement devices (DIA-Biotechnology Institute®), with CPAP (continuous positive airway pressure device) also employed in the most severe cases (2 patients). In all patients, a reduction in AHI was observed with treatment, with the device being adjusted in each case using the most effective tensioner and the minimal possible protrusion, monitored by respiratory polygraphy. Upon completion of treatment with the MAD, patients' mean AHI decreased from 33.29 (± 18.90) to a mean of 17.38 (± 10.37), these differences being statistically significant (p<0.001).

Patients were subsequently followed for a mean of 39 months (± 8) after completion of prosthetic treatment and placement of the MAD, not en no new mechanical prosthetic incidents or implant complications were observed during this period.

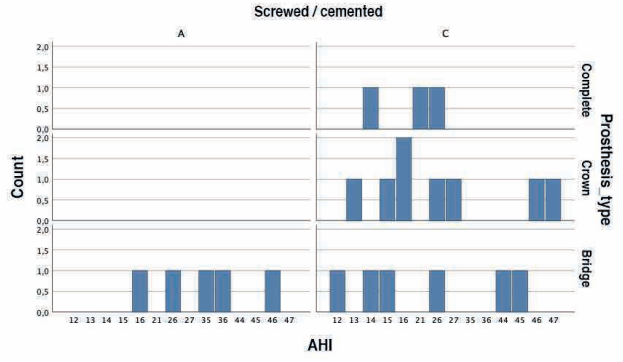


Figure 3. Prosthetic complications according to fixation (screw-retained/cemented), type of prosthesis, and location.

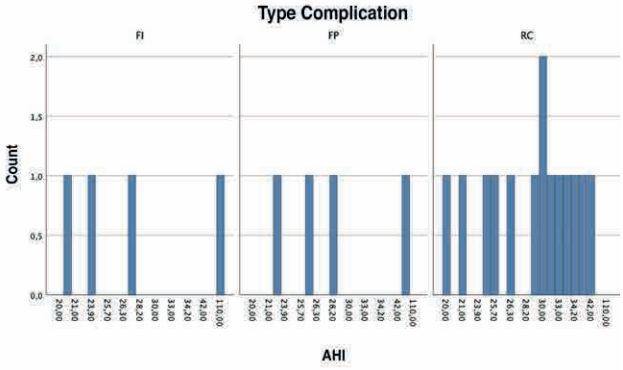
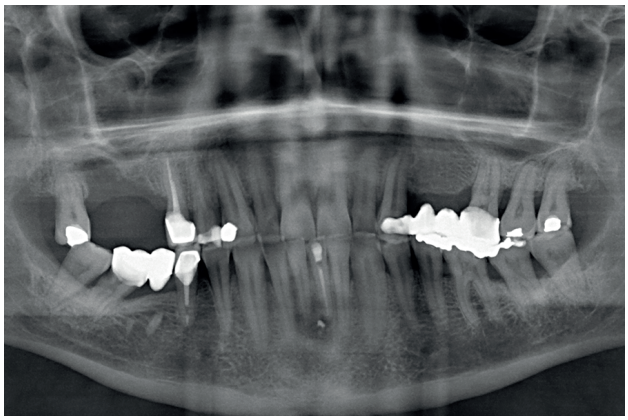
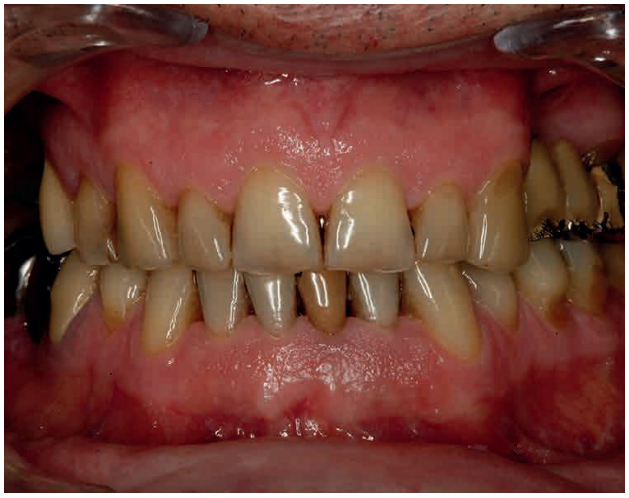


Figure 4. Type of complication (FI = implant fracture / FP = prosthesis fracture / RC = ceramic fracture) in relation to the AHI value.

Figures 5–13 present one of the cases included in the study.





Figures 5 and 6. Initial images of the patient, demonstrating generalised occlusal wear and several dental reconstructions, including the bridge in the second quadrant, where the patient reports pain on mastication.

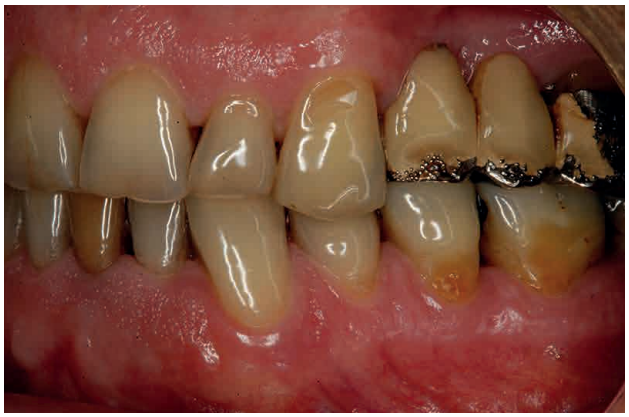


Figure 7. Detailed view of the incisal and occlusal wear, the fracture of the tooth-supported bridge, and the roots used as bridge abutments.

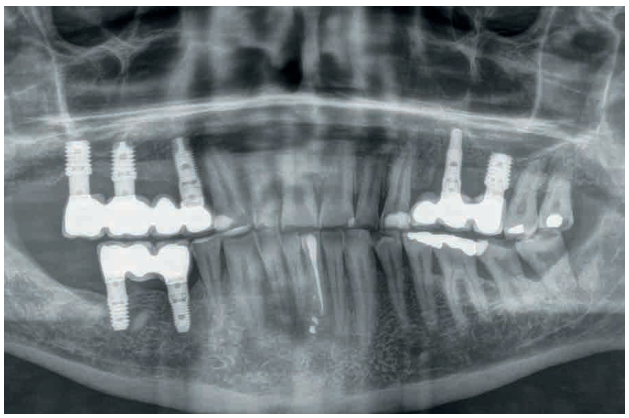


Figure 8. Final radiograph following completion of the implant treatment. Upon completion, a follow-up period is commenced.

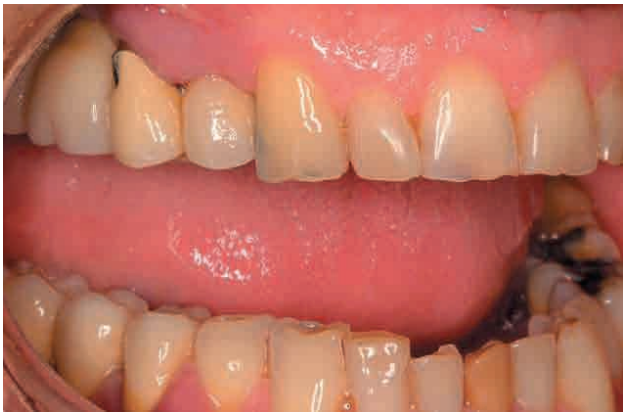


Figure 9. Adverse event of ceramic fracture at one-year follow-up, following restoration of the vertical dimension, for which a sleep study is conducted to ascertain whether the patient presents with obstructive sleep apnoea-hypopnoea (OSA).

***RESPIRATORY POLYGRAPHY:** Supervised Analysis*

Recording Time			09:48:50 (588,8 min.)	
Evaluated Time			09:17:08 (557,1 min.)	
Evaluated Oximetry Time			571,8 min.	
Wakefulness Suspected			0 min.	
RESPIRATORY EVENTS				
	Number	**Index per hour**		**Average Duration**
Apneas	79	AI	8,5	19
Unclassifieds	79	UAI	8,5	19
Obstructives	0	OAI	0	0
Centrals	0	CAI	0	0
Mixeds	0	MAI	0	0
Hypopneas	110	HI	11,8	23,2
Apneas + Hypopneas	**189**	**AHI**	**20,4**	**21,4**
Cheyne-Stokes Respiration	0	CSI	0	0
Border Events	56	BEI	6	21
APNEAS + HYPOPNEAS PER HOUR INDEX (AHI)				20,4
AHI per position	Supine	19	Non Supine	23,4
Time in supine (%)		68,7		

OXYGEN SATURATION (%SpO2)							
%SpO2		**Desaturations**		**%SpO2 < 90**		**%SpO2 < 85**	
Average Basal	91,7	Number	212	Minutes	115,4	Minutes	2,5
Minimum	79	Index per Hour	22,1	% time	20,2	% time	0,4
Average (%)	90,5	Average (%)	4,5				
		Average of Minimums (%)	88,2				

HEART RATE (pulse frequency in beats/min)							
Heart Rate	Minimum	53	Maximum	80	Average	64,2	

PRESENCE OF SNORES**						
Snores per position	Supine		Non Supine		Totals	
Number	171		324		495	
Time (minutes)	11,4		21,6		33	
% time snoring	3,1		12,9		6,2	
Snores per hour Index	26,8		111,4		53,3	
Intensity	High	Low	High	Low	High	Low
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**If sleeping next to a snoring person, consider this data with caution

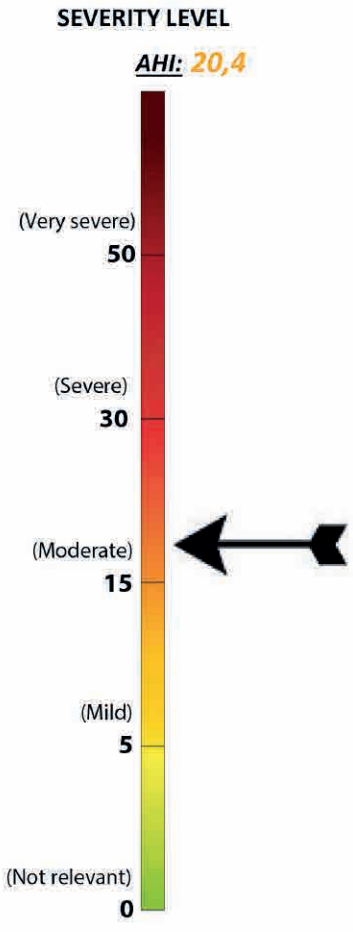


Figure 10. Initial respiratory polygraphy recording demonstrating the presence of moderate OSA. Treatment is commenced with a mandibular advancement device (MAD).

RESPIRATORY POLYGRAPHY: Supervised Analysis

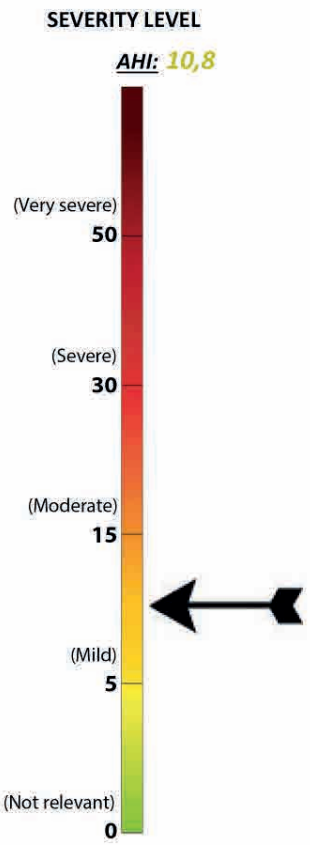
Recording Time			06:19:50 (379,8 min.)	
Evaluated Time			06:05:00 (365 min.)	
Evaluated Oximetry Time			365 min.	
Wakefulness Suspected			0 min.	
RESPIRATORY EVENTS				
	Number	**Index per hour**		**Average Duration**
Apneas	33	AI	5,4	19,3
Unclassifieds	33	UAI	5,4	19,3
Obstructives	0	OAI	0	0
Centrals	0	CAI	0	0
Mixeds	0	MAI	0	0
Hypopneas	33	HI	5,4	20,4
Apneas + Hypopneas	**66**	**AHI**	**10,8**	**19,9**
Cheyne-Stokes Respiration	0	CSI	0	0
Border Events	16	BEI	2,6	36,8
APNEAS + HYPOPNEAS PER HOUR INDEX (AHI)				10,8
AHI per position	Supine	11,5	Non Supine	9,9
Time in supine (%)		60,2		

OXYGEN SATURATION (%SpO2)							
%SpO2		**Desaturations**		**%SpO2 < 90**		**%SpO2 < 85**	
Average Basal	91,8	Number	73	Minutes	13	Minutes	0,9
Minimum	81	Index per Hour	11,3	% time	3,6	% time	0,3
Average (%)	91,8	Average (%)	4,5				
		Average of Minimums (%)	89,1				

HEART RATE (pulse frequency in beats/min)							
Heart Rate	Minimum	51	Maximum	74	Average	60,7	

PRESENCE OF SNORES**						
Snores per position	Supine		Non Supine		Totals	
Number	389		79		468	
Time (minutes)	25,9		5,3		31,2	
% time snoring	12,2		3,7		8,8	
Snores per hour Index	106,2		32,7		76,9	
Intensity	High	Low	High	Low	High	Low
	--	--	--	--	--	--

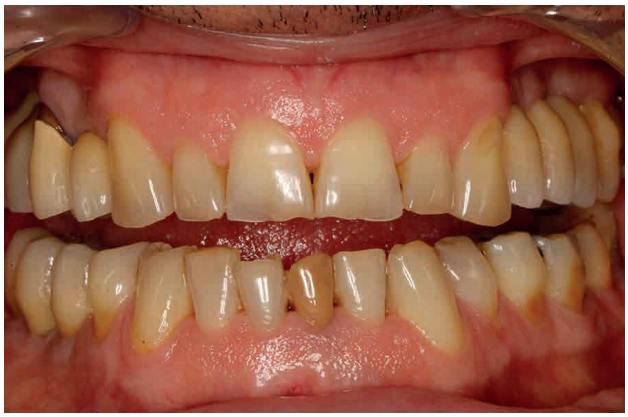
**If sleeping next to a snoring person, consider this data with caution

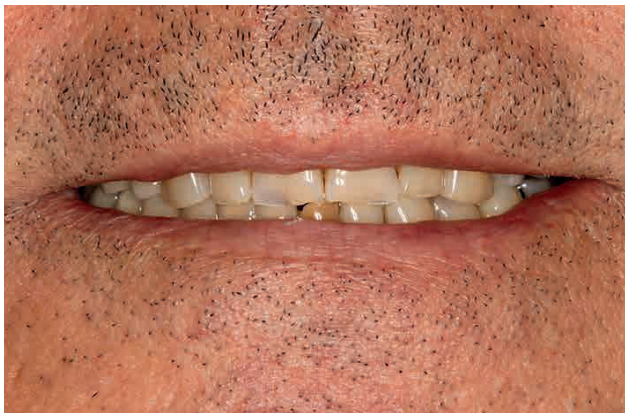


Quality of the record --> Flow: Good / Oxymetry: Good

(1) Approximate Oral Respiration (with respiratory events): [44%]
(2) Approximate Oral Respiration (without respiratory events): [27%]

Figure 11. Polygraphic recording following titration of the MAD, demonstrating a reduction in the parameters of the Apnoea-Hypopnoea Index. Additionally, a highly significant improvement is observed in the desaturation index (saturation below 90 for minutes), which decreases from 20.2% to 3.6%.





Figures 12 and 13. Images demonstrating progression three years following placement of the MAD, with no new adverse events and no increase in anterior occlusal wear.

DISCUSSION

Many patients with OSA exhibit oral signs and symptoms in addition to the classic features of systemic involvement. Consequently, a comprehensive medical history and thorough assessment at the initial consultation may enable the identification of individuals who are unaware that they suffer from this serious health condition, thereby facilitating the initiation of treatment[11,12]. Moreover, for an extended period, we have encountered patients in dental clinics with a high incidence of dental, prosthetic, and even implant fractures without any apparent explanation, with the presence of sleep disorders frequently representing the causal factor sought[11,12]. Epidemiological studies have found a high prevalence of bruxism in patients with OSA[3-7,11,12]. Similarly, our group, in studying a series of patients with dental wear who were being treated with mandibular advancement devices for suspected sleep bruxism, found that 93% had sleep apnoea, which was mild to moderate in 56% and severe in 37%[12]. Furthermore, a dose-response relationship was observed. That is, greater severity of dental wear corresponded to increased severity of OSA. These findings suggest that dental health professionals are in an optimal position to identify patients with suspected OSA. Such suspicion may be inferred both through the use of clinical questionnaires and by identifying anatomical and/or functional alterations, as in the case of bruxism or fracture of prostheses

Once the patient has been diagnosed, it is of vital importance to initiate treatment for both processes: the replacement of the rehabilitation affected by the mechanical incident, and the commencement of OSA treatment with mandibular advancement devices or with CPAP (continuous positive airway pressure device) in more severe cases, where the device alone may not constitute a sufficiently effective treatment[13-14]. In certain situations, both approaches (CPAP and mandibular advancement device) may be combined, thereby reducing the pressure required in CPAP, which in some cases results in loss of adherence to treatment, or in those bruxist patients where the mandibular advancement device may enhance the maintenance of the teeth and the rehabilitations supported by them.

CONCLUSIONS

Bruxism and OSA are intimately related, as are the dental signs of both conditions, such as wear and fracture of teeth, implants, or rehabilitations. Dentists can play a fundamental role in the treatment of these patients, including the presumptive diagnosis of undiagnosed cases of OSA, which may be identified through dental problems.

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ORIGINAL ARTICLE

From mild covid to long COVID: comprehensive oral health assessment

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ABSTRACT

Introduction. COVID-19 has caused a wide range of symptomatology, including that present in the oral cavity. A new related syndrome is gaining importance: Long COVID. The aim of this work is to analyse the effect of SARS-CoV-2 infection at the oral level in subjects diagnosed with Long COVID, compared to acute infection.

Methods. A case-control study was conducted with 102 subjects recruited between 2021 and 2022, from whom 34 oral health variables and possible risk factors were obtained.

Results. Statistical analysis revealed that Long COVID subjects had significantly higher prevalence of: adenopathies, TMJ pain, pharyngeal irritation, xerostomia, fillings, dental absences and dental crowns, higher CAOM and CAOD index values and higher total dental symptoms. In addition, stress appeared as a risk factor; those patients with Long COVID who presented a higher level of stress (7.73 ± 2.02) were also those who suffered, to a greater extent, from xerostomia or bruxism, responsible for TMJ pain, also more prevalent in this group.

Conclusions. Long COVID causes oral manifestations related, some of them, to the fact that the oral cavity is a route of entry of the virus, such as mucosal irritation; others, related to its possible autoimmune nature, such as mucosal irritation; others, related to its possible autoimmune nature, such as xerostomia and, in the same way, others related to stress, reflected in the presence of bruxism. It is essential to develop protocols that improve both the early diagnosis and management of these patients in our clinics.

KEY WORDS

COVID-19; Long COVID; Mucosal irritation; Xerostomia; Adenopathies; Bruxism and stress.

INTRODUCTION

The impact of the COVID-19 pandemic was profoundly transformative for humanity, affecting every aspect of our lives. When, at the end of 2019, the SARS-CoV-2 virus altered its evolution to make the leap to the human host, no one could have imagined the repercussions this would entail. Since the first cases were identified at the end of 2019, the virus spread rapidly worldwide, generating an unprecedented health crisis.

This is a highly contagious virus that has raised significant questions regarding community transmission processes, the pathogenesis of infections, and, above all, its involvement in the immune response. The latter was the catalyst for investigations that revealed how COVID-19 can exacerbate pre-existing autoimmune diseases and may trigger an exaggerated immune response in certain patients, thereby worsening the clinical picture[1].

Indeed, a proportion of infected individuals continue to manifest disease-related symptoms, of variable intensity, persisting over time. This proportion varies depending on the state of chronic inflammation prior to infection and the pre-existing diseases of each individual, although data published by the World Health Organization, as of March 2023, appear to indicate that approximately 10% to 20% of the population experiences medium- and long-term effects following the initial infection. These cases have been classified within a new category termed 'persistent COVID syndrome', 'post-COVID syndrome', 'post COVID-19 condition' or 'Long COVID'.

Long COVID can affect individuals of any age, sex, or medical condition and encompasses a wide range of clinical manifestations, which may involve various systems, including the cardiovascular, respiratory, and nervous systems[2].

In general, it is believed that the underlying pathological mechanisms of Long COVID may be related to a state of chronic inflammation and tissue damage induced by the virus. These processes may generate an exaggerated residual inflammatory response, which can result in organ damage and prolong the recovery of patients.

Furthermore, the immune response may account for Long COVID, as some patients have demonstrated a hyperactive and sustained immune response following infection, which may result in chronic inflammation and persistent organ damage[3].

Within the context of the pandemic, mechanisms related to stress cannot be disregarded. It should be understood, in principle, as a natural physiological and psychological response of the organism to adverse situations, constituting a natural protective mechanism. However, when such stress is prolonged, it may have detrimental effects on health[4]. In recent years, it has been demonstrated that chronic stress can affect the immune system and predispose individuals to the development of infectious diseases. This is attributable to the fact that stress can alter the immune response, modifying its capacity to combat infectious agents and thereby diminishing its competence to protect against diseases[5].

Finally, COVID-19 has caused a wide range of symptoms and complications across various bodily systems. Among others, a wide variety of oral symptoms have been reported, which must be addressed to ensure appropriate diagnosis and treatment of these patients[6]. However, it is important to emphasise that these oral manifestations associated with COVID-19 are not specific to this disease, but may also occur in other conditions, both infectious and non-infectious. They primarily present in the following forms:

- Oral lesions resembling recurrent aphthous stomatitis: these may be found in various areas within the oral cavity, including the buccal mucosa, lips, and palate[7].
- Oral ulcers: similar to those observed in other viral infections such as herpes simplex virus (HSV) and Epstein-Barr virus[8], and have even been considered an initial sign of COVID-19[9].
- Lesions on the tongue: similar to geographic tongue[10].
- Necrotising ulcerative gingivitis: more common in patients with COVID-19 than in individuals without the disease[11].

• Alterations in taste perception (dysgeusia): as well as anosmia, related to the sense of smell. Patients infected with COVID-19 may experience a reduction in their sense of taste, alterations in flavour, or a complete loss thereof. The majority of patients exhibit these changes temporarily; however, some may experience this symptom as a persistent long-term effect following recovery from the disease[12].

• Others: xerostomia, halitosis, vesiculobullous lesions, fissures or depapillation of the tongue, and oral candidiasis[13].

All these manifestations may be of concern to patients with COVID-19 and to dental health professionals, as they could indicate an active infection and the need for appropriate follow-up. Studies have demonstrated that SARS-CoV-2 is present in the saliva of infected patients from the early stages of infection and has also been detected in samples obtained from the tonsils, suggesting that the salivary glands may also serve as a potential reservoir for the virus. This could be due to the high expression of ACE2 receptors in the salivary glands[14], a demonstrated entry point for the virus into cells. It has also been proposed that oral manifestations associated with COVID-19 may be related to dysfunction of the immune system[15].

However, we found limited literature on oral health in patients with long COVID and the implications of the pandemic for the general population in this respect. Therefore, the objective of this study was to comprehensively evaluate the effect of SARS-CoV-2 infection on oral health status and, more specifically, its condition in individuals who developed long COVID.

MATERIALS AND METHODS

The present study is a sub-analysis of a broader investigation focused on the pathophysiology of long COVID-19, approved by the ethics committee of the

European University of Madrid (Internal code CIPI/20/207). All patients provided informed consent to participate prior to inclusion.

The definition of the study groups was as follows:

1. Case group: subjects diagnosed with long COVID-19. Sixty-three subjects, all adults, belonging to the Long Covid ACTS association of the Community of Madrid were recruited. None had active infection or severe systemic diseases in cases where examination is not recommended due to the life-threatening risk to the patient (ASA IV and V).

2. Control group: subjects who had experienced infection with the SARS-CoV-2 virus and either did not present with symptoms associated or whose symptoms resolved upon remission of the infection. Thirty-nine volunteer subjects were recruited via a social media campaign who met the inclusion criteria: over 18 years of age, from the Community of Madrid, and who had experienced the infection without sequelae.

The study was divided into two phases. In the first phase, the recruitment of the sample for both study groups was conducted, from September to November 2021. In the second phase, an oral examination and clinical interview of the subjects were performed.

This second phase was conducted at the University Dental Clinic of the European University of Madrid between November 2021 and April 2022. Before the clinical appointment, each patient completed a 20-item questionnaire covering demographic data, stress factors before and after infection, general health, and aspects related to SARS-CoV-2 infection. At the clinic, a full medical history and oral examination were performed, which included:

• Extraoral examination for the collection of data on pathologies and/or abnormalities such as tumours, cellulitis, adenopathies, cutaneous lesions, and asymmetries located in the head and neck regions.

• Assessment of temporomandibular joint (TMJ) status: degree of mouth opening, presence of articular clicks, deviation, and presence of pain on palpation during mouth opening and closure.

• Intraoral examination for the detection of soft tissue alterations (lips, buccal mucosa, tongue, floor of the mouth, retromolar region, palate, gingiva, and pharynx), evaluation of oral hygiene status (OHI-S index), recording of the number of carious lesions, ob Fillings, absences, fractures, root remnants, crowns, bridges, removable prostheses, as well as calculation of the DMFT and DMFM indices. Finally, periodontal status was assessed (probing depth, recessions, attachment loss, tooth mobility, furcation involvement) and the Community Periodontal Index of Treatment Needs (CPITN) was calculated.

Statistical analysis

For the descriptive study, relative frequencies were calculated for qualitative variables and, for quantitative variables, the mean and standard deviation were calculated.

In cases where the quantitative variables followed a normal distribution and were categorised by qualitative variables, parametric tests were performed. For variables with two categories, the Student's t-test was performed; if the variable had three or more categories, Levene's test for homogeneity of variances was conducted prior to ANOVA.

For those without a normal distribution, non-parametric tests were performed: the Mann-Whitney U test for variables with two categories, and the Kruskal-Wallis test for those with three or more.

Additionally, Pearson's Chi-square test was applied in cases where the independence between two qualitative variables was analysed. Similarly, in these tests of independence, when the p-value is significant ($p<0.05$), we can accept the hypothesis with 95% confidence that there is a statistically significant difference in the mean value of the variable between the different groups.

All statistical tests were conducted with a 95% confidence level, and version 26 of the IBM SPSS statistical software was utilised.

RESULTS

The study was conducted on a total of 102 subjects, of whom 20 were men (20%) and 82 were women (80%), with ages ranging from 23 to 68 years.

By study group, there was a higher proportion of subjects in the mild COVID group within the 26 to 45 years age range. However, in the long COVID group, there was a greater number of subjects within the age range of 36 to 65 years.

To analyse the level of oral health in subjects with long COVID, 34 related variables were examined. Of all these oral health markers explored both extraorally and intraorally, and subsequently analysed according to the

study group, the following were observed to a greater extent and with high statistical significance in the long COVID group (Table):

Table. Oral markers with statistical significance between study groups and their graphical representation.

Variable	Long COVID group	Mild COVID group	Figure
Adenopathies	12%	0%	1
TMJ pain	*37%*	8%	2
Pharyng eal irritation	*60%*	28%	3
Xerostomia	*63%*	21%	4
Fillings	*6.25 ± 4.15*	4.18 ± 3.4	5
Dental absences	*1.65 ± 1.98*	0.77 ± 1.77	6
Dental crowns	1.08 ± 1.44	0.46 ± 0.79	7
DMFT	3.1 ± 1.27	2.21 ± 1.4	8
DMFS	8.73 ± 4.28	5.97 ± 3.9	9
Sum of odontological symptoms	4.29 ± 1.54	3.56 ± 1.41	10

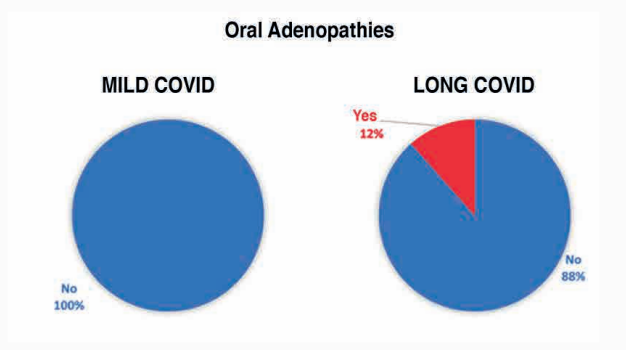

Figure 1. Presence of oral adenopathies in subjects with mild and long COVID. Fisher's exact test (p = 0.035).

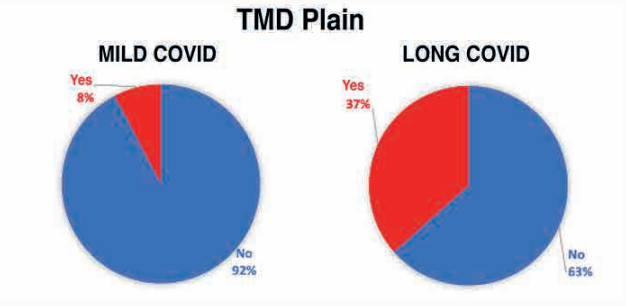

Figure 2. Temporomandibular joint pain in subjects with mild COVID and long COVID. Fisher's exact test (p < 0.01).

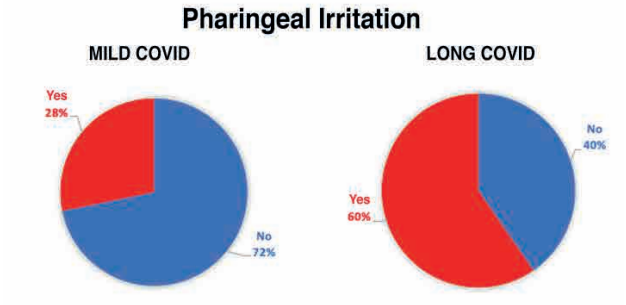

Figure 3. Presence of pharyngeal irritation in subjects with mild and long COVID. Fisher's exact test (p < 0.01).

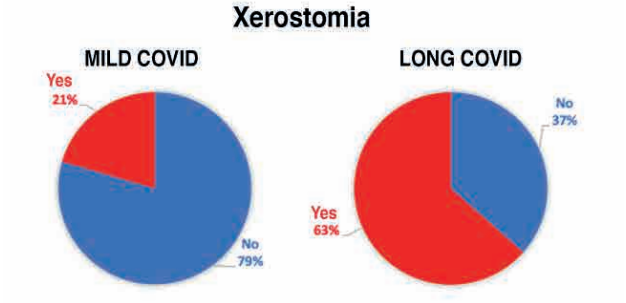

Figure 4. Presence of xerostomia in subjects with mild and long COVID. Fisher's exact test (p < 0.01).

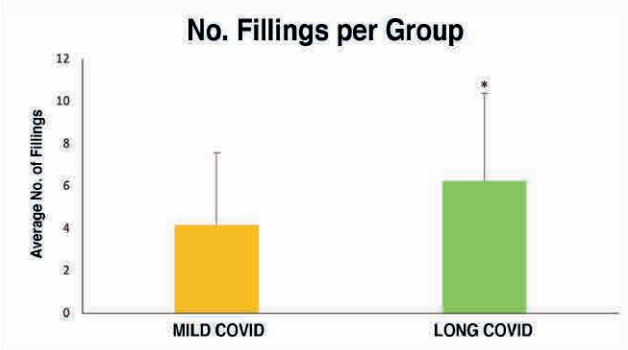

Figure 5. Number of fillings by study group. Mann-Whitney U statistic (p = 0.019).

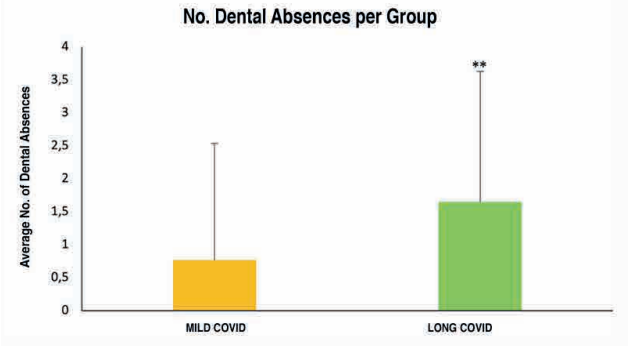

Figure 6. Number of dental absences by study group. Mann-Whitney U statistic (p = 0.002).

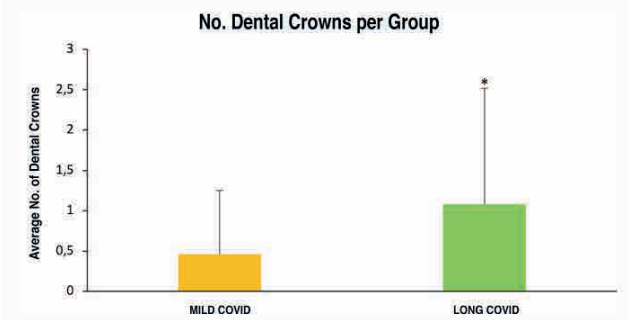

Figure 7. Number of crowns by study group. Mann-Whitney U statistic (p = 0.029).

Figure 8. DMFT index by study group. Mann-Whitney U statistic (p = 0.001).

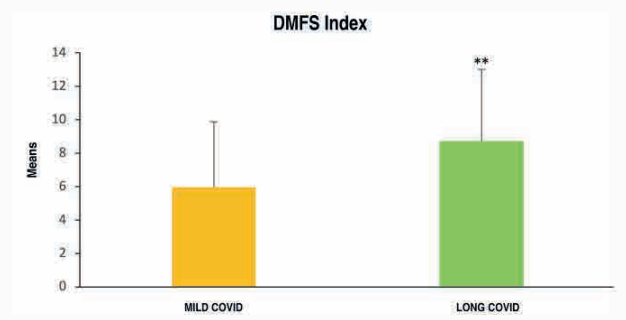

Figure 9. DMFS index by study group. Mann-Whitney U statistic (p = 0.003).

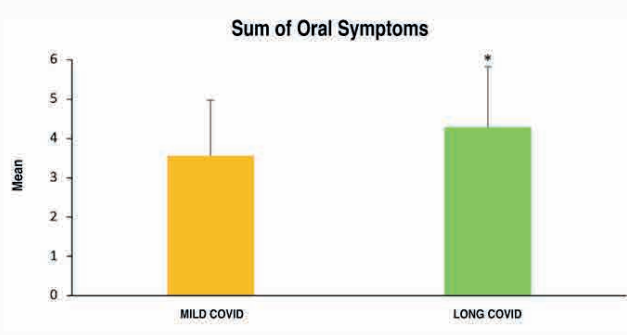

Figure 10. Sum of dental symptoms by study group. Mann-Whitney U statistic (p < 0.05).

Stress was identified as one of the most influential factors in oral health. As shown in Figure 11, mild COVID subjects with a higher current subjective stress level (7 ± 1.48) also exhibited greater pharyngeal irritation compared to those with a lower stress level (5.11 ± 2.69) and consequently an unaltered pharynx, this difference being statistically significant.

However, this did not occur in subjects with long COVID because, although they exhibited higher levels of stress, the differences observed in pharyngeal irritation were attributable to chance.

Conversely, it is the long COVID study subjects with higher levels of stress (7.73 ± 2.02) who experienced greater xerostomia compared to those with lower levels (5.63 ± 2.73), this difference being significant according to the Mann-Whitney U statistic (p<0.01) (Figure 12).

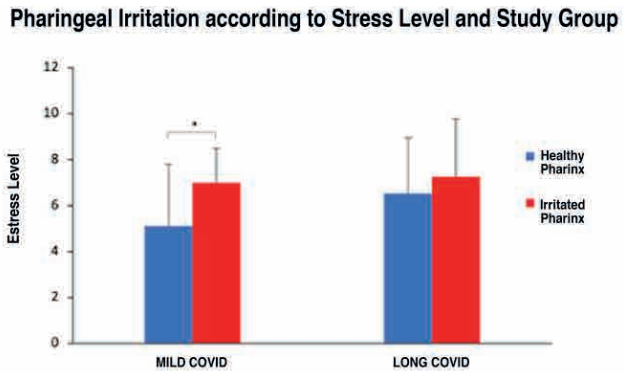

Figure 11. Pharyngeal irritation according to stress level and study group. Mann-Whitney U statistic (p<0.05) within the mild COVID group.

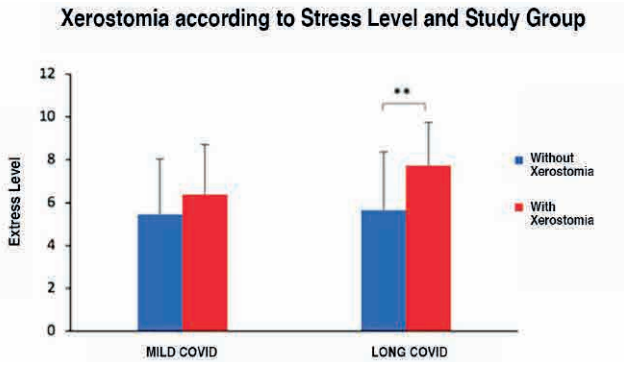

Figure 12. Xerostomia according to stress level and study group. Mann-Whitney U statistic (p<0.001) within the long COVID group.

DISCUSSION

Among the possible systemic conditions caused by the SARS-CoV-2 virus, it is necessary to analyse in depth its impact on the oral cavity. COVID-19 infection may give rise to various oral manifestations, primarily at the mucosal level. In the present study, it was observed that the number of dental symptoms—such as periodontal and peri-implant involvement, the presence of aphthae, mucosal irritation due to outbreaks, halitosis, dentine hypersensitivity, or the presence of caries—was higher in subjects belonging to the long COVID group. A possible explanation for this set of manifestations may be posited given that the oral cavity forms part of the upper respiratory tract and represents one of the potential direct routes for the entry of the SARS-

CoV-2 virus, owing to the presence of ACE2 receptors in the oral mucosa and in the epithelial cells of the salivary glands[16].

It should be emphasised that individuals who exhibited persistent systemic symptoms related to COVID-19 also presented certain oral manifestations, such as the presence of adenopathies, the subjective sensation of dry mouth (xerostomia), pharyngeal irritation, and temporomandibular joint pain as a consequence of bruxism. Of these, the presence of adenopathies, xerostomia, and mucosal irritation at the pharyngeal level are clinical manifestations that are likewise observed in certain autoimmune pathologies, such as Sjögren's syndrome, rheumatoid arthritis, systemic lupus erythematosus, type I diabetes, or multiple sclerosis, among others[17]. This raises the possibility of an autoimmune nature for long COVID.

In the case of pain experienced at the level of the temporomandibular joint, generated by dental clenching, predominantly nocturnal, it may be closely related to the level of stress currently perceived by individuals with long COVID, largely due to their complex medical condition[18].

Moreover, during the lockdown, dental clinics suspended their activities, limiting dental care solely to specific dental emergencies and, as far as possible, avoiding clinical treatments that generated aerosols[19]. This reduction in dental care, home confinement as a social distancing measure, the socio-economic crisis experienced, increased levels of stress, as well as anxious-depressive symptoms, together with the pathophysiological situation in which individuals with long COVID found themselves, complicated such a routine act as daily oral hygiene through tooth brushing and frequent visits to the dentist. This may account for the significant deterioration in oral health status observed in patients with long COVID, as evidenced by a higher number of restorations, missing teeth, crowns, and caries index in comparison with those with mild COVID.

Among the limitations, the biases of our study arise from the selection of cases from a single patient association, which hinders the extrapolation of the results. The imbalance between the number of cases and controls is also recognised, which was addressed through a multivariate analysis to adjust for variables that could affect the confidence level of the results. Robust studies are required to develop follow-up and control protocols at the onset of the disease, in order to evaluate the factors involved in resolution without sequelae or, conversely, in progression to long COVID.

Accordingly, the advancement of clinical practice in dentistry necessitates the promotion of research strategies that enable the expansion of our understanding of long COVID and its early diagnosis, as well as its prevention, potentially within the remit of dental professionals.

CONCLUSIONS

Individuals affected by long COVID demonstrate various related oral manifestations, some of which are attributable to the oral cavity serving as an entry route for the virus, such as mucosal irritation or the presence of aphthae; others to the possible autoimmune nature of this new syndrome, such as xerostomia or the presence of adenopathies, and, finally, other manifestations may be associated with stress, such as the presence of TMJ pain, indicative of bruxism.

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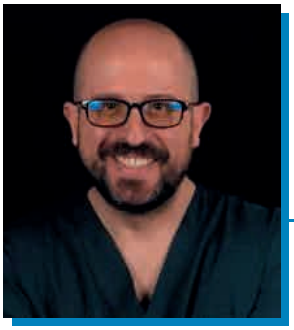

CASE REPORT

Clinical, radiographic and histomorphometric behaviour of the autologous tooth as a biomaterial in lateral access maxillary sinus elevation. Case report with six months of post-prosthetic loading follow-up.

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ABSTRACT

Introduction. Bone loss after extractions may require a sinus elevation to be performed in the posterior maxilla for the correct placement of implants. Autologous bone is considered the gold standard, but has a high rate of resorption and morbidity, leading to other alternatives such as autologous tooth, with good results in regenerative procedures. This case report evaluates at the clinical, radiographic and histomorphometric level the use of the autologous tooth in maxillary sinus elevation and the behaviour of two implants placed in a delayed manner.

Case report. The case is presented of a 48-year-old woman who came for consultation to replace the right posterior sector. The extraction of 4.8 as a donor tooth was performed to use it as a biomaterial in a lateral access sinus elevation, placing two implants six months after the intervention, and evaluating them six months after their prosthetic loading.

Discussion. The autologous tooth in this case report showed 30.56% of newly formed bone following a six-month wait, with better results than when allografts and xenografts were used. In addition, different cultural and ethnic aspects support the acceptance of the autologous tooth by patients. However, more long- term studies are needed to evaluate the stability of this type of graft in maxillary sinus elevation.

Conclusions. The autologous tooth in the sinus elevation offers biocompatibility, low incidence of complications and good patient acceptance, with good clinical and radiographic behaviour of the implants, despite the short time elapsed in this case after loading.

KEY WORDS

Autologous tooth; Lateral sinus elevation; Autologous dentine.

INTRODUCTION

Three months after dental extraction, there is a loss of 50% of the initial bone dimensions of the socket, which is particularly significant in the posterior region of the maxilla. In this anatomical region, the loss of antral teeth results in three-dimensional pneumatization of the maxillary sinus, which may extend to the alveolar crest and the anterior region, the tuberosity area, and the zygomatic bone. This dual process of pneumatization and bone remodelling reduces bone availability both horizontally and vertically, potentially compromising implant treatment and its long-term stability[1-6].

In such cases, the most predictable technique for bone reconstruction is the maxillary sinus elevation, which enables correct placement of implants and subsequent implant-supported restoration, thereby improving the quantity and quality of bone at the implant site. Among the maxillary sinus elevation techniques, the lateral approach is indicated when the vertical bone height is ≤ 4 mm, with delayed placement of the implants, whereas with a height ≥ 5 mm, the transcrestal sinus elevation technique and shorter implants are recommended, or the open technique with simultaneous placement of longer implants[7,8].

The lateral approach sinus lift, also known as the open technique, is a well-documented procedure, having been described by Tatum[9] in 1976 and subsequently published by Boyne and James[10] in 1980. This consists of raising a full-thickness flap to access the anterolateral wall of the maxillary sinus, and, by means of osteotomy, creating a window in the buccal cortical bone to expose the Schneiderian membrane. Once this membrane is exposed, it is carefully detached and elevated until it reaches a horizontal position to form the new sinus floor, after which a graft biomaterial is placed. A membrane may be placed,

either resorbable or non-resorbable, prior to suturing, to prevent displacement of the graft and colonisation of the sinus interior by periosteum originating from the flap[11,12].

Among the biomaterials employed in this technique, autologous bone is currently regarded as the gold standard, as it provides an effective scaffold for osteoconduction, contains growth factors to promote osteoinduction, and osteocompetent cells to facilitate osteogenesis. However, certain disadvantages, such as donor site morbidity, limited availability, and a high rate of resorption, may restrict its use[13,14].

For these reasons, various bone substitutes have been utilised (allografts, xenografts, and alloplastic materials). Most of these biomaterials exhibit only osteoconductive properties and have highly variable resorption times, ranging from very short (derived from polyglycolic and polylactic acid) to very long (hydroxyapatites), whilst others may provoke immune reactions (allografts). Owing to these disadvantages, studies on the clinical behaviour of tooth material in various regenerative procedures have increased in recent years, due to its similarity to human bone[15,16].

Kim et al.[17] described the osteoinductive and osteoconductive properties of tooth material, as well as lower morbidity and greater patient acceptance, with its favourable clinical and radiographic behaviour having been demonstrated in maxillary sinus elevation procedures, guided bone regeneration, and alveolar preservation[18].

The objective of this clinical case is to evaluate, clinically, radiographically, and histomorphometrically, the use of autologous tooth as a biomaterial in maxillary sinus elevation, as well as the clinical and radiographic behaviour of two implants placed in a delayed manner following the sinus elevation, and their progress six months after prosthetic loading.

CASE REPORT

This case report presents a 48-year-old woman who attended the clinic for restoration of the posterior region of the first quadrant.

The medical history revealed no relevant medical or surgical antecedents, no known drug allergies, and no harmful habits. Intraoral examination revealed the absence of 1.6 and 1.7, and the presence of 1.8 and 4.8 (Figure 1). Radiographic examination using cone

beam computed tomography (CBCT) revealed a residual height of 5.0 mm at 1.6, where an implant could be placed simultaneously, and 2.6 mm in the region of 1.7, making simultaneous implant placement with the lateral approach sinus elevation difficult (Figure 2).

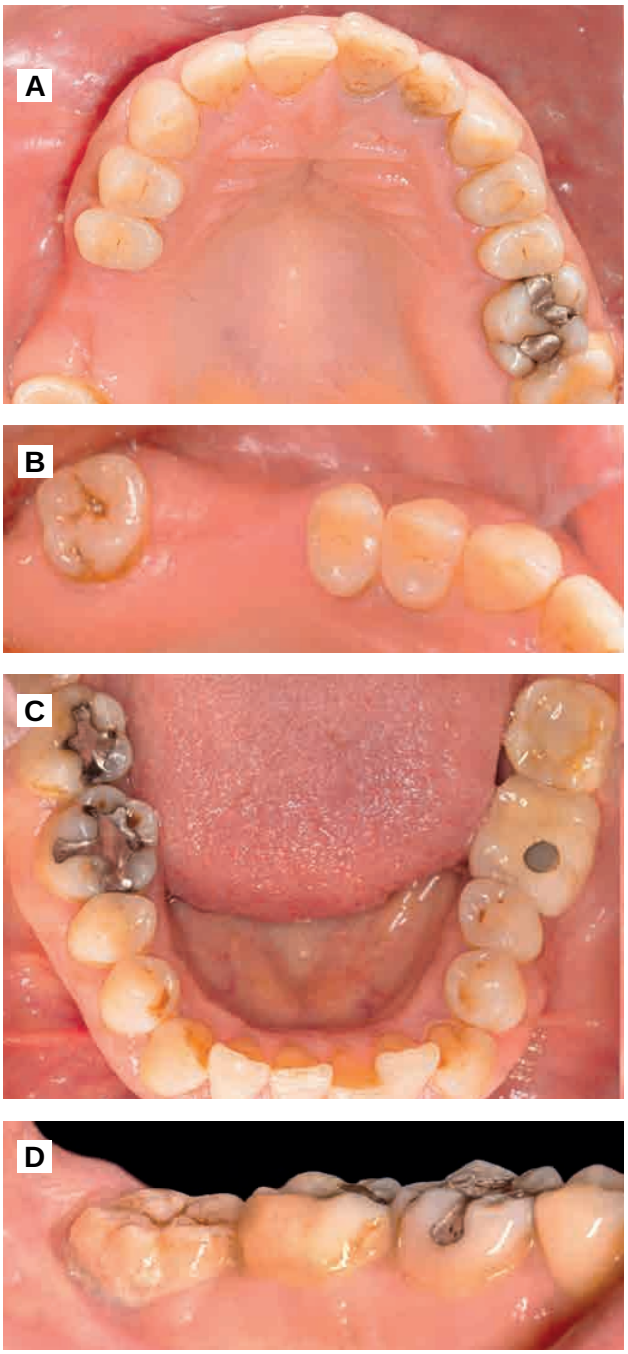

Figure 1. A. Maxillary occlusal view. B. Detail showing missing 1.6 and 1.7. C. Mandibular occlusal view. D. Lateral view of 4.8

Extraction of 4.8 was planned in order to use it as the donor tooth, for which informed consent was obtained in advance. An anaesthetic block was administered using 4% articaine (Inibsa®, Barcelona, Spain) with 1:100,000 adrenaline to the inferior dental nerve, the lingual nerve, and finally the buccal nerve. As the tooth had no associated infectious processes, only calculus was removed from the tooth using ultrasonic instrumentation and the extraction was performed as atraumatically as possible. The root surface was polished with turbine diamond burs under copious irrigation, thereby removing the periodontal ligament (Figure 3).

The weight of the tooth, once cleaned, was recorded using a precision balance (Ohaus® YA 102, YA Gold Series, New Jersey, USA), registering a weight of 2.1g. The tooth was then sectioned into fragments ≤ 5 mm, which were placed dry into the mill of the Tooth Transformer® device (S.R.L., Milan, Italy), as indicated by the manufacturer. Once introduced, it was placed inside the device and the container with the liquids was added, in order to demineralise the tooth, releasing BMP-2 and type I collagen, and eliminating any residual toxicity. When all components were inserted, the machine cover was closed and, by pressing the activation button, the process was initiated until the grinding of the fragments and the appropriate particle size was confirmed, thanks to the sieve present in the collecting container (400–800µm). Within 25 minutes, the autologous tooth graft was prepared and reweighed on the precision balance, recording a weight of 2.6g (Figure 4).

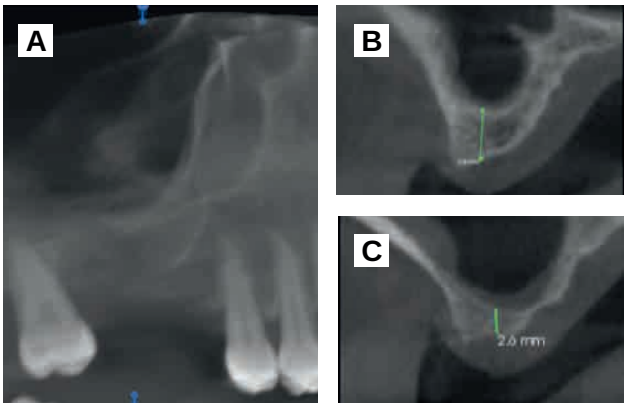

Figure 2. A. Pre-op CBCT. B. Residual height of 5.0 mm at 1.6. C. Residual height of 2.6 mm at 1.7.

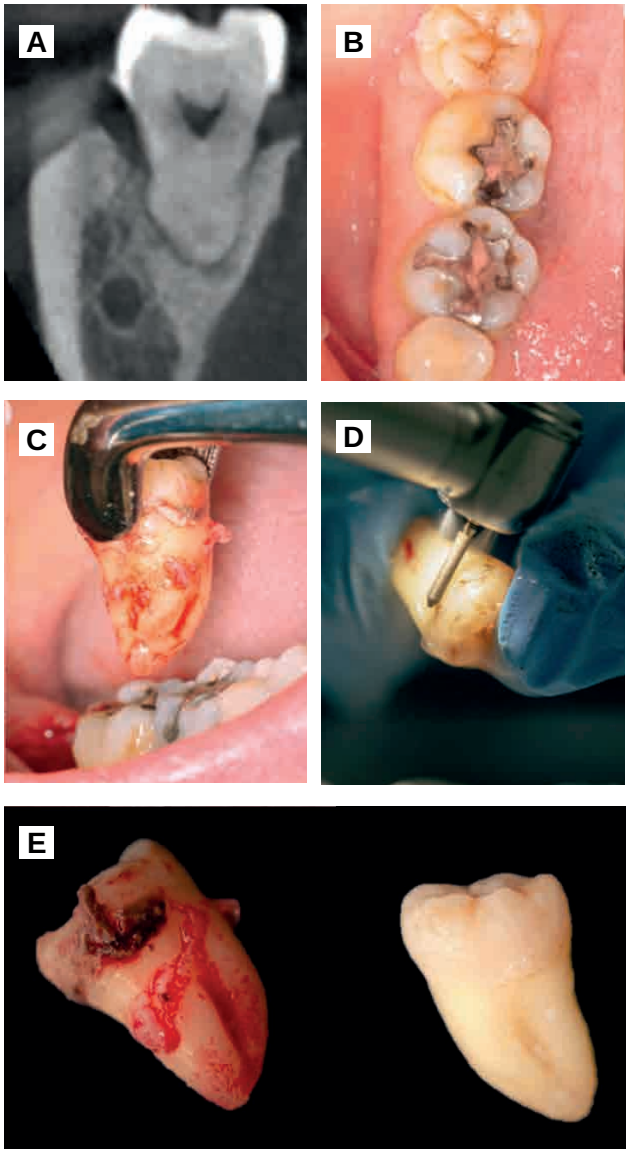

Figure 3. A. Orthoradial section of the CBCT at 4.8. B. Occlusal view of 4.8. C. Exodontia of 4.8. D. Cleaning of the root surface of 4.8 with a diamond turbine bur. E. Condition of 4.8 before and after preparation.

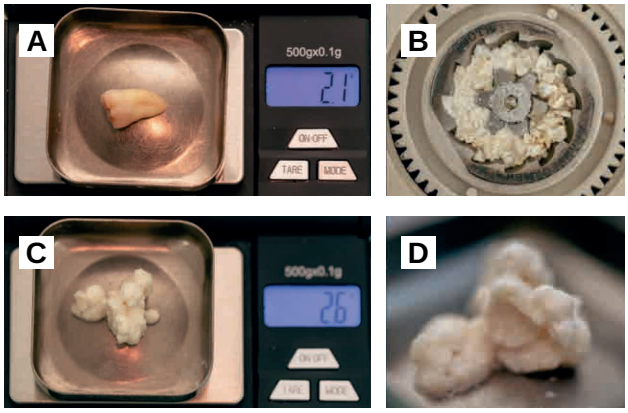

Figure 4. A. Recording of the preoperative weight of 4.8. B. Placement of the 4.8 specimen in the Tooth Transformer® device mill. C. Recording of the weight of 4.8 after processing. D. Appearance of the processed tooth.

During the preparation of the tooth in the Tooth Transformer® device, a lateral approach sinus elevation was performed using an anaesthetic block with 4% articaine and 1:100,000 adrenaline (Inibsa®, Barcelona, Spain) of the posterior and middle superior alveolar nerves and the greater palatine nerve. Following a partial Neumann incision with a vertical release at the mesial angle of tooth 1.5, a mucoperiosteal flap was raised, and a controlled osteotomy was performed using the Sinus Master III® system (MCTBIO, Gyeonggi-do, 17037, South Korea), employing hydraulic pressure and diamond burs. A processed tooth graft was placed inside the maxillary sinus, and a Lyoplant® resorbable collagen membrane (B. Braun Medical S.A., Barcelona, Spain) was positioned over the graft. After this step, suturing was performed using 4/0 non-resorbable monofilament suture (Supramid®, B. Braun, Barcelona, Spain) (Figures 5 and 6).

Six months after the maxillary sinus elevation surgery, re-entry was performed for the placement of implants. A 3 x 7mm bone tissue biopsy was obtained using a trephine, and histomorphometric analysis was requested, revealing 30.56% vital bone (Figure 7). After the biopsy sample was taken, two bone level Naturactis implants from ETK® (ETK Implants S.L, Sant Boi de Llobregat, Spain) were placed with an insertion torque of 35 Ncm,

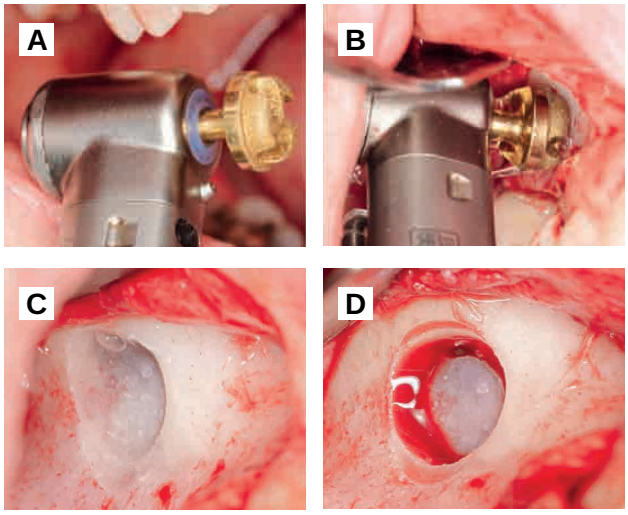

Figure 5. A. Diamond bur for lateral access. B. Application of the diamond bur to the buccal cortical bone. C. Verification of the osteotomy and thickness of the buccal cortical bone. D. Intact Schneiderian membrane.

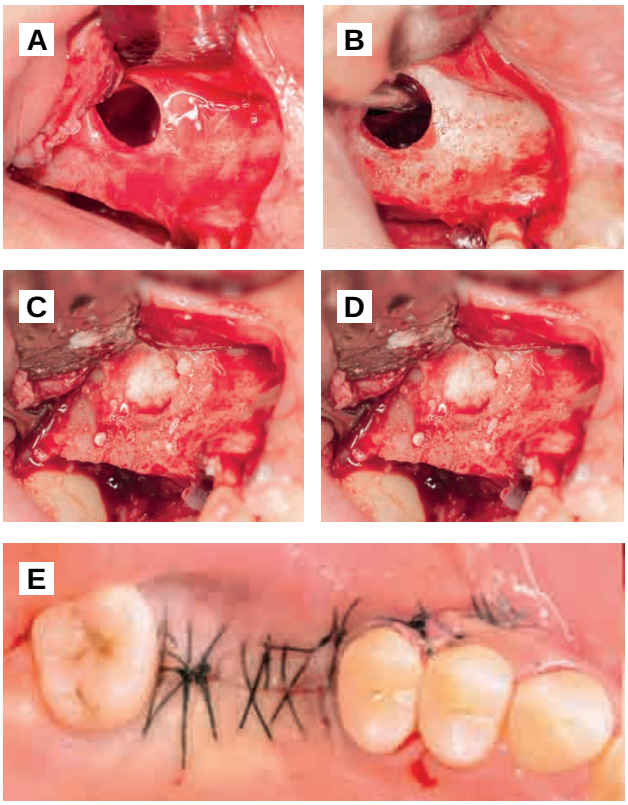

Figure 6. A and B. Elevation of the Schneiderian membrane. C. Placement of the dental biomaterial. D. Collagen membrane over the lateral window. E. Suturing of the surgical wound.

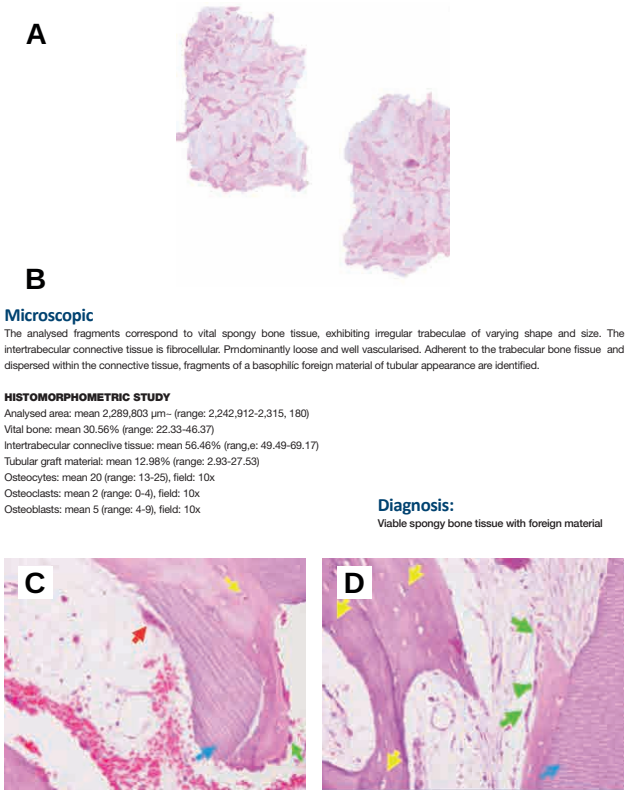

Figure 7. A. Histomorphometric slide. B. Histomorphometric study. C and D. Histological sections: Green: osteoblast. Yellow: osteocyte. Red: osteoclast. Blue: dentine.

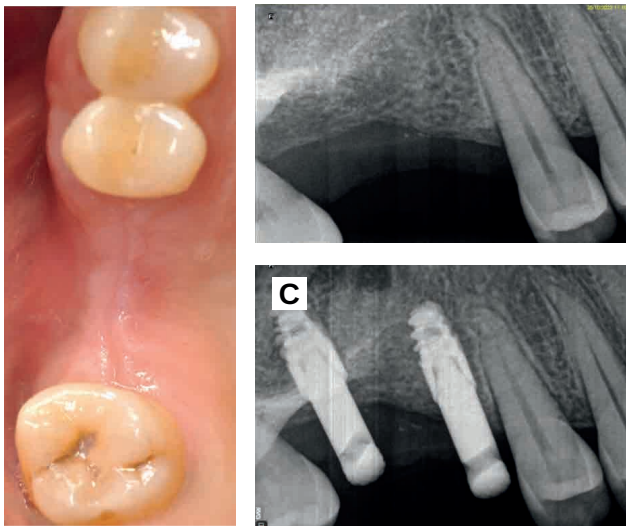

Figure 8. A. Postoperative appearance at 6 months. B. Preoperative periapical radiograph prior to implant placement. C. Placement of the implants.

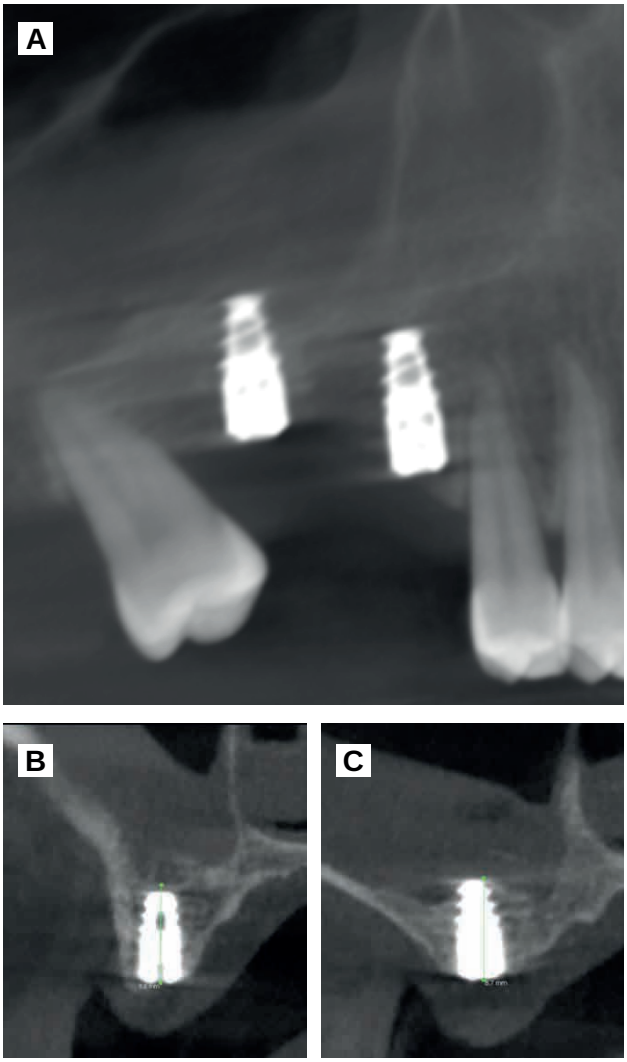

Figure 9. A. CBCT at six months following placement of the implants. B. Final height of 9.2 mm in the 1.6 region. C. Final height of 8.7 mm in the 1.7 region.

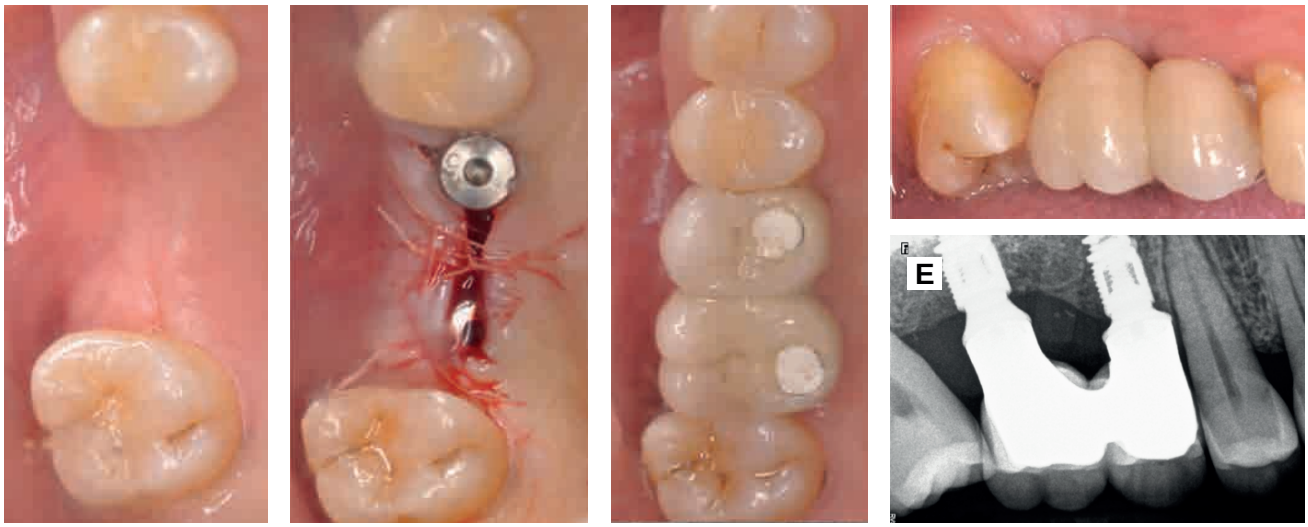

Figure 10. A. Occlusal view of the soft tissues prior to the second stage of the implants. B. Placement of healing abutments. C. Occlusal view with implant-supported crowns. D. Lateral view showing adjustment of the soft tissues. E. Periapical radiograph to confirm prosthesis fit.

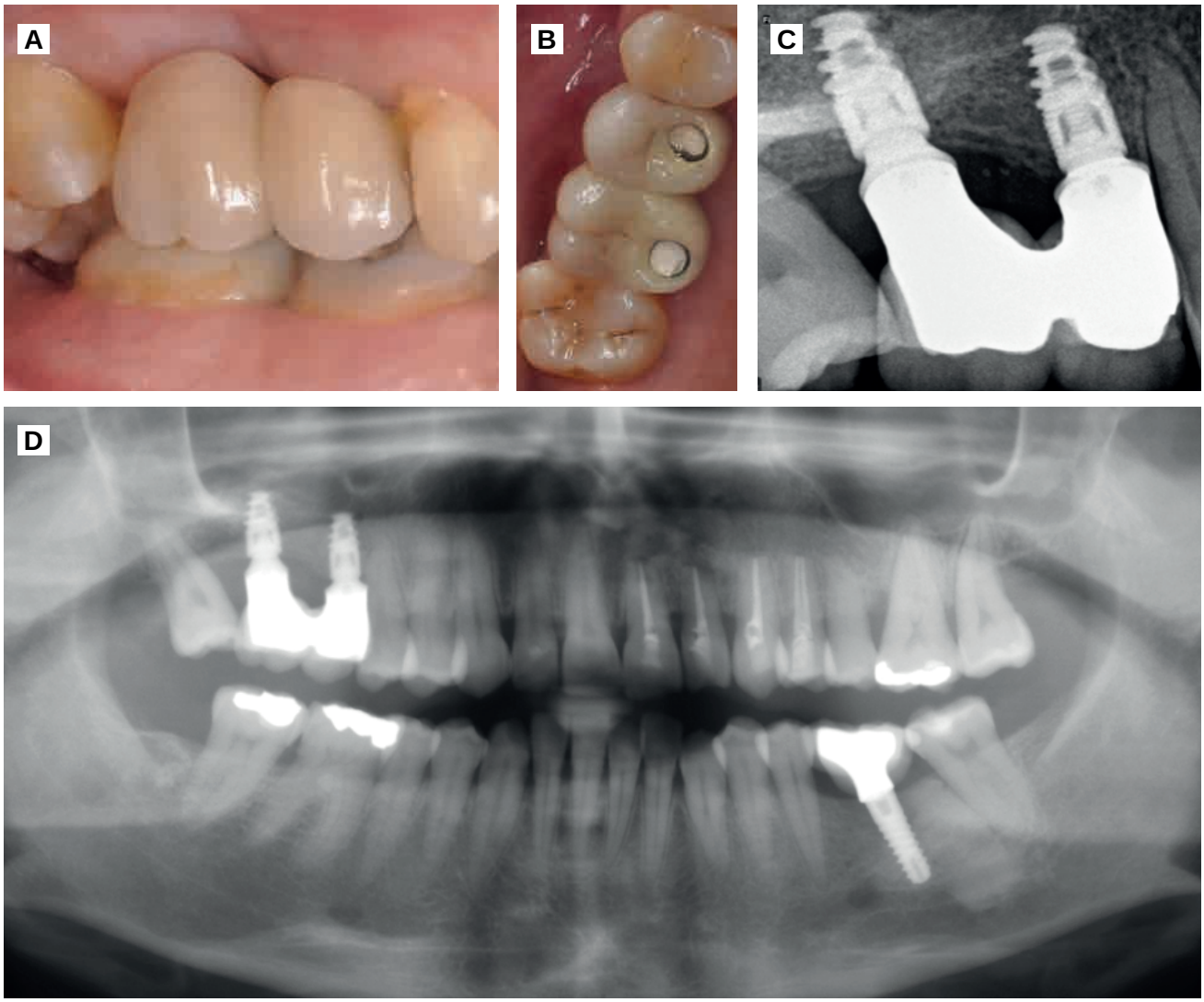

Figure 11. Images at six months post-loading. A. Lateral view of the implant-supported crowns. B. Occlusal view of the implant-supported crowns. C. Periapical radiograph. D. Panoramic radiograph.

and their correct positioning was confirmed in the immediate postoperative period by means of a periapical radiograph (Figure 8). Six months after the placement of the implants, the patient was able to attend for the second stage to place healing abutments. A verification CBCT was performed to assess the final bone height, revealing an increase of 4.2 mm in the region of 1.6 and 6.1 mm in the region of 1.7 (Figure 9).

Fifteen days after the second stage, impressions were taken for the fabrication of two splinted cement-screw-retained crowns on titanium bases, with the fit verified by a parallelised periapical radiograph (Figure 10). Six months after placement of the restoration, a clinical and radiographic review was conducted, noting the favourable condition of the soft tissues (Figure 11).

DISCUSSION

In recent decades, the use of biomaterials derived from dental structures, such as dentine and enamel, has been investigated in various bone regeneration procedures. This approach is based on the autologous nature of this material, eliminating the need for a second donor site, and on the structural and chemical similarity between tooth and bone tissue, which confers osteoconductive and osteoinductive properties.

Chemically, the inorganic composition of dentine is 70% compared to 65% in autologous bone, while the organic component of dentine is 20% compared to 25% in autologous bone, with a water content of 10% common to both. The inorganic content is primarily hydroxyapatite, while the organic matter consists mainly of type I collagen, as well as bone morphogenetic proteins (BMP)[19].

Some authors consider that different demineralisation processes favour the release of insulin-like growth factors (IGF), bone morphogenetic protein type 2 (BMP-2), transforming growth factor beta (TGF-beta), and type I collagen, all of which are directly involved in osteoinduction and angiogenesis. The mechanisms by which demineralised dentine stimulates bone regeneration are quite similar to the formation of newly formed bone when using autologous bone. Following demineralisation, both the bone matrix and the demineralised dentine matrix have an increased capacity to release type I collagen, growth factors, and BMP-2, thereby providing osteoinduction in regenerative procedures[20,21].

The inorganic content, consisting of four types of calcium phosphates (amorphous calcium phosphate, hydroxyapatite, octacalcium phosphate, and tricalcium phosphate), imparts osteoconductivity to the tooth, permitting a low resorption rate, lower than that of autologous bone, thereby ensuring greater stability over time[20,22].

Although the use of autologous bone in bone regeneration continues to be regarded as the gold standard among biomaterials, the use of tooth, compared to other biomaterials employed in maxillary sinus lift procedures, such as xenografts, has resulted in greater bone formation and a lower amount of residual biomaterial. Moreover, tooth as a biomaterial demonstrates a greater quantity of osteoid tissue surrounding the particles of the treated tooth, which are subsequently replaced by a greater amount of newly formed bone over time[18, 23-26].

The use of autologous bone in lateral approach sinus lift has demonstrated a higher rate of resorption compared to other biomaterials. Pesce et al.[27], in their 2021 systematic review, confirmed the varying rates of volumetric reduction among different biomaterials after a six-month waiting period, with xenograft being the material that exhibited the least volume reduction (7.30 ± 15.49%) and autologous bone experiencing the greatest volumetric reduction (41.71 ± 12.63%), with alloplastic grafts (27.82 ± 15.58%) and allografts (30.23 ± 1.61%) falling in between. Indeed, due to the high rate of resorption associated with autologous bone, Khijmatgar et al.[28], observed improved performance and a lower resorption rate when it was combined with different biomaterials (xenograft, alloplastic materials).

The percentage of newly formed bone obtained using the autologous tooth as a biomaterial in the present clinical case is 30.56%, six months after the lateral approach maxillary sinus lift. This value is similar to

that reported by other authors employing the tooth as a biomaterial, such as Jun SH et al.[29], with 31.07 ± 14.52% after four months post-intervention, or Minetti et al.[30] with 36.28% ± 9.77% after six months. Conversely, the amount of newly formed bone when using alloplastic grafts is 20.3–33.40% after six months of healing, 22.8% when using equine-derived xenograft, and 16.1–23.02% in the case of bovine-derived xenografts. However, the use of allografts yields higher percentages of newly formed bone, around 20.47–32.1%[31-34].

In a recent in vitro study, the physicochemical and biochemical characteristics of dentine and enamel matrix obtained following processing with the Tooth Transformer® device (S.R.L, Milan, Italy) have been described. It appears that particle size plays a significant role in enhancing soft tissue healing and the body's resorptive capacity, thereby promoting bone regeneration. In this context, the various devices available on the market enable a consistent particle size between 400–800 µm (Tooth Transformer®), 300–1200 µm (Smart Dentin Grinder®), and 425–1500 µm (Bone Maker®). When none of these devices are utilised, the particle sizes are highly heterogeneous, thereby delaying appropriate tissue healing and regeneration. Although, once the dentine is partially demineralised and the dentinal tubules are widened, osteoclasts can more readily release the organic content from within, inducing the differentiation of osteoblasts. With a particle size between 800–1000 µm, better bone formation results are achieved than with sizes of 426–600 µm, while results are very poor with particles of 180–212 µm[35–38.]

Apart from its potential to reduce costs, various cultural and ethnic factors may come into direct conflict with different types of biomaterials, such as xenografts and allografts, which, according to recent studies, appear to have the highest rates of rejection by pa patients, conferring another important advantage to the tooth when utilised[39].

In the clinical case presented, the autologous tooth graft demonstrated good clinical, radiographic and histomorphometric behaviour following a lateral approach maxillary sinus lift with delayed placement of two implants, despite the follow-up period being only six months after

prosthodontic restoration; therefore, studies evaluating other important parameters, such as marginal bone loss, over the long term are required.

CONCLUSIONS

The use of autologous tooth as a biomaterial in lateral maxillary sinus lift represents an alternative to other biomaterials, exhibiting excellent biocompatibility, a low rate of intraoperative complications, and good patient acceptance. It demonstrates a favourable radiographic appearance over time, although the follow-up period in this clinical case is only six months after prosthetic loading of the implants. The behaviour of the implants in the regenerated bone using tooth as a biomaterial exhibits good clinical and radiographic outcomes, despite the short period since prosthetic loading.

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CASE REPORT

Surgical and restorative management of a dental implant in the esthetic zone and volumetric evaluation following de-epithelialized connective tissue graft: a case report

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ABSTRACT

Introduction (basis and objectives). After tooth extraction, changes occur in the soft tissues associated with bone resorption in a vertical and horizontal direction. This collapse can be addressed through bone grafts and connective tissue grafts. The objective of this clinical case is to describe the treatment sequence carried out from extraction to delivery of the definitive crown, combining regenerative, guided surgery, mucogingival and prosthetic concepts. Furthermore, changes in vestibular mucosal thickness that occurred after the use of a connective tissue graft are described and analyzed using digital analysis software.

Methods. The surgical sequence consisted of performing alveolar preservation. After 4 months, a guided implant was planned and placed in position 1.2 with simultaneous connective tissue graft. After integration, the soft tissues were conditioned with a provisional crown and then the definitive screw-retained restoration was placed.

Results. The guided implant placement approach and application of a connective tissue graft showed aesthetic results and significant soft tissue volumetric gains.

Conclusions. Careful management of hard and soft tissues, as well as planning through guided surgery, increases precision regarding the ideal position of the implant, which will impact the long-term stability of hard and soft tissues.

KEY WORDS

Surgery; Computer-Assisted; Dental implants; Soft tissue; Connective tissue; Software tool.

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INTRODUCTION

In the field of implantology, digital technology has emerged as an advancement to enhance surgical procedures and achieve high-quality treatments with aesthetic outcomes. In this context, guided surgery, introduced in the 1990s, is regarded as a contemporary dental practice based on digital planning and the utilisation of advanced imaging technologies[1]. Implant placement is performed using 3D-printed surgical guides and a specific kit designed for each system[2]. Compared with the conventional technique, guided implant placement has been demonstrated to significantly optimise safety, minimise injury to adjacent anatomical structures, and reduce surgical time as well as intra- and postoperative morbidity[3–5]. However, guided surgery requires a financial investment, more meticulous advance planning, and a professional with broader experience for its appropriate management[2,6].

There is no doubt that the aesthetic outcome of treatment with implants in the anterior maxillary region is of great importance. For this purpose, it is essential to have adequate peri-implant tissue support, encompassing both hard and soft tissues. Each professional must assume responsibility for improving the phenotype of peri-implant soft tissues, focusing on three main components: gingival thickness, width of keratinised mucosa, and supracrestal tissue height[7,8]. Current research recognises soft tissue augmentation procedures as essential interventions. They not only enhance stability at the bone level but also control inflammatory signs and prevent future aesthetic complications[7,9–11].

Over the past decade, the quantitative evaluation of augmented tissues has primarily relied on clinical methods such as the periodontal probe and endodontic files. However, the analogue instruments employed lack three-dimensional accuracy for the precise assessment of volumetric changes[12]. Consequently, the utilisation of digital technologies such as computed tomography, ultrasound, and three-dimensional analysis of STL (Standard Tessellation Language) files derived from the digitisation of plaster models or intraoral scanning is advantageous[13–15]. These digital and computerised tools offer significant advantages in dental diagnosis, planning, and treatment. Thus, they provide non-invasive and comfortable measurements for patients, greater accuracy in 2D and 3D evaluations (achieving a precision of 0.01 mm), and enable long-term monitoring by analysing changes occurring in the tissues[16,17].

The objective of this clinical case is to present a treatment sequence in a clinical scenario where anatomical and restorative conditions precluded the placement of an immediate implant in the aesthetic sector. Furthermore, to describe and evaluate, using a non-invasive technique and three-dimensional analysis software, the volumetric changes of the soft tissue following the placement of a connective tissue graft on the buccal and occlusal aspects of the implant.

PATIENTS AND METHODS

1.1 Diagnosis and Treatment Plan

A 29-year-old female patient presented to our dental clinic following trauma to the right maxillary lateral incisor (1.2). The trauma resulted in a fracture of the entire anatomical crown; consequently, only a root remnant in a subgingival position remained. The root remnant was diagnosed as non-restorable, and the available therapeutic options were thoroughly discussed with the patient. It was decided to replace tooth 1.2 with a dental implant, and the following treatment plan and clinical sequence were established: Phase I: extraction of the root remnant 1.2 and reconstruction of the alveolar process using a minimally invasive alveolar preservation procedure. Immediate provisional restoration using a removable partial acrylic prosthesis. Phase II: guided placement of an implant and augmentation of mucosal thickness with a connective tissue graft. Phase III: shaping and modelling of the emergence profile using a direct implant provisional prosthesis and definitive ceramic implant restoration.

1.2 Treatment

- Phase I: atraumatic extraction of the root remnant 1.2 was performed, followed by curettage of the granulation tissue. Subsequently, the alveolus was filled with an inorganic bovine bone graft (0.25–1

mm) combined with autologous platelet- and leukocyte-rich fibrin. Finally, the edges were approximated and sutured with four simple stitches from the vestibular mucosal margin to the palatal aspect. Subsequently, the patient continued using her removable partial denture as a provisional restoration (Figure 1).

• Phase II: healing proceeded without complications. After 5 months from the alveolar preservation surgery, guided implant surgery was planned at position 1.2 (Figure 2). For this purpose, a DICOM file from cone beam computed tomography (CBCT) and an STL file obtained from scanning with

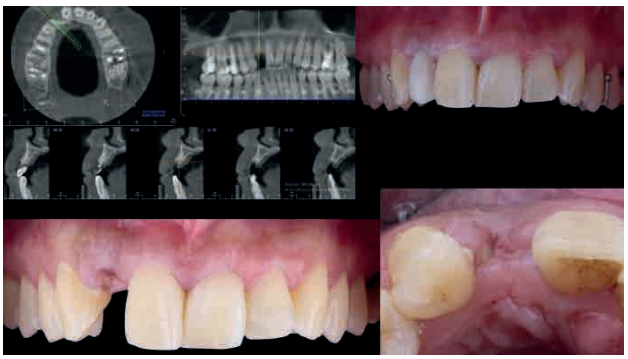

Figure 1. Pre-surgical CBCT image and removable acrylic provisional prosthesis. The lower images show healing at 2 weeks following alveolar preservation (xenograft + L-PRF).

an intraoral optical scanner were used. Using this information, a dental support surgical guide was fabricated (Figure 3). The surgical guide was anchored onto the teeth and guided the preparation of the implant bed and the placement of the implant. The guided surgery technique consisted of flap surgery, preparing and inserting the implant (3.5 x 11.5 mm) according to the standardised Nobel Active® guided surgery protocol (Nobel Biocare AB, Gothenburg, Sweden). Once implant 1.2 was placed, a gingival graft composed of epithelium and connective tissue from the palatal masticatory mucosa was obtained. Subsequently, the superficial epithelial layer of this graft was deepithelialised extraorally using a 15C scalpel blade in order to obtain a connective tissue graft from the underlying layer[18].

The de-epithelialised graft was inserted and positioned buccally and occlusally using horizontal mattress sutures with 5-0 non-resorbable suture (Figure 4)[19].

Post-surgical medication included an antibiotic (1g of amoxicillin twice daily for 7 days) and an antiinflammatory (25 mg of dexketoprofen three times daily for 5 days). The sutures were removed 10 days after the procedure.

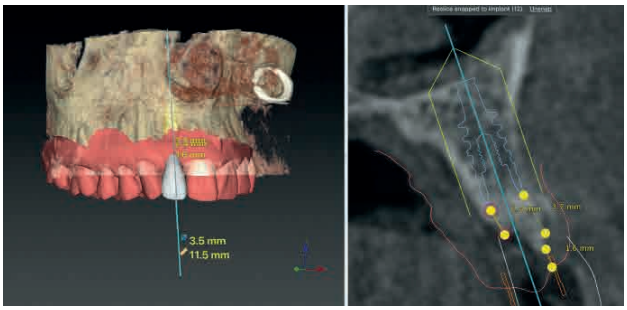

Figure 2. Images from the software and guided implant planning.

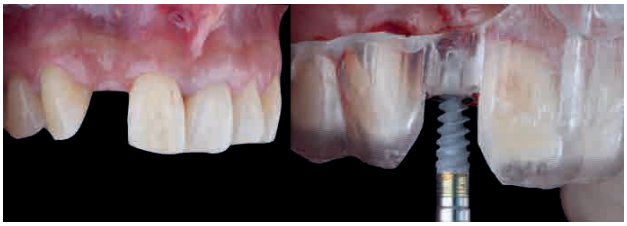

Figure 3. Intraoperative images of the guided implant placement.

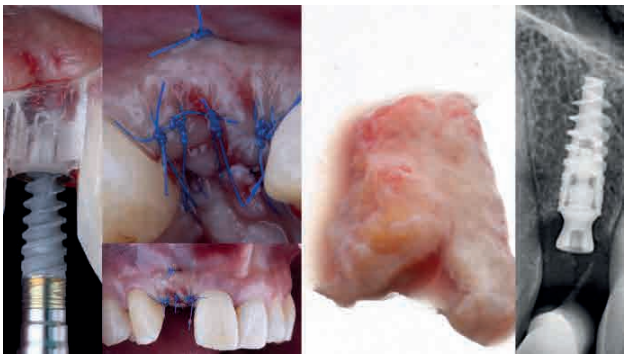

Figure 4. Placement of implant 1.2 and suturing of the connective tissue graft buccally and occlusally to implant 1.2, along with the placement of a customised healing abutment.

• Phase III: three months after implant placement, the soft tissue condition was favourable (Figures 5 and 6). A digital impression was obtained using an intraoral scanner for the fabrication of a screw-retained polymethyl methacrylate (PMMA) provisional restoration. Regarding the definitive implant crown, a cement-screw-retained restoration was fabricated with a titanium nitride interface, adapting the design to the emergence profile already consolidated with the provisional prosthesis. The crown was produced by CAD-CAM in zirconia with full reduction and feldspathic ceramic veneering for zirconia (Figure 7)

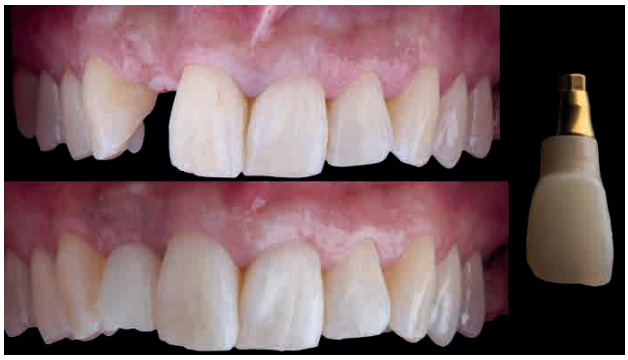

Figure 5. Direct implant provisional. A milled polymethyl methacrylate (PMMA) restoration was placed.polimetilmetacrilato fresada (PMMA).

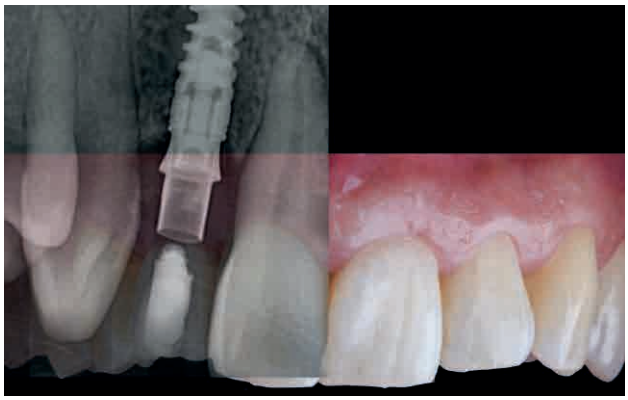

Figure 6. Clinical and radiographic appearance with the provisional crown on implant 1.2.

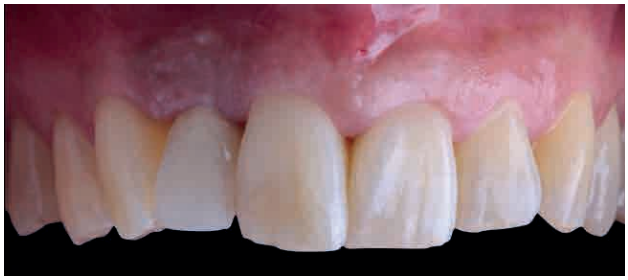

Figure 7. Image taken on the same day as the delivery of the definitive crown.

1.3 Digital measurements of the augmented vestibular soft tissue.

The site where the surgery was performed (implant 1.2), together with its complete arch, was scanned using an intraoral optical scanner at different time points; three weeks before the surgery (T0), immediately after the surgery (T1), and one and a half months post-surgery (T2). The generated digital models were exported and saved as STL files to be subsequently imported into image analysis software (Geomagic® Control X™; 3D Systems, Rockhill, SC). An analysis of preoperative (T0) versus postoperative (T1 and T2) thickness changes was conducted. These longitudinal thickness changes were analysed on the vestibular aspect of the implantsupported crown using the "3D Compare" function, which enabled the creation of a colour map following model superimposition to quantitatively assess the variations occurring in the intervention areas. The colour map ranges from +3 mm to -3 mm, with a tolerance of ± 0.15 mm, and is interpreted as follows: green areas correspond to perfect alignment of the models; red, orange, and yellow colours are interpreted as volume again, while dark and light blue colours respectively represent volumetric loss (Figures 8 and 9). Subsequently, a rectangular region of interest was designed to study the intervention area, where linear changes of the peri-implant mucosa were evaluated (Figures 8 and 9). The horizontal extension of the region of interest encompassed both papillae (mesial and distal), covering the marginal contour of the implant crown up to the marginal surface of the adjacent teeth. To report the results of interest, points were identified on the horizontal plane previously designed on the vestibular aspect of the implant, starting from the mesial and extending 0.5 mm distally. Positive values indicated that the peri-implant soft tissues were located more buccally (> thickness), whereas negative values indicated that the peri-implant soft tissues were located more palatally (< thickness).

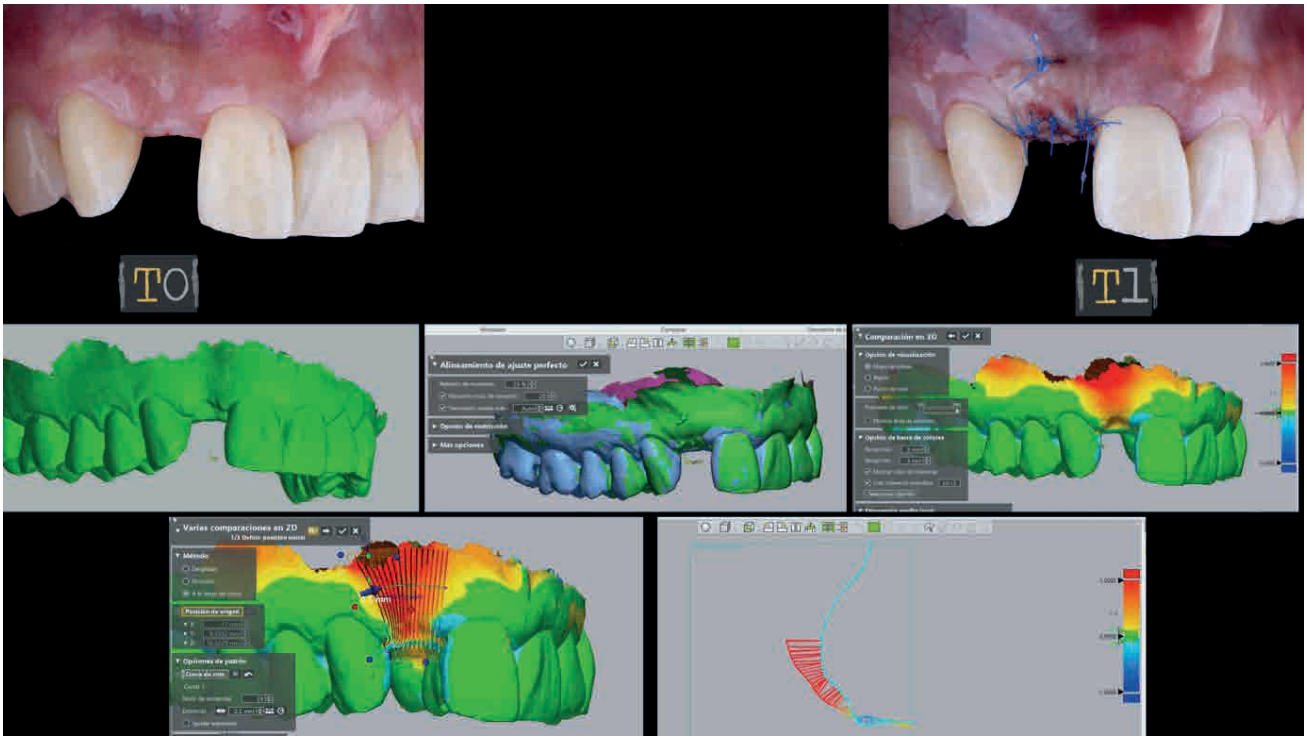

Figure 8. 3D evaluation during the follow-up period (T0–T1) shows an extensive gain marked in red and orange.

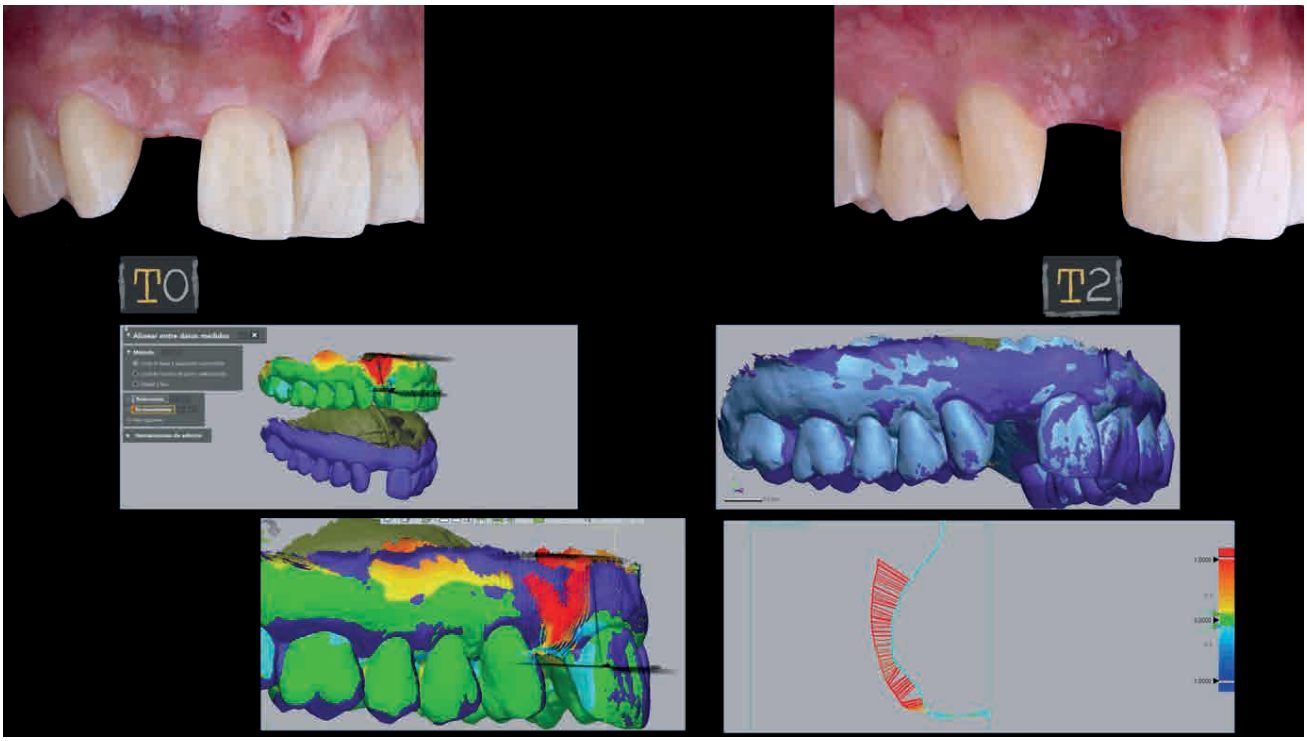

Figure 9. Three-dimensional evaluation during the follow-up periods (T0–T2) shows the gain marked in red and orange.

RESULTS

The final clinical outcome was satisfactory, fulfilling the patient's aesthetic requirements. The soft tissues were morphologically and dimensionally stable, with no signs of inflammation. However, changes in the peri-implant soft tissue (vestibular volumetric thickness) were demonstrated both qualitatively and quantitatively (Figures 8 and 9). In the immediate postoperative period (T1), the mean gain obtained when comparing T0 to T1 was 0.88 ± 0.15 mm, with a maximum increase of 1.1 mm. When comparing T0–T2, a mean gain of 0.73 ± 0.23 mm was observed. That is, a volume contraction of 0.16 mm occurred from the time of graft placement (T1) until one and a half months later (T2).

DISCUSSION

The loss of a tooth in the aesthetic sector represents a challenge for the clinician, as it requires a multidisciplinary and comprehensive approach to restore function and aesthetics. To optimise aesthetic outcomes and reduce the dimensional bone changes that occur following tooth extraction, the use of bone substitutes has demonstrated advantages compared to alveolar healing without bone grafts[20,21]. Regarding the use of autologous platelet-rich fibrin in platelets and leukocytes, Pichotano et al. demonstrated that its application, together with a xenograft in bone regeneration, accelerates the bone healing process, resulting in an increase in new bone formation[22].

Conversely, the use of connective tissue grafts is considered the technique of choice to compensate for the contraction of peri-implant soft tissues, thereby favouring pink aesthetics. Sharma et al. In their clinical study, gingival measurements were taken around the maxillary and mandibular lateral incisors[23]. These authors found that mean gingival thickness ranged between 0.56 and 1.02 mm. These mean values indicate or recommend increasing mucosal thickness over implants, as the patient's own tissues are not sufficiently thick (<2 mm mucosal thickness)[8].

In the present clinical case, a de-epithelialised connective tissue graft was placed on the buccal and occlusal aspects, resulting in greater mucosal thickness and increased height of the supracrestal tissue. The literature describes the advantages of peri-implant soft tissue augmentation, which is beneficial not only to minimise recession of the buccal mucosa but also to support peri-implant bone stability[9,23–25]. The study by Thoma et al. With a follow-up period of up to 3 years, they observed minimal changes in peri-implant soft tissue thickness at implant sites previously grafted with a xenogeneic membrane (-0.2 mm) compared to a subepithelial connective tissue graft (-0.1 mm)[26]. Furthermore, they found greater increases in mucosal thickness with the use of autologous connective tissue grafts compared to the xenogeneic substitute (on average 0.3 mm greater with autologous connective tissue grafts). However, the data obtained in our study regarding mucosal thickness cannot be compared with that of Thoma et al., as our study has a short follow-up period (approximately one and a half months) and only analyses the changes occurring between T0–T1 and T0–T2, without assessing the initial peri-implant mucosal tissue thickness[26]. In our study, it was observed that between T1 and T2 the connective tissue graft undergoes contraction during its healing process (an average of 0.16 mm).

Furthermore, guided implant surgery has been described in the literature as a promising technique that enhances accuracy both in pre-surgical planning and implant placement[3]. Additionally, tooth-supported surgical guides exhibit greater accuracy compared to bone-supported guides[27]. Similarly, the use of a tooth-supported guide without raising extensive flaps may be the optimal choice for both the clinician and the patient[28]. Moreover, virtual planning enables optimisation of implant placement in areas with complex anatomy and bone atrophy by allowing direct visualisation of the available bone volume[29]. Conversely, it provides the possibility of performing immediate loading procedures in a safe and predictable manner[28].

Among the limitations associated with this technique are its higher cost compared to the conventional approach, potential fractures of the surgical guide during the intervention, and the requirement to be

conducted under favourable anatomical conditions, as it necessitates the use of specialised instruments that may be limited to cases without restricted mouth opening. Moreover, the fabrication of an immediate provisional restoration may be compromised by minor discrepancies between the actual and planned implant positions, potentially resulting in slight misfits[3,29–32]. An additional disadvantage concerning the various phases of the presented surgical protocol is the increased number of surgical procedures performed.

CONCLUSIONS

The presented case exemplifies a multidisciplinary approach to the loss of a tooth in the aesthetic sector. It is important to emphasise that meticulous management of hard and soft tissues, as well as planning via guided surgery, enhances precision concerning the ideal position from a prosthodontic standpoint, thereby influencing the long-term stability of hard and soft tissues. The present volumetric analysis suggests that following the execution of a connective tissue graft, there is an initial gain which diminishes after one and a half months.

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LITERATURE REVIEW

Pulp regeneration / revitalization in immature permanent teeth

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SUMMARY

Introduction. Treatment of affected immature teeth is a challenging procedure. Immature teeth have wide canals, thin dentin walls and open apices, in addition to being more prone to fracture and with a poor long-term prognosis. Revascularization of an immature tooth attempts to preserve the teeth as long as possible, but there are failures because it is difficult to achieve optimal disinfection of the root canal system.

Methods. An exhaustive search was carried out by consulting the electronic databases PubMed and Web of Science of the last 10 years, using keywords and eligibility criteria.

Results. The search process yielded 635 total articles. After applying filters, eliminating duplicates and selecting articles by title and abstract, only 27 were for the present study.

Conclusions. Pulp revitalization has high survival rates in the treatment of necrotic immature permanent teeth. Randomized clinical trials are needed to compare the effect of platelet-rich fibrin, platelet-rich plasma, and induced bleeding on the revitalization of a tooth with necrotic pulp. One of the main problems of pulp revitalization is coronal discoloration. Triple antibiotic paste is a very effective antimicrobial agent, but high concentrations could have a detrimental effect on stem cell survival.

KEYWORDS

Apical closure; Open apex; Immature teeth; Permanent teeth, Platelet-rich fibrin; MTA; Non-vital traumatized immature permanent; Pulp necrosis; Dental pulp regeneration.

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- IBECS
- LATINDEX
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INTRODUCTION

During childhood and adolescence, traumatic dental injuries are common, causing damage to the tooth and its supporting structures, including root fractures, bone loss, and tooth loss[1]. The loss of permanent teeth at an early age may result in arrested growth of the alveolar bone, thereby impeding subsequent aesthetic and functional reconstruction[2]. Given the increasing desire to preserve natural teeth, a tooth with a poor prognosis presents a new challenge for dentists[1].

The principal characteristic of young permanent teeth is incomplete root development. This results in an open apical foramen, thinner and more fragile root walls, an inadequate crown-root ratio, and an unformed root structure[3]. These particular characteristics of young permanent teeth mean that the required pulp treatments are different and should be as conservative as possible.

The management of affected immature teeth is among the most challenging procedures in endodontics. Owing to the fact that such immature teeth possess very wide canals, thin dentinal walls, and open apices, they present increased difficulty for the clinician during biomechanical preparation[1,3]. Furthermore, these are more prone to fracture and, therefore, have a poor long-term prognosis[3,4].

Traditionally, immature teeth diagnosed with necrotic pulp are treated by apexification with calcium hydroxide ($Ca(OH)_2$) or mineral trioxide aggregate (MTA)[5,6]. However, neither procedure allows for thickening of the root wall or continued root development[7]; consequently, these teeth become fragile and susceptible to fracture[5].

Regenerative endodontic procedures represent a novel therapeutic approach that promotes continued root growth in necrotic immature teeth, potentially preventing root fracture[5]. The revascularisation of a traumatised immature tooth seeks to preserve the teeth for as long as possible[2].

In pulpal revascularisation, the root canal is disinfected with antibiotics or antimicrobial agents[8]. Promotion of the blood clot is necessary following disinfection of the root canal system. In recent years, this promotion of the conventional clot (induced by over-instrumentation) has been replaced by the use of platelet-rich plasma or platelet-rich fibrin, which offer enhanced efficacy and a higher concentration of growth factors to promote dental bleeding[7].

However, a significant concern in teeth undergoing regenerative endodontic treatment is achieving optimal disinfection of the root canal system[6]. Although revascularisation is an increasingly utilised treatment, clinical failure rates in the revitalisation of immature teeth may reach up to 40%[8].

When pulp regeneration or revitalisation is performed, a significant proportion of cases fail. Therefore, it is necessary to identify the most effective techniques to undertake this treatment with minimal risk.

MATERIALS AND METHODS

Sources of information and search strategy

A comprehensive search was conducted to ensure that as many studies as possible were identified through electronic searching.

For the search strategy, the following electronic databases were consulted: 1) PubMed and 2) Web of Science, covering the past 10 years, using the following MeSH keywords: “apical closure”, “open apex”, “immature teeth”, “permanent teeth”, “platelet-rich fibrin”, “MTA”, “non-vital traumatised immature permanent”, “pulp necrosis”, “dental pulp regeneration”.

Boolean operators were used, such as: “immature” NOT “mature”, “permanent” NOT “temporal”, “Blood Clot” OR “Platelet-rich Fibrin”.

Eligibility Criteria

The selection of articles for this study was conducted by applying the following selection criteria (Table 1).

All identified articles were assessed according to the title, keywords, and abstract to exclude those not relevant to the review question.

Table 1. Inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
- Publications from the last 10 years - Studies: • Conducted in young permanent teeth • In vivo • Using the revascularisation/ revitalisation	- Publications in languages other than Spanish or English - Studies with clinical follow-up of less than 3 months - Animal study

RESULTS

Selection of studies

The search process yielded a total of 635 articles. After applying the filter of "publications from the last 10 years", 135 articles were excluded, leaving 500 articles remaining. After removing duplicates in both databases (218 articles), a total of 282 publications remained.

The remaining publications were filtered for "randomised controlled trials" and "clinical trials". In PubMed, the search was reduced to 17 articles, while in Web of Science, it was reduced to 212, resulting in a total of 229 articles.

Following selection of the articles by title and abstract, 53 were chosen for full-text review. Twelve of these were excluded for being systematic reviews; three for

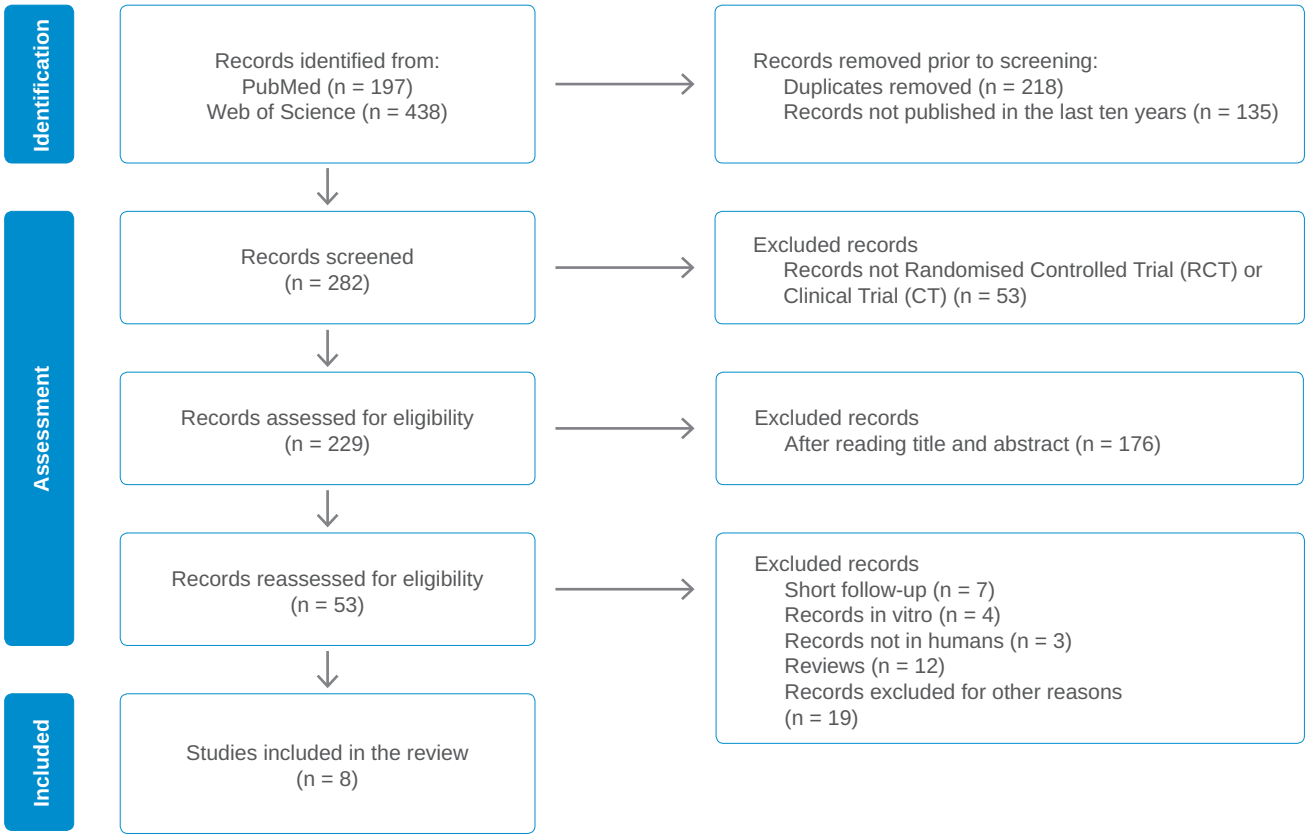

Figure. Flow diagram of the search conducted..

involving non-human samples; four of them, for being in vitro studies; seven, for having a follow-up period of less than three months; and the remainder, for other reasons. Thus, only eight were selected for full-text review, and all of these were included in the present study (Figure).

Characteristics of the studies

For this search, various types of studies were consulted, excluding, as previously mentioned, systematic reviews. Furthermore, sample size, case follow-up, and aetiology have also been considered (Table 2).

Patient characteristics

The sampling unit in these studies is the immature necrotic permanent tooth. A total of 227 immature necrotic permanent teeth are included The majority are maxillary incisors (193), although mandibular incisors (1), premolars (5), maxillary molars (3), and mandibular molars (25) have also been studied (Table 2).

Revascularisation technique

In half of the studies selected for this review, pulp revascularisation was performed by inducing bleeding (blood clot formation) (BC)[2, 8-10]. Only one study utilised platelet-rich fibrin (PRF)[11] and another employed platelet-rich plasma (PRP)[12]. The remaining two were conducted using platelet-rich fibrin in half of the sample, and in the other half, blood clot induction was performed[13,14] (Table 3).

Use of MTA

Of the eight studies selected for this review, five used MTA exclusively to create a coronal plug[2, 11-14].

Two other studies divided the sample into two groups, using MTA in one group and either Bioceramic Root Repair[8] or EndoSequence Bioceramic Putty[9] in the other. Only one study used NeoMTA Plus[10] (Table 3).

Intracanal medication

Triple antibiotic paste (TAP) was used in five studies[9,11–14]. Another study used TAP in half the sample and $Ca(OH)_2$ in the rest[10]. In one study, either $Ca(OH)_2$ or 2% chlorhexidine digluconate gel was used[8]. In the eighth study included in this review, tetracycline and triamcinolone were used as intracanal medication[2] (Table 3).

Table 2. Descriptive characteristics of the studies.

Author and year	Type of study	Sample size	Sample unit (tooth)	Cause of necrosis	Follow-up (months)
Bukhari S, 2016	Retrospective case series	28	21 anterior teeth, 5 premolars and 2 molars. 22 maxillary and 6 mandibular	Caries or trauma	7-31
Ragab RA, 2019	Randomised clinical trial	22	Incisors	Not specified	6 y 12
Mittmann CW, 2020	Retrospective study	16	Maxillary incisors	Trauma	22
Rizk HM, 2020	Randomised clinical trial	30	Maxillary incisors	Trauma	3, 6, 9 y 12
Wikström A, 2022	Prospective cohort study	75	Maxillary incisors	Trauma	≥ 24
Al-Qudah A, 2023	Prospective randomised clinical study	50	23 maxillary anterior teeth, 1 anterior mandibular tooth, 3 maxillary molars and 23 mandibular molars	Caries or trauma	3, 6, 12, 24 y 36
Kumar JK, 2023	Prospective clinical study	1	Maxillary incisor (11)	Trauma	12
Biradar N, 2023	Case series	5	Maxillary incisors	Not specified	12

Discolouration

Four studies reported the occurrence of coronal discolouration, either caused by MTA or after blood clot induction[2, 8, 11, 14]. Only one study reported the absence of coronal discolouration, coinciding with the use of NeoMTA Plus[10]. Three studies made no reference to the presence or absence of discolouration[9, 12, 13] (Table 3).

Failures / exclusion

A total of 54 treatments failed. Failures could be early or late[8]. The former (19) are characterised by an absence of bleeding on induction or failure to form a blood clot; whereas in the latter group (11 teeth), patients exhibited persistent clinical symptoms. Others failed due to severe resorption (3) or non-attendance at follow-up visits (1)[2].

Other unfavourable outcomes included root resorption (1 case), association with the sinus tract (1), sensitivity to percussion (2), and persistence or increase in the size of the apical radiolucency without symptoms (3)[10]. In some cases, failure was due to the need for additional treatment (3) or incomplete healing (4)[9] (Table 3).

DISCUSSION

Regenerative therapy has demonstrated excellent success rates[3] and has proven to be the technique offering the greatest benefit for the long-term management of non-vital permanent teeth[11].

Revascularisation is a promising approach for treating immature incisors, helping to restore sensitivity and promote apical closure[2], increase dentinal wall thickness[11] and at least preserve the alveolar bone in terms of socket preservation. Further studies are needed to determine the ideal conditions for revascularisation, such as trauma type, age, and apical foramen width[2].

The success of revascularisation is considered to depend on reducing bacterial load[18]. The main reported side effect was discolouration, seen only in damaged teeth. The most consistently observed radiographic finding was narrowing of the apical diameter[3]. Yang et al. (2022) followed up at 6, 12, 24, and 36 months, showing further radiographic evidence of healing in immature necrotic teeth[16].

Table 3. Description of clinical outcomes.

Author and year	Revascularisa tion technique	Intracanal medication	Sealing material	Discolouratio n	Failures / exclusions (teeth)
Mittmann CW, 2020	BC	Tetracycline and triamcinolone	MTA	Yes	4
Wikström A, 2022	BC	Ca(OH)2 or 2% chlorhexidine digluconate gel	MTA or Bioceramic Root Repair	Yes	30
Al-Qudah A, 2023	BC	Ca(OH)2 o TAP	NeoMTA Plus	No	7
Kumar JK, 2023	FRP	TAP	MTA	Yes	0
Biradar N, 2023	PRP	TAP	MTA	Not specified	0
Rizk HM, 2020	FRP o BC	TAP	MTA	Yes	6
Ragab RA, 2019	FRP o BC	TAP	MTA	Not specified	Not specified
Bukhari S, 2016	BC	TAP	MTA or EndoSequence Bioceramic Putty	Not specified	7

BC (blood clot);
MTA = Mineral Trioxide Aggregate
Ca(OH)2 = calcium hydroxide;
TAP = triple antibiotic paste
PRF = platelet-rich fibrin;
PRP = platelet-rich plasma

In a prospective study, Wikström et al. (2022) reported successful pulpal revitalisation, with resolution of clinical and radiographic signs and continued root development.

Continuous root development was observed in 60% of the teeth in which the procedure was performed, with failed cases being associated with the absence of bleeding (n=19) and persistent infections (n=11)[8], as well as crown fractures[19].

Use of MTA

In the study by Tawfeek et al. (2023) demonstrated that clinical and radiographic success, whether using NeoMTA or conventional MTA (WMTA), was 100%. Discolouration was detected in only one tooth with NeoMTA (9.1%) and in three teeth (27.3%) with MTA, but the difference between the groups was not statistically significant[15].

Similarly, Ajram et al. (2019) demonstrated that the regenerative endodontic technique is feasible and can be successfully performed using Ca(OH) and MM-MTA[5]. In the randomised clinical trial by Abuelniel et al. (2020), it was demonstrated that teeth treated with MTA exhibited significant discolouration from 6 to 18 months of follow-up. It was observed that 23 of the 25 teeth treated with MTA had developed discolouration at the 6-month follow-up visit[20].

The case series conducted by Hajizadeh et al. (2019), illustrated 12-month follow-ups of revascularisation in three necrotic immature teeth using MTA as a coronal barrier. The treatments were considered successful, as the teeth were functional, all unfavourable signs and symptoms were alleviated, and some degree of root development was achieved[17].

In the study conducted by Sajjad et al. (2022), 40 cases were treated with MTA and 32 were successful. A complete resolution of signs and symptoms was observed, with absence of periapical radiolucency, in most cases, elongation of root length, increased thickness of the root canal walls, and apical closure[21].

Use of platelet-rich fibrin, platelet-rich plasma, and stimulation of the blood clot

The randomised controlled trial (RCT) conducted by Rizk et al. (2020), demonstrated that the teeth in which platelet-rich fibrin was used (examined group) exhibited a statistically significant increase in radiographic root length and width, an increase in periapical bone density, and a reduction in apical diameter compared to the control group (in which bleeding was induced, resulting in the formation of a blood clot). At the end of the follow-up period, all treated teeth were negative in the sensitivity test. The control group exhibited greater coronal discolouration compared to the examined group[14].

In the prospective case series by Nawal et al. (2020), immature necrotic permanent maxillary anterior teeth (n=6) underwent pulp regeneration using platelet-rich fibrin. None of the teeth demonstrated improved responsiveness to pulp sensitivity tests at the end of the 5-year follow-up; however, all exhibited a reduction in apical diameter (mean of 30.96%), which was statistically significant. An increase in root thickness (40.20%) and root length (13.18%) was also observed[7].

Ragab et al. (2019) stated, in their RCT, that the use of platelet-rich fibrin is effective for controlling the placement of MTA at the desired level, with only slight pressure exerted on the MTA during placement; It is also stated, however, that the use of platelet-rich fibrin may not be necessary for pulp revitalisation in immature permanent anterior teeth[13]. Similarly, Sakthivel et al. (2020) confirmed that platelet-rich fibrin is an ideal biomaterial for regeneration[6].

In the RCT conducted by Rizk et al. (2020), they conducted a 12-month follow-up (n=24). Platelet-rich fibrin demonstrated a marginal increase in radiographic root length and width, periapical bone density, and a reduction in apical diameter. No statistically significant differences were observed when compared with the blood clot. The treated teeth did not respond to the sensitivity test at the conclusion of the study. The blood clot exhibited a statistically significantly greater degree of coronal discolouration compared to the platelet-rich fibrin group[14].

Ragab et al. (2019) stated, in their randomised clinical trial, that the blood clot was important for creating vital tissue within the empty sterile canals[13].

In the prospective clinical trial conducted by Markandey et al. (2022), a follow-up period of 12 to 24 months was conducted, yielding the following results: the use of a blood clot, platelet-rich plasma, and platelet-rich fibrin demonstrated similar potential for the healing of periapical lesions and apical closure, as well as for radicular wall thickness and root length in immature teeth[22].

Platelet-rich plasma is superior to platelet-rich fibrin and induced bleeding with regard to the healing of periapical wounds; however, they produce comparable outcomes in terms of lateral wall thickening, root lengthening, and response to vitality tests[23].

A disadvantage of platelet-rich plasma and platelet-rich fibrin techniques is that additional time is required to extract and centrifuge blood prior to its introduction into the root canals[23].

Canal disinfection

Sakthivel et al. (2020) confirmed that revitalisation of an immature necrotic infected tooth is possible under conditions of complete canal disinfection[6].

Biradar et al. (2023) once again demonstrated the role of antibiotics in creating a favourable environment for the growth of pulpal and periapical tissues; furthermore, they make particular mention of triple antibiotic pastes (TAP), which play an important role as intracanal medicaments in regeneration and revascularisation procedures[12]. Hajizadeh et al. (2019) stated that the concentrations of medicaments are important in achieving a balance between canal disinfection, the release of growth factors from the dentine matrix, and the survival/proliferation of stem cells from the apical papilla[17]. It should be noted that triple antibiotic paste is a highly effective antimicrobial agent; however, high concentrations of this mixture may have a detrimental effect on the survival of stem cells[24].

Ragab et al. (2019) stated, in their RCT, that ciprofloxacin and metronidazole in addition to sodium hypochlorite are effective in controlling infection, although in some cases an extension of the treatment period is required[13].

Adverse effects

Higher concentrations of antibiotic medications, as well as $Ca(OH)_2$, may cause adverse effects on the mechanical, physical, and chemical properties of radicular dentine; that is, it may negatively affect fracture resistance in the cervical third of the roots[25,26].

When used at high concentrations, antibiotic medicaments (TAP) may demonstrate superior antimicrobial properties compared to $Ca(OH)_2$. However, high concentrations of TAP have been associated with several complications, such as antibiotic resistance, high cytotoxicity, and discolouration of the teeth[10].

There is a low incidence of adverse effects. The most frequently reported drawback in the reviewed publications was tooth discolouration caused by MTA.

Endodontic regeneration failed in some cases due to discolouration and recurrent caries, crown fracture[4] or loss of the coronal restoration of the treated teeth[9].

CONCLUSIONS

According to this literature review, pulp revitalisation demonstrates high survival rates in the treatment of immature necrotic permanent teeth, with satisfactory clinical and radiographic outcomes.

Revascularisation facilitates improved apical closure, increased dentinal wall thickness, and greater root length. It also preserves the alveolar bone.

Randomised clinical trials are required to compare the effect of platelet-rich fibrin and induced bleeding on the long-term revitalisation of teeth with necrotic pulp and open apices. Platelet-rich plasma results in superior apical healing, with root lengthening and thickening of the dentinal walls.

Clinical and radiographic success can be achieved using either MTA or Ca(OH2). One of the principal challenges of pulp revitalisation is coronal discolouration. NeoMTA is a material that has demonstrated less discolouration compared to conventional MTA. Likewise, it has been shown that the use of platelet-rich fibrin results in less discolouration than induction of bleeding and clot formation.

Triple antibiotic paste is a highly effective antimicrobial agent; however, high concentrations may have a detrimental effect on the survival of stem cells.

Although current research in regenerative therapy is highly promising, its outcomes remain unpredictable due to the histological nature of the regenerated tissue. Consequently, further studies are required to assess the follow-up and efficacy of each of these treatments.

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LITERATURE REVIEW

Osteonecrosis of the jaws in patients treated with monoclonal antibodies: A review of the literature

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ABSTRACT

Introduction. In the last decade, monoclonal antibodies have revolutionized the field of modern medicine. These are proteins designed to bind specifically to certain molecules for the treatment of certain types of cancer and autoimmune disease.

The aim of this study was to analyze the relationship between treatment with monoclonal antibodies and osteonecrosis of the jaws by analyzing the incidence and associated risk factors.

Methods. A total of 3057 results were initially obtained. After an initial screening of articles that did not meet the inclusion criteria, 42 articles were selected for full-text reading. Finally, 13 randomized clinical trials were included.

Results. The total number of patients included was 16259. The mean incidence of osteonecrosis cases was 3.87%. There were 51 mild cases of osteonecrosis (stage 1-2) and 16 severe cases (stage 3). The risk factors analyzed were the use of mismatched prostheses, invasive dental procedures, periodontal disease and the use of corticosteroids.

Conclusions. The mean incidence of monoclonal antibody-induced osteonecrosis was 3.87%. The use of misaligned prostheses, tooth extraction, periodontal disease and the use of corticosteroids may favor the development of monoclonal antibody-induced osteonecrosis.

Studies of higher quality and with longer follow-up time are necessary to reach more conclusive statements.

KEY WORDS

Monoclonal antibodies; Antiresorptive drugs; Osteonecrosis of the jaws.

INTRODUCTION

Monoclonal antibodies (MAs) are molecules that act as substitutes for endogenous antibodies to restore, enhance, or mimic the activity of the immune system[1]. MAs have revolutionised the treatment of autoimmune, allergic, and infectious diseases, being useful in cases of multiple sclerosis, bone metastases, and osteoporosis[2-4].

Four types of monoclonal antibodies are distinguished according to their origin: murine, chimeric, humanised, and human. The most commonly used and prescribed at present are the humanised antibodies, identified by the suffix -zumab (romosozumab), and the human antibodies, identified by the suffix -umab (denosumab); the latter are less antigenic, better tolerated, and possess a longer half-life. Both act by inhibiting osteoclast activity, thereby reducing bone resorption and increasing bone density[3], with a highly specific mechanism of action through inhibition of the receptor activator of nuclear factor-kappa B ligand (RANKL)[5].

RANKL is a critical factor in bone resorption, as it plays a fundamental role in the formation, function, and survival of osteoclasts. The RANKL inhibitor is osteoprotegerin, which, similarly to monoclonal antibodies, competes with RANKL for binding to RANK, thereby neutralising its effects. Thus, inhibition of RANKL permits an increase in bone density[6,7].

Owing to their mechanism of action, these agents may have several adverse effects, including increased susceptibility to infections, hepatic injury, and osteonecrosis of the jaws (ONJ), which is an uncommon but serious condition characterised by one or more necrotic bone lesions that are exposed or can be palpated through an intraoral or extraoral fistula in the maxillofacial region, and persist for at least 8 weeks without response to appropriate treatment[8,9].

The American Association of Oral and Maxillofacial Surgeons (AAOMS) introduced the staging system to classify the symptomatology of ONJ and facilitate decision-making for its treatment[8]. (Table 1)

In the past decade, the use of monoclonal antibodies has increased; therefore, the aim of this literature review was to analyse the association between monoclonal antibody therapy and the incidence of ONJ, as well as the risk factors in patients with ONJ treated with monoclonal antibodies.

MATERIALS AND METHODS

Sources and search strategy: A literature search was conducted using the PubMed/Medline database, employing the following keywords: [(monoclonal antibodies) OR (antiresorptive drugs)] AND [(osteonecrosis of the jaw) OR (ONJ)].

Inclusion criteria: Randomised controlled trials (RCTs) from the past 10 years describing the incidence of ONJ in patients treated with monoclonal antibodies (MAs) were included.

Exclusion criteria: In vitro studies, animal studies, and observational studies were excluded. RCTs reporting ONJ caused by drugs other than MAs were also excluded.

Selected articles: Following the initial search, a total of 3,057 results were obtained. An initial screening was conducted, excluding articles that did not meet the inclusion criteria based on title and abstract. Subsequently, 42 articles were read in full, and ultimately, 12 articles were included in the review (Figure).

Information recorded from the articles: The names of the authors, year of publication, number, sex and age of the patients, follow-up period, type, dose and frequency of administration of the monoclonal antibody (MA) used, number of reported cases, severity, and risk factors were recorded.

RESULTS

In total, 13 RCTs were analysed, as the article by Stopeck et al.[13] presented two studies. The total number of patients was 16,259, 15,027 women and 1,232 men, with a mean age of 65.22 years.

The most frequently used MA was denosumab, which was analysed in 10 studies and administered at doses ranging from 60 mg every 6 months to 120 mg monthly. The other MA, analysed in three studies, was romosozumab, administered at a dose of 210 mg

monthly. The follow-up period for patients ranged from 6 to 120 months.

In five studies[11,12,15,18,21] no cases of ONJ were reported, whereas in the remaining seven studies[10,13,14,16,17,19,20] an incidence ranging from 0.028% to 8% (mean 3.87%) was observed. The severity of ONJ cases was analysed in only three studies[13,17], with 51 mild cases (stage 1–2) and 16 severe cases (stage 3) reported. Finally, the factors associated with the development of ONJ were analysed in three studies[14,17,20] in which the use of ill-fitting prostheses, extractions, invasive dental procedures, periodontal disease, and the use of corticosteroids were described (Table 2).

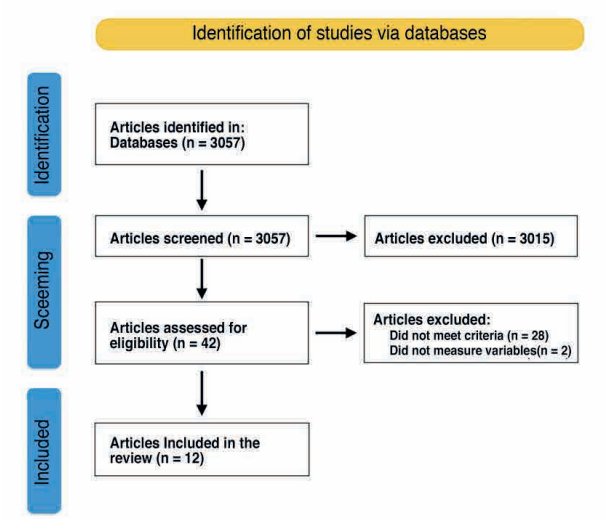

Figure. PRISMA flow diagram.

DISCUSSION

ONJ is a rare pathology that considerably impairs patients' quality of life. In this literature review, 12 studies were included in which cases of patients receiving monoclonal antibody therapy were documented, with denosumab (60 mg every 6 months)[11,12,16,18] being the most frequently utilised.

The majority of cases studied were women (92.4%), which may be explained by the high prevalence of osteoporosis following menopause. The most commonly utilised treatments for osteoporosis are zoledronic acid, denosumab, and teriparatide, as they demonstrate high efficacy in reducing the risk of bone fractures[22].

ONJ is most frequently localised in the mandible[22,23]; however, it may also be detected in the maxilla[24]. Furthermore, it may be accompanied by pain, inflammation, erythema, suppuration, and tooth loss. Although ONJ may occur spontaneously, in the majority of cases it results from a surgical procedure in the oral cavity[25].

With regard to the incidence of ONJ, a variation between 0% and 8% was observed, which may be attributable to differences in sample sizes among the studies and the follow-up period. Furthermore, when comparing the mean incidence obtained in this review (3.87%) with other drugs that may also induce ONJ, such as intravenous bisphosphonates (1.3–3.2% after 3 years of follow-up) and oral bisphosphonates

TABLE 1. Staging classification of onj according to the american association of oral and maxillofacial surgeons (AAOMS)[8]

Stage 0	Non-specific symptomatology and clinical findings without evidence of necrotic bone
Stage 1	Exposed and necrotic bone, or a fistula reaching the bone, in patients who do not present with symptoms or evidence of infection or inflammation.
Stage 2	Exposed and necrotic bone, or a fistula reaching the bone, in symptomatic patients
Stage 3	Stage 2 plus one or more of the following: • Exposed necrotic bone extending beyond the alveolar region • Pathological fracture • Extraoral fistula • Oroantral or oronasal communication • Osteolysis extending beyond the inferior border of the mandible or the floor of the sinus

TABLE 2. Descriptive characteristics and clinical outcomes of the selected articles

Authors/Journal/ Year	Type of study	Number of patients (start/end)	Mean age	Sex (♀ / ♂)	Medication	Dose (mg)	Administration frequency (subcutaneous)	Follow-up (months)	Cases of ONJ	Severity	Risk factors
Henry y cols. Support Care Cancer 2014[10]	RCT	800/792	59	269/531	Denosumab	120 mg	1 month	30	6	-	-
Gnant y cols. Lancet 2015[11]	RCT	1636/1636	-	1636/0	Denosumab	60 mg	6 months	72	0	-	-
Sugimoto y cols. Osteoporos Int. 2015[12]	RCT	404/404	71,5	383/21	Denosumab	60 mg	6 months	36	0	-	-
Stopeck y cols. Support Care Cancer 2016[13]	RCT	325/318	56	325/0	Denosumab	120 mg	1 month	54	20	18 stage 1-2 2 stage 3	-
Stopeck y cols. Support Care Cancer 2016[13]	RCT	153/147	70	0/153	Denosumab	120 mg	1 month	51	12	9 stage 1-2 3 stage 3	-
Cosman y cols. N Engl J Med. 2016[14]	RCT	3589/3581	70,9	3589/0	Romosozumab	210 mg	1 month	12	1	-	Ill-fitting prosthesis/ extraction
Saag y cols. N Engl J Med. 2017[15]	RCT	2046/2040	74,4	2046/0	Romosozumab	210 mg	1 month	12	0	-	-
Bone, y cols. Lancet Diabetes Endocrinol. 2017[16]	RCT	2343/1451	74,9	2343/0	Denosumab	60 mg	6 months	120	7	-	-
Raje y cols. Lancet Oncol. 2018[17]	RCT	859/850	63	397/462	Denosumab	120 mg	1 month	42	35	24 stage 1-2 11 sta-ge 3	Invasive dental procedures and standard use of corticosteroids
Gnant y cols. Lancet Oncol. 2019[18]	RCT	1711/1709	-	1711/0	Denosumab	60 mg	6 meses	120	0	-	-
Huang y cols. Adv Ther. 2020[19]	RCT	103/102	61	38/65	Denosumab	120 mg	1 month	39	7	-	-
Coleman y cols. Lancet Oncol. 2020[20]	RCT	2256/2241	50	2256/0	Denosumab	120 mg	1 month	78	122	-	Previous extraction, dental prosthesis, periodontal diseasel
Baek y cols. Endocrinol Metab. (Seoul) 2021[21]	RCT	34/34	66,7	34/0	Romosozumab	210 mg	1 month	6	0	-	-

No: Number; ♀ : Female; ♂ : Male; RCT: Randomised controlled trial.

(between 1–2.3% after 3 years of follow-up), the incidence of MRONJ is observed to be higher in patients taking antiresorptive agents (ARs)[26,27]. This increased incidence was already noted by Loyson et al.[28], who

confirmed a higher risk of MRONJ in patients who switched from bisphosphonates to ARs. It is worth noting, however, that the effects of bisphosphonates on bone can last up to three years after the last dose, unlike ARs, which do not have a cumulative effect[22]. The risk factors for ONJ associated with monoclonal antibody therapy were described in three studies[14,17,20]. The risk factors for ONJ related to the use of monoclonal antibodies that were identified are similar to those for ONJ induced by bisphosphonates: use of ill-fitting prostheses, extractions, invasive dental procedures, periodontal disease, and use of corticosteroids. Additionally, ONJ caused by bisphosphonates presents further risk factors such as the cumulative dose of bisphosphonates in the blood and tobacco use[29].

In this context, it is important to implement a review programme for patients treated with monoclonal antibodies, as the majority of diagnosed cases of ONJ associated with monoclonal antibody therapy are mild (stages 1–2). Seventy-six per cent of cases in which the stage is recorded are mild, thereby underscoring the particular importance of early diagnosis of ONJ[30].

With regard to the management of ONJ, the literature describes adjuvant treatments (antibiotics, oral rinses) for mild cases (stages 1–2). In stage 3, for those cases that do not respond to adjuvant treatment, surgical procedures (debridement, curettage, removal of sequestra, and bone resection) should be employed, ensuring complete removal of necrotic bone, smoothing of the bone margins, and meticulous wound closure[31]. Other therapeutic alternatives are currently under investigation, such as the use of platelet concentrates, teriparatide, laser therapy, hyperbaric oxygen, and ozone applications. These therapies may be effective, although at present they exhibit a low level of evidence and a limited sample size[32].

One of the limitations of the present review is the short follow-up period (< 5 years) in nine of the thirteen included studies. Furthermore, in eight of the thirteen included studies, the sample comprises exclusively women; thus, it would be of interest to determine the incidence according to gender. Finally, it would be beneficial to compare the incidence of ONJ between monoclonal antibodies and other antiresorptive agents.

CONCLUSIONS

The incidence of ONJ induced by monoclonal antibodies in this review is higher than that of other agents, such as oral and intravenous bisphosphonates. Furthermore, it appears that the use of ill-fitting prostheses, extractions, periodontal disease, and corticosteroid use may promote the development of ONJ associated with the administration of monoclonal antibodies. Nevertheless, further randomised clinical trials comparing monoclonal antibodies with other antiresorptive agents are required to more precisely determine the incidence, severity, and risk factors.

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