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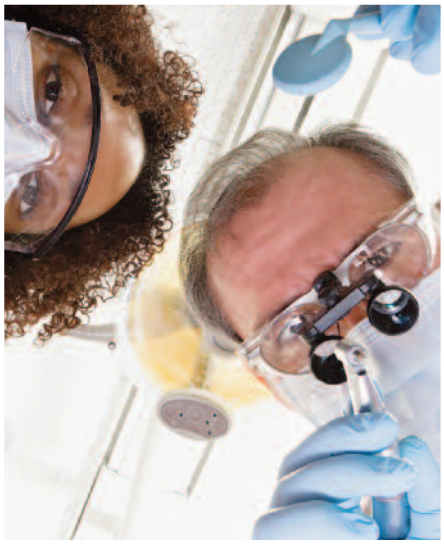

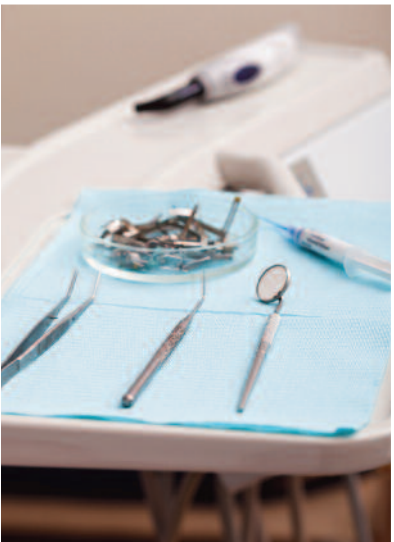

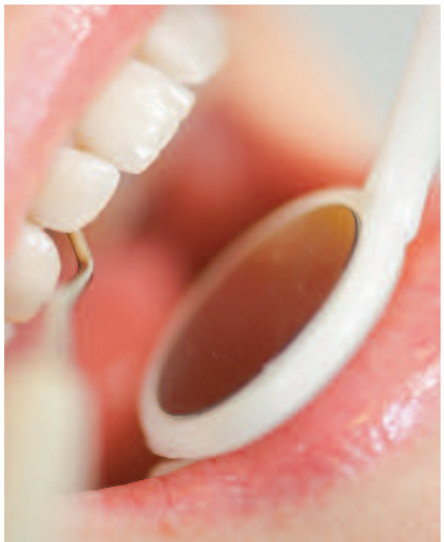

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editorial

Dr. Jesús Calatayud Sierra
Director of *Científica Dental*.

As it does every year, *Científica Dental* is pleased to issue this special English language supplement containing articles published during 2017 which received awards in the three categories of: best scientific article, best clinical case, and best first scientific work by a new author. We have also included the three finalists in each of these categories, for a total of six best works of the year that readers can browse in open access on our website, www.cientificadental.es. And of course, readers who wish to do so may also access these works in Spanish at the same Internet address, as they have already been published online.

I cannot thank enough all the people who through their efforts make this magazine possible (editors, reviewers, ...), especially the authors for their many contributions and the quality of the work that they have bestowed upon our readers who are, after all, the intended beneficiaries of our common endeavours.

A cordial greeting to all,

Dr. Jesús Calatayud
Director of *Científica Dental*

Clinical case

Is periodontal regeneration effective in a long-term maintenance of teeth with advanced periodontitis? a case report

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ABSTRACT

Objective: The purpose of this article is to describe a clinical case on periodontal regeneration and to determine the efficacy and predictability of the different regenerative techniques in the treatment of intraosseous defects caused by periodontitis.

Clinical case: This is the case of a 65-year-old patient with advanced chronic periodontal disease located in the right superior central incisor where regenerative surgery was planned during the reevaluation stage due to a radiographically visible intraosseous defect with a pocket depth of 11 mm. The lesion, which affected the buccal, distal and palatal walls, was treated with a combination of bone xenograft (BGs), absorbable collagen membrane (GTR) and enamel matrix proteins (EMPs), resulting in a reduction in pocket depth up to 7 mm after nine months.

Conclusion: Periodontal regeneration has been shown to be effective for the treatment of an intra-bone defect that compromises tooth survival by helping the patient maintain proper oral health and function.

KEYWORDS

Periodontal regeneration; Enamel matrix proteins; Bone grafts; Guided tissue regeneration.

INTRODUCTION

Periodontitis is a chronic inflammatory disease of infectious origin that causes progressive deterioration and destruction of the tissues that support the tooth, made up of alveolar bone, the periodontal ligament and radicular cement.[1] The extent and severity of bone loss must be diagnosed with radiographs and clinical examination.[1, 2]

There are two types of bone loss in periodontitis: horizontal and vertical bone loss patterns. The first, in which the alveolar crest migrates horizontally towards the apex, is more common. The second form is less frequent and is usually found more locally, making these cases of vertical bone loss susceptible to regeneration techniques.[2-4]

Periodontal regeneration is defined, according to the American Academy of Periodontics (AAP), as the restoration of tissue lost due to periodontitis, including the radicular cement, periodontal ligament and alveolar bone. However, it must be made clear which types of bone defects are susceptible to regenerative surgery.[1]

According to Papapanou and Tonetti5, we can distinguish between supraosseous or horizontal defects, intraosseous or vertical defects and interradicular or furcation defects. Supraosseous defects are those found coronally to the alveolar crest. In infraosseous defects, the lesion is apical to the residual alveolar wall. Interradicular defects are those that occur in the area of separation of multiradicular tooth roots, called furcation, which leads to loss of said bone and may make the furcation clinically detectable.

Regarding infraosseous defects, these are classified as intraosseous defects and craters. In intraosseous defects, one or several walls of the same bone are affected, with the defect named according to the number of walls that are intact: single-wall defects, two-wall, three walls or combined intraosseous defects. Craters, on the other hand, are defects in which there is similar bone loss in the roots of two contiguous teeth with no bone between them[5] (Figure 1).

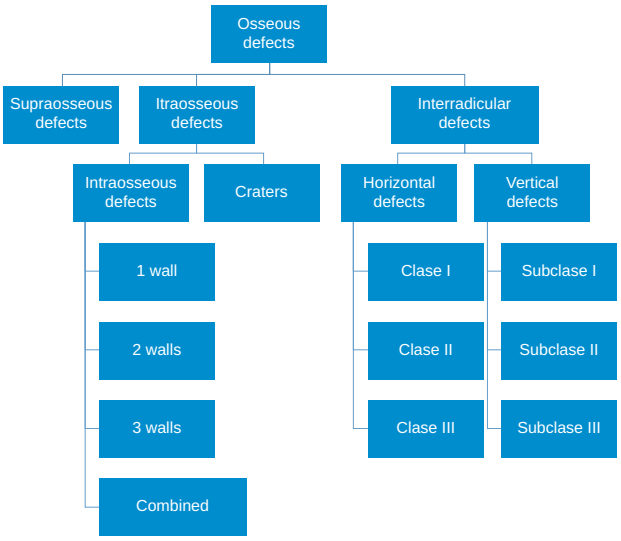

Figure 1. Classification of periodontal bone defects.

Periodontal regeneration is possible in intraosseous defects and class I and class II interadicular defects, both mandibular and maxillary. It is not predictable in horizontal or supraosseous defects, intraosseous craters or class III intraradicular defects.[6,7]

Among the most widely used regeneration techniques is guided tissue regeneration (GTR), the use of enamel matrix proteins (EMP) or the use of bone grafts (BG).

GTR consists of placing a biocompatible membrane between the epithelium and connective tissue of the defect, which can be to serve as a physical barrier, acting as a cellular exclusion mechanism, thereby promoting the migration of cells from the periodontal ligament and impeding the entry of epithelial cells.[8-10]

EMPs, extracted from embryonic enamel of young pigs, are not a physical barrier per se, but rather a material in gel form that is placed precisely inside the defect, promoting true periodontal regeneration. EMPs modulate tissue regeneration, simulating events that occur during formation of the root and promoting the formation of new alveolar bone, radicular cement and periodontal ligament. Among the properties of EMPs are its antimicrobial ability and inhibition of epithelial migration by direct contact.[3, 11, 12]

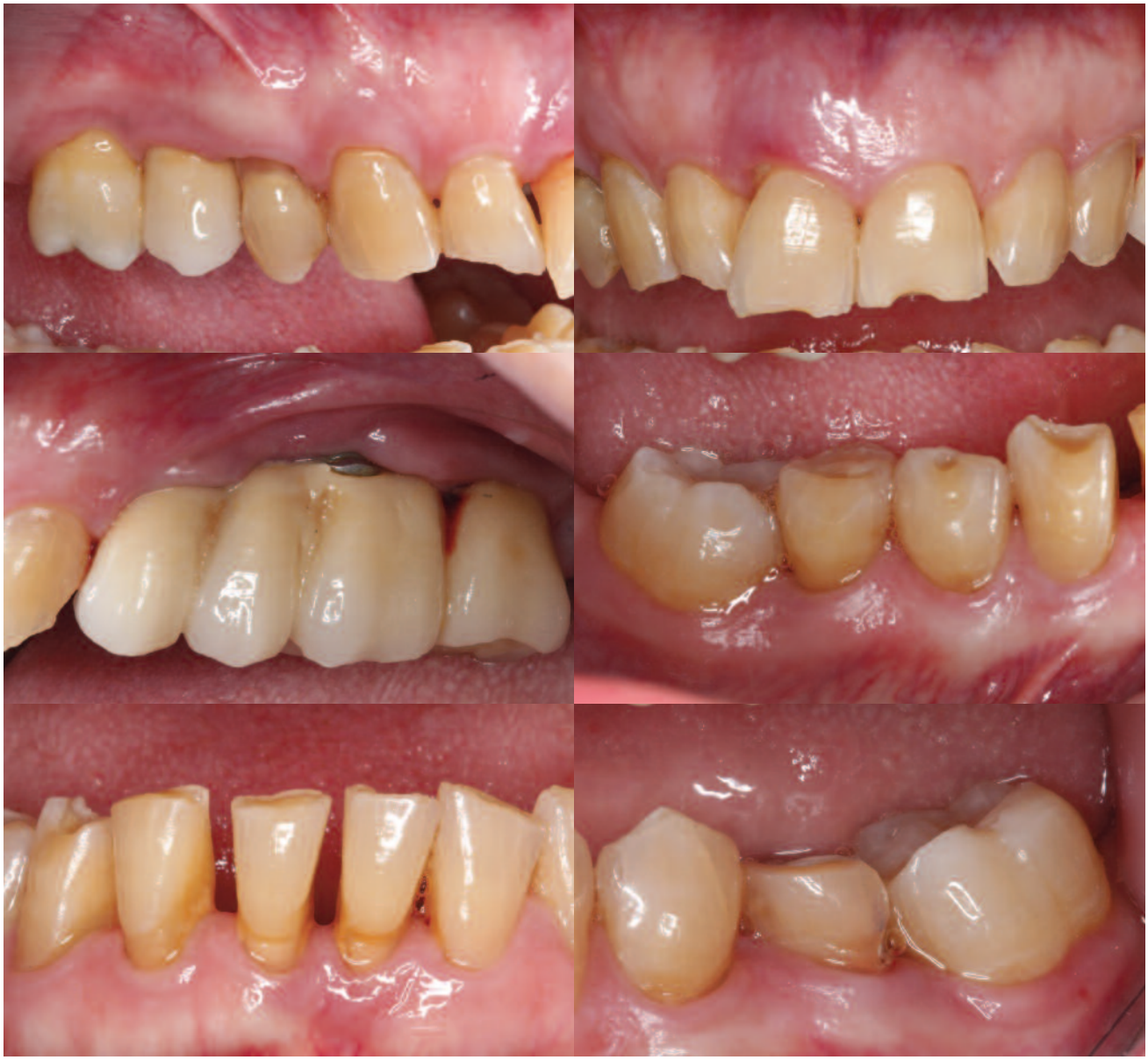

Figure 2. Initial photographs by sextants.

BGs can be obtained from the patient (autograft), another human (allograft), another animal species (xenograft) or from alloplastic materials. The BGs most widely used in periodontal regeneration are bone xenografts extracted from lyophilized bone usually of bovine origin. Regarding the application of BGs alone in periodontal regeneration, it has been shown that they are ineffective in achieving satisfactory results, so they are used in combination with GTR and EMP. The combination of EMP+BG and GTR+BG shows additional improvement in the reduction of pocket depth and gains in clinical insertion versus EMP or membranes alone, though the results in some cases are not significant.[6,10,13]

The purpose of this article is to describe a clinical case on periodontal regeneration and to determine the efficacy and predictability of the different regenerative techniques in the treatment of intraosseous defects caused by periodontitis.

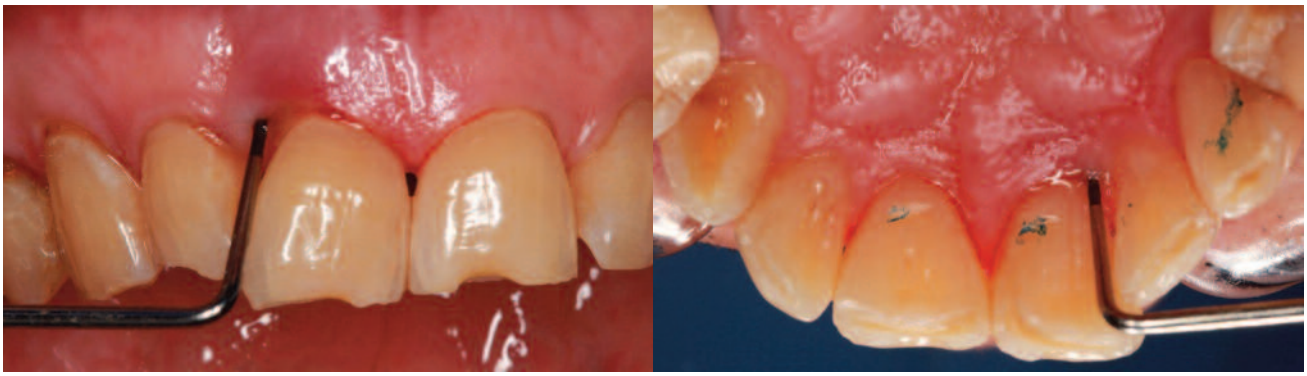

Figure 3. Photograph of the pocket in RSCI.

CLINICAL CASE

This is the case of a 65-year-old retired male who was referred to the periodontics clinic for a possible endo-periodontal lesion of the right superior central incisor (RSCI).

The history is significant for mild sleep apnea-hypopnea syndrome (SAHS) and hypertension, currently treated with Enalapril 20 mg. This is therefore an ASA type II patient.

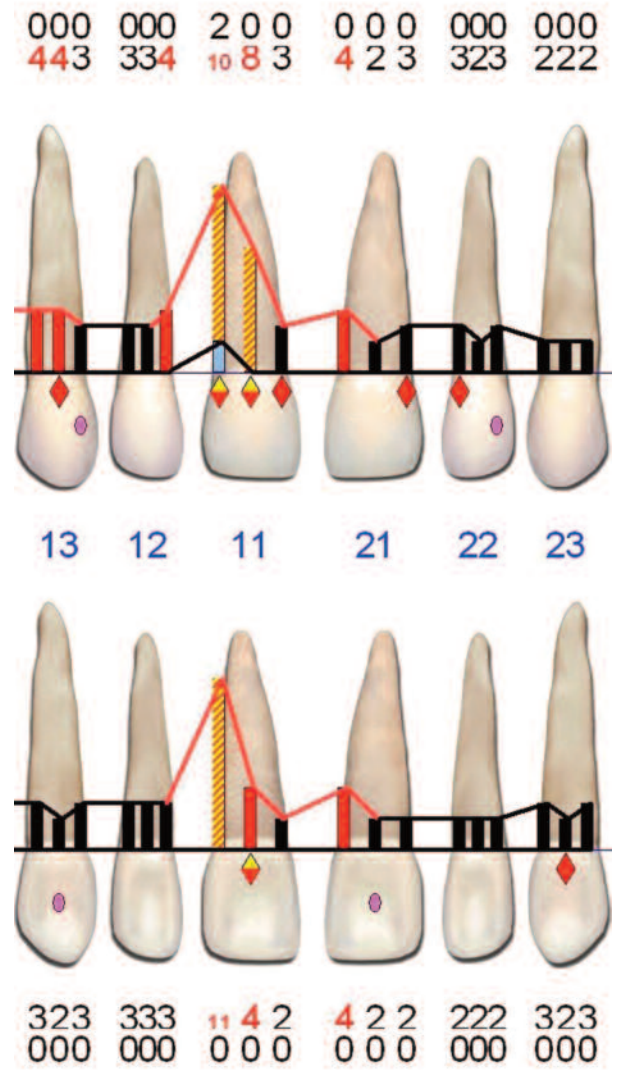

Figure 4. Initial periodontogram of the second sextant.

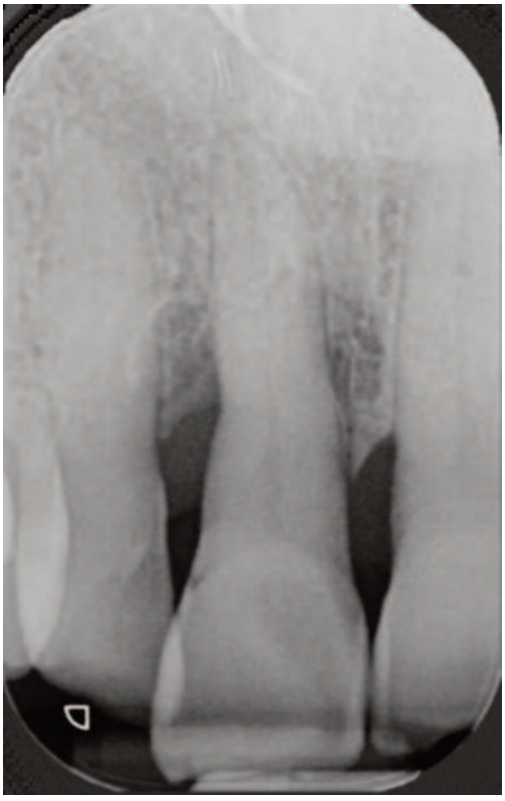

Figure 5. Initial periapical radiograph of the RSCI.

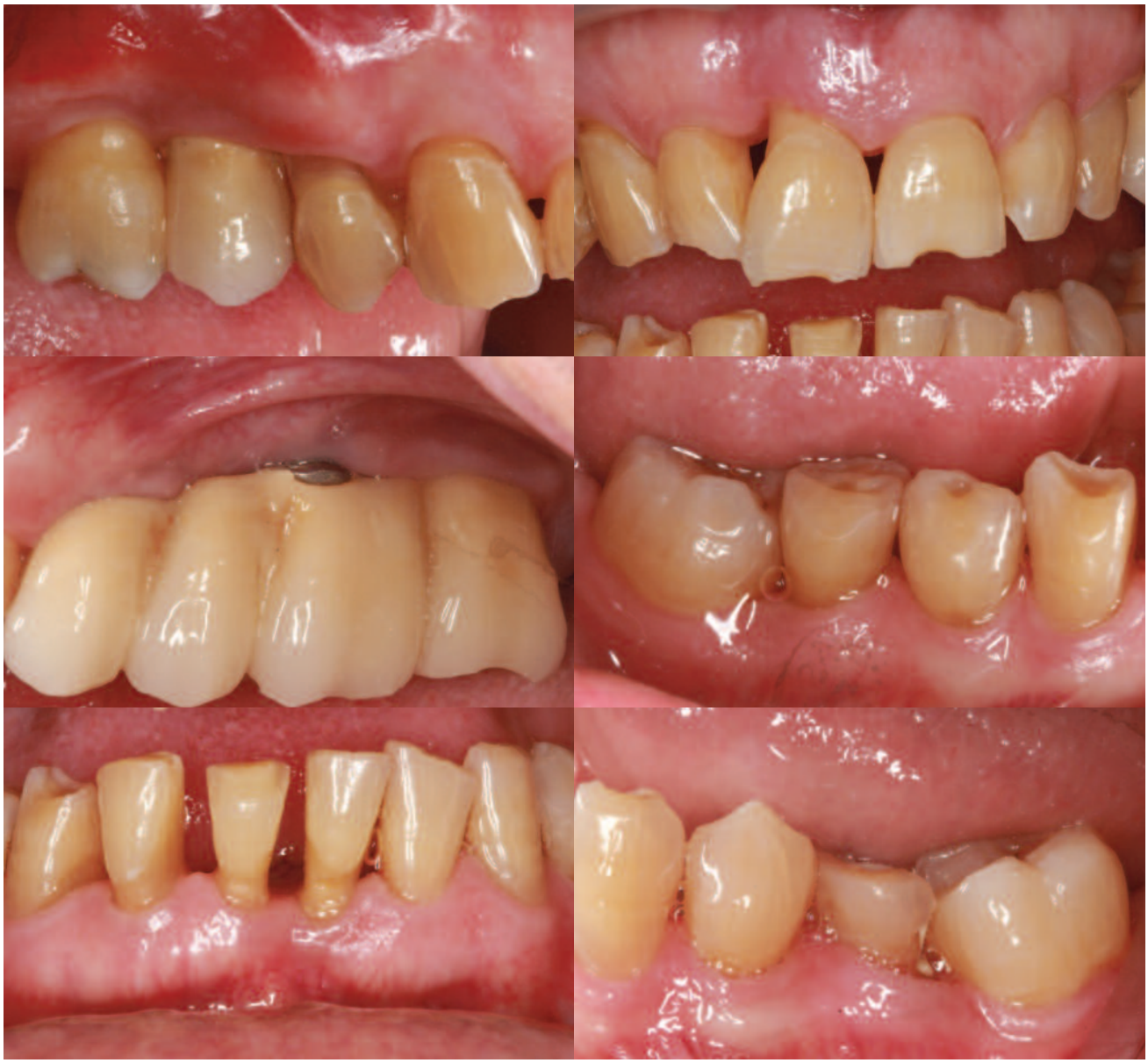

Figure 6. Photographs by sextants after post-RAR reevaluation.

Examination and diagnosis

Intraoral examination revealed an increased overbite, generalized abrasions and anterior attrition due to bruxism. From a periodontal point of view, there were generalized vestibular recessions and

gingival inflammation, plaque and calculi accumulation in all the posterior sectors. Regarding the patient's implants, there were some cemented crowns that were over-routed and poorly fitted at the gingival margin which had resulted in difficulty maintaining oral hygiene in this area (Figure 2).

A complete periodontogram was carried out which revealed pocket depths up to 6 mm, primarily in the molars and premolars, and pocket depths of up to 9 mm in the third sextant implants, as well as detectable furcation lesions in the first inferior and superior molars, 40% plaque and 37% bleeding. In addition, the RSCI revealed a localized pocket depth of 10 mm

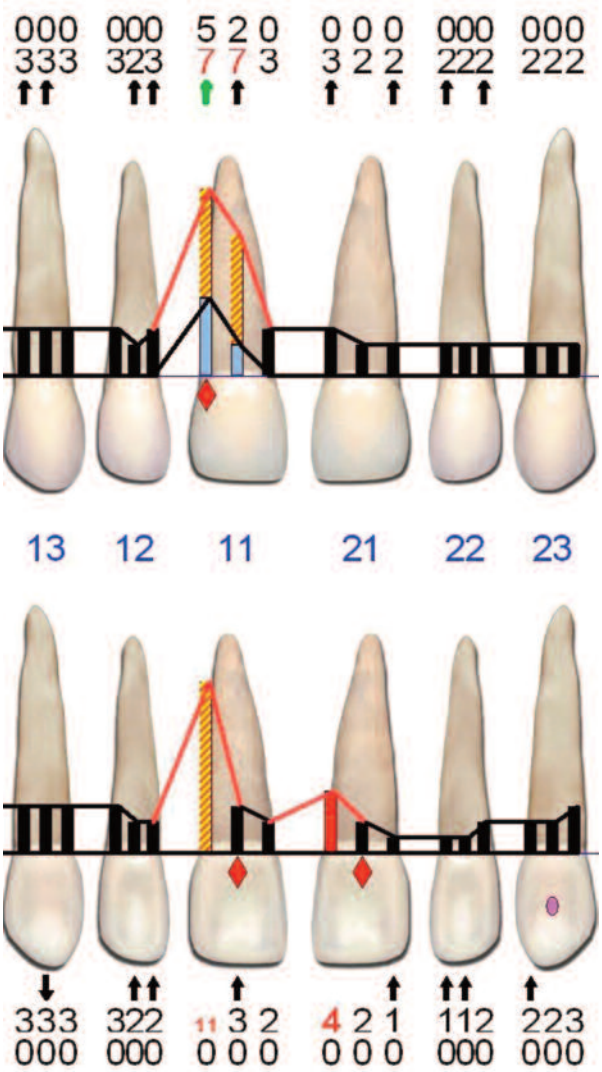

Figure 7. Periodontal chart of the second sextant after reevaluation.

distovestibular, 8 mm mesiovestibular and 11 mm distopalatal, suspicious for a possible endoperiodontal lesion, given the magnitude of the loss in that tooth. In addition, there was bleeding, suppuration and type-I mobility (Figures 3 and 4).

Clinically, the right superior central incisor (RSCI) was mildly vestibulized with respect to the left central, leading to the suspicion that there may be occlusal trauma at that level. Radiographic examination revealed a moderate generalized bone loss pattern with no bone loss at the implants. The RSCI exhibited a marked

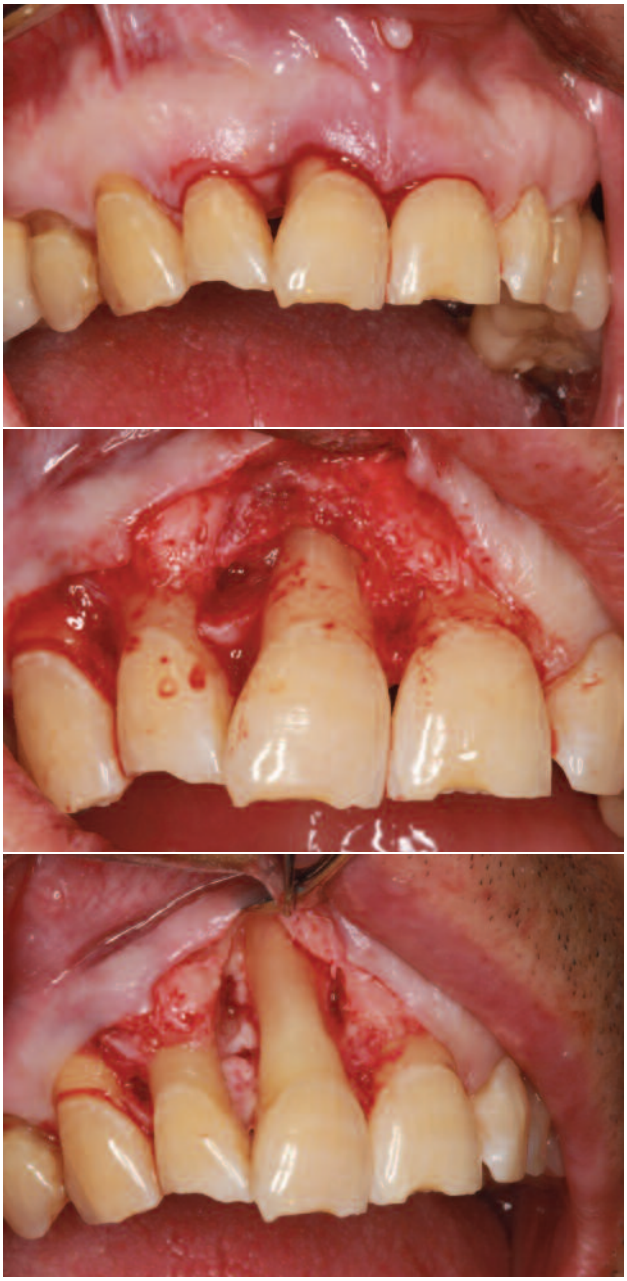

Figure 8. Photos of the surgery. Incision, detachment and cleaning of the defect.

intraosseous defect that involved almost the entire tooth (Figure 5). In addition, vitality tests were negative.

Microbiological samples were taken from each sextant, revealing the presence of Prevotella intermedia, Porphyromonas gingivalis, Fusobacterium nucleatum in a proportion of 18.19%, 33.59% and 1.59% of the entire oral microflora, respectively (6.288x108 CFU).

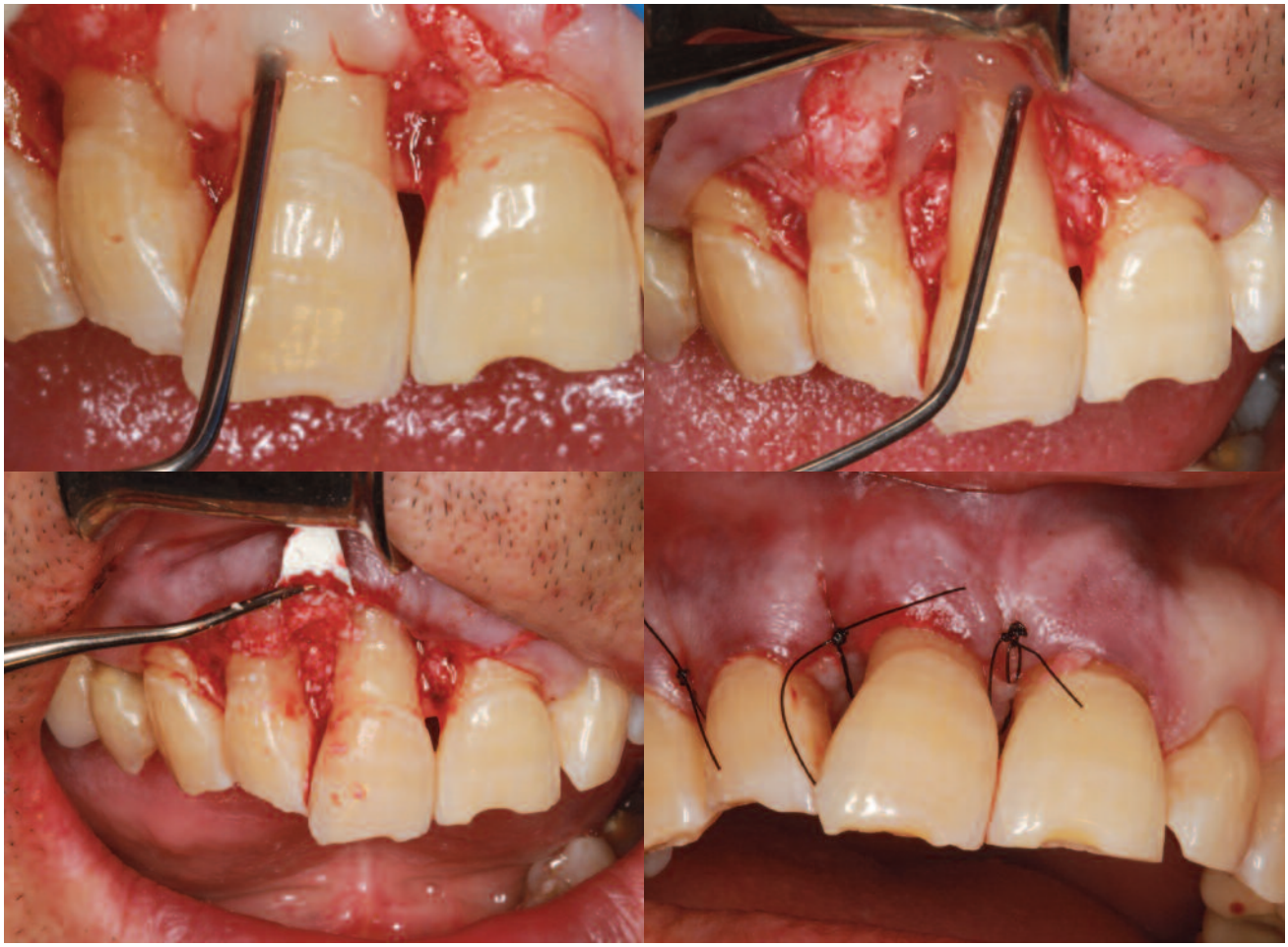

Figure 9. Photos of the surgery. Application of enamel matrix proteins, absorbable collagen membrane and xenograft. Suture.

After clinical and radiological examination, it was concluded that the patient had moderate generalized/advanced localized periodontitis and peri-implant mucositis.

Prognosis

A favorable prognosis was made for all of the teeth except the RSCI, which was given a poor prognosis due to the loss of periodontal support.

Treatment plan

After analyzing the occlusion, the presence of rubbing detected in the RSCI was relieved by selective sculpting on the palatal surface of the tooth. The basic phase of periodontal treatment was carried out, consisting of instructions on oral hygiene, professional prophylaxis, radicular filing and polishing, 0.12% chlorhexidine + 0.05% cetylpyridine chloride rinses (Perio-aid®; Barcelona, Spain) every

12 hours for 2 weeks, in addition to a prescription for metronidazole 500 mg every 8 hours for 7 days due to the presence of P. gingivalis.

Reevaluation at one month revealed clear improvement of inflammation, plaque and bleeding, reduced up to 15 and 19%, respectively (Figure 6).

However, given the limitations of basic periodontal treatment, especially in the deep pockets of more than 6 mm, the RSCI maintained high pocket depths, 7 mm distovestibular with a 5 mm recession (10 and 2 mm at baseline, respectively) and 11 mm distopalatal (Figure 7).

Therefore, given the clinical and radiographic findings,

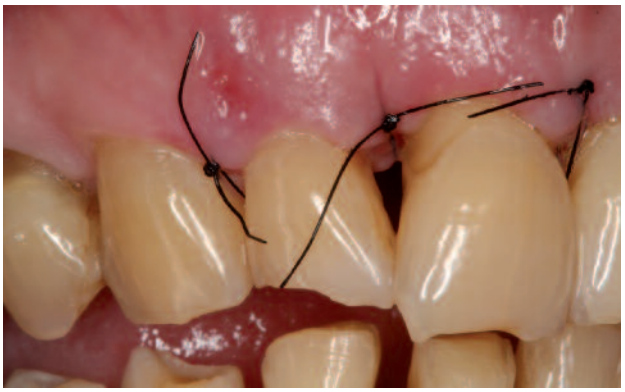

Figure 10. Healing at one week after surgery.

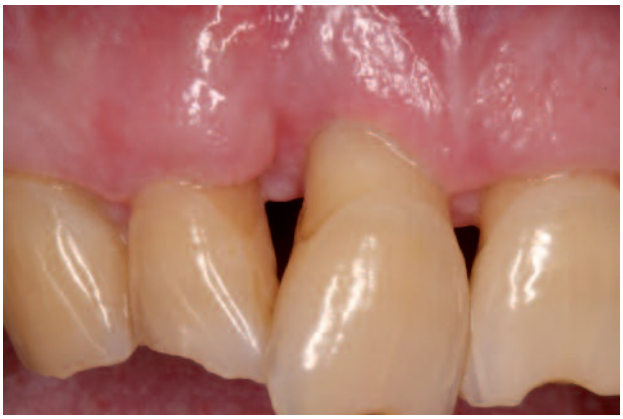

Figure 11. Healing at one month after surgery.

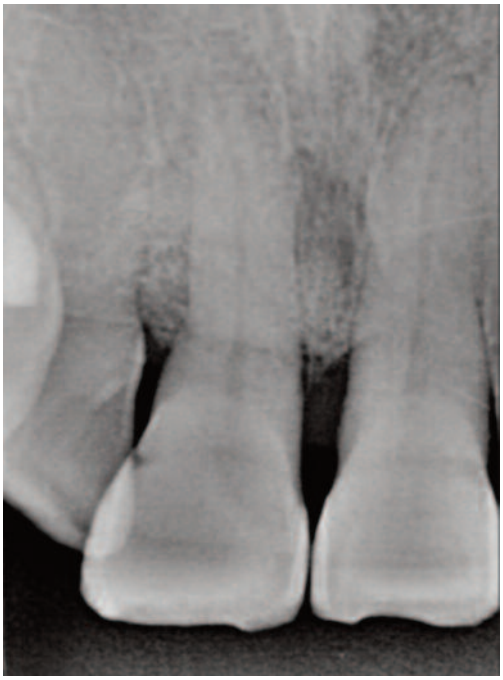

Figure 12. Follow-up periapical radiograph at 2 months after surgery.

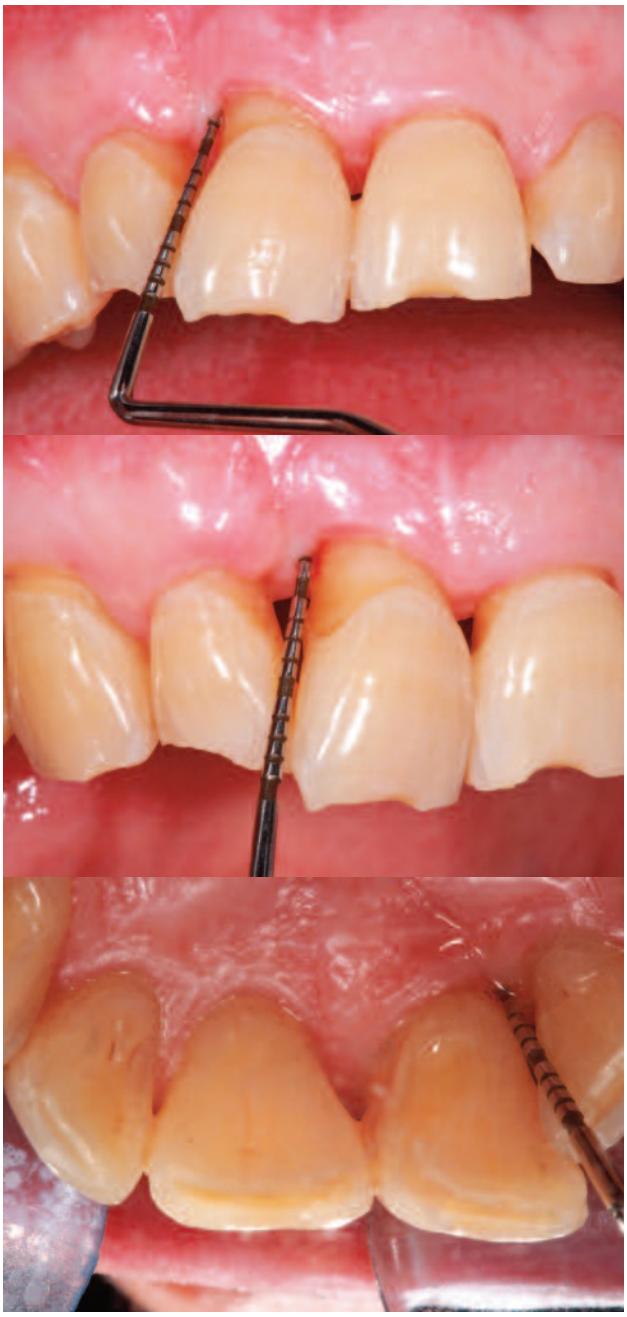

Figure 13. Photograph of pocket at 9 months after surgery.

a regenerative surgery was selected for the RSC., This procedure was thus indicated aimed to improve the prognosis of the RCSI and to achieve healthy pocket depths.

A simplified papilla preservation technique was used in interdental spaces of less than 2 mm and a modified

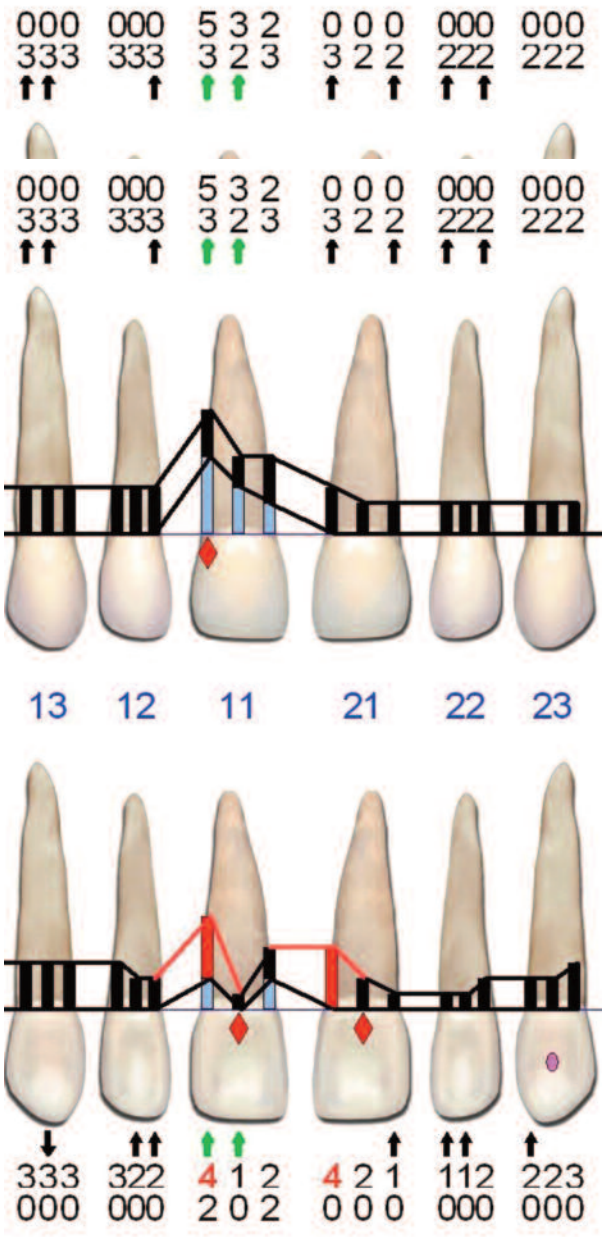

Figure 14. Periodontal chart of the second sextant at 9 months after surgery.

papilla technique for interdental spaces greater than 2 mm. After complete thickness separation and elimination of granulation tissue, an intraosseous defect was observed with complete loss of the vestibular bone, the distal wall and part of the palatal wall of the RSCI that extended almost to the apex. Given the importance of the lesion, a combined technique using guided tissue regeneration (GTR) using absorbable collagen membrane, bovine bone xenograft (Bio-Oss®) and enamel matrix proteins (Emdogain®) was proposed in order to reconstruct the lost vestibular bone (Figures 8 and 9).

Table 1. Clinical trials that use GTR or GTR + BG.

Study	Time (months)	Treatment (number of defects)	Mean reduction in PD[1] (mm)	P	Mean GCI[2] (mm)	P
Sculean et al.[14] (2008	12	PMEs (10)	4.1	<0.001	3.4	<0.001
		RTG (10)	4.2	<0.001	4.2	<0.001
		PMEs + RTG (9)	4.3	<0.001	3.3	<0.001
		CAD (9)	3.7	<0.001	2.0	<0.001
	120	PMEs (10)	4.6	NS3	2.9	<0.001
		RTG (10)	3.4	NS3	2.8	<0.001
		PMEs + RTG (9)	3.6	NS3	2.9	<0.001
		CAD (9)	3.5	NS3	1.8	<0.001
Siciliano et al[15] (2011)	12	RTG (20)	5.5	<0.001	4.1	<0.001
		PMEs (20)	2.9	<0.001	2.4	<0.001
Nygaard-Østby et al.[16] (2010)	9	IOs (20)	2.9	<0.05	2.5	<0.05
		IOs + RTG (20)	3.2	<0.05	2.5	<0.05
	120	IOs (13)	2.7	<0.05	2.2	<0.05
		IOs + RTG (13)	4.2	<0.05	3.8	<0.05
Slotte et al.[17] (2007)	12	RTG + IOs (52)	5.2	ND[4]	4.2	ND[4]
	36		5.6	ND[4]	4.1	ND[4]
	60		5.3	ND[4]	4.3	ND[4]
Cortellini et al.[18] (2011)	12	RTG (25) Ext/implante	8.8	<0.001	7.7	<0.001
			ND[4]	ND[4]	ND[4]	ND[4]
	60	RTG (25) Ext/implante	8.9	NS[3]	7.7	NS[3]
			ND[4]	ND[4]	ND[4]	ND[4]

[1] Pocket Depth; [2]Gained Clinical Insertion; [3]Not significant; [4]Not defined.

Follow-up and outcomes

After the surgery, weekly follow-up visits were scheduled in the first month, and prophylaxis of the area was carried out at each visit. Brushing was prohibited in the first week, restarting after the first seven days after removal of the sutures (Figure 10). After one month, healing of the area was very satisfactory (Figure 11). After the first month, follow-up visits were carried out every 3 months, emphasizing the importance of good hygiene, especially at the interproximal level.

A detailed reevaluation was performed nine months after regenerative surgery.

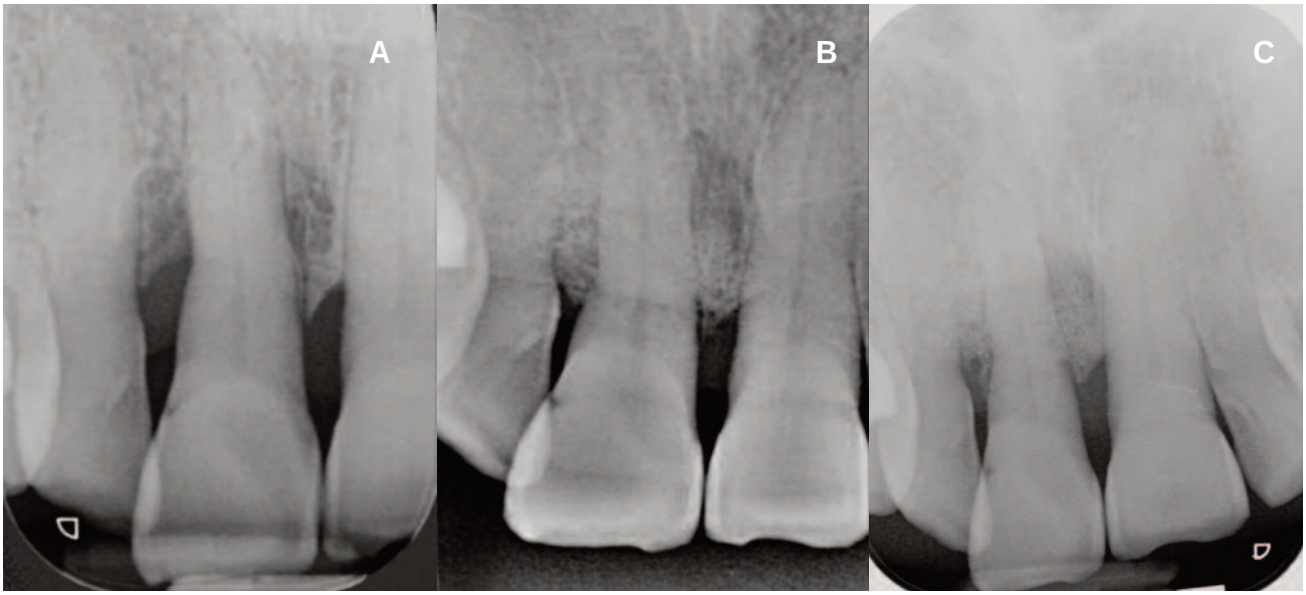

Figure 15. Radiographic progression of the case up to 9 months after surgery: a. Initial radiograph; b. Radiograph at 2 months; c. Radiograph at 9 months.

A periapical radiograph of the RSCI revealed radiographic bone refilling of the entire defect. Clinically, the pocket depth in the area was measured, revealing 2 mm mediovestibular, 3 mm distovestibular and 4 mm distopalatal, with a reduction in pocket depth of 6 and 7 mm, respectively, for vestibular depts and 7 mm for palatal compared to baseline. As expected after periodontal treatment that involved a reduction in gingival inflammation, an 2 mm distoplanal and 3 mm distovestibular and mediovestibular increase in the recession was observed (Figures 12-15).

DISCUSSION

In this case we were able to achieved a reduction in pocket depth of up to 7 mm and a notable gain in the clinical insertion depth of the defect that reached up to 5 mm distopalatal. This demonstrates the efficacy of periodontal regeneration in the treatment of teeth with advanced periodontitis and a poor prognosis.

Regarding this case, a limited search of the literature on periodontal regeneration over the last 10 years was carried out, revealing that the regenerative treatment of

Table 2. Clinical trials that use GTR or GTR + BG

Study	Time (months)	Treatment (number of defects)	Mean reduction in PD[1] (mm)	P	Mean GCI[2] (mm)	P
Grusovin et Esposito[19] (2009)	12	PMEs (15) CAD (15)	4.2 3.9	NS[3]	3.4 3.3	NS[3]
Chambrone et al.[20] (2010)	12	PMEs CAD	4.00 3.49	NS[3]	3.46 3.65	NS[3]
	24	PMEs CAD	4.21 3.28	<0.05	5.69 5.24	NS[3]
Sculean et al.[21] (2007)	48	PMEs (12) PMEs + IOs (13)	4.2 4.1	NS[3]	3.4 3.4	NS[3]
Kuro et al.[22] (2006)	8	PMEs (26) PMEs + IOs (26)	5.03 5.73	<0'05	4.06 5.17	<0.05
Cortellini et al.[18] (2011)	12	PMEs (25) Ext/implante	8.3 ND[4]	<0.001 ND4	7.8 ND[4]	<0.001 ND[4]
	60	PMEs (25) Ext/implante	8.7 ND[4]	NS[3] ND[4]	8.1 ND[4]	NS[3] ND[4]
Sculean et al.[14] (2008)	12	PMEs (10) RTG (10) PMEs + RTG (9) CAD (9)	4.1 4.2 4.3 3.7	<0.001 <0.001 <0.001 <0.001	3.4 4.2 3.3 2.0	<0.001 <0.001 <0.001 <0.001
	120	PMEs (10) RTG (10) PMEs + RTG (9) CAD (9)	4.6 3.4 3.6 3.5	NS[3] NS[3] NS[3] NS[3]	2.9 2.8 2.9 1.8	<0.001 <0.001 <0.001 <0.001

[1]Pocket Depth; [2]Gained Clinical Insertion; [3]Not significant; [4]Not defined

Table 3. Clinical trials that compare GTR vs. EMP

Study	Time (months)	Treatment (number of defects)	Mean reduction in PD[1] (mm)	P	Mean GCI[2] (mm)	P
Sculean et al [23] (2006)	12	PMEs (10) RTG (10)	4.1 4.6	NS[3]	3.2 3.0	NS[3]
	96	PMEs (10) RTG (10)	3.4 3.7	NS[3]	2.8 2.9	NS[3]
Crea et al.[24] (2008)	12	PMEs (19) RTG (20)	3.5 3.5	NS[3]	2.9 2.5	<0.05
	36	PMEs (19) RTG (20)	3.1 3.2	NS[3]	2.4 2.0	<0.05
Siciliano et al .[15] (2011)	12	PMEs (20) RTG (20)	2.9 5.5	<0.001	2.4 4.1	<0.001
Siciliano *et al .*[25] (2014)	12	PMEs + BG (20) RTG + IOs (20)	4,6 4,4	NS[3]	3,8 3,7	NS[3]

[1] Pocket Depth; [2]Gained Clinical Insertion; [3]Not significant; [4]Not defined.

intraosseous defects that resulted from progression of periodontitis is a predictable therapeutic procedure that has been widely studied in the field of periodontics.[3-32]

There are currently two main techniques in regenerative periodontal therapy: GTR and the use of EMPs, alone or in combination with BG. The efficacy of these two procedures have been evaluated separately in comparison with the Open Flap and Debridement (OFD), used alone or in combination with BG, as well as other studies that compare both techniques (Tables 1 to 3).

GTR, commonly using absorbable collagen membranes, is a procedure that has been shown in recent years to provide results superior to OFD, both in reducing pocket depth and in gains in clinical insertion. This has been shown in the recent publication by Sculean et al.[14] in which, though a very similar reduction in pocket depth was found for both GTR and OFD, a greater clinical insertion of up to 2.2 mm was seen in cases treated with GTR. In the study by Siciliano et al.[15], results favoring the use of GTR over OFD were also found, with a reduction in pocket depth of up to 5.5 mm and a gain in clinical insertion of between 3.2 and 4.1 mm. The papers published by Nygaard-Østby et al.[16] and Slotte et al.[17] which employed GTR and BG together revealed that the combination of collagen membranes together with bone xenografts provides significant improvement in reducing pocket depth and gaining clinical insertion compared to the use of both techniques separately (Table 1).

Regarding enamel matrix proteins, the first article to compare the effectiveness of EMP versus the OFD procedure was published by Heijl et al.[26] in 1997 in which the authors observed a statistically significant reduction of pocket depth and gains in clinical insertion favoring EMPs. Subsequently, the studies by Grusovin and Esposito[27] and Chambrone et al.[28] compared the efficacy of EMP versus OFD, primarily in three-wall defects6, showed a reduction in pocket depth of up to 5 mm and a gain in clinical insertion of between 3.4-5.6 mm. These results are very similar to those obtained using GTR, although it has been shown that treatment with EMP has a lower number of postoperative complications and, therefore, lower morbidity compared to GTR29. The study published by Sculean et al.[21] evaluated the efficacy of the EMP+BG combination. This study failed to demonstrate a statistically significant difference against EMP alone. However, the article published by Kuro et al.[22] revealed that the combination of EMP+BG resulted in a greater reduction in pocket depth and, especially, a greater gain in clinical insertion 8 months after surgery. In the systematic review y meta-analysis by Matarasso et al.[13] published in 2015 on the use of EMP and BG, the authors analyzed a total of 20 studies and 548 intraosseous defects. It was observed that the combination of EMP + BG provided additional improvement in gain in clinical insertion (3.76±1.07 mm after treatment with EMP + BG vs 3.32±1.04 mm after treatment with EMP alone) and pocket depth (4.22±1.20 mm after treatment with EMP + BG vs 4.12±1.07 mm after treatment with EMP alone). These data suggest that the use of EMP combined with BG should be evaluated based on the morphology of the defect, since combined use does not necessarily lead to better outcomes. In the randomized trial published by Siciliano in 2014[25], EMP and GTR were compared, both combined with BG. The authors did not find statistically

significant differences between procedures with regards to pocket depth and gain in clinical insertion. However, outcome was slightly better in the EMP + BG group (Tables 2 and 3).

Therefore, for the use of xenografts, both combined with GTR or EMPs, the most recent literature indicates that in many cases, the addition of a BG does not provide truly significant improvements in reducing pocket depth and gaining clinical insertion. This indicates that the use of bone xenografts is not really necessary in certain cases of intraosseous defects and outcome will depend on its morphology.[14,21,30,31] In addition, it is important to keep in mind the number of complications related to both technologies. Sanz et al.[32] observed a 100% complication rate associated with GTR compared to a 6% in EMP. Conversely, one should consider whether the clinical outcomes would improve by combining the use of the three techniques in periodontal regeneration. In a study by Lekovic et al.[33] published in 2001, the combination of EMP + GTR + BG was compared to OFD in the treatment of different intraosseous defects. The authors achieved a reduction in pocket depth of 4.95±1.52 mm and a gain in clinical insertion of 3.89±1.16 mm. However, this study should ideally compare the results of this combination against a positive control group in which the defects would be treated with GTR, currently the gold standard. Therefore, methodological issues preclude a definitive conclusion.

Conversely, all intraosseous defects are not equal nor istheir prognosis. Often times, bone loss around some teeth is very extensive, where the prognosis for said teeth can be very poor to non-viable, thereby leading to extraction. y cols.[18] Given the efficacy of periodontal regenerative therapy in deep intraosseous defects 60 Ext/implante also be effective in teeth with a very poor or non-viable prognosis. Cortellini et al.[18] carried out a randomized clinical trial that compared regenerative treatment of teeth with advanced periodontitis and a poor or even impossible prognosis to extraction of those teeth and subsequent treatment with implants. Different techniques were used in regenerative treatment, including the combination of GTR + EMP + BG, in very deep circumferential defects with loss of various walls, obtaining results of up to 12 mm in reduction of pocket depth and more than 10 mm in gain in clinical insertion. After completion of the study, they did not find differences in comfort, both in function and esthetics in both groups. In the clinical case presented (a RSCI with a very poor prognosis), there was a circumferential three-wall defect with extension almost to the apex and loss of the entire vestibular plate. Given the complexity of the case, and in an attempt to achieve an ideal regeneration of all of the walls of the defect including the external plate, it was decided to use, according to the article by Cortellini et al.18 in which very similar cases were treated, a combination of absorbable collagen membrane, bone xenograft and enamel matrix protein. This treatment achieved a reduction in pocket depth of 7 mm and a gain in clinical insertion of up to 5 mm, thereby obtaining healthy values and improving the tooth's prognosis.

These results demonstrate that, even in the most severe cases, periodontal regeneration is truly effective and may be considered as a real alternative to extraction in teeth with severely affected periodontal support. However, one must keep in mind that the combination of the three techniques significantly increases the cost of treatment, so this article should not be taken to suggest that it is the treatment of choice but rather reserved for very advanced disease states.

CONCLUSIONS

Periodontal regeneration has been shown to be effective in the treatment of vertical intraosseous defects, including teeth with a poor prognosis.

The combination of GTR + BG, EMP + BG has led to a benefit in outcomes and prognosis, which should be selected based on the amount of loss and the characteristics of the defect. However, the higher level of complexity with the technique and especially the higher cost makes the combination of the three periodontal regeneration materials reserved only for very specific cases and always with the patient's consent.

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Literature review

Pathogenesis of oral cancer caused by human papilloma virus

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ABSTRACT

Introduction: Oral cancer represents 1-2% of all cancers in the body, 90% of which is correspond to oral squamous cell carcinoma (OSCC). Risk factors traditionally involved in the development of oral cancer are advanced age, male sex, and prolonged expo-sure to habits such as alcohol, tobacco, and betel nut. In recent years, the increasing incidence of OSCC in young patients without exposure to classical risk factors suggests the presence of other possible pathogenic agents, especially the Human Papilloma Virus (HPV).

Objectives: To reveal on the molecular development of OSCC by HPV as an oncovirus and its characteristics.

Results: The studies show the high oncogenic risk presented by HPV subtypes 16 and 18 acting via their E6 and E7 proteins, directly affecting p53, on retinoblastoma (pRb) and other enzymes involved in regulation of the cell cycle like PI3K, thereby altering processes of cellular apoptosis, proliferation and differentiation.

Conclusions: HPV plays an important role as a carcinogen in the onset of OSCC associating a more favorable prognosis compared to other etiologic factors. The process of oncogenesis in the development of OSCC caused by HPV is linked to the high-risk subtypes, as well as the expression of viral proteins E6 and E7, which are responsible for inhibiting the activity of cell cycle tumor suppressor genes.

KEYWORDS

Oral cancer; Human papilloma virus; Oncoproteins; Oncogenesis

INTRODUCTION

Oral cancer comprises 1-2% of all cancers in the body, making it the sixth most common neoplasm worldwide.[1,2] Within this group, the most common entity is oral squamous cell carcinoma (OSCC), which constitutes 90% of all cancers of the oral cavity.[2] The prognosis for OSCC is determined by the stage at diagnosis, following the T (Tumor), N (Metastasis to lymph nodes, M (Distant metastasis) classification.[3] Tumors in the floor of the mouth associates the worst prognosis. The survival rate depends primarily on the tumor stage at the time of diagnosis, generally abut 50% at 5 years. Risk factors traditionally involved in the development of oral cancer are advanced age, male sex, and prolonged exposure to habits such as alcohol, tobacco, and betel nut.[4-8] There are also other predisposing factors like radiation therapy, immunosuppression and chronic irritation.[9] In recent years, different authors have studied infectious carcinogens, specifically the participation of the human papilloma virus (HPV), since there is evidence that it may play an important role in the development of this type of cancer, especially in carcinoma of the cervix.

The increase in the incidence of OSCC in young patients without exposure to classical risk factors suggests the presence of other possible pathogenic agents, especially HPV[9], which is the most common sexually transmitted viral infection, being present in 12-63% of all OSCC cases.[10,11] HPV is widely known to be a pathogenic agent that causes different benign mucocutaneous lesions such as verruca vulgaris, squamous papilloma and condyloma acuminatum.[4,6] In the oral cavity, this virus is responsible for different oral lesions according to its subtype, with 6 and 11 being responsible for squamous cell papilloma and 2 and 4 for verruca vulgaris[2], 13 and 32 for lesions such as Heck's disease or focal epithelial hyperplasia, while subtypes 16 and 18 have a high potential for malignancy affecting the head and neck region (subtypes 31, 33, 51, 55, 58...).[4,6,10]

Some studies show that 70.59% of OSCC are positive to HPV and have shown a higher prevalence in subtype 18 compared to subtype 16.[12] In addition, one study concludes that 48% of OSCC located in the tongue are positive for this virus.[13] A systematic review revealed a lower prevalence of HPV-16 in OSCC (0-2%), being greater in oropharyngeal carcinomas (50-80%).[14]

In general, HPV-associated OSCC occurs more frequently than HPV-negative OSCC in young people, with a mean age difference of 4-10 years. This may be associated with a current increase in the number of sexual partners in young people and adolescents compared to previous decades. OSCC has also been shown to be positive for HPV in individuals who have higher levels of education, being 5 times more frequent in men.[1,15]

TABLE 1. DIFFERENCES BETWEEN HPV-POSITIVE AND HPV-NEGATIVE[3, 6, 16].

Therapy	HPV-positive tumors	HPV-negative tumors
Molecular characteristics	Altered p53, increased expression of p16, decrease in RB expression, degraded p53.	Mutación Mutation in p53, genomic instability.
Pathogenic characteristics	Direct transformation by oncoproteins E6 and E7.	Use of ethanol and tobacco and poor oral hygiene - chronic inflammatory state with free radicals - damage in DNA.
Cellular composition	T Cells (CD3+, CD4+, CD8+, CD34+), NK cells, B cells and monocytes.	Endothelial cells, keratinocytes and fibroblasts in the epidermis.
Epidemiological characteristics	Male, young, Caucasian race, increased number of sexual partners, marihuana use.	Older population, African-Americans, tobacco and ethanol users, poor oral hygiene
Clinical Characteristics	Early T stage with extensive lymph node involvement. Cystic or multilevel tumor phenotype.	Late T stage. Generally, less lymph node involvement.
Metastatic characteristics	Distant metastasis occurs after chemotherapy with a distinct pattern to the lung, liver, bone and other tissues. Requires alternative monitoring strategies.	Local and lung metastasis. Reduction of the distant metastasis pattern in bone, liver and other sites.

Table 2. Histopathology differences between HPV-positive and HPV-negative[6].

HPV-positive tumors	HPV-negative tumors
Not associated with epithelial dysplasia or keratinization.	Keratinization present.
Well differentiated or undifferentiated.	Moderately differentiated.
Has lymphocyte invasion.	Not invaded by lymphocytes.
Lobular growth.	No lobular growth.
Basaloid morphology.	No basaloid variants present.

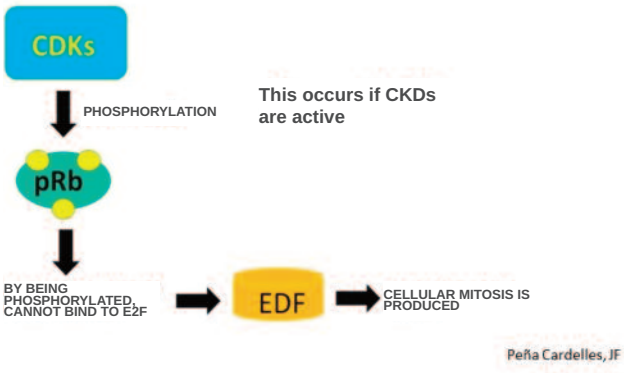

Figure 1. Phosphorylation of pRb.

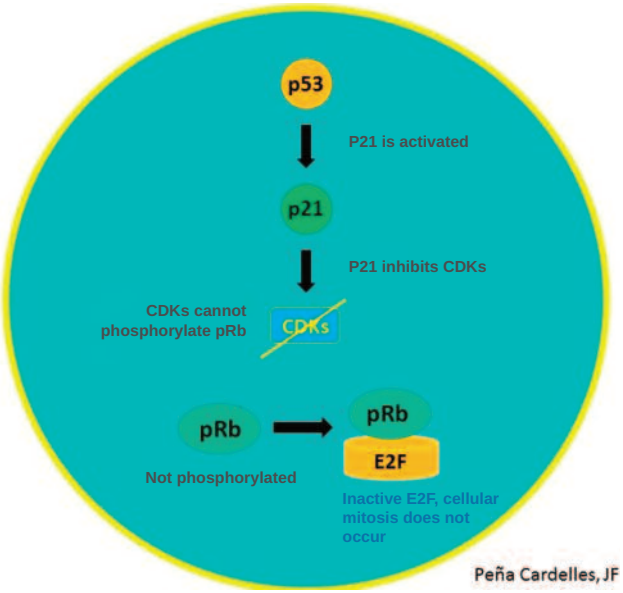

Figure 2. Action of tumor suppression proteins p53 and pRb.

HPV induces a series of changes in chromosomal profiles and gene expression in the tumor lesions where it is present, constituting a different biological type in comparison to tumor lesions associated with traditional risk factors, to the point that patients with HPV-positive tumors have a greater long-term survival rate[5] (Table 1). Histopathologically, there are also differences between HPV-positive and HPV-negative tumors[17] (Table 2).

The purpose of this article is to describe the pathogenesis of OSCC by HPV through a review of the most recent scientific literature, aimed to understand the most important molecular processes responsible for the development of tumor pathology, as well as the specific characteristics of the entity.

HPV AND CARCINOGENESIS

Viruses are microorganisms that need a host cell to complete their lifecycle, making them obligate intracellular parasites. According to this relationship, cells have developed strategies to control viral replication and, at the same time, viruses have developed mechanisms to evade the host cell's defenses.

The defense mechanisms of host cells occur during the cell cycle, which is the process by which the cell can carry out cellular mitosis and replication of its genetic material. The cell cycle comprises different phases: G1, S, G2, M and a fifth phase known as G0 in which the cell remains out of the cell cycle.[3]

Table 3. HPV proteins and their respective functions[19-24].

Protein	Protein function
L1	Largest protein, involved in the virion assembly process.
L2	Essential for the transport of DNA to the interior of the host cell's nucleus.
E1	Helps E2 form a protein complex for replication of the viral DNA.
E2	Viral transcription factor. Helps E1 facilitate replication of viral DNA.
E4	Involved in the modification of viral DNA after transcription.
E5	Regulates growth factors and cell proliferation.
E6	Inhibits p53.
E7	Inhibits pRb, activates E2F, altering the G1/S control point.

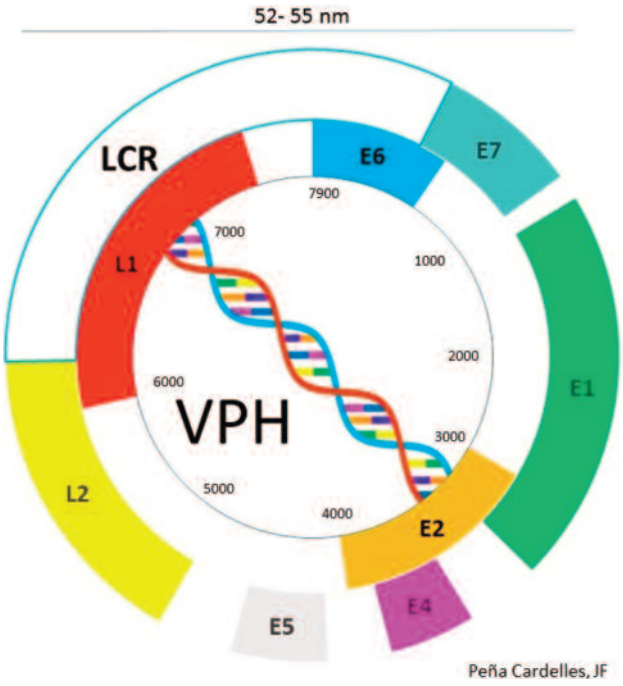

Figure 3. Structure of the human papilloma virus (HPV).

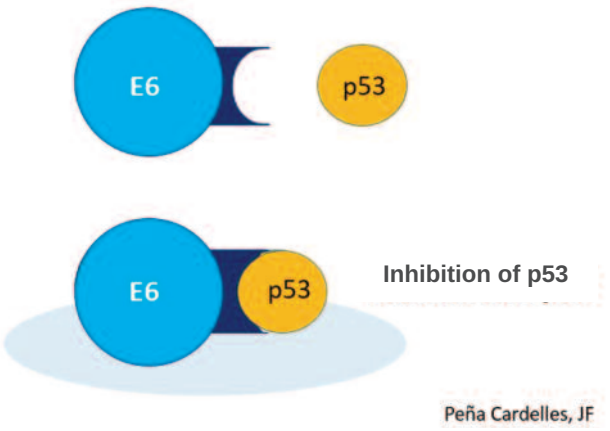

Figure 4. Inhibition of p53 by the E6 viral protein.

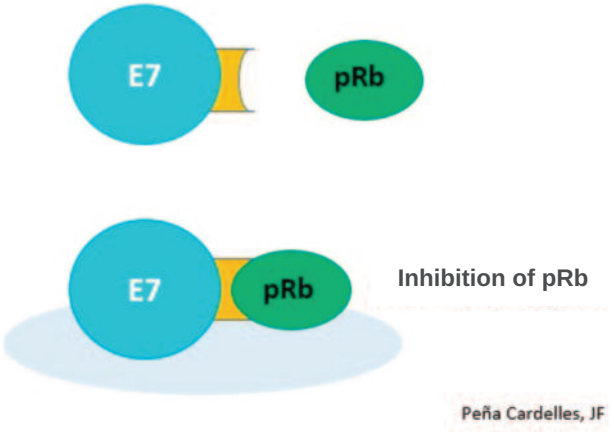

Figure 5. Inhibition of pRb by viral protein E7

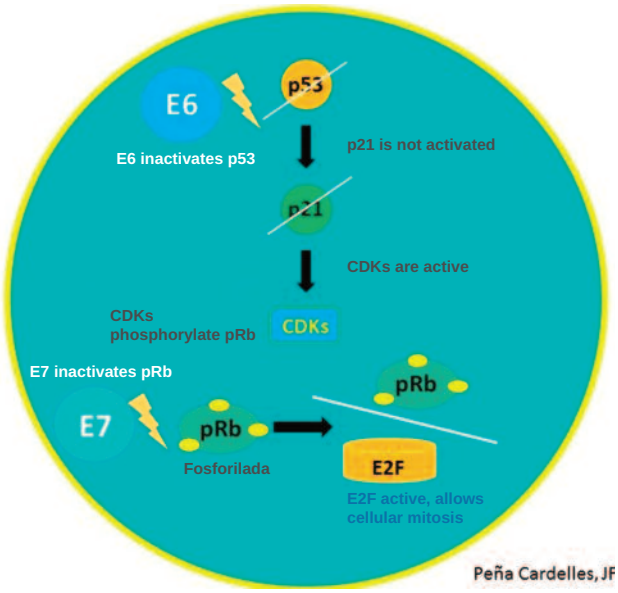

Figure 6. Inhibition of tumor suppression proteins p53 and pRb by viral proteins E6 and E7. Consequences of the mutation occurring in cell DNA due to HPV.

In order to understand the carcinogenesis process caused by HPV, it is important to remember that the tumor suppression protein involved in the cellular cycle is known as p53 (named after its molecular weight). P53 is normally found in small amounts in the cell, but in the face of cell damage, it is synthesized in large quantities. The p53 gene is capable of stopping the cell cycle in the G1, S and G2 phases. In addition, if cell damage continues, it can cause controlled apoptosis of the cell.[3]

P53 acts as a transcriptor in order to activate the p21 gene, which produces the protein p21 capable of inhibiting cyclin-dependent kinases (CDKs), thereby inhibiting the cell's mitotic activity via the retinoblastoma (pRb) protein's hypophosphorylation state (not being phosphorolysed by CKDs). PRb can be found in two states: hypophosphorylated and hyperphosphorylated. In the hypophosphorylated state, pRb is active and can perform its tumor suppressor function by binding and blocking E2F (a protein that, unbound, allows for the

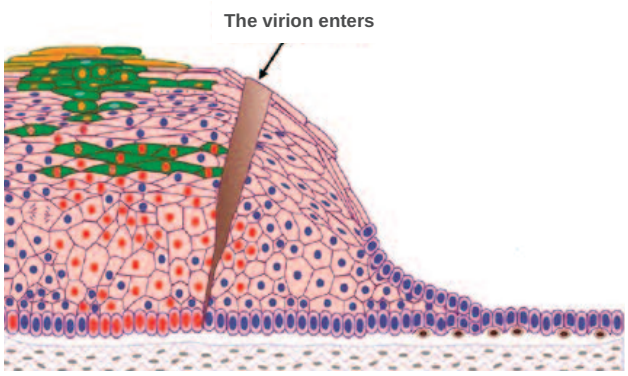

Figure 7. The virion enters the basal membrane through micro-cracks present in the oral mucosa in order to infect basal keratinocytes. Modified from Doorbar et al.[28]

progression of G1 to S), thereby impeding the cell's progression through the cell cycle[3] (Figures 1 and 2).

The process of HPV-related carcinogenesis is related to the cell cycle inside the host cell. HPV is a 52-55 nm virus made up of a double chain of DNA. The virus genome contains three early genes called E (Early), some late genes called L (Late) and some genes called LCR (Long Control Region). The E region is crucial for viral replication and transcription. The L region is responsible for making structural proteins (L1 and L2) that are essential for assembly of the virions. LCR participates in replication and transcription of the viral DNA (Figure 3).

The virus has proteins such as E1 to control its own replication. Upon entry into the cell nucleus, the viral genome produces a mutation in the DNA, inhibiting the E6 protein for p53 and the E7 protein for pRb (the transcription of proteins E6 and E7 become regulated by the viral E2 protein)[3,6,18] (Table 3).

P53, the function of which we specified above (regulation of the cell cycle and apoptosis) will not activate p21 since p53 is inhibited by the E6 viral protein. Therefore, the CDKs will phosphorylate pRb, leaving the E2F transcription factor free (when it is bound to pRb, E2F is inactivated) and leading to both the progression from G1 to S of the cell cycle and cell mitosis[10,25] (Figure 4).

In addition, the E7 gene codes for the E7 protein which inactivates it if bound to pRb (a key protein in avoiding cell mitosis). This prevents it from binding to the E2F transcription factor, thereby promoting progression of the cell cycle[1,5,7,10,25] (Figures 5 and 6).

This functional inactivation of pRb includes increased expression of the p16 tumor suppression protein.[1,25] This protein plays an important role in regulation of the cell cycle and mutations that occur increase the risk of developing various cancers. In fact, according to some studies, the majority of HPV-positive OSCC show an overexpression of the p16 protein.[26] For this reason, various studies have suggested that p16 positivity may be used as a biomarker for HPV-associated tumors and as a prognostic factor for OSCC.[27]

Finally, E5 increases the action of CDKs, thereby promoting proliferation and inhibiting cell differentiation. The E4 protein helps in the assembly of

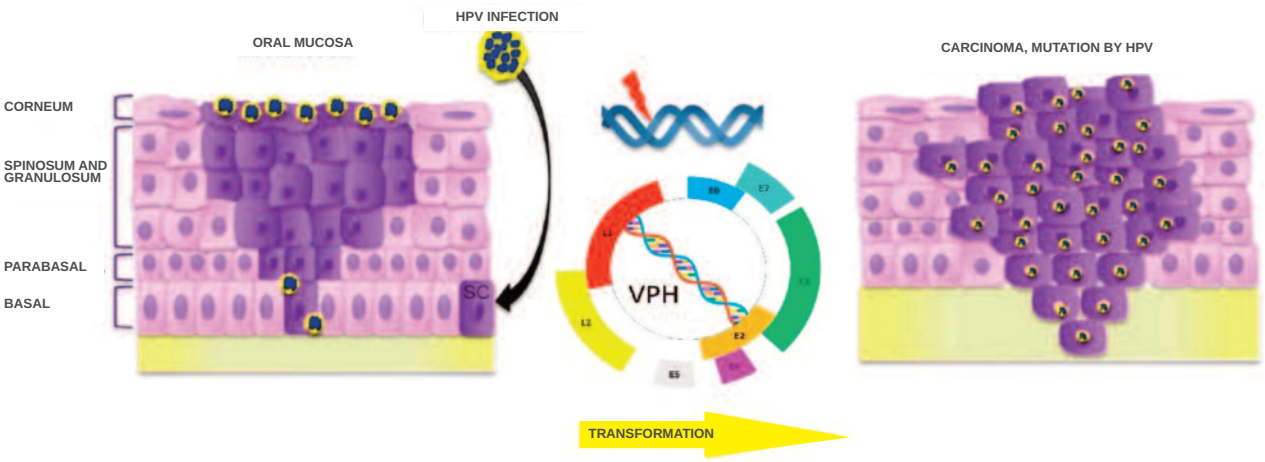

Figure 8. Mitosis of cells with a mutation caused by HPV, until reaching the stratus corneum and making the presence of a tumor in the oral epithelium apparent. Modified from Pullos et. al.[29]

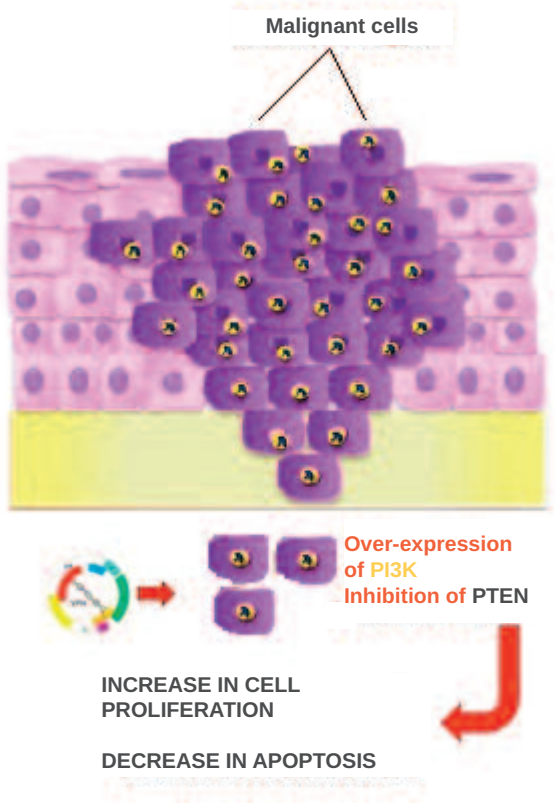

Figure 9. Action of HPV on PI3K and PTEN. Modified from Pullos et. al[29]

proteins L1 and L2 for the formation of virions, as well as the entry of the virus into the cell nucleus.[4,6,10] Thus, there is an infected cell whose genetic material, suppressor genes and tumor suppressor proteins are altered in such a way that it is not capable of controlling its own cell cycle, thereby transforming into potentially malignant cell.

The HPV virion passes through micro-cracks to infect oral basal epithelial cells. Once there, the process of DNA mutation begins inside the host cell. The virion enters the interior of the cell and, through the action of the L2 protein, is capable of integrating its genome into the nuclear DNA structure of the host cell[6] (Figure 7).

When the host cell later divides and starts to differentiate into mature keratinocytes, the DNA alterations increase, as does the number of malignant cells. Finally, the cells, initially the basal cells, begin to increase in number within the epithelial layers until reaching the stratum corneum and the presence of the tumor becomes evident in the oral epithelium (Figure 8).

Several studies have shown that OSCCs likely caused by HPV have a better prognosis than those that are HPV-negative. This can be explained by studying tumor stem cells (TSC). A TSC is defined as a cell within a tumor that can renew itself automatically, supporting tumor growth and generating cancerous cell lines that make up the majority of tumor cells, which is why they are known as tumor-initiating cells or tumorigenic cells. The tumor cells present in OSCCs that express high levels of CD44 antigen may have TSC properties, having increased metastatic potential and higher resistance to treatment. Curiously, the marker for CD44 enrichment is lower in patients with HPV-positive OSCC than in patients with HPV-negative OSCC. An initial idea was that patients with HPV-positive OSCC would respond more favorably to treatment than patients with HPV-negative OSCC because HPV-positive tumors could harbor fewer TSCs. However, several studies revealed that the appearance of TSC is greater in HPV-positive tumors than in HPV-negative tumors. It has been shown that patients with HPV-positive OSCC have a better prognosis and respond more favorably to radiation and chemotherapy than patients with HPV-negative OSCC, probably due to the TSC phenotype or quality regardless of its quantity. They have some properties that make them more susceptible to anti-tumor therapy.[29,30]

The most widely studied route for explaining the existing relationship between HPV and OSCC is inhibition of p53 and pRb. However, other mechanisms of action related to the cell cycle are currently being described and may ultimately explain the appearance of a tumor cell. In this regard, the best prognosis for HPV-related OSCC may also be explained by some studies that investigate the route by which HPV may improve its replication, involving deactivation of DNA repair (DDR), specifically on ATM and ATR kinases. This suppression of DDR may partially explain why HPV-positive cells are more susceptible to radiation therapy since it is not possible to counteract the accumulated damaging process in DNA prior to oncological treatment when DDR is not activated.

Other studies investigate the phosphoinositide 3-kinase (PI3K) signaling route. These enzymes are crucial in numerous cell functions involved in cell growth and

survival, promoting cell proliferation and avoiding apoptosis. It has been confirmed that 55% of cases of HPV-positive carcinoma contain a mutation and overexpression of PI3K. This alteration in PI3K is also related to suppression of phosphatidilin-sitol-3,4,5-triphosphate 3-phosphatase (PTEN), an enzyme considered to be a tumor suppressor that acts as an agonist in the PI3K signally pathway and has been shown to be altered in the presence of HPV[29,32] (Figure 9).

Currently under research is the role played by HPV in autophagia, an intracellular homeostatic process in which aged organelles and long-chain proteins are degrading, which acts as a mechanism of cellular recycling. It has been observed that the virulence of HPV can be mediated by autophagy in such a way that biomolecular inhibition of this process would increase the invasive capability of the virus.[33-35] This is because HPV-16 pseudovirions activate Akt and mTOR pathways in human keratinocytes, thereby inhibiting the first stages of autophagy during interaction of the virus with the cell.[23] The Akt route is an enzyme group that participates in the cell growth and survival process while mTOR regulates cell functions for multiplication and survival.[35,36]

The oncoproteins above-mentioned, E6 and E7, also modulate autophagy through two different pathways. First, E6 causes a restriction of nutrients in keratinocytes that leads to an increase in mTORC1 activity. This inhibits autophagy due to an increase in AKT activity. However, it has been shown that E7 produces the opposite effect, inducing autophagy in keratinocytes.[35] This binds with pyruvate-kinase-M2 (PK-M2), an enzyme that catalyzes the final step of glycolysis. This binding results in the dimerization of PK-M2, restoring nucleic acid synthesis and promoting cell proliferation. This dimerization of PK-M2 results in partial inhibition of glycolysis, which increases its intermediaries[36], thereby promoting synthesis of nucleic acids, lipids and amino acids and increasing autophagy-mediated cell survival mechanisms. This results in rapid cell proliferation and a resulting increase in tumor growth.[35,36] For this reason, it is believed that there may be a balance between oncoproteins E6 and E7 that would determine the role of autophagy in the pathogenesis of head and neck cancer.[34-36]

To a lesser degree, alterations of the tumor suppressor genes such as PBXW7 have been studied. This gene codes for a specific group of proteins called F-box that constitute the ubiquitin ligase complex involved in phosphorylation-dependent ubiquitination.

Ubiquitination is a process by which altered or unusable proteins are destroyed in proteasomes. Therefore, an alteration in this cellular recycling process would contribute to a higher probability of the appearance of potentially tumorous cells.[29]

Another gene that has been confirmed to be altered in the presence of HPV is NOTCH1, which codes for different transmembrane proteins involved in cell growth and in the regulation of interactions that occur with adjacent cells. Mutations in these proteins seem to contribute to alterations of the tumor cycle and promote the appearance of cancer. Viral protein E6 is also considered to have the ability to increase the expression of the EGFR (epidermal growth factor receptor) HBD3 protein. This protein promotes proliferation of keratinocytes in the mucosa, facilitating malignant transformation of the tissue.[8,29]

CONCLUSIONS

HPV plays an important role as a carcinogen in the onset of OSCC with a more favorable prognosis compared to tumors associated with other etiologic factors. The process of OSCC oncogenesis by HPV is determined by its high-risk subtypes, as well as the expression of viral proteins E6 and E7, which are responsible for inhibiting the activity of tumor suppressor genes of the cell cycle.

Other pathways that may be involved in the development of OSCC are currently under research, the majority of which are related to alterations in the cell cycle. It is important to clarify the pathogenic process in order to improve prevention at a clinical level, especially by vaccinating against HPV.

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Original article

Atraumatic extraction of implants: predictability of the technique and the re-implanted implant

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ABSTRACT

Introduction: Reversibility of implant treatment is currently one of the key points for retreatment in cases in which there has been peri-implantitis or bone loss that leads to implant failure. A technique that allows for atraumatic extraction of the implant and reinsertion in the same surgical phase effectively resolves the problem.

Methods: This is a pilot study on nine patients who underwent implant removal and implantation in the same surgical phase and location. These reinserted implants were monitored over time to evaluate survival.

Results: Implants were monitored for 50±2 months from insertion (range 48-52 months) and 43±3 months from loading (range 40 to 48 months). No failed implant was observed during follow-up. Mesial bone loss was 1.0 ± 0.8 mm and distal bone loss was 1.0 ± 0.8 mm.

Conclusions: The atraumatic removal technique is safe and predictable and can be used without risk in the majority of implants currently on the market.

KEYWORDS

Implant removal; Peri-implantitis; Reimplanted implant

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INTRODUCTION

Removal of failed implants for various reasons is a growing challenge in our practice. In order to solve this new problem, different techniques have been developed other than complete trephining and removal of the implant with surrounding bone cylinder, which are considered the traditional techniques.

Several studies on the implant removal techniques can be found in the international literature. The study by Covani *et al.* in 2006 and 2009[1,2] shows a more conservative technique than conventional trephines for the removal of implants using a low-revolution drill with irrigation that is capable of removing the bone around the implant. When the bone is removed, the structural union is broken from the integration and the implant can be removed. This technique, besides being more conservative than conventional trephining, leaves defects of greater diameter than the extracted implant, resulting in loss of part of the bone bed.

Counter-torque-based techniques have been reported in humans, to remove small-diameter implants, as in the study by Simon *et al.*[3] These authors use a device to remove the implants without the intermediate extractor piece. Despite being implants of smaller diameter, they found various negative effects such as: fracture, deformation of the implant and fracture of bone fragments.

The technique reported by our study group (Anitua *et al.*)[4] allows for atraumatic counter-torque removal of the implant, leaving a completely preserved bone bed. The extractors remove the implant without damaging the area where it was placed and, usually it allows for the insertion of a new implant in the same place during the same surgical act.

In addition, follow-up of these implants inserted in the area of the previous removal is not well documented. There are many studies that report cases of implants placed immediately following extraction, but only a few describes follow-up of implants placed in the same site of tooth removal performed in the same surgical procedure.

MATERIALS AND METHODS

Implant removals were carried out using the explantation kit (BTI Biotechnology Institute, Vitoria, Spain). The kit consists of a wrench that is used to transmit the counter-torque force to the implant through a connector (extractor) that is inserted in the implant's connection. The wrench is set to 200 Ncm so that it disarms automatically when it reaches this level of force, thereby avoiding lesions caused by shearing or bone rupture caused by levels of force greater than 200 Ncm,

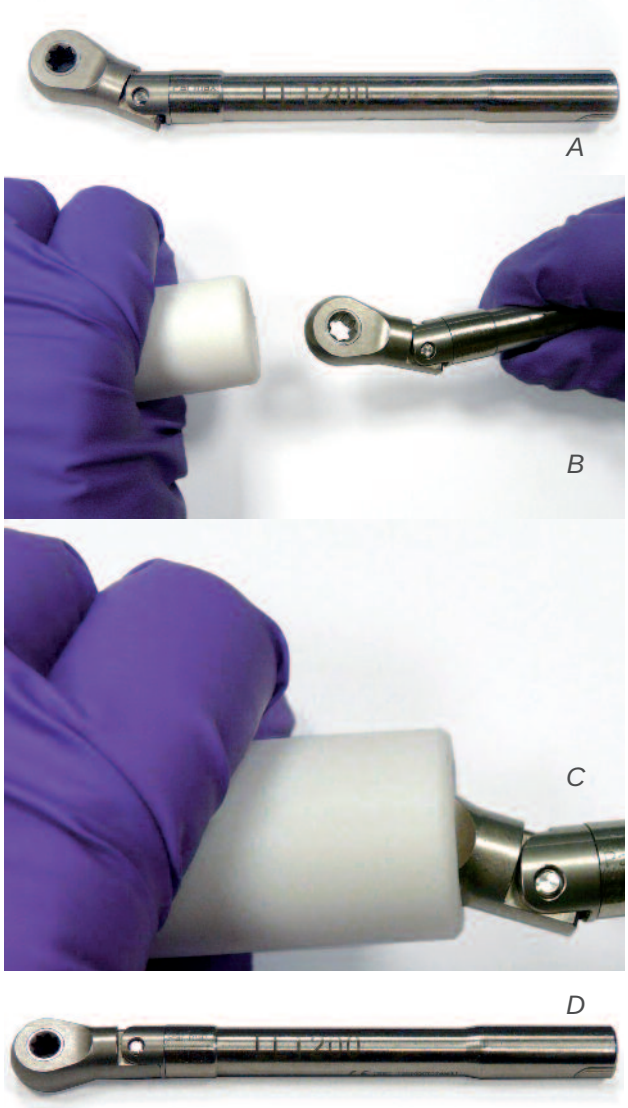

Figure 1.
A) Wrench that has deactivated upon reaching 200 Ncm.
B) In order to bypass the deactivation and be able to use it, we introduce the plastic rearming tube.
C) We apply pressure to move the wrench to its original position (armed).
D) We remove the wrench from the plastic tube.

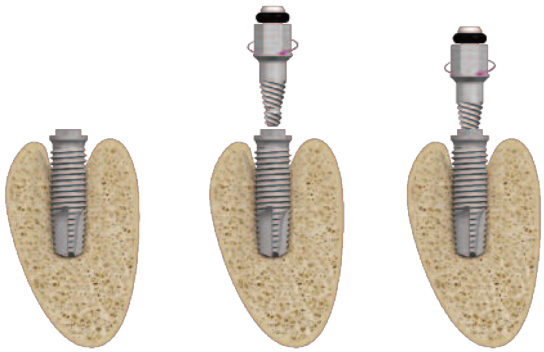

Figure 2. Introduction of the extractor in a counterclockwise direction in the implant connection.

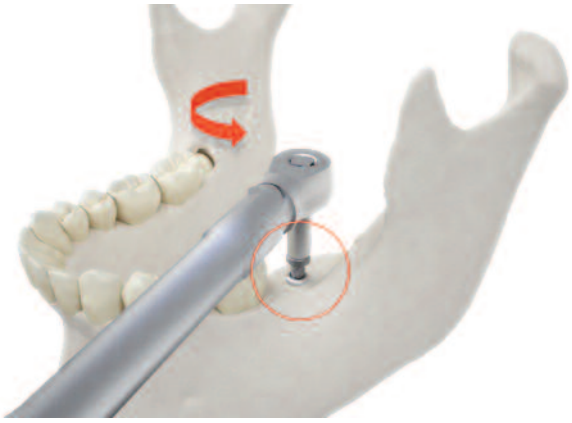

Figure 3. We continue the counterclockwise movement with the torque wrench. It is important that this movement is kept axial to the implant at all times.

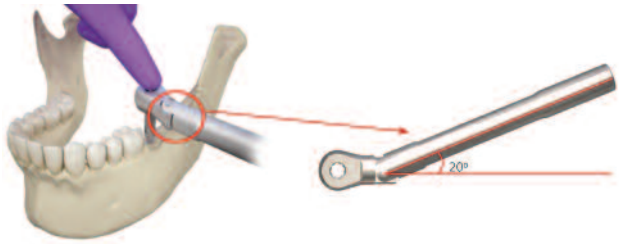

Figure 4. Disarticulation of the torque wrench which indicates that we have reached 200 Ncm.

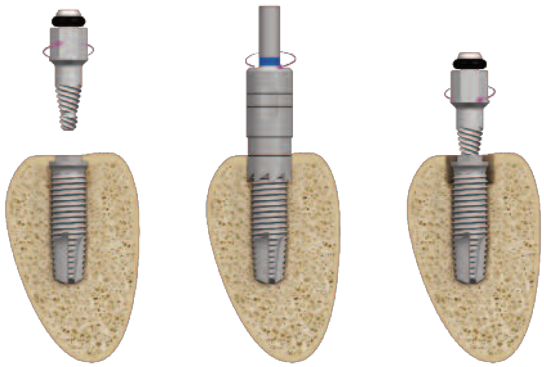

Figure 5. Trephining of the first 2-3 mm of the implant to break the cortical union of the first threads and then an attempt to remove the implant with the extractor.

or fracture of the extractor in the interior of the implant. When the wrench is disarmed, it can be rearmed by applying a counter force in a plastic cylinder that allows for its introduction and righting[7] (Figure 1).

The extractor is positioned using a manual socket wrench in a counterclockwise direction and then with the anticlockwise force is applied with the wrench (counter-torque) to the implant-extractor set which will cause rupture of the bone-implant union, resulting in loss of osseointegration (Figures 2 and 3).

For cases exceeding 200 Ncm (the removal torque) allowed by the wrench, thereby making it impossible to continue with the removal, ultrafine trephining is performed around the implant (1-2 mm) in the most coronal bone. The maneuver is then attempted again with a new extractor. Elimination of these first millimeters of cortical bone drastically reduces the removal torque and, therefore, we are now able to remove the implant with a counter-torque of less than 200 ncm[7] (Figures 4 and 5).

Once the new implants were inserted, they were monitored in order to evaluate the predictability of the reimplanted implant.

RESULTS

Nine removals were carried out in nine patients in which new implants were placed in the same bed and surgical act.

Six of the patients were women with a mean age of 61±4 years. Six of the implants were inserted in the superior maxillary and three in the mandible. The mean extraction torque for the failed implants was 162±41 Ncm.

The implants inserted in the post-removal beds had a mean torque of 36±16 Ncm. Only two implants were inserted with a torque of less than 15 Ncm.

Two implants were short (5.5 mm x 5.5 mm and 5.5 mm x 7.5 mm). Three of the implants were 8.5 mm in length with diameters of 4, 4.5 and 5.5 mm. The remaining implants were 10 to 13 mm in length and 3.75 to 5 mm in diameter.

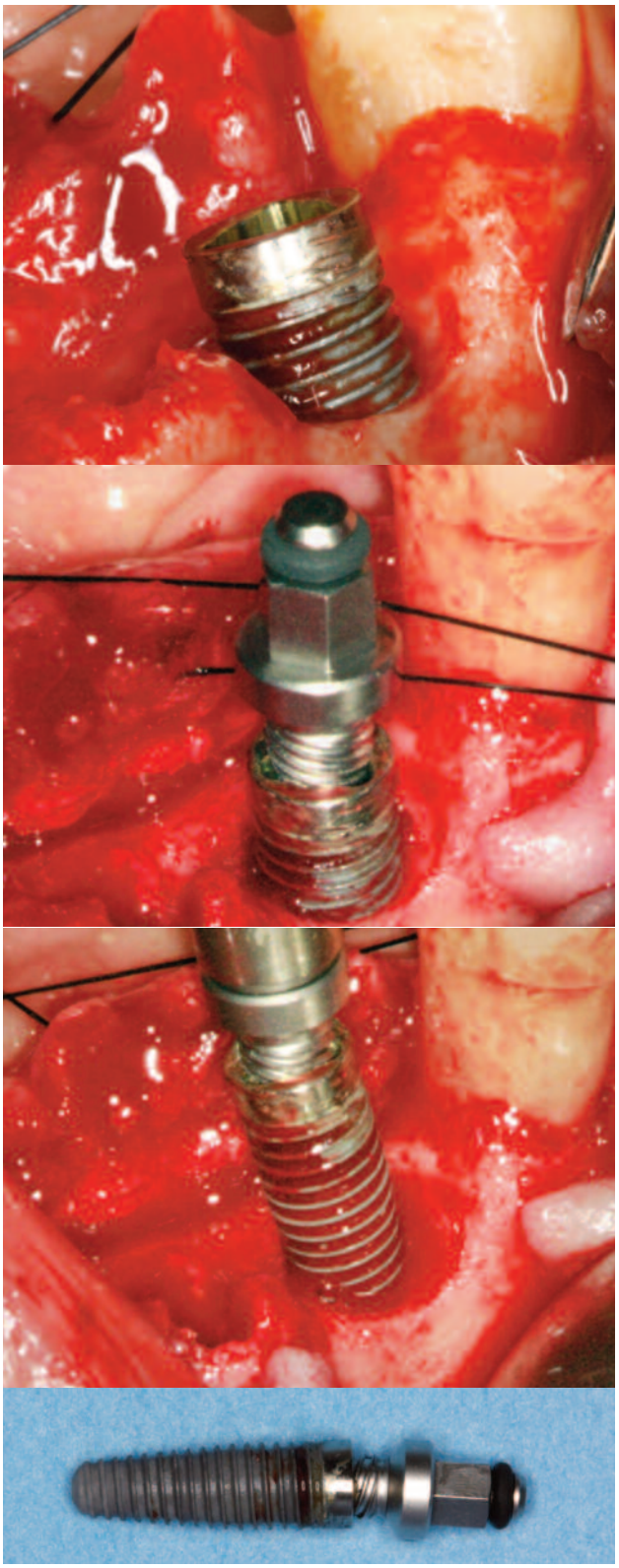

Figure 6. Initial images of the case where the situation of the implant in position 34 can be observed.

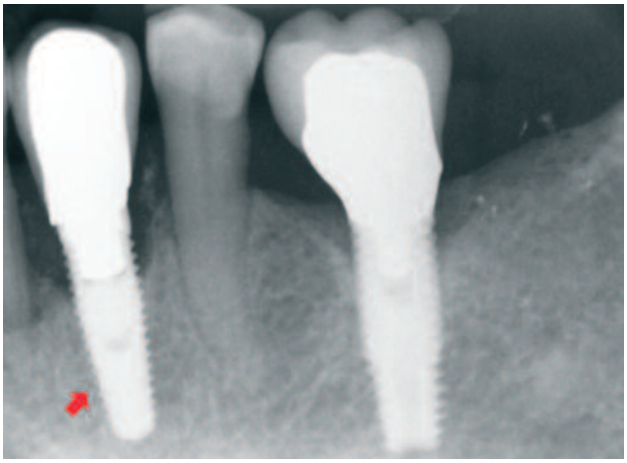

Figure 7. Initial radiograph. We can observe the poor periodontal situation of the antero-interior face. In addition to removal of the implant in position 34, we decided to extract the affected teeth and place implants in the area.

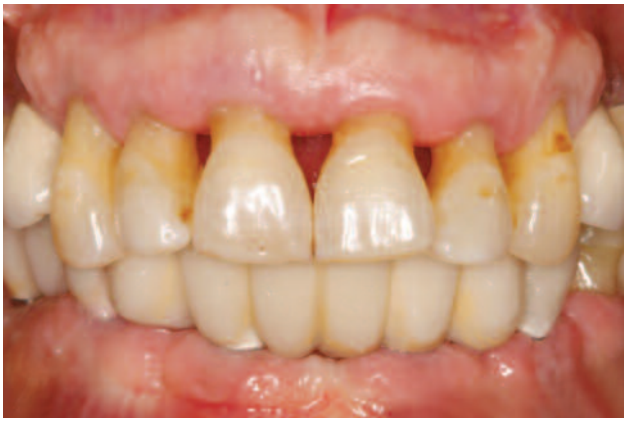

Figure 8. Image of the patient with definitive prosthesis. We can observe the state of the peri-implant and periodontal tissues.

Implants were monitored for 50±2 months from insertion (range 48-52 months) and 43±3 months from loading (range 40 to 48 months). No failed implant was observed during follow-up.

Mesial bone loss was 1.0 ± 0.8 mm and distal bone loss was 1.0 ± 0.8 mm.

DISCUSSION

Many studies report cases of implants placed immediately following extraction, but only a few describe the follow-up of implants placed in the same site of tooth removal performed in the same surgical act.

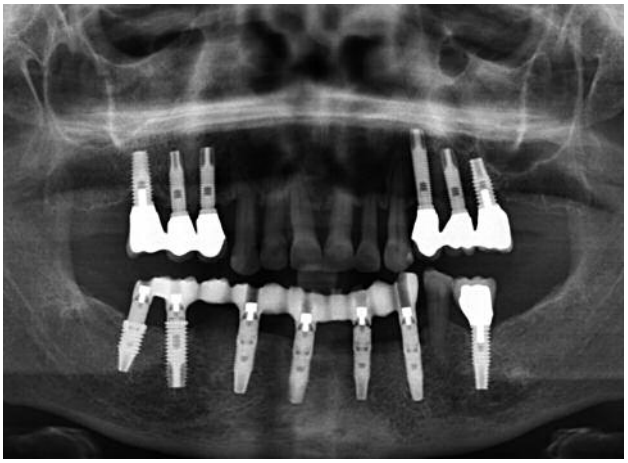

Figure 9. Radiographic image of the definitive prosthetic at one year. We can see the stability of all of the implants placed.

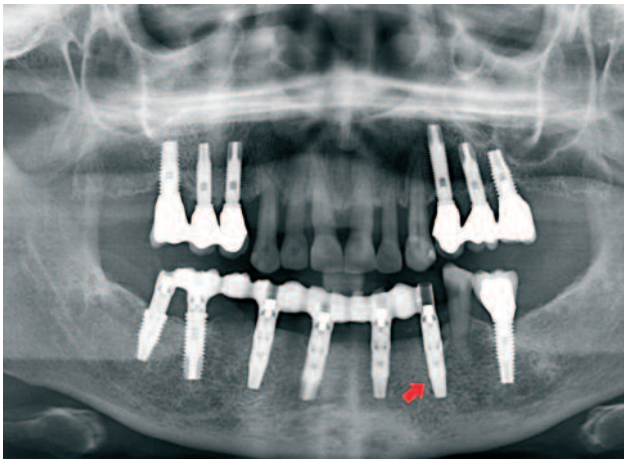

Figure 10. Radiographic image at 3 years. Stability of tissues is maintained.

The first studies on the possibility of dental reimplantation after removal in humans and follow-up of the reimplanted implant were by Covani *et al.* (2006, 2009 and 2010).[1,2,8] In these studies, removal was performed preserving the maximum amount of alveolar bone in the peri-implant bed through the separation of bone that was in contact with the implant by drilling with a fine low speed drill with irrigation. The implants were then placed after another drilling according to the manufacturer's technical specifications with a new drilling to prepare a new slightly wider bed in order to be able to stabilize the implant. All of the implants treated with this method were implants that were removed by fracture at different levels as they were cylindrical threaded implants.

The total number of cases recorded is 9 implants in 9 patients. All of these were rehabilitated after an osseointegration period and there was no sign of early failure at the reentry site. Following prosthetic rehabilitation, all implants were followed for 6 months (12 months in total from the time of insertion), revealing no failure of any of the implants or bone loss greater than that described after normal loading.

The second reference found in the literature was published by Grossmann *et al*. in 2007.[9] In this study, follow-up was carried out on 31 implants re-implanted in the area of explantation of a previous implant, placed in 28 patients. The mean follow-up was 19.4 months from placement with a range of between 6 and 46 months. During the follow-up period, nine of the re-implanted implants failed, making the survival rate of 71%, lower than the survival rate for implants placed conventionally. All failures occurred within the first year after placement.

In our study, none of the implants placed in areas where there was previous peri-implantitis had failed. Therefore, immediate insertion of a new implant for the treatment of failed implants may be an alternative to reduce costs, time and surgical morbidity. The atraumatic removal technique is safe and predictable and can be used without risk in the majority of implants currently on the market.

Figures 6 to 10 show surgical images and radiographs of a treated patient in which removals and placements were made in areas of implant extractions.

CONCLUSIONS

The atraumatic removal technique is safe and predictable and can be used without risk in the majority of implants currently on the market.

Insertion of the implants in the same surgical act and bed must be taken into consideration and analyzed together with other factors specific to the receiving bed and the patient, in order to achieve success rates similar to those of implants placed in a primary bed with no previous treatment.

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Original article

A study on the prevalence of radiographic manifestations caused by pulp failure in deciduous dentition

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ABSTRACT

The purpose of this research was to study the pathological signs observed in temporary molars that had undergone pulpotomy.

Materials and methods. 79 intraoral radiographs of molars that had undergone pulpotomy were evaluated. Internal and external resorption patterns and the presence of radiolucent lesions in the furcation were studied.

Results. Pathological internal radicular reabsorption was observed in 43% of temporary molars and pathological external radicular resorption was observed in 34.2% of the sample. The radiolucent lesions of the radicular furcation were present in 39.1% of temporary molars.

Conclusions. The most common radiographic manifestation was pathological internal root resorption. However, this radiographic failure may be considered only a secondary effect if it is not accompanied by clinical manifestations and does not compromise tooth function before physiological exfoliation.

KEYWORDS

Pulpotomy; Temporary molars; Radiographic manifestations.

INTRODUCTION

Pulpotomy in temporary dentition is a treatment that is commonly performed in cases of extensive cavities with healthy pulp or reversible affectation. Intraoral radiographs provide key information on the extent of cavities, the proximity of restorations to the pulp horns, the presence of any type of peri-radicular pathology, the level of physiological or pathological reabsorption and the presence or absence of the successor tooth.[1]

During pulpotomy, the coronal pulp is resected and different materials are placed in the entrance to the radicular canals, which gives the name to the pulpotomy (formocresol pulpotomy, glutaraldehyde pulpotomy, calcium hydroxide pulpotomy...).[2]

Pulpotomy treatment is considered successful when there is vitality in the major portion of the radicular pulp until its physiological change.[2,3]

Failure of a pulpotomy in temporary teeth rarely causes pain, so it is important to perform adequate clinical and radiological follow-up.[2-5]

A pulpotomy is considered a failure when any of the following are observed in the treatment revision and follow-up phase:

- Pathological symptoms; pain, swelling or sensitivity.
- Radiological signs of internal and/or external resorption.
- Pathology in the peri-radicular tissues.
- Lesions in the permanent teeth.[2]

Resorption is the disappearance of structures through a biological mechanism of cellular phagocytosis, similar to osteoclasia. Cells developed with phagocytic function arise from primary cells from connective, bone and cement or pulp tissue that, accompanied by other macrophages, eliminate one or various hard tissues. In tooth reabsorption, this process affects the dentin or cement (not the enamel) sometimes being physiological, as in the tooth eruption process.[6]

Histologically, internal dentin resorption is done by odontoclasts with invasion of the pulp in the resorbed area. It may occur in the chamber or in the radicular canals and extends centrifugally, being able to reach the radicular cement. In order for odontoclast action to take place, there must be vital pulp tissue, which is generally inflamed. This is the most common cause for pulpotomy treatment.[6] Internal radicular resorption has been described as the most common radiographic sign in molars that have undergone pulpotomy and it has been attributed to inflammation of the residual pulp since it is generally observed in the area where the drug is applied.[2,3,7] Some studies have attributed it to the use of calcium hydroxide compounds but it can also occur with other techniques, though the radiographic appearance may be different. Histological studies have revealed that this occurs independently of the medication used.[8]

Internal resorption is diagnosed by radiographic examination which reveals a radiolucent image with irregular enlargement of the wall of the canal. Symptoms are generally absent and vitality tests are usually normal. If the resorption results in a communication with the periodontium, pulp necrosis prevails. When the entirety of the pulp tissue dies, resorption stops.[6] Sometimes there is also external radicular resorption and in temporary molars, a radiotransparent zone appears in the area of the bifurcation or trifurcation (Figure 1), while in anterior teeth this transparency may be present in the apices or to the side of the roots. The differential diagnosis between internal and external resorption is difficult when total perforation of the tooth wall has occurred. The greater the destruction, the greater the mobility of the tooth; additionally, a fistula usually appears.[6]

Although the presence of radicular resorption processes is considered a radiological failure, it may not necessarily mean a clinical failure.[7]

The appearance of radiolucent lesions at the radicular bifurcation or trifurcation (Figure 2) may indicate treatment failure. In addition, the appearance of peri-radicular cystic lesions has been described.[6,8]

The purpose of our study was to evaluate the pathological radiographic manifestations of temporary molars that had undergone pulpotomy.

MATERIALS AND METHODS

The study universe consisted of 664 patients seen at the School of Pediatric Dentistry at Universidad Complutense de Madrid. A selection of 209 medical records was made along with a convenient sample of radiographs. The criteria applied to carry out the study were:

Inclusion criteria:

1. Healthy child patients with bitewing or periapical radiographs of the 1st and 2nd temporary molars treated with the formocresol or ferrous sulphate pulpotomy technique.
2. Diagnostic intraoral radiographs prior to pulp treatment with no signs of pulp-periodontal pathology.
3. Follow-up post-treatment intraoral radiographs at least one month after pulp treatment.

Exclusion criteria:

1. Intraoral radiograph records of insufficient quality.
2. No documentation of the drug used in the pulpotomy.
3. Patients with allergies, severe systemic pathology or on pharmacological treatment.
4. Absence of informed consent.

After applying the above criteria, the principal investigator selected 79 radiographs that were digitalized using an Epson ScanJet 7400® digital scanner with VueScan 9X32® in transparency mode at 600 dpi. All of the images were coded to hide the patient-related data and the pulpotomy technique used. Two qualified investigators analyzed the radiographic records independently using the same portable computer, an Acer Travel Mate 290®, and completed the "Pulpotomy Evaluation" table according to the following criteria:

1. - Internal radicular resorption: radiolucent image with irregular enlargement of the wall of the canal.
2. - Pathological external radicular resorption: radiolucent image with irregular resorption of the radicular wall.
3. - Radiolucent lesion of the radicular furcation: radiolucent image in the radicular bifurcation or trifurcation and/or broadening of the periodontal ligament at this level.

RESULTS

Of the temporary molars submitted for the study, 40 were first molars and 39 were second molars. According to their location on the dental arch, 19 were superior and 60 were inferior (Figure 3). Regarding the medication used, 41 were treated with formocresol and 38 with ferrous sulphate.

Forty-three percent of the temporary teeth in the study (N=34) had pathological internal radicular resorption. In 34.2% of these (N=27) pathological radicular resorption was observed and in 39.2% (N=31), a radiolucent lesion at the furcation was detected.

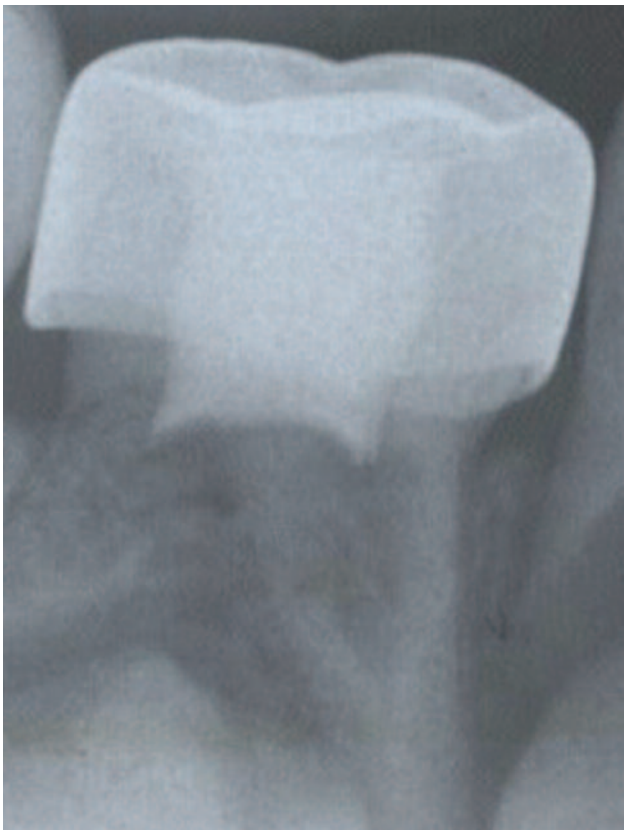

Figure 1. Inferior molar with pulpotomy. Area of internal and external radicular reabsorption.

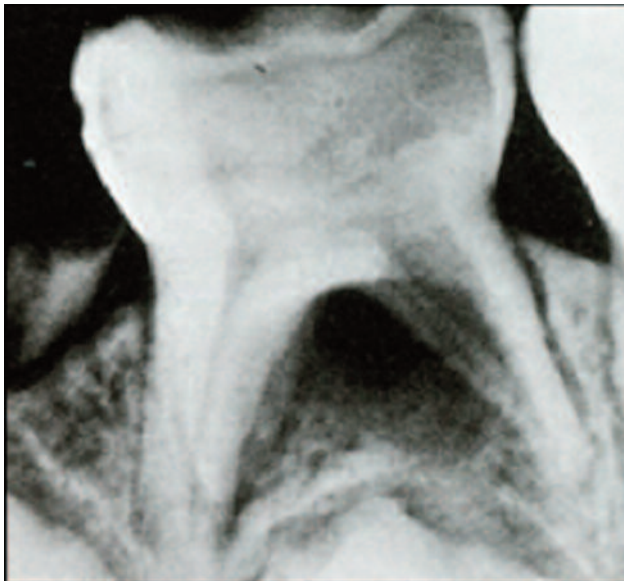

Figure 2. Radiographic image of a temporary inferior molar with an interradicular lesion[8]

Of the sample, 7 were first right superior temporary molars; 42.9% of these had pathological internal radicular resorption, 57.1% had pathological external radicular resorption and 57.1% had an interradicular radiolucent lesion.

Study of the radiographic findings in the 5 second right superior second molars revealed that 40% had pathological internal and external radicular resorption and 20% had a pathological interradicular radiolucent lesion.

When analyzing the radiographs of the 4 left superior temporary molars, 50% of the sample had pathological internal radicular resorption and 75% had an interradicular radiolucent lesion.

Regarding the 3 left superior temporary molars, 33.3% had pathological internal and external resorption as well as a pathological inter- or peri-radicular radiolucent image.

A study of the 17 left inferior temporary molars revealed that 47.1% of these had pathological internal radicular resorption. In addition, 29.4% had external radicular resorption as well as a pathological image in the furcation in 41.2%.

A study of the 15 left inferior temporary second molars revealed pathological internal radicular resorption in 53.3%, pathological external resorption in 26.7% and a pathological interradicular image in 40%.

Of the 12 right inferior temporary first molars evaluated, 66.7% had pathological internal radicular resorption, 41.7% had pathological external radicular resorption and a pathological interradicular radiolucent image was present in 58.3%.

Finally, analysis of the 16 right inferior temporary second molars revealed pathology in 12.5% according to the criteria for pathological internal and external radicular resorption and a pathological radiolucent lesion at the level of the interradicular furcation (Figure 4).

DISCUSSION

Pulpotomy allows for preservation of vital temporary teeth affected by deep cavities that would otherwise have to be extracted.[9,10] The most common radiographic finding observed in our study was internal radicular resorption, in coincidence with other studies.[5,11-13]

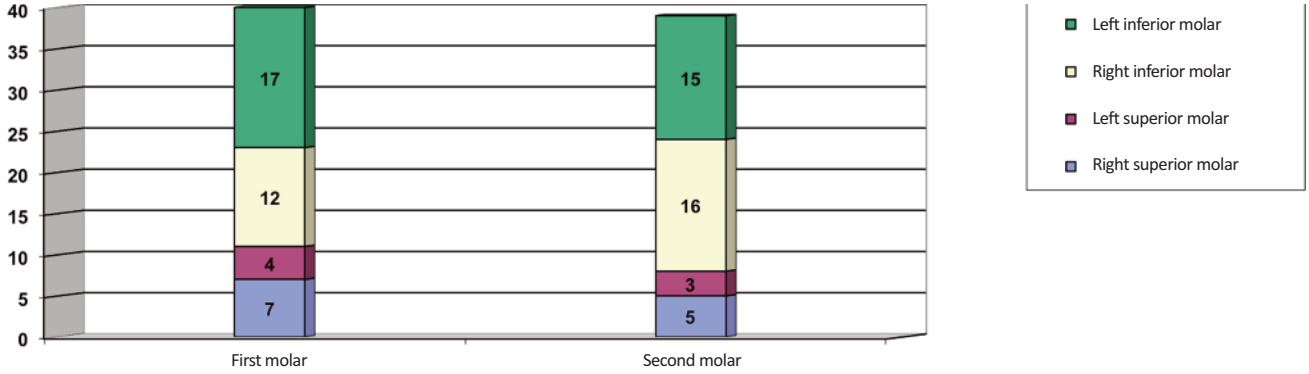

Figure 3. Distribution of the study sample.

In order to affirm that pulpotomy treatment has been adequate, the clinical and radiographic signs are considered separately. Therefore, the presence long-term vitality in the majority of the radicular pulp and the absence of painful symptoms (pain, swelling, fistula,...) are favorable. However, the presence of radiographic signs of resorption or periapical radiolucent images indicate that a pulpotomy that was clinically considered a success contains chronic inflammation in the radicular pulp.[6,8]

Some investigators do not consider the presence of internal reabsorption to be a sign of radiographic failure but rather a secondary effect that in some cases does not compromise tooth function until physiological exfoliation.[5,11-13] Nevertheless, in the research by Kurji *et al.*, 41% of cases with internal resorption resulted in bone involvement and/or clinical signs and symptoms which ultimately led to extraction.[14]

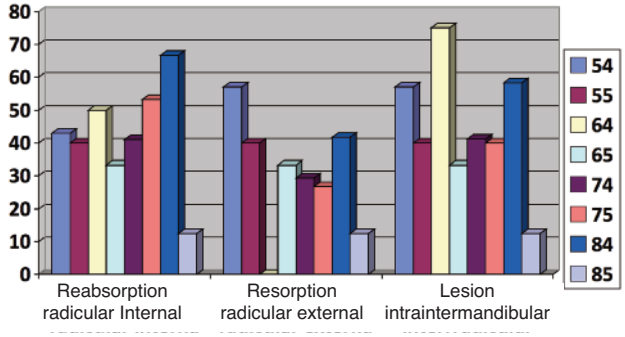

Figure 4. Percentage of pathological radiographic signs in temporary molars in those who had undergone pulpotomy.

Early exfoliation of temporary teeth that have received this treatment is attributed to the chronic inflammatory process of periodontal tissues generated by filtration of the drug or the zinc-eugenol oxide cement from the pulp chamber.[15,16] However, ferrous sulphate may not be the cement of choice in pulpotomies since the eugenol may irritate pulp tissue.[9] Ferrous sulphate, unlike formocresol, does not cause pulp mummification when it is applied in the chamber. For this reason, zinc-eugenol oxide cement in ferrous sulphate pulpotomies may be associated with the presence of pathological radicular resorption. However, the specific role of direct application of this cement to the pulp tissue has not been analyzed in this study and more research on the subject is needed.

Radiographic evaluation of resorption patterns was more complicated for the roots of superior molars versus inferior molars. We agree with Kurji *et al.* and Maroto *et al.* that this difficulty is due to the superposition of the maxillary sinuses and the radicular anatomy itself.[2,14] In fact, some investigators only use mandibular molars in the evaluation of pulp stenosis and/or internal radicular resorption phenomena given that these radiographic changes are much more evident than in maxillary molars.[2,14,17,18]

CONCLUSIONS

The most common radiographic manifestation was pathological internal radicular reabsorption. However, this radiographic failure may be considered only a secondary effect if it is not accompanied by clinical manifestations and does not compromise tooth function before physiological exfoliation.

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Original article

Management of soft tissues in bone regeneration/reconstruction using the modified double-flap incision technique. Periostium preservation technique

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ABSTRACT

Introduction: Implant techniques require the presence of bone structures that are adequate in quality and quantity in order to place osteointegrated fixations in a predictable manner. On occasions, the bone substrate is insufficient and bone reconstruction/regeneration techniques that require complete primary closure are needed in order to ensure success in the formation of new bone tissue. The purpose of this study is to describe a series of eight clinical cases in which the Modified Double-Flap Incision Technique was used to reconstruct areas of bone defect in the posterior mandibular region that limited placement of osteointegrated fixations.

Methods: This is a prospective study of eight clinical cases, from our private practice, with bone deficit in the posterior mandibular region, who required rehabilitation treatment with fixed implant-supported prosthetics. The Modified Double Flap Incision Technique (DFITm) was used in all cases.

Results: We achieved a complete primary closure at 15 days and proper placement of the implants in the regenerated area was possible in all cases.

Conclusion: The modified double flap incision technique allows to carry out adequate primary closure without tension in cases that require bone reconstruction or regeneration, avoiding the appearance of dehiscence that would lead to treatment failure.

KEYWORDS

Bone transplantation; Alveolar ridge augmentation; Surgical flaps; Dental implants.

INTRODUCTION

Implant techniques require the presence of bone structures that are adequate in quality and quantity in order to place osteointegrated fixations in a predictable manner. When the bone substrate is insufficient because of an esthetic problem, an anatomical circumstance (pneumatized maxillary sinus), a physiological circumstance (loss of bone volume secondary to tooth extraction) or because of sequelae from iatrogenic incidents (removal of infected dental implants), we need to use bone regeneration or reconstruction techniques.[1-7]

There are currently a large variety of predictable techniques[1-7]: bloc grafts, bone layers or split block bone technique (SBBT), osteoperiostial flaps, particulated grafts or guided tissue regeneration (GTR) techniques, among others. Professionals select a certain technique taking into account the type of defect, the esthetic requirements of the case and the patient's characteristics. In addition, other factors may also play a role like the surgeon's preferences, the type of practice (dental center, hospital center) or the patient's opinion.[1-5]

Regardless of all of these circumstances, bone regeneration will occur if the constructed matrix intended for transformation into bone tissue is perfectly isolated from the oral environment. This means that a complete primary closure is needed in order to ensure that the phenomena that would lead to new bone tissue take place.

For this purpose, several authors have proposed different incision and flap designs.[7-12;15-25] The double flap incision technique (DFIT)[9.10] has been shown to be particularly useful for regeneration in the posterior mandibular area with results comparable to other approaches. In addition, due to its characteristics, it appears to be especially useful in the dental clinic.

The present study describes a series of eight clinical cases in which the modified double flap incision technique was used to reconstruct areas of bone defect in the posterior mandibular region that limited placement of osteointegrated fixations.

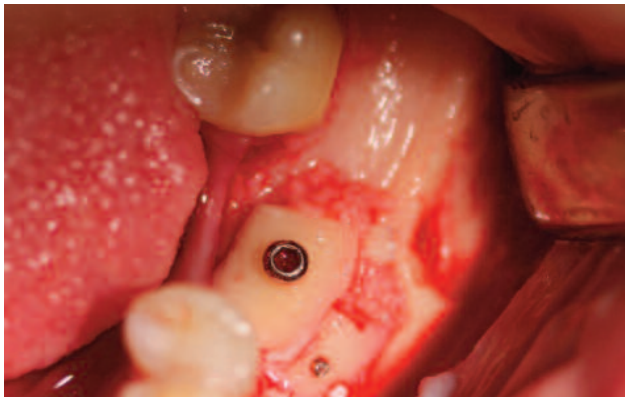

Figure 1. Bone reconstruction using the SBBT technique (clinical case 3).

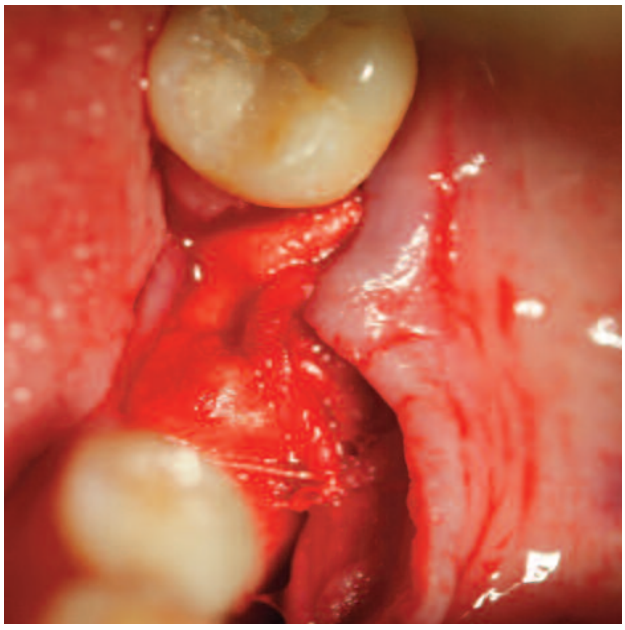

Figure 2. Primary closure of the periostial layer of the double flap (clinical case 3).

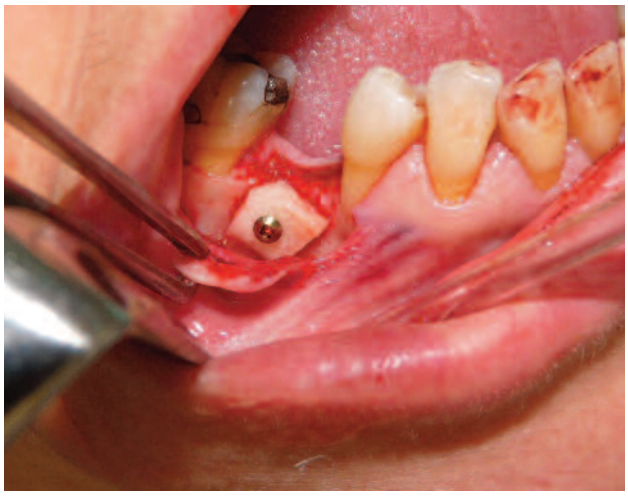

Figure 3. Non-laminated autologous bone graft with microscrew for exclusively horizontal bone gain (clinical case 4).

MATERIALS AND METHODS

This is a prospective study of eight clinical cases, from our private practice, with bone deficit in the posterior mandibular region who require rehabilitation treatment with fixed implant-supported prosthetics.

Regarding sample selection criteria, none of the patients had pathology or treatments that could compromise the bone regeneration outcome (osteoporosis under bisphosphonate treatment, decompensated diabetes, patients undergoing oncology treatment, smokers of more than 10 cigarettes per day). The age of patients participating in the study ranged between 20 and 60 years.

In all cases, regeneration techniques were performed using bone obtained from the same incision, either from the external oblique line or from the retromolar zone.

In four defects with a vertical and horizontal component, a laminated bone graft (SBBT) was used with a 3D reconstruction similar to the Khoury technique[4] (Figures 1 and 2).

In three defects with a horizontal component, autologous blocks obtained without lamination were used, and they were fixed with micro-screws for exclusively horizontal bone gain (Figures 3 and 4).

In one defect with a vertical and horizontal component, an autologous bone block was used in the central zone, without laminating, and the areas lateral to the graft were filled with a mixture of autologous bone mixed with 50% bovine biomaterial (Figures 5, 6 and 7).

The Modified Double Flap Incision Technique (DFITm) was used in all cases. Compared to other techniques, it provides greater mobilization of the epithelial and connective tissues, favoring primary closure without tension. In addition, preservation of the periostium promotes vascularization of the bone graft and the flap created.[11]

Knowledge of oral mucosal histology is important for understanding this double flap. The most superficial part is the epithelial layer, which is bound to a deeper layer called the lamina propia (connective tissue) thanks to the basal membrane. The border between the lamina propia and the periostium is marked by the submucosal layer, which is not always well defined. Therefore, when practicing this surgical technique, we make two layers in which the most superficial one is made up of the epithelial tissue, basal membrane, lamina propia and submucosa, while the deepest plane consists exclusively of periostium.[12.13]

When performing a DFIT, first a partial thickness supraperiostial incision with mesial unloading is made and a mucosal flap is fashioned. After this step, another periostial flap is made by making a second incision, now deepened to the mandibular bone (Figure 8).

We prefer to modify the DFIT by first making a full-thickness mucoperiostial incision that can be accompanied by an accessory mesial unloading. We raise the flap to full thickness and identify the structures that we are interested in, thus being able to access and observe the mandibular branch and the external oblique line, there by facilitating the location of mental nerve foramen.

We then make an incision 2 mm away from the border of the flap, along its edge. This should only be periostial, and we free the periostial flap with a Buser or Back Action blunt separator. We prefer to make this modification (DFITm) because it is a faster and simpler procedure than fashioning the flap to partial thickness, especially because it minimizes the possibility of fenestration or tearing of the mucosal flap which, logically, has a very small thickness (Figure 9).

It is recommended that this double flap be made at the beginning of the operation, in order to achieve proper hemostatic management and, so the final suture maneuver and closure of the two planes are greatly simplified.

As we have already mentioned, this flap design achieves a wide surgical field with access to the external oblique line and/or retromolar zone from which the autologous graft can be easily obtained (Figures 10, 11 and 12).

After this step, we carry out the selected bone regeneration technique, we fix the grafts and place the absorbable membranes. There are arguments for and against their use.[26-31] We prefer to use them in order to help maintain the volume of regenerated bone tissue,

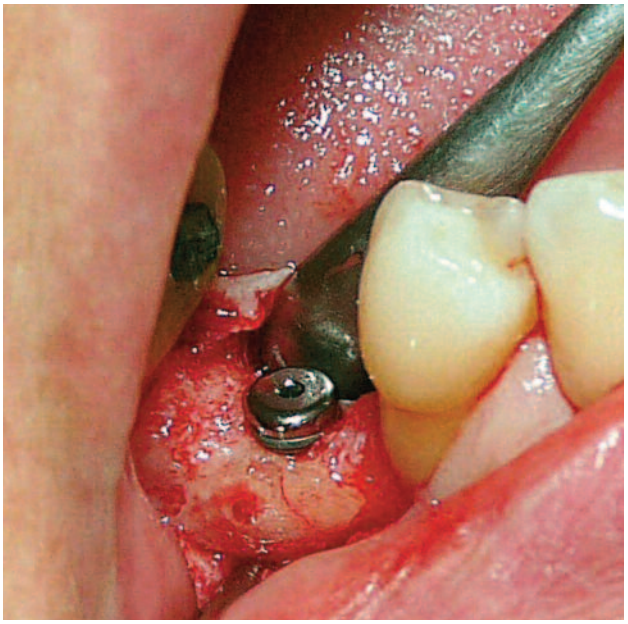

Figure 4. Reentry and placement of the implant in the most favorable prosthodontic position (clinical case 4).

decrease its resorption, help stabilize it in its immobilized position and avoid penetration of soft tissues.[26-31]

Finally, we proceed to close the periostial plane with absorbable 4-0 suture, trying to cover as much bone graft as possible. We suture the mucosal plane with 5-0 silk or 5-0 monofilament, which slides easily over the area to be regenerated, thereby allowing for a comfortable closure without tension on the area. We keep this suture for at least 15 days in order to ensure complete primary closure of the wound and to avoid dehiscence, which would lead to exposure of the graft

Table 1. Bone reconstruction/regeneration phase.

CASE	AGE	SURGICAL TECHNIQUE	TYPE OF DEFECT	NEUROLOGICAL/ INFECTIOUS COMPLICATIONS	PRIMARY CLOSURE (15 DAYS)
1	45	Non-laminated block	Horizontal	NO	YES
2	60	Non-laminated block and particulated graft (autologous+bovine)	Horizontal and vertical	NO	YES
3	42	SBBT	Horizontal and vertical	NO	YES
4	40	SBBT	Horizontal and vertical	NO	YES
5	50	Non-laminated block	Horizontal	NO	YES
6	47	SBBT	Horizontal and vertical	NO	YES
7	60	SBBT	Horizontal and vertical	NO	YES
8	47	Non-laminated block	Horizontal	NO	YES

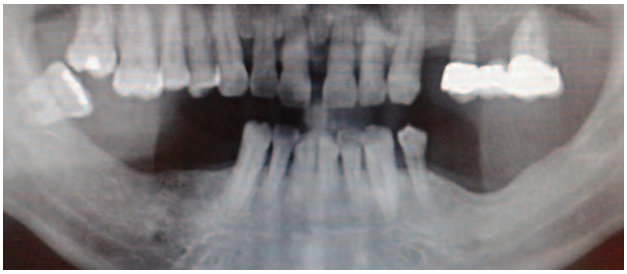

Figure 5. Initial situation of the vertical and horizontal bone defect in zone 34- 36 (clinical case 2).

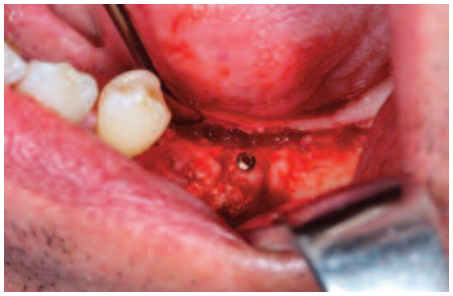

Figure 6. Situation at reentry of the area regenerated with a block of autologous bone, obtained from the external oblique line, placed in the center of the defect with a lateral filling of particulated autologous bone mixed with bovine biomaterial (clinical case 2).

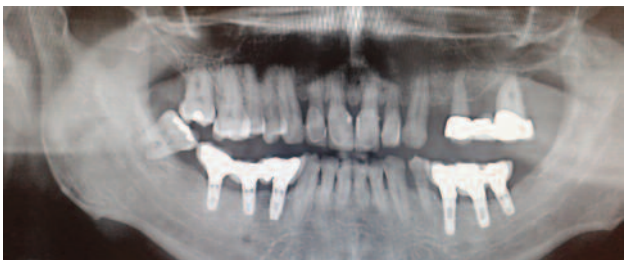

Figure 7. Follow-up orthopantomography for monitoring of regeneration and implants at two years with no clear reabsorption (clinical case 2).

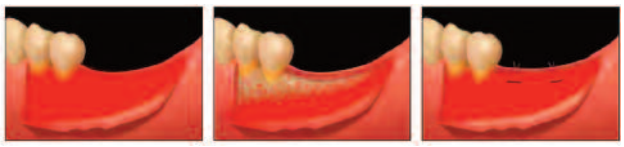

Figure 8. Double flap incision technique design. Image redrawn from the article by Ogata et al.9

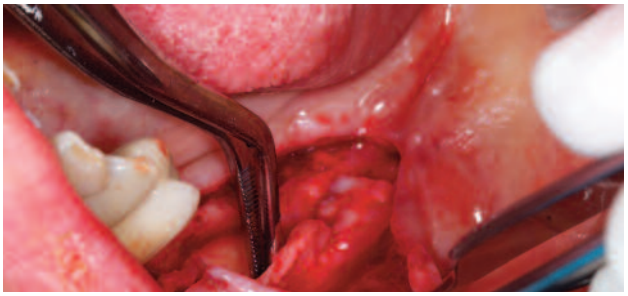

Figure 9. Intraoperative image which shows the double flap obtained, revealing a mucous layer and another deep periostial layer.

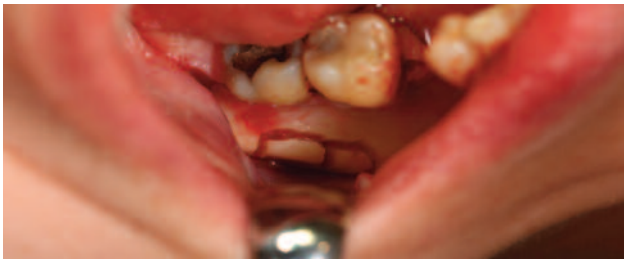

Figure 10. With a single incision, we obtain an operative field that allows us to obtain the material from the autologous graft, as well as its fixation to resolve the bone defect present (clinical case 5).

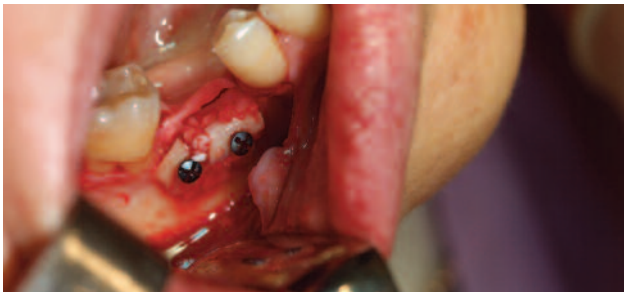

Figure 11. Fixation of the autologous bone graft material (clinical case 5).

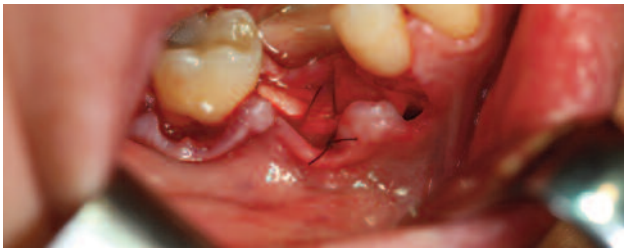

Figure 12. Suture of the periostial layer of the clinical case shown in figure 11 (clinical case 5).

material. The duration of surgery was less than one hour for all procedures (Figures 2 and 12).

Primary closure was evaluated at 15 days and considered complete when there was absence of dehiscence, signs of infection, inflammation or abnormal coloration. The

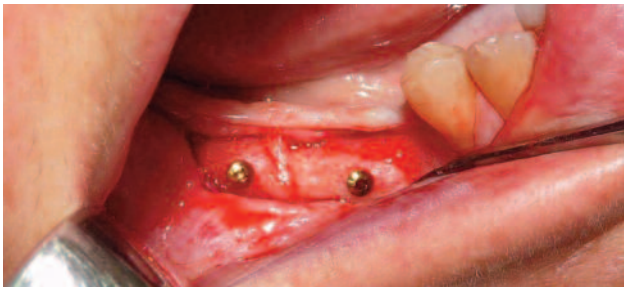

Figure 13. Reentry in which the proper state of the autologous bone block grafts is seen (clinical case 1).

occurrence of neurological complications of the inferior dental and mentonian nerves was assessed (anesthesia, hypoesthesia, paresthesia, disesthesia), as well as the presence of immediate infectious complications.

At 5 months after surgery, reentry was carried out in order to place the implants, and the volume and appearance of the regenerated bone (optimal/acceptable/inadequate) was evaluated. We also checked whether placing the implants in the regenerated area was possible, using prosthetic-guided criteria, graded as correct or incorrect, according to the need to regraft or use techniques with angled implants (Figures 13 and 14).

RESULTS

We achieved complete primary closure in all cases at 15 days, without any neurological or infectious complication (Table 1).

In seven cases, the volume of the regenerated bone tissue was considered optimal and in one case it was acceptable, as there was mild resorption of the graft caused by a small exposure of the head of the fixation screw in a block of laminate (SBBT) in the fourth month after surgery. This did not preclude precise placement of the bindings from a prosthodontic point of view (Figures 15 A and B).

Placement of the implants in the regenerated area, with prosthetically-guided criteria was possible in all cases, so it was not necessary to regraft or place the implants in an angled fashion in any of the operated cases (Figures 16, 17 A and B, 18 A, B and C) (Table 2).

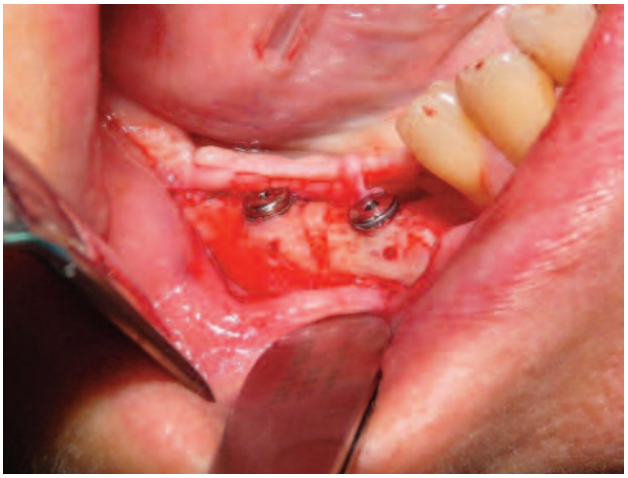

Figure 14. Placement of the implants in their ideal positions, following prosthodontic criteria, by having direct monitoring of the three-dimensional situation of the autologous bone grafts in the reconstructive phase (clinical case 1).

DISCUSSION

The incisions should always preserve the vascularization of the flap, paying special attention to the mandible due to its poorer irrigation. Given that it is a bone with a greater cortical component, special care is needed to avoid exposure of the grafted material. This is of greater importance in patients who are smokers and diabetics due to their known vascular deficiency and diminished healing ability.[33]

From this premise, it is possible to design any type of flap in the maxilla and mandible with the objective of allowing access to the area to be regenerated with a primarly closure of optimal quality. Several authors have made all types of proposals in search of this objective: Langer 1990[15] proposes a palate approach technique; Buser 1993[16] and 1995[17], Tinti and Parma-Befenati 1995[18], Fugazzotto 1999[19] propose a 3-4 mm horizontal incision in the oral vestibule, apical to the vertical unloading and away from it; Khoury 1999[34] proposes the two-incision consistent tunnel approach, one mesial and the other distal, through which two laminated blocks are introduced for reconstruction of bone defects, being especially indicated in the posterior mandibular sector; Cranin 2002[20] avoids making incisions in the periostium, so they make a partial-thickness incision below the mucogingival line that facilitates coronal advancement of the flap; Sclar 2003[21] proposes a biselated (45º-60º)

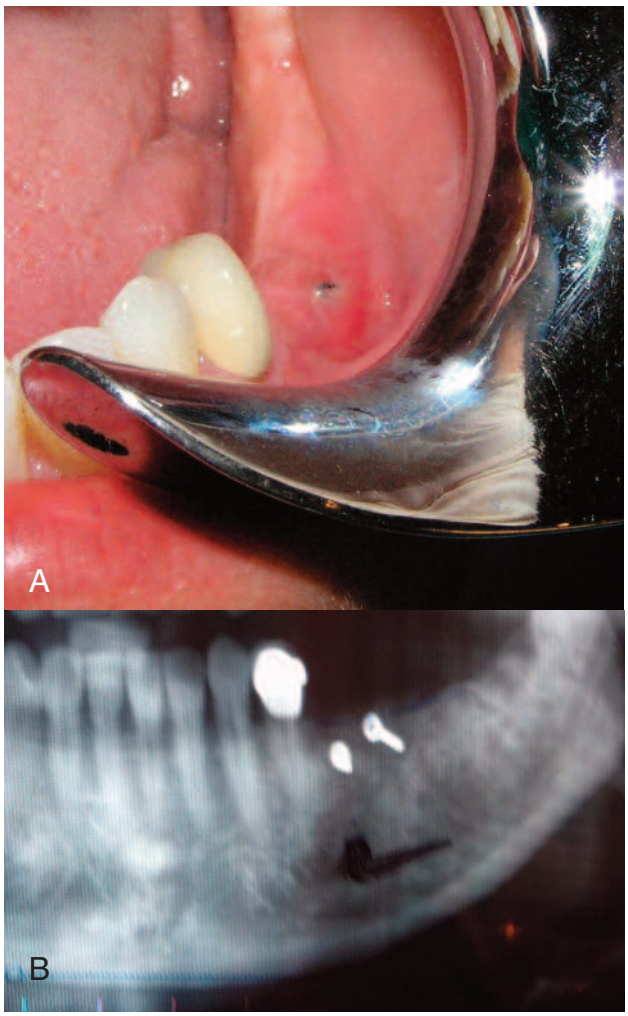

Figure 15. Clinical case 7. A, image in which minimal exposure of the head of the fixation screw is seen at the fourth postoperative month. B, radiographic follow-up image at the fourth postoperative month.

horizontal incision at the base of the vertical unloadings towards the center of the flap; Herford 2011[22] designs a flap of vascularized connective tissue by making incisions that separate the soft tissue, thereby increasing its quantity, promoting primary closure of the operative field; Ronda and Stacchi 2011[23] design a lingual advancement flap; Steigmann 2012[24] designs the "periosteal pocket flap" technique; Park 2012[25] uses the PRI technique with one or two vertical unloaded in order to achieve greater coronal advancement; Restoy 2015[7] proposes the use of an access and closure with two planes using the inverted technique (inverted double flap), similar to that proposed by Kan 2016[35] in

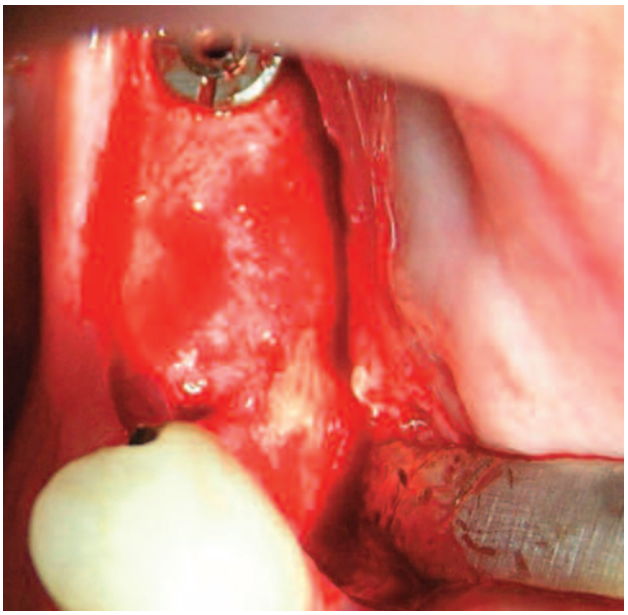

Figure 16. Reentry that allows for placement of the implants in the positions predetermined with prosthetic criteria (clinical case 7).

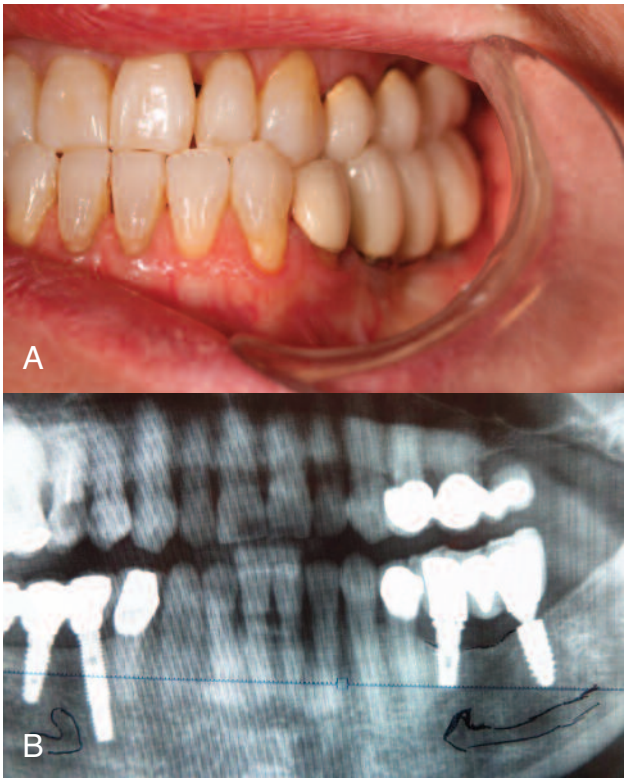

Figure 17. Clinical case 7. A, clinical follow-up at 4 years postop (3i Osseotite and Ankylos implants). B, radiological follow-up image at 4 years postop.

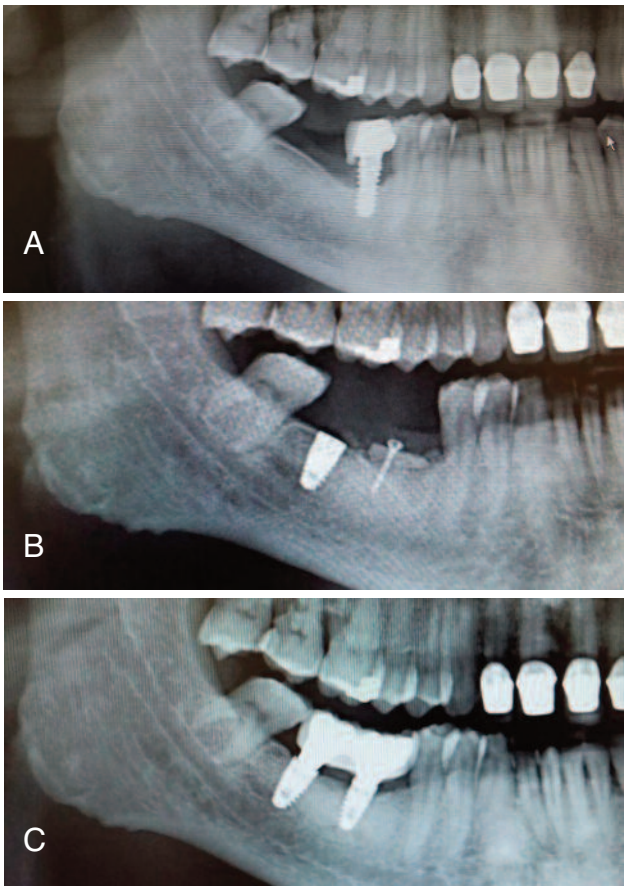

Figure 18. Clinical case 6 A, preoperative radiographic image in which it was decided to remove the implant in zone 46 in order to do a subsequent reconstruction with an autologous graft that would allow for the residual bone defect to be overcome. B, radiological image in which the autologous bone graft is seen. C, postoperative radiological image at one year of follow-up.

order to carry out extensive reconstructions in the maxilla with cranial bone.

The DFITm has shown better results compared to the displacement or a coronal reposition flap. The primary advantage of this surgical technique is the preservation of the periosteal vascularization, thereby avoiding deep incisions in the submucosa. For this reason, it achieves greater coronal advancement with less postoperative morbidity, thereby decreasing the incidence of dehiscence, necrosis and exposure of bone regeneration/reconstruction material.[8-10]

Regarding the lower postoperative morbidity for the patient, special mention should be made of the lower level of postoperative inflammation and edema shown by patients due to preservation of the periosteal vascularization.[8-10]

TABLE 2. IMPLANTATION PHASE

Case	Assessment (Integrated)	Reentry Assessment	Nº Implants Prosthodontics
1	OPTIMAL	46-47	CORRECT
2	OPTIMAL	34-35-36	CORRECT
3	OPTIMAL	36	CORRECT
4	OPTIMAL	46	CORRECT
5	OPTIMAL	45-46	CORRECT
6	OPTIMAL	46-47	CORRECT
7	ACCEPTABLE (MILD BONE REABSORPTION)	36-37	CORRECT
8	OPTIMAL	45	CORRECT

Regarding the tunneling technique[34], our technique appears to provide promising results that should ideally be confirmed in larger blinded trials. We believe it is particularly useful in cases of regeneration with a reduced vertical or exclusively horizontal component.

Among the advantages[8-10] it provides greater intraoperative safety due to direct vision and control of the foramen of the mentonian nerve; greater control of the position of the graft and the anatomy to be regenerated, which is very important for the subsequent placement of the implants under prosthodontic criteria, since it is not a blind technique. In addition, this is a less invasive surgical technique since the donor zone comes from the same surgical field, accessed by the same incision. It is also a technique that, though requiring delicate and expert handling of the soft tissue, is generally faster. All our cases were operated on in less than an hour. This is very useful for patients being operated exclusively under local anesthesia.

Finally, it should be noted that in those clinical cases in which the soft tissue is of reduced thickness, we are currently introducing modifications like the use of dermal membranes or thin layers of palate connective tissue that we place at the supraperiosteal level.

CONCLUSION

The modified double flap incision technique allows to carry out adequate primary closure without tension in cases that require bone reconstruction or regeneration, avoiding the appearance of dehiscence that would lead to treatment failure. In addition, this surgical technique is faster and safer compared to other techniques, since it allows for good visualization of the operative field, precise location of the mentonian foramen and adequate three-dimensional placement of the grafts, with proper positioning of the implants using prosthodontic criteria.

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Clinical case

Denosumab-induced osteonecrosis of the jaw: A case report

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ABSTRACT

Osteonecrosis of the jaw (ONJ) induced by antiresorptive drugs, mainly bisphosphonates (BP), is widely described in the scientific literature. In recent years, there have been reports of ONJ induced by other antiresorptive drugs such as Denosumab, Bevacizumab and Sunitinib used in cancer patients. Denosumab is a monoclonal antibody used in the treatment of osteoporosis and in the prevention of fractures following treatment of some types of cancer.

In this article, we present the case of a patient who developed ONJ. The patient had periodontal disease and osteoporosis, which had been treated for years with Alendronate (oral bisphosphonate) and currently with Denosumab. In addition, she had a poorly adapted removable prosthesis. This paper discusses the risk of ONJ associated with such drugs, and the possible influence of certain local factors on the occurrence of this condition, as well as the preventive and therapeutic measures that should be adopted in these cases.

KEYWORDS

Osteonecrosis of the jaw; Denosumab; Oral bisphosphonates; Osteoporosis.

INTRODUCTION

Osteonecrosis of the jaw (ONJ) is a clinical entity associated with alteration of the blood supply, inhibition of osteogenesis, and an increase in osteocyte apoptosis. It results in ulcerated mandibular or maxillary lesions with exposure of necrotic bone. ONJ has been associated with diseases such as lupus, falciform cell anemia and Caisson's disease. It has also been related to the use of some drugs like corticosteroids and bisphosphonates, and with radiation therapy of the head and neck.[1-8]

Currently, cases of ONJ caused by the use of new antiresorptive drugs such as Denosumab, Bevacizumab and Sunitinib have been reported.[2,5] Denosumab (Prolia®) was approved in 2010 by the European Medicines Agency. It is used for the treatment of osteoporosis in postmenopausal women who are at an increased risk of fractures and for the treatment of bone loss associated with hormone suppression therapy in men with prostate cancer and women with breast cancer who are treated with aromatase inhibitors. Denosumab is a human monoclonal antibody (IgG2) that, due to its mechanism of action, leads to inhibition of the formation, function and survival of osteoclasts, which results in a decrease in bone resorption in cortical and trabecular bone. It acts by increasing bone mineral density on the one hand, but also reducing bone remodeling ability or bone turnover on the other.[9]

Evaluating the long-term efficacy and safety of Denosumab is important when it is used for the treatment of osteoporosis, given that it is a chronic disease that requires long-term treatment. Although few studies, analyze these complications over the long term, there seems to be an increased risk of ONJ in the group treated with Denosumab compared with controls. [10]

The occurrence of this complication makes its management and considerations equivalent to those of bisphosphonates.

CLINICAL CASE

We present the case of a 63-year-old patient, nonsmoker, with osteoporosis (initially treated with oral bisphosphonates and currently with Denosumab) with no other systemic pathology who came in for consultation due to two-month history of an ulcer at the right inferior alveolar border that caused pain.

The patient has been taking Alendronate 70 mg 1 tablet weekly since 2006 as treatment for osteoporosis. Treatment with the bisphosphonate was discontinued in 2013 and after one year without medication in 2014, the rheumatologist decided to start treatment with Denosumab (Prolia®), 60 mg subcutaneously every 6 months. Two months after the first injection, the patient came in for consult complaining of jaw pain associated with the appearance of an ulcer on the lingual surface of the right inferior alveolar ridge.

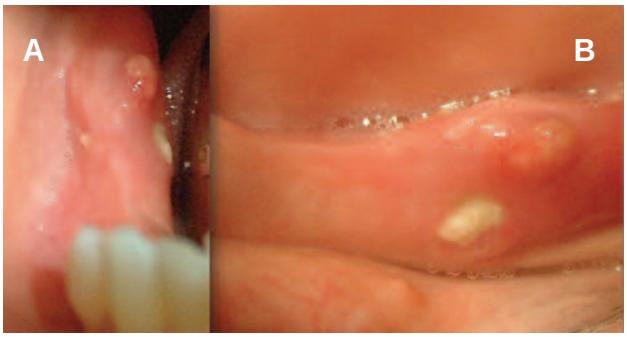

Figure 1. Initial images. a) Image on the left shows the frontal view of the right inferior alveolar border. Ulceration of the internal surface is seen along with the presence of two fistulas, one distal to the ulcer and the other on the vestibular surface. b) Image on the right, coronal view of the ulcer and distal fistula.

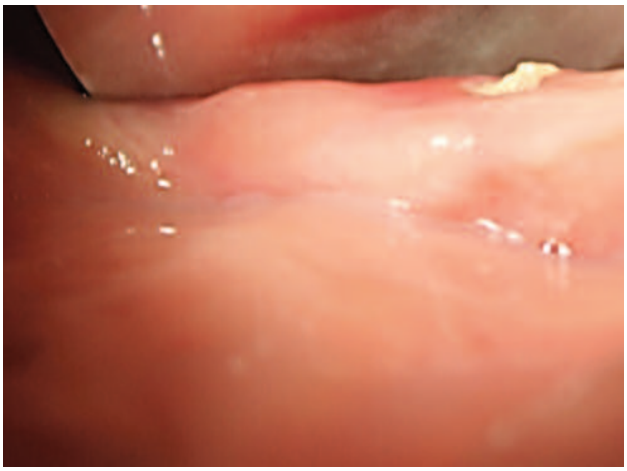

Figure 2. Image seen from the coronal view at one month. We observe ulceration of the internal surface of the mandible, the fistulas have disappeared.

The patient had only been treated for periodontal disease in 2008 and subsequently followed with periodontal reviews every 6 months. Her plaque control was optimal and she did not have any other oral pathology. For the past 8 years, she has had a removable inferior prosthetic with insufficient adjustment and adaptation. The patient has repeatedly shown her refusal to replace it despite professional recommendations.

Intraoral examination revealed a round ulcer at the lingual zone of the inferior alveolar ridge with an erythematous halo measuring 6 mm in diameter (Figure 1) with bone exposure. The lesion coincided with the area of support for the removable inferior prosthesis. A few millimeters more coronal to the ulceration, in the area near the retromolar trigone, we detected two fistulas with purulent exudation.

In addition to insisting on the need to maintain adequate oral hygiene, the patient was prescribed Augmentin Plus® (1000/62.5 mg), 2 tablets twice daily for 10 days and chlorhexidine 0.12% every 12 hours for 15 days. Moreover, she was instructed not to use the removable prosthesis in order to avoid local trauma and was referred to to her rheumatologist in order to assess discontinuation of Denosumab treatment.

The patient was reviewed 15 days later, observing a reduction in the size of the ulcer, although the fistula remained, so it was decided to prolong use of the chlorhexidine mouthwash. The patient came in for

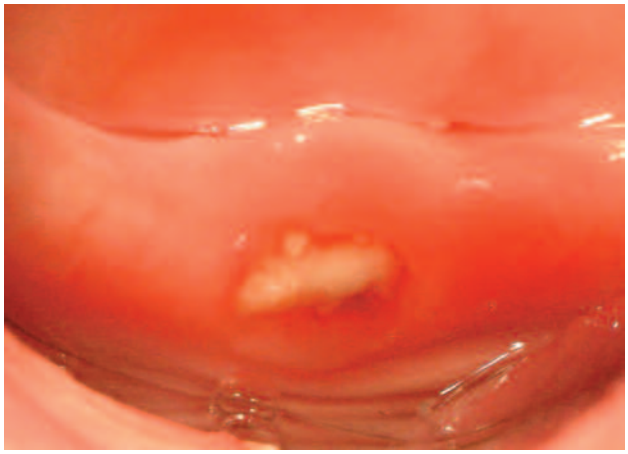

Figure 3. Image seen from the lingual view at one month. We observe ulceration with bone exposure.

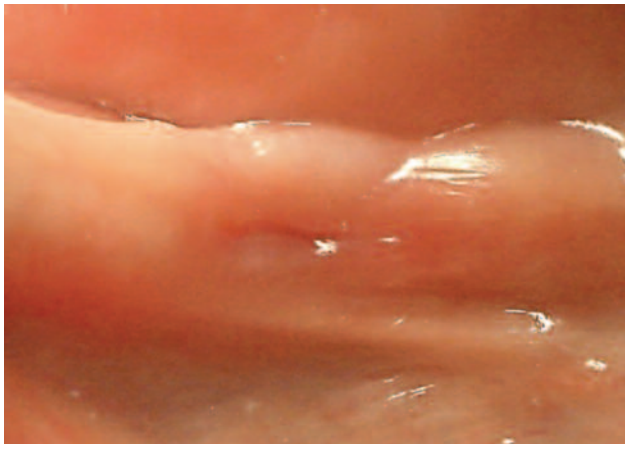

Figure 5. Image of the right inferior alveolar border 6 months after the appearance of the lesion and one month after the surgical intervention.

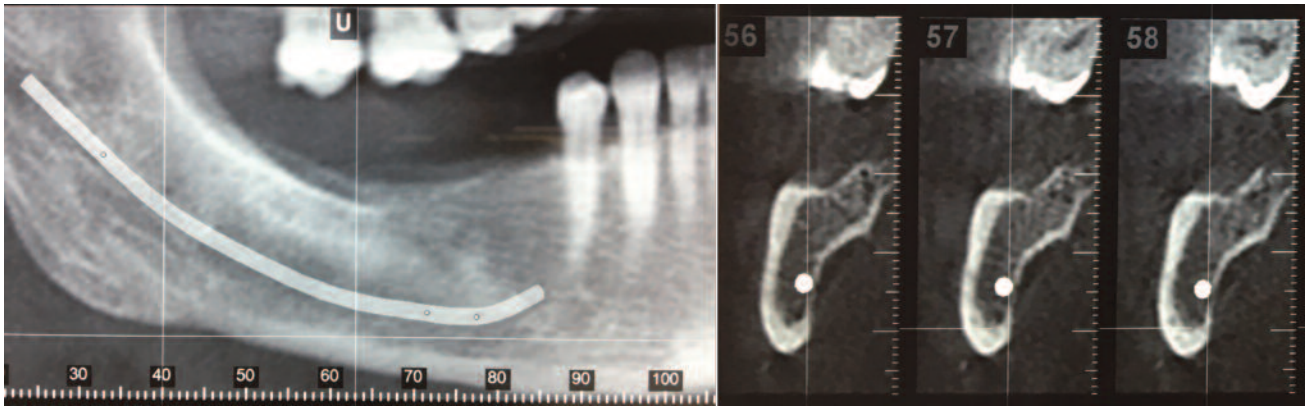

Figure 4. Mandibular CT. Image from the left, frontal slice. Image from the right, sagittal slice. We observe some bone rarification, radiodense and radiotransparent areas.

follow-up at one month. The fistula had disappeared but the bone exposure had increased (Figures 2 and 3).

A Computed axial tomography (CT) of the jaw was performed, revealing images compatible with bone rarefication in the mandibular body. It was possible to distinguish areas of osteocondensation surrounded by radiotransparent zones (Figure 4).

Due to clinical manifestations such as the appearance of an ulcer with bone exposure, purulent exudate and radiographic alterations, as well as the history of pharmacological treatment, a possible ONJ associated with the use of treatment for osteoporosis was suspected.

The patient was referred to the Maxillofacial Surgery Unit at Ciudad Real General Hospital where curettage and extirpation of the sequestered bone together with application of local antiseptic measures were performed. The patient was followed one month after surgery, observing adequate healing of the area (Figure 5).

Currently, the patient is free from recurrence. Her old prosthesis was replaced by another properly fitted and, although she is still being followed, her rheumatologist has not considered it suitable to restart treatment with any antiresorption drug.

DISCUSSION

ONJ is a bone alteration seen in patients treated with radiation therapy or with different antiresorption drugs used to control osteoporosis. Although the exact etiology is not known, certain risk factors favoring its development have been identified: previous treatment with bisphosphonates, advance age, deficient oral hygiene, dental procedures (endodontics and oral surgery), use of removable prosthetics, oral trauma, presence of certain comorbidities (like preexisting oral disease, anemia, coagulopathy, infection), tobacco use and certain concomitant treatments (like chemotherapy, anti-angiogenic biological medications, corticosteroids, radiation therapy of the head and neck).[1,11]

Denosumab has become a suitable option for the treatment of osteoporosis because it contributes to a constant increase in bone mineral density. Even so, cases of ONJ associated with this drug have been described in the literature. A review by Ramirez *et al.*[2] found thirty-five articles published between 2007 and 2012 that related antiresorption and anti-angiogenic drugs with the risk of the appearance of ONJ. Of these, nine associated Denosumab with ONJ.[2-5]

A subsequent review by Oliveira *et al.*[12] arrived at the conclusion that the majority of cases of ONJ caused by Denosumab occurred in women around 60 years of age who received the drug for the treatment of osteoporosis (47%). The most common location for the appearance of ONJ was the mandible.[12]

As bisphosphonates, Denosumab is an antiresorption drug that shares similar mechanisms of action. Denosumab is a humanized monoclonal antibody (IgG2) that is directed at and binds with high affinity and specificity to for RANKL (nuclear factor-kappa B receptor activator), impeding activation of its receptor, RANK, on the surface of precursors of osteoclasts and in osteoclasts. By blocking RANKL/RANK interaction, it inhibits the formation, function and survival of osteoclasts, which leads to a decrease in bone reabsorption in trabecular and cortical bone. Therefore, Denosumab may have the same adverse effects as bisphosphonates, as described in the technical sheet, and in the previously mentioned bibliography.[2-5]

Although there are not many studies evaluating the long-term risk of ONJ in patients treated with Denosumab. Some studies consider it to be similar to oral bisphosphonates, oscillating between 0.09% and 0.34%[2]. Other studies indicate that if the only treatment for osteoporosis is Denosumab, administered in short periods, the risk of ONJ is similar to that of controls, although the risk increases with the duration of treatment.[10]

The patient presented had received previous treatment with oral bisphosphonates for 7 years (Alendronate, 70 mg/weekly). Eighty-eight percent of ONJ cases associated with oral bisphosphonates are related to the

use of Alendronate. In these cases, the risk of ONJ increases starting at 3 years of use, but this time period is shortened when administration is also associated with other drugs also involved in the pathogenesis of ONJ.[7] In addition, some authors state that the effect of bisphosphonates persists for a very long time after discontinuing the drug and may, in some cases, last as long as 10 years.[8,13,14] Many of the reported cases of Denosumab-associated ONJ had received previous treatment with bisphosphonates for a time of no less than 5 years.[15,16] Therefore, the use of Alendronate in our case may be considered an additional etiological factor in the development of ONJ.

We have found only one case report of ONJ induced by the administration of Denosumab and bisphosphonates simultaneously, which may indicate the existence of a possible synergistic action between both antiresorptive drugs. Further research is needed to demonstrate this synergistic relationship of both treatments when administered simultaneously.[17]

In the appearance of ONJ associated with antiresorptive drugs, the possible influence of certain local factors has been highlighted: tooth extractions, poor oral hygiene and poorly fitting prosthetics, among others.[13] The case described included a poorly fitting removable inferior prosthetic as a risk factor. This is related to repeated microtrauma in the alveolar mucosa that may promote the development of ONJ in this patient. The pathogenic participation of ONJ produced by antiresorption drugs on the presence of poorly fitting prosthetics has been previously documented in the literature. Sopeck *et al.*[15] in 2010 performed a randomized double-blind study in which 1026 patients were treated with Denosumab and 1020 with zoledronic acid. In this trial, after three years receiving treatment, 2% of patients treated with Denosumab and 1.4% of those treated with intravenous bisphosphonates developed ONJ. In the majority of cases, the associated etiological cause was a poorly fitting prosthetic (90% vs. 75%), so we believe it is important to check the fit of removable dental prosthetics in all patients who are going to start or are on treatment with these drugs.[13,15,18,19]

As with bisphosphonates, longer duration treatment with Denosumab increases the risk of developing ONJ.[13] It has been shown that the risk of ONJ in the first year of Denosumab administration is 0.5%, 1.1% at 2 years and 1.3% at 3 years.[21] In our case, the time of administration did not determine the risk of developing ONJ as it appeared early after administration of a single dose of the drug. We have found similar cases in the literature.[12,13] This suggests that the combined administration of Denosumab with previous use of Alendronate may be the cause of ONJ.

Although we lack sound data in this regard, the possible risk of ONJ associated with the use of Denosumab suggests that the same protocols recommended for the administration of bisphosphonates apply. According to different authors, implementation of preventive measures is important, as is the use of dental screening prior to starting treatment with antiresorptive drugs in order minimize the risk of ONJ.[20] The Spanish Medicines and Health Products Agency issued an informative note in 2014 in which they informed the healthcare community about the association between Denosumab and the appearance of ONJ in order to apply the measures necessary to prevent this disease.[21]

Therefore, prior to starting treatment with Denosumab, risk factors for the development of ONJ should be taken into account, dental examination should be performed and appropriate dental treatment applied. In addition, it is recommended that Denosumab not be administered to patients with dental or jaw pathologies that require surgery, nor to patients who have not recovered from previous maxillofacial surgery.[21,22]

It is also recommended that during Denosumab treatment, avoid exposing patients with risk factors for invasive dental procedures, inform patients who are to be treated with Denosumab about the importance of maintaining good oral hygiene, and the need to undergo periodic dental examinations. In addition, patients exposed to risk factors should avoid invasive dental procedures, and contact their healthcare professional immediately at the first sign of any anomaly in the mouth (like loose tooth, pain or inflammation).[21]

In patients developing ONJ during treatment, an individualized plan should be established in close collaboration with a dentist or maxillofacial surgeon with experience in ONJ. It is also considered pertinent to temporarily interrupt treatment with Denosumab until the condition resolves and possible risk factors present are minimized as much as possible.[21]

Discontinuation of the drug as a therapeutic and preventative measure is a controversial issue because bisphosphonates store in the bone matrix and due to its long half-life, the risk remains high despite discontinuing the drug. Even so, periods of drug discontinuation have been established allowing invasive dental procedures, like extractions, to be performed safely.

Denosumab, unlike bisphosphonates, is not stored in the bone matrix, so discontinuation would be more effective in resolving the ONJ process than in the case of bisphosphonates.[2]

In the case presented, after the appearance of signs and symptoms of ONJ, treatment with Denosumab was discontinued, with ONJ resolving after 6 months from the onset of the first symptoms.

The cases reviewed in the literature do not reflect the cure times for ONJ, nor do they explain whether or not the drug was discontinued. As with the case of bisphosphonates, it would be necessary to establish action protocols that indicate the waiting times for performing certain dental interventions, as well as studies that demonstrate de relation between discontinuation of Denosumab and resolution of ONJ.[2,22]

CONCLUSIONS

Denosumab is a drug with a mechanism of action similar to bisphosphonates and may therefore be directly related with the development of ONJ, with a similar incidence to oral bisphosphonates. Because Denosumab prescriptions are increasing for the treatment of patients with osteoporosis, we need to be aware of the risk for patients, control possible risk factors, and take the measures necessary, prior and during treatment with the drug, to prevent the development of ONJ. Further scientific studies are needed to provide evidence on the relationship between Denosumab and the risk of ONJ, that may allow for the establishment of preventive action protocols, and suitable treatments for these patients.

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