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Facultat d'Odontologia

Tesis doctoral

Ridge preservation in molar extraction sites comparing xenograft versus mineralized freeze-dried bone allograft: a randomized clinical trial.

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Ridge preservation in molar extraction sites comparing xenograft versus mineralized freeze-dried bone allograft: a randomized clinical trial

DOCTORAL THESIS

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A mi familia y a mi amigo Fran,

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Resumen

La pérdida dental conlleva una serie de cambios volumétricos en el reborde alveolar como respuesta adaptativa a la pérdida o cambio en la función. Esta reducción es más pronunciada en la zona vestibular, tanto del maxilar como de la mandíbula, y especialmente en el área de los molares. Estudios científicos han concluido que los cambios volumétricos que se producen tras la extracción dental, son mayores en sentido horizontal que vertical, pudiendo suponer más de un 50% de pérdida ósea en anchura a los 6 meses de la extracción. Estos cambios reducen considerablemente la disponibilidad ósea, dificultando los tratamientos con implantes dentales.

Con el fin de minimizar dichos cambios, se ha propuesto la realización de técnicas de preservación alveolar. Estos procedimientos consisten en la aplicación de un material biocompatible en el alveolo post-extracción con el propósito de reducir el remodelado óseo que se produce tras la extracción dental.

El término preservación alveolar incluye una variabilidad de técnicas quirúrgicas, las cuales pueden incluir la utilización de un biomaterial de relleno óseo, una membrana barrera o la combinación de ambos. Además, el material puede quedar expuesto, dejando cicatrizar por segunda intención, o cubierto mediante un avance del colgajo.

Los resultados de las revisiones sistemáticas han demostrado que la preservación alveolar reduce los cambios dimensionales, tanto en sentido horizontal como vertical, pero no puede prevenirlos completamente. Además, se ha sugerido, que el grosor de la cortical vestibular puede influenciar en los cambios dimensionales, determinando que corticales vestibulares finas pueden beneficiarse más de estos procedimientos. Sin embargo, hasta la fecha no hay evidencia científica de superioridad de una técnica con respecto a otra en cuanto a los cambios dimensionales o histológicos, aunque se recomienda el uso de materiales de relleno óseo en combinación con una membrana barrera.

El uso de xenoinjerto bovino o aloinjerto mineralizado han sido ampliamente analizados en la literatura demostrando beneficios clínicos e histológicos en procedimientos de preservación alveolar. Aunque hay evidencia de que el uso de aloinjertos parece producir mayor porcentaje de hueso vital comparado con el uso de xenoinjertos, hasta hoy no se han podido determinar diferencias estadísticamente significativas a nivel histológico con respecto al uso de diferentes biomateriales.

Por el momento, la mayoría de estudios de preservación alveolar se han enfocado en el sector anterior y en premolares. Sin embargo, la evidencia científica con respecto a la preservación alveolar en molares es limitada. Estudios clínicos en humanos han demostrado que la realización de preservación alveolar en molares reduce el remodelado óseo que se produce tras la extracción dental limitando la necesidad de efectuar elevaciones de seno lateral en casos maxilares, y reduciendo la proximidad a estructuras anatómicas, como el nervio dentario inferior, en casos mandibulares, minimizando la necesidad de llevar a cabo técnicas de regeneración más invasivas.

Los resultados de este estudio demuestran que tanto el uso de xenoinjerto como aloinjerto en técnicas de preservación alveolar en molares, son efectivos de manera similar en cuanto reducción del remodelado óseo y composición del tejido. Además, el grosor de la cortical vestibular presenta una correlación positiva con la cantidad de pérdida ósea, determinando que las corticales más finas están a asociadas a mayor remodelación ósea.

Por último, la preservación alveolar en molares minimiza la necesidad de elevación de seno, favoreciendo un abordaje transcrestal, y la realización de regeneración ósea horizontal simultánea a la colocación de implante. Por lo tanto, la preservación alveolar parece un método sencillo y eficaz que permite minimizar el llevar a cabo técnicas de regeneración ósea más invasivas.

Summary

Tooth loss leads to a series of volumetric changes in the alveolar ridge as an adaptive response to the loss or change of function. Such reduction is more pronounced in the buccal aspect both in the maxilla and the mandible, and in molar regions. Scientific evidence has concluded that volumetric changes after ridge preservation are greater in width than in height as more than 50% of the ridge width can be resorbed after 6 months following tooth extraction in some patients. Those changes considerably reduce bone availability for future implant placement.

In order to minimize these changes after tooth removal, ridge preservation procedures have been developed. These techniques aim to introduce a biocompatible material into the extraction socket to prevent bone remodelling after tooth loss.

Alveolar ridge preservation refers to a general term which includes a variety of surgical therapies. Such procedures may include the use of a graft biomaterial, or a barrier membrane, or the combination of both. In such interventions, the socket may be left to heal with the biomaterial exposed, by secondary healing, or covered, by flap advancement.

The existing evidence has demonstrated that ridge preservation limits the bone loss of the alveolar ridge, in both height and width, but does not completely prevent bone dimensional changes. Moreover, it has been suggested that the thickness of the buccal bone plate may influence bone loss, meaning that thin bone plates may benefit more from these procedures. However, to date there is no evidence regarding which technique provides superior results in terms of morphometric or histological changes, although the use of graft biomaterials is strongly recommended with the addition of a barrier to protect the underlying bone.

The use of bovine xenografts (DBBM) or mineralized allografts (FDBA) has been widely used in the literature demonstrating clinical and histological benefits in ridge preservation procedures. Although scientific evidence suggests that the use of allografts results in greater percentages of vital bone compared to DBBM, to date no significant differences have been found in terms of tissue composition between the use of different biomaterials.

The beneficial effect of alveolar ridge preservation procedures has been widely investigated in the anterior and premolar areas. However, research focusing on ridge preservation in the molar region is limited. Clinical studies performed in humans have demonstrated that ridge preservation in molar sites results in less bone remodelling following tooth extraction limiting the need of lateral sinus lift in maxillary cases, and reducing the proximity to anatomy structures, such as the alveolar inferior nerve, minimizing more invasive bone augmentation techniques.

Results from this investigation demonstrate that the use of DBBM or FDBA in ridge preservation procedures in molar sites, result in similar bone remodelling and tissue composition after 5 months. Moreover, the thickness of the buccal bone plate has demonstrated a positive correlation, demonstrating that thin buccal bone plates are associated with more bone remodelling. Lastly, performing ridge preservation procedures minimizes the need of sinus lift procedures, favouring a transcrestal approach, and the realization of simultaneous horizontal bone regeneration at the time of implant placement. Therefore, ridge preservation procedures are a useful and simple technique that prevents from performing more invasive bone augmentation procedures.

INTRODUCTION

Reasons for tooth loss

The impossibility to maintain teeth in a status compatible with health, function, and/or adequate aesthetics, as well as strategic purposes, may indicate tooth extraction (Kao, 2008; Tonetti, et al., 2000). Those situations may be related to the presence of advance caries, developmental defects, traumatisms, endodontic lesions or due to advanced periodontitis (Lundgren, et al., 2008).

Among the different treatment options to replace the missing tooth, fixed dental prostheses, have demonstrated high predictability and patient satisfaction (Wolleb, et al., 2012). However, these treatments are not excluded from complications as caries, periodontitis or root fracture on the abutment teeth may occur (Tan, et al., 2004; Wolleb, et al., 2012) or periimplantitis (Schwarz, et al., 2018).

Dental implants have demonstrated to be a predictable alternative with high survival rates (Quirynen, et al., 2014). However, many factors are critical for the long-term implant and prosthesis survival. Among them, having a sufficient amount of bone is crucial to allow osseointegration of the endosseous implant (Benic & Hämmerle, 2014).

Bone remodelling following tooth extraction may difficult prosthetically driving implant placement, and require bone augmentation procedures which may result in more morbidity for the patient and more complex clinical procedures (Milinkovic & Cordaro, 2014). Thus, an understanding of the healing process that occurs following tooth extraction is essential when planning implant therapy (Vignoletti, et al., 2012).

Anatomy of the periodontium

The periodontium is constituted by the tissues that surround the tooth, and comprises the gingiva, the periodontal ligament, the root cementum and the alveolar bone (figure 1).

The main function of the periodontium is tooth attachment on bone and maintenance of the integrity of the masticatory mucosa (Lang & Lindhe, 2015).

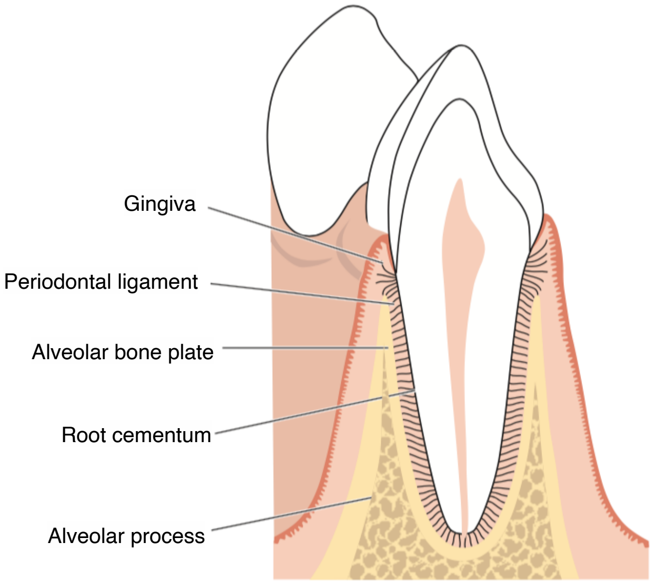

Figure 1. Anatomy of the periodontium. Image obtained and adapted from Lang & Lindhe 2015.

The alveolar bone is compounded of the alveolar process, which extends from basal bone of both maxillary and mandibular bones, and the alveolar proper bone, also called "bundle bone" (histologic term) which lines the thin bone plate that covers the alveolar socket. The periodontal ligament is a specialized connective tissue organized in fiber bundles that are embedded in the cementum and the bundle bone surrounding the teeth. The fibers inserted into root cementum and bundle bone are called Sharpey fiber's. The presence of periodontal ligament allows forces transmission to be distributed and resorbed by the alveolar process and confer the capacity of proprioception (Nanci & Bosshardt, 2006; Lang & Lindhe, 2015).

The relation between the teeth and their supporting structures remain dynamic after tooth eruption, generating a spontaneous migration of the teeth within the alveolar process as soon as the teeth begin its functionality. This results in a series of adaptive mechanisms to preserve bone anchorage and the integrity of periodontal ligament, which provides the major source of renewing cells (Saffar, et al., 1997).

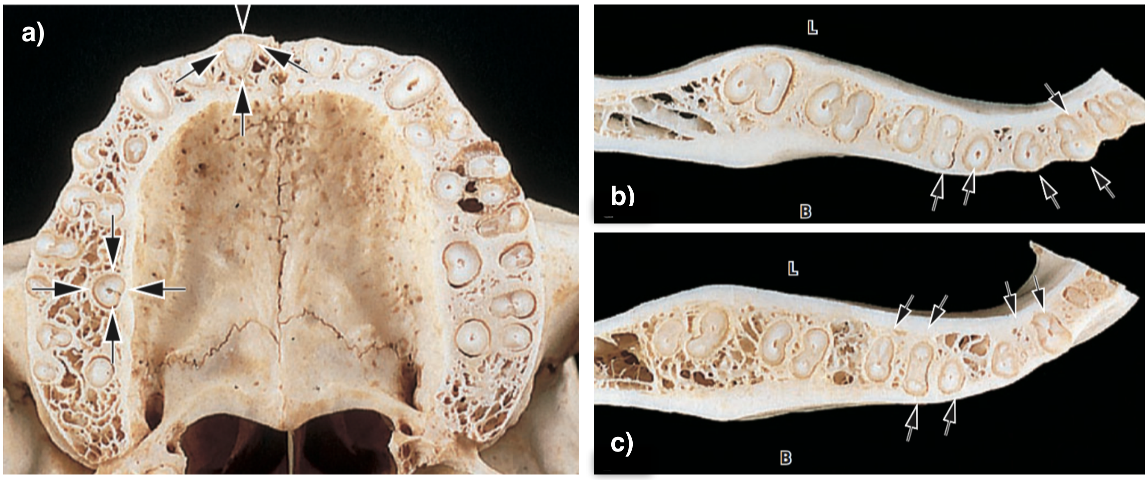

Figure 2. Cross sections of maxillary (a) and mandibular (b, c) alveolar process at the mid-root level of the teeth. (B: buccal, L: lingual). Image obtained from Lang & Lindhe, 2015.

The alveolar process its formed by an outer portion of cortical bone, the bundle bone, which lines the alveolar socket, and a central part of trabecular bone (Nanci & Bosshardt, 2006). The bundle bone is frequently in continuity with the buccal and lingual cortical bone. Its thickness varies between regions (figure 2), which has been estimated to oscillate between 0.1 - 0.4mm (Schroeder, 1986). Trabecular bone occupies most of the interdental bone but a small part of the buccal and lingual bone walls (Lang & Lindhe, 2015). Thus, the volumen and the shape of the alveolar process is determined by tooth eruption, location, size and inclination of the roots (Schroeder, 1986).

Bone covering the root surfaces, varies among different areas of the maxillary and mandibular bones. In some areas of the buccal bone of the maxilla or mandible, it is frequent to find dehiscences (absence of bone at the coronal part of the root) or fenestrations (absence of part of the bone wall, but where a coronal bone bridge is present). These findings are more frequent in the anterior teeth than in the posteriors, and are commonly associated to a too buccal position of the teeth. In those cases, the roots of the teeth are mainly covered by periodontal ligament and gingiva (Lang & Lindhe, 2015).

Generally, in the anterior and premolar area, the buccal bone plate is thinner than the lingual while in the molars the bone is thicker in the buccal region (figure 3) (Lang & Lindhe, 2015).

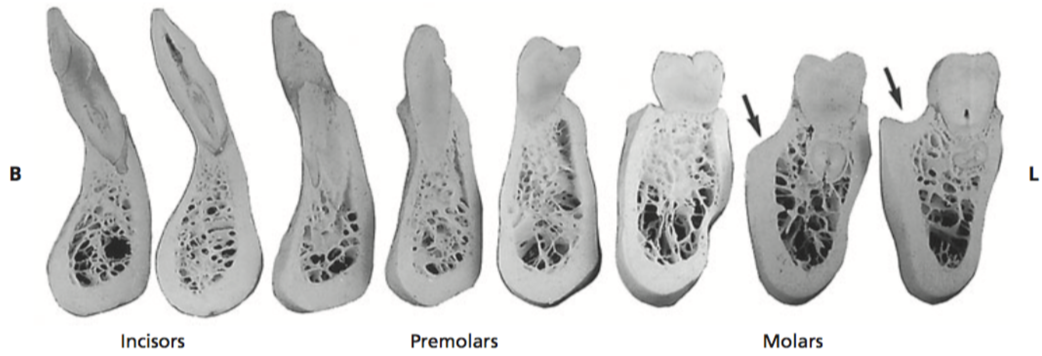

Figure 3. Thickness of the buccal and lingual bone plates at incisor, premolar and molar sites. (B: buccal, L: lingual). Image obtained from Lang & Lindhe, 2015.

In the anterior segment, 85% of the cases present a buccal bone wall of ≤ 1.0 mm in thickness while in between 40 - 60% of the sites is inferior to 0.5mm. Moreover, this thickness seems to follow a uniform patterns from the crest to the apical area as similar bone thickness has been observed at 1, 3 and 5 mm from the cemento-enamel junction (Januario, et al., 2011).

The dimensions of buccal bone plate in posterior teeth have been analyzed by the use of cone beam computed tomography (CBCT) (Temple, et al., 2016) demonstrating that tooth type, tooth location and jaw play a significant role on buccal bone dimensions in the posterior areas. This study reported that buccal bone plates perform differently in the maxilla than in the mandible. While in the maxilla there is a decrease in thickness from coronal to apical, the mandible behaves in an opposite manner. Thus, buccal bone thickness increases from anterior to posterior in both jaws and the tooth positioning in the arch has been determined as an influential factor for the thickness of the buccal plate, being thinner at the first premolar and the first molar mesial root and the thickest at the second molar at both mesial and distal roots in the mandible. These results are in agreement with other studies which observed that absence of the buccal bone plate was more frequent in mandibular premolars (Braut, et al., 2012) and that a thin (<1.0 mm) buccal bone plate was a common finding in maxillary and mandibular first premolars, mesial root of the first molar, and mandibular second premolars (Temple, et al., 2017). Still, 76.7% of the teeth representing the anterior and posterior areas, have a thickness of the alveolar buccal bone less than 1 mm (dos Santos, et al., 2019).

Thus, we can assume that the width of the buccal bone plate in most cases is mainly composed by bundle bone and cortical bone and solely of bundle bone in the coronal regions, which is greater in height at the buccal (≥ 1 mm) than at the lingual bone plate (< 0.5 mm) (Araújo & Lindhe, 2005).

Healing after tooth extraction

Following tooth extraction, a blood clot is formed and retained in the socket during the first 24 hours (Amler, 1969; Lin, 1994; Cardaropoli, et al., 2003). During the first week of healing, the coagulum is partially replaced by granulation tissue (GT) in the marginal area of the socket while in central and apical regions is substituted by provisional matrix. It has been suggested that GT formation might form in response to bacterial contamination to protect the more apical parts of the socket (Araújo, et al., 1997). This may lead to a delayed bone formation, as at 14 days, hard tissue formation has already started with more of 50% of the central and apical part of the alveolus filled with woven bone which is only present in 15% of the marginal tissue. The presence of inflammatory cells in the marginal area decrease at 1 month showing a keratinized epithelium covering the mucosa.

At this time, the socket is mainly filled by mineralized bone which presents areas under osteoclastic resorption indicating that modelling/remodelling process is taking place. The formation of a bone bridge in the marginal portion of the socket can be found after 60, 90, 120, and 180 days of socket healing. This process is called "corticalization" (Ohnishi, et al., 2000) and includes the formation of a bone wall to which the lining mucosa is attached. It includes proliferative and resorptive changes involving the formation and remodelling of woven bone and formation of layers of lamellar bone strengthening the bone bridge and the set-up of periostium. From day 30 to 180 of healing, the tissue within the socket has been found to be occupied at 85% by bone marrow (BM), (figure 4). This may be explained by the absence of load in the area and consequently low demand of mineralized tissue (Cardaropoli, et al., 2003).

Table 1. Overall proportion (%) of the various tissues in the healing socket during the different time intervals, mean (SD)

	1 day	3 days	7 days	14 days	30 days	60 days	90 days	120 days	180 days
CLOT	99.5 (0.6)	99.5 (0.6)	48 (41.9)	0	0	0	0	0	0
GT	0.5 (0.6)	0.5 (0.6)	4 (7.5)	3 (5.7)	0	0	0	0	0
PCT	0	0	48 (47.1)	49 (23.8)	12 (8.6)	0	0	0	0
MB	0	0	0	48 (29.4)	88 (8.7)	23 (15.2)	37 (12)	29 (14.7)	15 (11.1)
BM	0	0	0	0	0	77 (15.1)	63 (11.4)	71 (14.3)	85 (11.2)

CLOT: blood clot; GT: granulation tissue; PCT: provisional matrix; MB: mineralized bone; BM: bone marrow.

Figure 4. Tissue composition and proportions at different time intervals following tooth extraction. Image obtained from Cardaropoli, et al., 2003.

Inmunohistochemically, the density of vascular tissue in extraction sockets seems to be high after 2-4 and 6-8 weeks of healing and decreases at 12-24 weeks. The presence of osteoblasts reaches it highest point at 6-8 weeks and stay stable thereafter. Macrophages decrease from 2-4 weeks on, and only in a few samples at 2-4, 6-8, 12-24 weeks osteoclasts could be observed. Thus, tissue modelling in human extraction sockets seems to be a fast process, while the remodelling of the recently formed tissue seems to be slow. The process of healing has been demonstrated to vary between subjects and was not completed at some of them after 24 weeks following tooth extraction (Trombelli, et al., 2008).

Additionally, tooth loss will consequently lead to a series of morphological changes in the alveolar ridge as an adaptive response to the loss or change of function. These changes have been widely study (Pietrovski and Massler, 1967; Amler, 1969; Cardaropoli, et al., 2003; Schropp, et al., 2003; Araújo & Lindhe 2005; Trombelli, et al., 2008).

The magnitude of the alveolar ridge alterations following tooth extraction result in a substantial reduction of the ridge which is more pronounced in the buccal aspect both in maxilla and in the mandible. These changes, cause a shift of the center of the edentulous ridge towards the palatal or lingual aspect with a reduction of the total arch length. The amount of tissue resorption has been found to be greater in molar regions than in the area of premolars and incisors (figure 5) (Pietrovski and Massler, 1967).

Table 1
Average amount of resorption after tooth extraction in different tooth areas*

	Average amount of resorption (mm.)		
	Buccal surface	*Lingual surface*	*Difference*
Mandibular teeth			
Central incisor	2.08	0.91	1.17
Lateral incisor	3.54	1.41	2.13
Canine	3.25	1.59	1.66
First premolar	3.45	1.40	2.05
Second premolar	3.28	0.75	2.53
First molar	4.69	2.79	1.90
Second molar	4.30	3.00	1.30
Maxillary teeth		*Palatal surface*	
Central incisor	3.03	1.46	1.57
Lateral incisor	3.47	0.86	2.61
Canine	3.33	1.91	1.42
First premolar	3.33	2.04	1.29
Second premolar	2.58	1.62	0.96
First molar	5.25	3.12	2.13
Second molar	4.10	2.93	1.07

Figure 5. Amount of bone ridge resorption at different tooth areas following tooth extraction. Image obtained from Pietrovski and Massler, 1967.

These findings have been supported by other studies. In 2003, Schropp and coworkers, evaluated the dimensional changes, in soft and hard tissues, that occur after tooth extraction in molars and premolars areas at 3, 6, and 12 months. The authors observed that, after 12 months of healing, there was a reduction of 50% in width, two-thirds of which occurred within the first three months after tooth extraction. A displacement of the level of the crest of 1.2 mm more apically was observed after 12 months. During the first three months of healing, bone formation in the socket and loss of the alveolar bone crest took place. An additional bone gain was observed between the period of 3-6 months, while from 6-12 months, a remodelation of the newly formed bone occurred (Schropp, et al., 2003).

In 2005, Araújo and Lindhe performed an observational study in dog model to evaluate the dimensional changes that occur following tooth extraction. After tooth extraction, bundle bone looses its function and is completely resorbed after 4 weeks of healing and replaced with woven bone. The buccal bone plate was observed to be thinner than the lingual, being comprised solely in the crestal region by bundle bone while the lingual counterpart was composed by a combination of lamellar bone and bundle bone. After 8 weeks of healing, a reduction in height and width was observed. The buccal bone crest, which was at the beginning of the study coronal to the lingual, was located 2 mm apical from de lingual crest (figure 6). The considerable resorption of bundle bone may explain the reduction of height found in the buccal bone plate between 1 and 4 weeks of healing. However, since this study determined the alterations in the buccal bone crest levels by taking as a reference the lingual counterpart, which was also presenting signs of resorption, these changes may be underestimated. Yet, the authors concluded that after 8 weeks of healing, the process of modelling is not completed (Araújo & Lindhe, 2005).

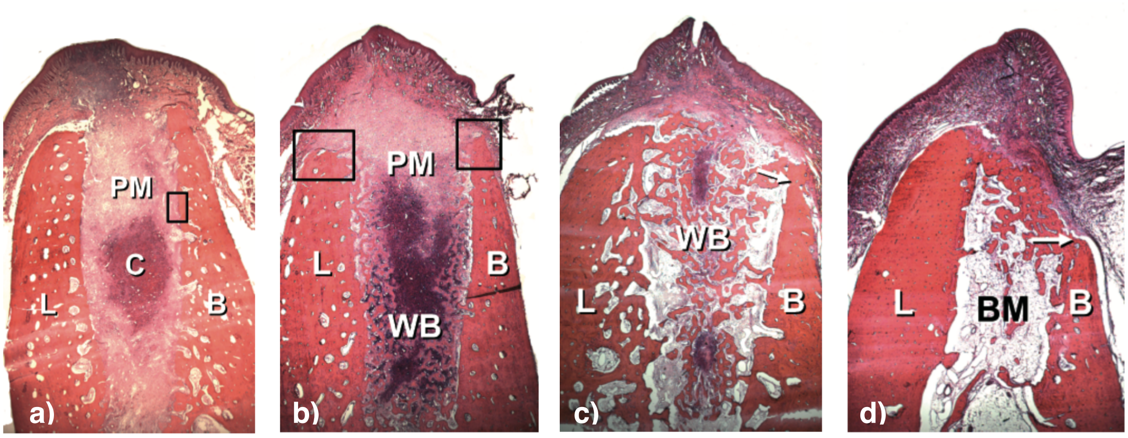

Figure 6. Ridge alterations following tooth extraction. a) One week of healing. b) Two weeks of healing. c) Four weeks of healing. d) Eight weeks of healing. C: Coagulum (blood clot), PM: provisional matrix, B: buccal bone wall, L: lingual bone wall, WB: woven bone, BM: bone marrow. Images obtained from Araújo & Lindhe, 2005.

Dimensional changes of the alveolar socket following tooth extraction

Volumetric changes that occur after tooth extraction have been widely documented. A systematic review that evaluated ridge dimensional changes in humans 12 months following tooth extraction, outlined a vertical reduction of 1.24 ± 0.11 mm, ranging from 11-22%, and a horizontal width reduction of 3.79 ± 0.23 mm after 6 months of tooth extraction, from which 32% and 29-63% occur after 3 and 6-7 months, respectively. Hence, more than 50% of the ridge width can be resorbed after 6 months in some patients. This study observed a greater reduction of the buccal and lingual bone crests in comparison to mesial and distal, with the major changes occurring during the first 3 months. The successive changes that take place after this period are more subtle. Nevertheless, the horizontal reduction is always larger than the vertical (Tan, et al., 2012). These results are in agreement with other investigations that reported a reduction in height and width of 1.67 mm and 3.87 mm, respectively (Van der Weijden, et al., 2009). However, as the distance from the crest augments, the horizontal bone reduction decreases (Kerr, et al., 2008; Araújo & Lindhe, 2009).

To date, the majority of the studies regarding dimensional changes following tooth extraction have been performed in the anterior area and premolars not including molar region, thus, evidence regarding ridge dimensional changes in molar sites remains scarce. Hence, studies evaluating dimensional changes in posterior sites have reported that a reduction in width and height of 4.48 mm and 1.43 mm, respectively, can be expected after 4 months (Cardaropoli, et al., 2012). These changes may be influenced by several factors. First, buccal bone thickness has been shown to play an important role in the amount of bone resorption as thinner buccal bone plates (< 1.5 mm) seem to result in a greater reduction in width than thicker buccal bone plates (≥ 1.5 mm) (Barone, et al., 2017). Similarly, results from the latest european workshop regarding ridge preservation procedures have suggested that, sites with a thickness of the buccal bone plate > 1.0 - 1.5 mm present less bone remodelling following tooth extraction (Tonetti, et al., 2019). Thus, some studies in molar sites have failed to find any correlation (Walker, et al., 2017; Al Harthi, et al., 2019).

Furthermore, other possible contributing factors that may influence bone healing have also been studied. Primary closure entails the elevation of full thickness flaps which may cause attachment loss and 0.62 mm of bone resorption (Wood, et al.,1972). However, differences between flap and flapless approaches seem to be negligible after 6 months of healing (Araújo & Lindhe, 2009). Contiguous tooth extraction may lead to an enhanced bone resorption compared to single tooth extractions (Al-Askar, et al., 2013**).** Smoking may result in an increased bone resorption expecting 0.5mm more of crestal bone reduction after tooth extraction (Saldanha, et al., 2006). Moreover, rinsing with clorhexidine digluconate twice daily for 1 month have demonstrated positive effects on the healing of periodontal tissues with an increase in bone density in the apposition phase and less bone remodelling (Brägger, et al., 1994). Also, it has been speculated that over eruption of adjacent teeth may affect the pattern of dimensional changes (Mizutani & Ishihata, 1976). Thus, the use of immediate dentures may affect in the short-term alveolar dimensional changes although the differences versus delayed ones were imperceptible after two years of healing (Carlsson, et al., 1967).

It was suggested, that the placement of dental implants in the fresh extraction sockets could prevent bone remodelling maintaining the original dimensions of the ridge **(**Paolantonio, et al., 2001). However, findings from animal (Araújo, et al., 2005; Araújo, et al., 2006; Blanco, et al., 2008) and clinical studies (Sanz, et al., 2010) have failed to support this hypothesis. Thus, the placement of an implant in a fresh extraction socket failed to prevent bone dimensional changes, resulting in similar loss of buccal bone height compared to natural spontaneous healing.

The dimensional changes that occur following tooth extraction may play a role, not only in high demanding aesthetic areas but also in the posterior region, at which insufficient availability of bone, particularly in height, and the proximity with anatomic structures, such as the maxillary sinus or the inferior alveolar nerve, may hinder the placement of dental implants.

In order to minimize the dimensional changes that occur after tooth loss, ridge preservation techniques have been proposed.

Principles of regenerative procedures

Bone regeneration techniques are based on the biological principle of guided tissue regeneration discovered by Nyman & Karring in the 1980s. These investigators found that the cells that first populate a wound determine the type of tissue that is formed in a specific area. For that purpose, they introduced the use of barrier membranes in regenerative periodontal surgery in order to isolate the growth of undesired cells from the wound allowing exclusively the proliferation of certain cell populations (Nymann, et al., 1987).

The placement of a stable membrane on native bone covering the bony defect, excludes the epithelial and connective tissue cells and promotes the growth of undifferentiated mesenchymal cells in the submembranous-protected leading to periodontal regeneration.

Bone regeneration techniques are based on this principle and have demonstrated to be a successful method to augment bone in areas with insufficient amount of hard tissue to place dental implants (Milinkovic & Cordaro, 2014, Elnayef, et al., 2019).

For this purpose, several barrier membranes and bone grafts have been developed. The barrier membranes used for bone regeneration procedures can be classified as resorbable and non-resorbable. Thus, depending on their origin, resorbable membranes can be classified as natural or synthetic (table 1).

NON-RESORBABLE	**RESORBABLE**	
	Natural	**Synthetic**
e-PTFE	Native collagen	Polyglactin
d-PTFE	Cross-linked collagen	Polyurethane
Titanium foil	Freeze-dried fascia lata	Polylactic acid
Micro titanium mesh	Freeze-dried dura mater	Polyglycolic acid
		Polylactic acid/polyglycolic acid copolymers
		Polyethylene glycol

Table 1. Description of the materials used in resorbable and non-resorbable membranes.
Table obtained and adapted from Benic & Hämmerle, 2014.

In general, barrier membranes should be biocompatible, non-toxic or allergenic and induce low or none inflammatory response or immune reaction. Moreover, they should provide tissue integration, cell occlusion, space maintenance, be adaptable and easy to handle. Its maintenance in place should last time enough to provide bone growth, and in case of resorbable, its resorption should not infer in bone healing (Gottlow, 1993).

Historically, the first barrier membranes used were non-resorbable and they were composed of expanded polytetrafluoroethylene (ePTFE). e-PTFE, is a synthetic polymer with a porous structure, that resists enzymatic degradation and does not induce immune reactions. e-PTFE membranes can be reinforced by titanium to facilitate its adaptation in shape to the bone defect and augment its stability (Benic & Hämmerle, 2014). Although this material provides good results in bone regeneration procedures, one of its main disadvantages is that these type of membranes require a second surgery for their removal and have a high risk of exposure to the oral cavity during healing which normally results in bacterial contamination and poor regenerative outcomes (Selvig, et al., 1992). In order to overcome these problems, resorbable membranes have been developed.

Resorbable membranes do not need a second surgery to be removed presenting less morbidity, are cost-effective and can be used in a wide range of surgical techniques. However, its degradation can difficult the maintenance of the barrier function during an appropriate period of time (Benic & Hämmerle, 2014). Natural resorbable membranes are mainly composed of collagen, and have been widely used in guided tissue and bone regeneration procedures. This material presents similar results to non-resorbable membranes with the advantage that they do not usually get exposed to the oral cavity, and if so, its exposure involves no infection (Tal, et al., 2008). The process of resorption of collagen membranes is caused by the enzymatic activity of macrophages and polymorphonuclear leukocytes. Further, the collagenase activity of periodontal pathogens can degrade the membranes when exposed to the oral cavity (Moses, et al., 2005).

For that, aims to retard the process of resorption of the collagen membranes have been attempted with the use of cross-linking technology, in order to increase its durability. However, studies evaluating the duration of both cross-linked, and non-cross-linked membranes have found complete degradation of both, when exposed to the oral cavity at 7 days (Tal, et al., 2008). Despite this fact, the absence of primary closure and the intentionally exposure of cross-linked collagen membranes seems not to affect to the residual graft or the amount of new vital bone formation in bone regeneration procedures (Kim, et al., 2013). Among the resorbable collagen membranes, Mem-Lok® RCM is a cross-linked (CLCM) highly purified collagen type I membrane which macromolecular pore size permeability that allows for exchange of nutrients during the period of healing . This characteristic also facilitates its adaptation to several bony defects and ensures resorption period of 26-28 weeks. CLCM has been widely applied in bone regeneration techniques (Guarnieri, et al., 2015; Kim, et al., 2013).

Regarding bone grafting materials, they should be biocompatible, similar in structure to bone, be able to promote angiogenesis and display osteoinductive or osteoconductive capacity to promote human bone growth in direct contact with the graft material.

Besides, the resorption rate of the graft should be similar to the rate of new bone formation in order to ensure its effectiveness in bone augmentation (Bartold, et al., 2016). Depending on their origin, bone grafts can be classified as autograft, allograft, xenograft or alloplast (table 2).

GRAFT MATERIAL	ORIGIN	EXAMPLES
Autograft	Tissue from the own patient	Harvested intra or extra-orally
Allograft	Tissue from individuals on the same species	Fresh-frozen bone, Freeze-dried bone, demineralized freeze-dried bone
Xenograft	Tissue from other species	Origin: bovine, equine, porcine.
Alloplast	Material synthetically fabricated	Tricalcium phosphate, hydroxyapatite, hydroxyapatite/ tricalcium phosphate composite, calcium phosphate cement, calcium sulfate, bioactive glass, polymers.

Table 2. Description of the most commonly type of graft materials used. Table obtained and adapted from Benic & Hämmerle, 2014.

Among the graft materials employed for bone regeneration procedures, two of the most widely used are deproteinized bovine bone mineral (DBBM) and freeze-dried bone allograft (FDBA).

DBBM, is a xenograft composed by hydroxyapatite bone mineral to which the organic components have been removed from without altering its mineral part and microstructure. Structurally and chemically it resembles human bone and its mineral content and porosity confers its property of osteoconduction (Buser, et al., 1998). DDBM has been used successfully in guided bone regeneration (Norton, et al., 2003; Carmagnola, et al., 2003; Mardas, et al., 2011; Nart, et al., 2016), guided tissue regeneration (Sculean, et al., 2004), and sinus lift (Schmidth, et al., 2012) procedures.

FDBA, is a bone allograft prepared in a freeze-dried form. Allograft materials can be prepared in two different forms: freeze-dried; at which the bone is cryo-dried to eliminate the liquid component but preserving its structure, or treated with hydrochloric acid; to produce demineralized forms and expose the bone morphogenetic proteins present in the bone matrix (Bartold, et al., 2016). FDBA has osteoconductive capacity and provides an appropriate scaffold for space maintenance in bone regeneration procedures. However, FDBA is also demineralized after implantation in bone as osteoclasts break down its mineral component. This may lead to the availability of osteoinductive proteins with a prolonged and beneficial protein release (Wood & Mealey, 2012). Freeze-dried bone allografts have been used in guided tissue regeneration (Listgarten & Rosenberg, 1979; Gothi, et al., 2015), guided bone regeneration (Wang & Tsao, 2008; Demetter, et al., 2017) and sinus lift procedures (Avila-Ortiz, et al., 2012) with successful results.

The use of barrier membranes alone (Carmagnola, et al., 2003; Formiga, et al., 2019) or in combination (Cardaropoli, et al., 2012; Norton, et al., 2003, Barone, et al., 2008, Mardas, et al., 2011) with graft materials has been widely applied in ridge preservation and bone regeneration techniques.

Ridge preservation

Among different periodontal regeneration techniques, ridge preservation procedures have been developed to minimize the dimensional changes that occur after tooth extraction. This technique was first described by Sheer & Boyne (1987) and aimed to introduce a biocompatible material into the extraction socket to prevent bone remodelling after tooth loss. Since then, several materials and techniques have been used.

Ridge preservation techniques have been defined as "any therapeutic approach carried out immediately after tooth extraction aimed to preserve the alveolar socket architecture and to provide the maximum bone availability for implant placement" (Vignoletti, et al., 2012).

For that purpose, graft materials such as; allografts (Engler-Hamm, et al., 2011; Avila-Ortiz, et al., 2014), xenografts (Flickl, et al., 2008; Araújo, et al., 2008; Araújo & Lindhe, 2009; Araújo & Lindhe, 2011; Ackermann, 2009; Nart, et al., 2016; Carmagnola, et al., 2003; Mardas, et al., 2011; Molly, et al., 2008; Norton, et al., 2003; Barone, et al., 2008; Barone, et al., 2014; Alkan, et al., 2013), autografts (Araújo & Lindhe, 2011), and alloplasts (Kim, et al., 2013; Mardas, et al., 2011, Molly, et al., 2008; Oghli & Steveling, 2010) have been commonly used. Growth factors in combination with a carrier (Fiorellini, et al., 2005) have also been tested. Resorbable barrier membranes with natural origin (Flickl, et al., 2008; Barone, et al., 2008; Barone, et al., 2014; Kim, et al., 2013; Mardas, et al., 2011; Norton, et al., 2003; Nart, et al., 2016; Cardaropoli & Cardaropoli, 2008), or synthetic origin (Engler-Hamm, et al., 2011), non-resorbable barrier membranes (Avila-Ortiz, et al., 2014; Molly, et al., 2008) free gingival grafts (Flickl, et al., 2008; Oghli & Steveling, 2010; Alkan, et al., 2013) or soft tissue substitutes (Jung, et al., 2013) have also been used.

The use of graft materials have been employed alone (Flickl, et al., 2008; Araújo, et al., 2008; Araújo & Lindhe, 2009; Ackermann, 2009), in combination with barrier membranes (Flickl, et al., 2008; Carmagnola, et al., 2003; Nart, et al., 2016; Mardas, et al., 2011; Norton, et al., 2003, Cardaropoli & Cardaropoli, 2008; Avila-Ortiz, et al., 2014; Barone, et al., 2008; Barone, et al., 2014; Kim, et al., 2013), free gingival grafts (Flickl, et al., 2008; Oghli & Steveling, 2010; Alkan, et al., 2013) or soft tissue substitutes. Furthermore, the use of membranes alone has also been tested (Carmagnola, et al., 2003).

Additionally, some authors have aimed to achieve primary closure so the graft material is covered by a barrier membrane or soft tissue graft and the flap (Engler-Hamm, et al., 2011; Araújo & Lindhe, 2009; Barone, et al., 2008; Barone, et al., 2014; Kim, et al., 2013; Norton, et al., 2003), while other studies leave the barriers intentionally exposed (Flickl, et al., 2008; Engler-Hamm, et al., 2011; Cardaropoli & Cardaropoli, 2008; Barone, et al., 2014; Kim, et al., 2013; Nart, et al., 2016; Norton, et al., 2003).

Systematic reviews have demonstrated that ridge preservation procedures do not completely prevent bone dimensional changes, but limit the bone loss of the alveolar ridge, in both height and width, after tooth extraction (Vignoletti, et al., 2012; Ten Heggeler, et al., 2011; Vittorini Orgeas, et al., 2013; Avila-Ortiz, et al., 2014; MacBeth, et al., 2016; Avila-Ortiz, et al., 2019). After ridge preservation techniques, a reduction in width up to 3.48 mm and 2.64 mm in height may still be expected (Ten Heggeler, et al., 2011). Thus, according to a recent systematic review, when compared to extraction alone, ridge preservation prevents 1.99 mm of horizontal, 1.72 mm vertical mid-buccal and 1.16 mm mid-lingual bone resorption (Avila-Ortiz, et al., 2019).

To date, there is no evidence of which technique or material provide better results in terms of alveolar ridge preservation (Willembacher, et al., 2016; MacBeth, et al., 2016; Tonetti, et al., 2019; Avila-Ortiz, et al., 2019). However, it has been suggested that the use of membranes, flap procedures and primary closure provides better results horizontally (Vignoletti, et al., 2012). Regarding graft materials, the use of xenografts or allografts in combination with a collagen membrane or a collagen sponge seem to result in a better preservation of the ridge width (Avila-Ortiz, et al., 2019).

Several studies have performed an histologic and histomorphometric evaluation of the regenerated bony areas to quantify the amount of vital bone, graft particles, and non-mineralized connective tissue present in the site (Eskow, et al., 2014; Demetter, et al., 2017). This analysis provides information to the clinician regarding the type of tissue formed and the time needed to achieve a proper healing. However, there is no firm evidence that confirms any benefit with the use of different ridge preservation techniques in terms of histological and histomorphometric analysis in comparison to spontaneous healing (De Risi, et al., 2015).

Moreover, since the majority of the studies regarding ridge preservation techniques do not include molar regions, further studies are required to evaluate how healing of molar extraction sites are influenced by the use of these techniques.

Analysis of dimensional changes

Traditionally, different methods have been proposed for evaluation of the dimensional changes of the alveolar ridge. This includes the use of study casts (Pietrovski & Massler, 1967; Schropp, et al., 2003; Flick, et al., 2008), and clinical measurements by means of a periodontal probe (Barone, et al., 2008) or a caliper (Cardaropoli & Cardaropoli, 2008; Spinato, et al., 2012).

Radiographic osseous changes have been evaluated with the use of standardized periapical radiographs (Schropp, et al., 2003; Mardas, et al., 2011; Parashis, et al., 2016), subtraction radiography (Schropp, et al., 2003; Mardas, et al., 2011) or cone beam computed tomography (CBCT) (Januario, et al., 2008; Jung, et al., 2013; Nart, et al., 2016; Lombardi, et al., 2018; Formiga, et al., 2019). Although, periapical radiographs are used to measure and evaluate the level of the interproximal bone dimensions, some image magnification can be expected (Schropp, et al., 2003).

Nowadays, CBCT is the cross-sectional imaging modality of choice as this technology entails a submillimetric precision for linear measurements. Further, it is available at reduce expense, and produce less radiation than conventional computed tomography (Braut, et al., 2012).

CBCTs have demonstrated to be accurate in the visualization of both hard (Januario, et al., 2011; Braut, et al., 2012; Temple, et al., 2016; Gomes dos Santos, et al., 2019) and soft tissues (Januario, et al., 2008) being able to analyze the structures of the periodontium and dentogingival attachment apparatus.

Studies comparing direct measurements in skulls versus CBCT images have demonstrated its accuracy and have determined that, with an appropriate selection and definition of the landmarks and proper three-dimensional measuring tools, this accuracy provides unambiguous anatomical information (Lascala, et al., 2004; Ludlow, et al., 2007; Kamburoğlu, et al., 2011). This accuracy has shown to be within 0.28 - 0.29 mm in comparison with direct measurements at the buccal and lingual plates after tooth extraction (Behnia, et al., 2015).

The superimposition of CBCT images was proposed by Jung and coworkers (2013). This technique aimed to compare different CBCT images of the same patient on different periods of time. In this way, dimensional changes of the ridge can be evaluated and compared after natural healing and/or bone regeneration procedures in time. In order to perform this evaluation, several anatomic craneal points which have not been involved in any dimensional change procedure are taken as reference, which allows to measure clinical changes occurred in the region of interest.

Justification

Ridge preservation has demonstrated to be a successful treatment minimizing ridge resorption following tooth extraction and consequently maintaining a sufficient area of bone to place dental implants (Choi, et al., 2017; Lim, et al., 2019).

To date, several techniques and biomaterials have been widely investigated with the purpose to determine which technique and biomaterial provide better results. So far, there is no consensus with regard to which technique is superior in terms of bone ridge reduction or tissue composition (Vignoletti, et al., 2012; Vittorini Orgeas, et al., 2013; De Risi, et al., 2015; Avila-Ortiz, et al., 2019).

It has been suggested that sites with a thickness of the buccal bone plate > 1.0-1.5 mm present less bone remodelling following tooth extraction so that thin bone plates may benefit more from ridge preservation procedures (Tonetti, et al., 2019).

Moreover, the proximity of molar teeth to anatomic structures such as the maxillary sinus or the inferior alveolar nerve, may imply that ridge remodelling after molar extraction result in a decreased length of the ridge augmenting the need of bone regeneration with more invasive techniques. Thus, taking into consideration the proximity of maxillary and mandibular molars to relevant anatomic areas, ridge preservation therapy would be anatomically indicated in many cases.

To date, scientific evidence regarding ridge preservation in molar sites remains scarce and, to our knowledge, there is no previous investigation comparing the use of DBBM and FDBA in ridge preservation in molar sites.

HYPOTHESES

Main hypothesis

Ha0: No differences will be observed in terms of ridge dimensional changes between the use of FDBA or DBBM, in combination with a resorbable membrane.

Ha1: Differences in ridge dimensional changes will be observed between the use of FDBA or DBBM, in combination with a resorbable membrane.

Secondary hypotheses

Hb0: The thickness of buccal and lingual bone plates will not have an influence on ridge dimensional changes.

Hb1: The thickness of buccal and lingual bone plates will influence ridge dimensional changes.

Hc0: No differences will be observed regarding new bone formation, amount of residual bone particles and connective tissue formation between the use of FDBA or DBBM, after 5 months of healing.

Hc1: Differences will be observed regarding new bone formation, amount of residual bone particle and connective tissue formation between the use of FDBA or DBBM, after 5 months of healing.

Hd0: The use of ridge preservation techniques will not limit the need of lateral sinus lift previous to implant placement.

Hd1: The use of ridge preservation techniques will limit the need of lateral sinus lift previous to implant placement.

OBJECTIVES

Main objective

The aim of the present investigation was to evaluate the dimensional changes that occur after ridge preservation techniques in molar sites and compare the use of freeze dried bone allograft or xenograft, in combination with a resorbable membrane.

Secondary objectives

- To evaluate the influence of the thickness of buccal and lingual bone plates on dimensional changes.
- To determine the histologic composition of the regenerated areas in terms of new bone formation, non-mineralized connective tissue and residual graft particles after 5 months of healing.
- To evaluate the need of lateral sinus lift previous to implant placement in previously preserved areas.

MATERIAL & METHODS

Material and methods

This randomized clinical trial was performed at the Clínica Universitaria de Odontología of the Universitat Internacional de Catalunya (UIC) (Barcelona, Spain). The Ethics Committee for Scientific Research (UIC) reviewed and approved the protocol of the present study (2013-M-PER-ECL-2013-04) and CONSORT guidelines for randomized clinical trials were followed. Experimental procedures were conducted from December 2013 to May 2019. All patients included accepted and signed the informed consent.

Sample size calculation was made considering a difference in ridge width (primary outcome variable) of 1.2 mm to be of clinical relevance. To detect such a difference with a power of 80% and a $\propto$ - level of 5% in bilateral contrast, a total of 10 subjects per group were needed. Assuming a 15% of dropouts, a sample size of 24 subjects were recruited. For both analysis, Stata Software was used.

Patient selection

Inclusion criteria: adult patients aged 18 and older in need of removal of a maxillary or mandibular first or second molar and posterior implant placement, were selected. The molars to be extracted had to be bordered by at least one tooth, have a presence of ≥ 2 mm of keratinized gingiva and three intact bony walls. A dehiscence on the fourth wall, if any, had to be less than 2 mm in height. Only one extraction per patient was accepted. In case that one patient presented more than one extraction site complying inclusion criteria, the included site was selected by randomization with sealed envelopes. Patients were informed of all the phases of the treatment and the inform consent form (ICF) was accepted and signed.

Exclusion criteria was the following: presence of acute periodontal or periapical infections, pregnancy or lactancy, smokers of more than 10 cigarettes per day, previous adverse reactions to the biomaterials used in the study, metabolic diseases affecting the mechanism of bone remodelling, medications or treatments taken in the last twelve months and known to affect bone "turnover" and systemic diseases that impedes the successful outcome of treatment or result on impair healing. Furthermore, patients with poor plaque control -more than 20% (O'Leary, et al., 1972)- and absence of periodontal health maintenance or postoperative recommendations compliance were also excluded.

Patients were excluded from the study if they violated any of the following criteria during the trial: failure to comply with postoperative instructions correctly, failure to comply with the maintenance program correctly, become pregnant during the study, desire to leave the study and have any adverse reactions due to the use of any of the materials discussed above.

Randomization

Once patients were recruited, a computer-generated randomization list was used for treatment assignment by means of a software and opaque and sealed envelopes were prepared. An operator blinded to the experiment, opened the envelope just after tooth extraction.

Study groups

A randomized comparison of two biomaterials; Bio-Oss® (cancellous xenograft) (DBBM), 0,5 gr (Geistlish, Pharma Wolhausen, Switzerland) versus MinerOss® (cortical and cancellous allograft) (FDBA) 1cc, (BioHorizons, Birmingham, AL, USA) in combination with a cross-linked resorbable membrane Mem-lok®, 15x20 mm (BioHorizons, Birmingham, AL, USA) in ridge preservation techniques was performed.

Recruitment

Patient recruitment was carried out orally within the Universitat Internacional de Catalunya (UIC) by the dental students, practice coordinators, residents and clinical faculty members in accordance with the inclusion criteria. Patients were consecutively referred to the postgraduate clinic of the Periodontology Department at UIC. After confirming that the patient complied with the inclusion criteria in the study, the patient was informed orally and given a ICF. The procedure and possible alternatives were explained and discussed. All questions or doubts that the subjects formulated were clarified so that they fully understood all the steps to be followed in the study before they sign the ICF.

Clinical appointments

In the first appointment, evaluation of the molar to be extracted was performed considering the need of extraction and subsequent feasibility of implant placement. Moreover, medical and dental history of participants were reviewed and updated and comprehensive oral and periodontal examination including periapical radiographs, study casts, and clinical photographs was performed. Furthermore, participants received information of the study, surgical procedures, details of the post-surgical follow-up and the importance of dental care and oral hygiene maintenance was emphasized.

Following screening, patients were treated with a full mouth debridement and/or scaling and root planing, if necessary, to provide an improved oral environment and wound healing prior to surgery.

After molar extraction, an initial CBCT (CBCT1) was obtained. Following surgery, participants were scheduled at one week for visual examination and one week later for suture removal. The following visits were scheduled at 6 weeks and 4 months after surgery. All the visits included clinical photographs.

Five months later, a second CBCT (CBCT2) was obtained and implant placement was planned. At implant surgery, a tissue biopsy was obtained (figure 7).

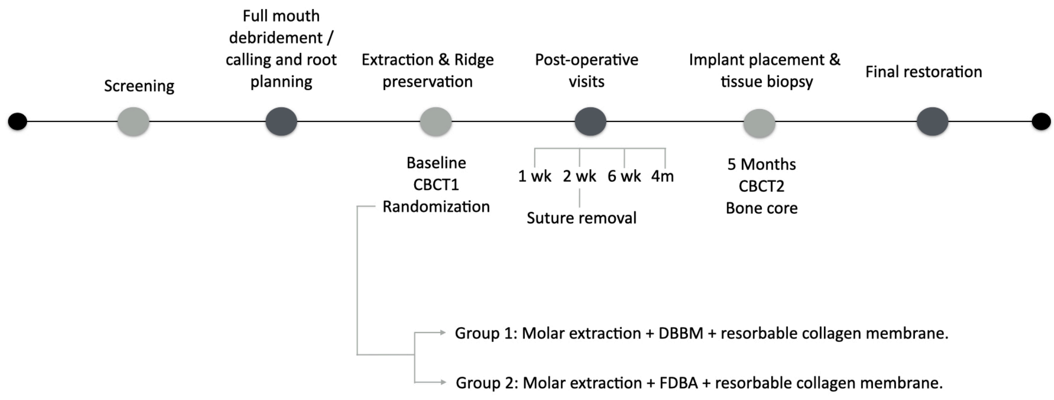

Figure 7. Clinical appointments schedule and study design. 1 week (1 wk), 2 weeks (2 wk), 6 weeks (6 wk), 4 months (4 m), baseline CBCT (CBCT1) and final CBCT (CBCT2).

Risk/benefit assessment

The risk of infection is considered to be similar whether teeth are extracted with or without bone grafting. Subsequently, there is no higher risk in comparison to the alternative treatment (extraction without bone grafting). The risk associated with dental extractions and graft procedures are:

- Bleeding.
- Dry socket.
- Infection.
- Bone sequestrates or tooth fragments.
- Swelling.
- Pain.
- Paresthesia.
- Necrosis.

In addition, the risk of infection in the present study was considered to be very low as a post-operative antimicrobial mouth rinse and post-operative systemic antibiotics were prescribed. In addition, the patient underwent Phase I mechanical scaling and root planing, if necessary, and extensive training in oral hygiene to control periodontitis before entering into the surgical phase of the study. In the unlikely event of an infection, the bone graft in the extraction site was treated accordingly, allowed to heal, and re-treated at a later time at no cost to the subject. Other than that, there are no known risks (physical/psychological/social/economic, etc.) to having extraction sites grafted and sealed with the two described surgical techniques.

A list of possible adverse events (AE) was created. At each visit, after the surgical procedure, we interviewed each subject specifically about adverse events.

Ridge preservation procedure

A minimal full-thickness mucoperiosteal flap was raised to expose the buccal and lingual bone without reaching the mucogingival line. Teeth were extracted as atraumatically as possible and sectioned when necessary. The extraction sockets were curetted to remove all soft and granulation tissue. After debridement, presence of intact bone walls or the extent of dehiscence, if any, was evaluated.

Subsequently, a Cone Beam Computed Tomography (CBCT) (iCAT Vision®; Imaging Sciences International LLC, USA) of the maxilla or mandible was carried out to analyse the dimensions of the alveolar ridge in width and height, as well as the thickness of the bone walls (CBCT1). After obtaining the 3D image, ridge preservation was performed.

Subjects were treated with DBMM or FDBA in combination with a resorbable collagen membrane. DBBM or FDBA were hydrated with sterile saline and placed into the extraction socket. A collagen membrane was trimmed, hydrated in sterile saline for 5 minutes and adapted to completely cover the socket extending at least 3 mm beyond the alveolar crest. Flaps were then replaced and sutured with 5/0 polypropylene interrupted and mattress sutures (figure 8).

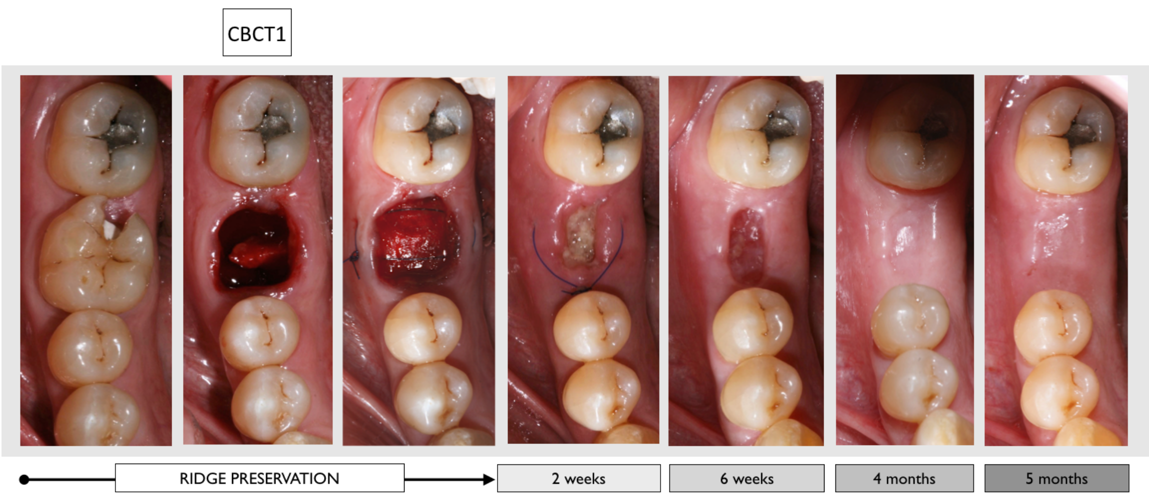

Figure 8. Surgical procedure of ridge preservation. Initial CBCT (CBCT1).

Post surgical care

All subjects were instructed to rinse with 0.12% chlorhexidine digluconate and 0.05% cetylpyridinium chloride (Perio-Aid®, Dentaid, Barcelona, Spain) twice daily for 2 weeks. As systemic antibiotic, Amoxicillin (500 mg every 8 hours for 7 days) or, in case of allergy to penicillin, Clindamycin (300 mg every 8 hours for 7 days) was prescribed. Analgesics such as Ibuprofen (600 mg every 8 hours) or Paracetamol (650 mg every 8 hours) were recommended as needed. Sutures were removed 2 weeks after the surgery and all patients were supervised weekly until full soft tissue closure was achieved. Post-operative follow-up was recorded at 1, 2, and 6 weeks, and at 4 and 5 months after surgery.

5 months reentry for implant placement

After 5 months of healing, a second CBCT (CBCT2) was obtained and implant placement was planned. Prior to surgery, Amoxicillin (2 g 1 hour before implant placement) or, in case of allergy to penicillin, Clindamycin (600 mg 1 hour before implant placement) was prescribed to the patient.

Full-thickness flaps were elevated and a trephine core of 2x6 mm (2 mm of inner and 2.5 mm of external diameter) was used with saline irrigation to obtain a core from the preserved area. The core was removed from the trephine bur with the use of a periodontal probe and placed in 10% formaline. The implant site was prepared with the use of a surgical handpiece. Implants were inserted and flaps were repositioned and sutured with 5/0 polypropylene suture (figure 9). Subjects followed the same analgesic and antiseptic postoperative care regime as in the previous surgical procedure and were checked until implant loading was completed.

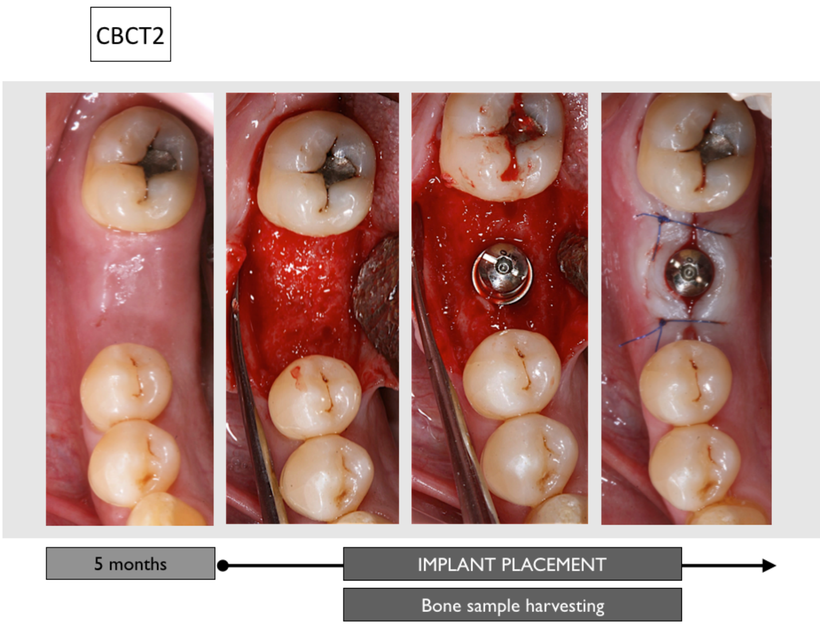

Figure 9. Surgical procedure, after 5 months of ridge preservation, at the time of implant placement. Final CBCT (CBCT2).

Dimensional changes evaluation

To evaluate dimensional changes, the initial (CBCT1) and 5 months (CBCT2) CBCT images were processed and superimposed with the use of a specialized software image Simplant® O&O (Denstply Sirona, Charlotte, NC, USA). The analysis was carried out by a blinded examiner (D.A) who was unaware of treatment assignment. Before superimposition, images were processed individually to eliminate undesired structures and possible artefacts, and each image was saved in a different colour. Once processed, the two CBCT scans (CBCT1 and CBCT2) were overlapped (Figure 10) with help of three or more anatomical landmarks settled manually in cranial areas where no changes had occurred during the healing period.

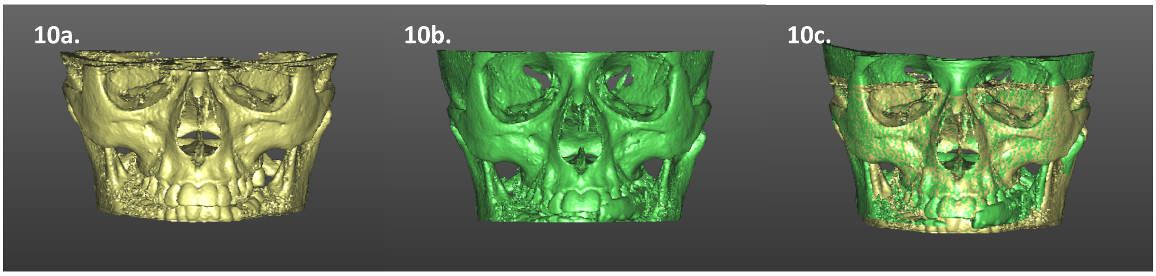

Figure 10. Dimensional changes evaluation with CBCT. Baseline CBCT (CBCT1) and final CBCT (CBCT2). 10a) CBCT1. 10b) CBCT2. 10c) CBCT1 and CBCT2 superimposition with anatomical landmarks.

A reference apical point, corresponding to the apex of the extraction socket was settled. Two reference lines were determined according to this location, a vertical line crossing the center of the socket and the apical reference point, and a horizontal line located on the base of the apex of the extraction socket and perpendicular to the vertical line (Jung, et al., 2013) (Figure 11). All measurements were made encompassing these references. The thickness of the buccal bone plate (BP) was measured at 1 mm (BP-1), 3 mm (BP-3) and 5 mm (BP-5) below the lingual bone crest at baseline. The thickness of the lingual bone plate (LP) was also determined at 1 mm (LP-1), 3 mm (LP-3) and 5 mm (LP-5). The height of the buccal and lingual bone plate was measured at the mid-buccal (BH) and mid-lingual (LH) aspect, as well as the height of the ridge at the center of the socket (CH). The width of the bone ridge (RW) was measured at 1 mm (RW-1), 3 mm (RW-3) and 5 mm (RW-5) below the bone crest.

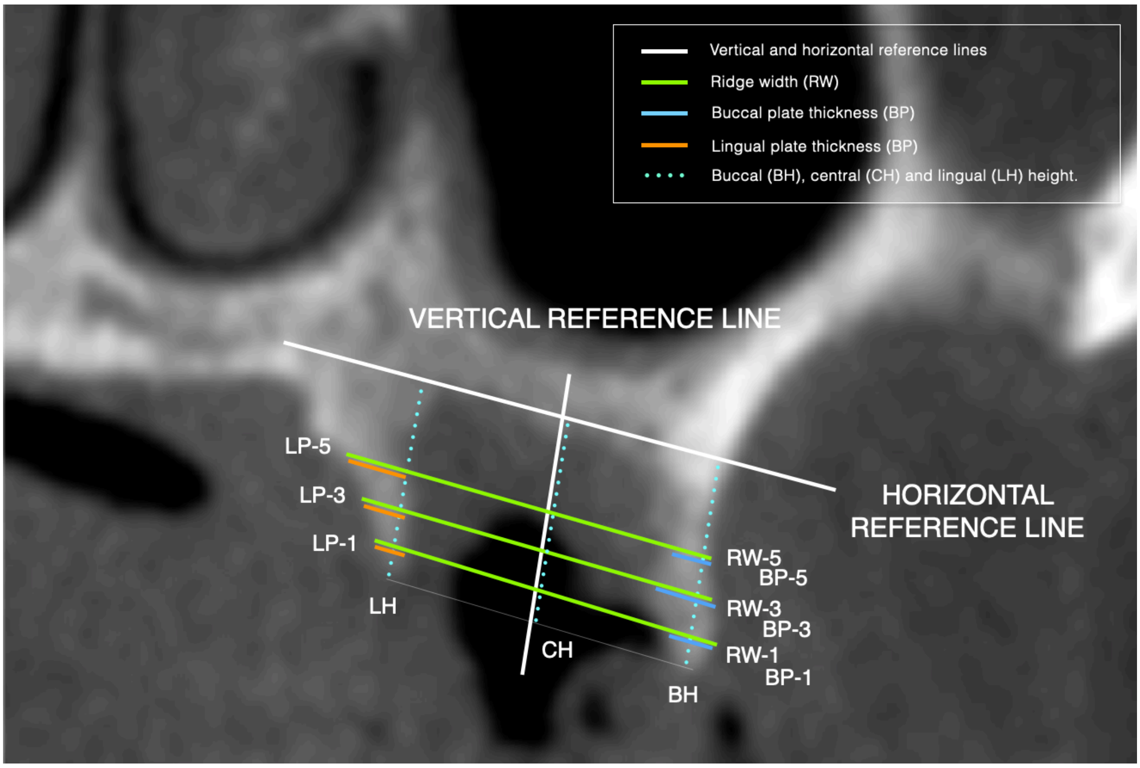

Figure 11. Coronal section of the ridge with measurement reference lines. Vertical measurements: buccal bone (BH), center of the ridge (CH) and lingual height (LH). Horizontal measurements: ridge width (RW) at 1 mm (RW-1), 3 mm (RW-3) and 5 mm (RW-5) from the bone crest. Buccal (BP) and lingual plate (LP) thickness at 1 mm (BP-1) (LP-1), 3 mm (BP-3) (LP-3) and 5 mm (BP-5)(LP-5) from the bone crest, respectively.

Dimensional changes were assessed based on the measurements performed on CBCT1 and CBCT2 (figure 12) after superposition. Measurements were expressed in millimetres (mm) and percentages showing changes in (i) RW-1, RW-3 and RW-5 and (ii) BH, CH and LH. A possible correlation between the initial BP and LP (≥ 1.5 mm or < 1.5 mm) and vertical or horizontal bone changes was also assessed.

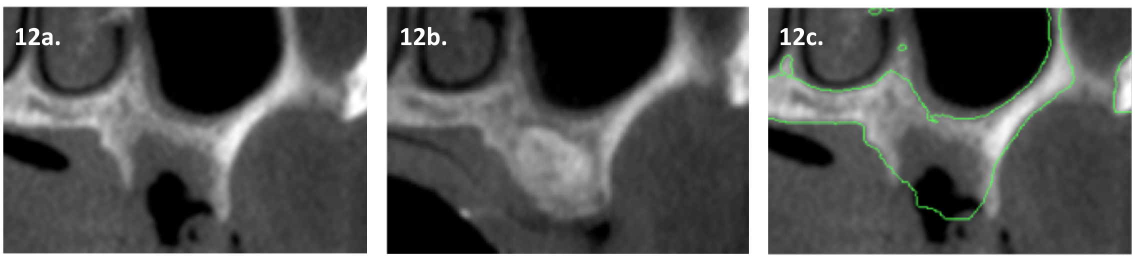

Figure 12. Radiographic evaluation . 12a. Baseline CBCT (CBCT1). 12b. Final CBCT image after 5 months (CBCT2). 12c. Superimposition of CBCT1 and CBCT2.

Histological and histomorphometric analysis

Samples were processed by M.C. and coworkers at the Anatomopathology Department of the Hospital General de Catalunya and analyzed by an examiner (D.A.), who was not aware of the treatment assignment, although blinding could not be possible due to visual particle type differences. Biopsies were decalcified, embedded in paraffin, sectioned longitudinally and prepared for histological analysis using a hematoxylin-eosin staining. Each section was examined at 40x magnification and standardized photographs from the selected sections were taken. The histomorphometric analysis was performed by the use of a specific software image (Image J®, Image Processing and Analysis in Java) and the areas occupied by vital bone (VB), non-mineralized connective tissue (NMCT) and graft particles (GP) were evaluated. The analysis of each tissue volume was expressed in percentages (%).

Need of sinus lift elevation following ridge preservation

In order to evaluate the need of sinus lift procedures following ridge preservation, the height of the alveolar crest (CH), was evaluated after 5 months, previously to the implant placement planning. A threshold of 8mm in initial ridge length was settled to evaluate the need of sinus lift after ridge preservation procedures. This threshold of 8 mm of vertical residual bone has been also followed in previous studies (Rasperini, et al., 2010).

Statistical analysis

Intra-examiner reliability was conducted by measuring CBCT distances between reference points two-days apart. For assessing its individual reproducibility, intraclass correlation coefficient (ICC) was performed. Descriptive data was expressed as mean, standard deviation (SD), median and percentages.

Data normality distribution was assessed by means of Shapiro-Wilk tests. As data did not follow a normal distribution intra and intergroup comparisons of quantitative data were assessed by using Wilcoxon and U-Mann Whitney tests, respectively. Moreover, Fisher's exact Chi square test was applied for assessing possible associations between two categorical variables. Therefore, intra-group volumetric changes were analyzed with Wilcoxon test. Age, dimensional changes and histological differences were analyzed with U-Mann Whitney test, while gender, location (maxilla or mandible) and smoking habit were presented using frequency and percentages and evaluated with Fischer's exact Chi square test.

A Spearman correlation test was performed to analyze the influence of buccal and lingual/palatal plate thickness on dimensional changes at 1, 3 and 5 mm below crest. All the statistical procedures were performed using Stata (v.15.2) software. A p-value < 0.05 was considered as statistically significant (*).

<u>Confidentiality</u>

All the information was coded with numbers assigned to each subject participating in the study; therefore, no name appeared on the sheet in which all clinical measurements were registered. Each subject was assigned a number according to the sequence of enrollment in the study. After recording the clinical data, all forms were archived.

RESULTS

Demographic data

Twenty-one patients (13 males (61.9%) and 8 females (38.1%), with a mean age of 44.84 ± 8.62 years) were included in the study. From the initial sample of twenty-four recruited patients, two dropped out for economic reasons and one female was excluded due to pregnancy during the evaluation period of the study. Moreover, seven more participants did not accept final implant placement and yet, histological analysis in those cases was not performed.

All patients fulfilled the inclusion criteria and 4 (19%) were smokers of less than 10 cigarettes per day, while 17 (81%) were non-smokers. The sample included 10 and 11 subjects in FDBA and DBBM group, respectively. A total of 13 procedures were performed in the upper maxilla (61.9%), while 8 were performed in the mandible (38.1%). No statistically significant differences were observed among gender, age and smoking habit between the two groups at baseline *($p > 0.05$).* However, the distribution of the procedures showed a major frequency of the sites treated with DBBM to be located in the maxilla and sites treated with FDBA in the mandible *($p = 0.049$)* (table 3).

	Biomaterial						
	DBBM		**FDBA**		Total (n=21)		p-value
Age (years)							
Mean (±SD)	43 ± 9.53		46.90 ± 7.51		44.84 ± 8.62		0.460
median	42		50		43		
IQR	12		11		11		
Gender (frequency and percentages)							
Male	5	45.45%	3	30.00%	8	38.10 %	0.392
Female	6	54.55%	7	70.00%	13	61.90%	
Location (frequency and percentages)							
Mandible	2	18.18%	6	60.00%	8	38.10%	0.049*
Maxilla	9	81.82%	4	40.00%	13	61.90%	
Smoking habit							
No	9	81,8 %	8	80 %	17	81 %	0.916
Yes	2	18,2 %	2	20 %	4	19 %	

Table 3. Baseline demographic data of the enrolled sample. Statistically, gender analysis was performed with U- Mann Whitney test, while gender, location and smoking habit were evaluated with Fischer's exact Chi square test.

The reasons for tooth extraction were associated with an absence of healthy dental structure and consequently restorative reasons. All the clinical procedures were performed in accordance to the study protocol. All extraction sites healed uneventfully, and no complications or post-operative infections were recorded during the study period.

<u>Horizontal and vertical dimensional changes evaluation by *CBCT analysis*</u>

The intra-examiner reliability for the CBCT measurements showed an ICC of 0.96 (95% CI 0.88 to 0.99; *p < 0.05)*. Bland-Altman analysis shows a risk of bias of -0.39 (CI 95% -0.86 to 0.08) and a correlation coefficient of absolute success of 0.975.

Horizontal dimensional changes

Baseline measurements of the RW showed no statistically significant differences between groups at RW-1 *(p = 0.27),* RW-3 *(p = 0.89)* and RW-5 *(p = 0.29)*, respectively. In order to provide a general understanding of horizontal ridge dimensional changes, a volumetric analysis was performed without differentiating the type of material used. Overall, mean dimensional ridge changes were more pronounced in the coronal aspect of the ridge. As such, a mean reduction of -2.93 ± 2.28 mm *(p = 0.0002)*, -1.01 ± 1.50 mm *(p = 0.007),* and -0.37 ± 1.11 mm *(p = 0.051)* was observed at RW-1, RW-3 and RW-5, respectively after 5 months; showing a tendency to decrease from the coronal to the apical aspect. Besides, the greater standard deviation in the coronal aspect indicates more variability in this area (figure 13).

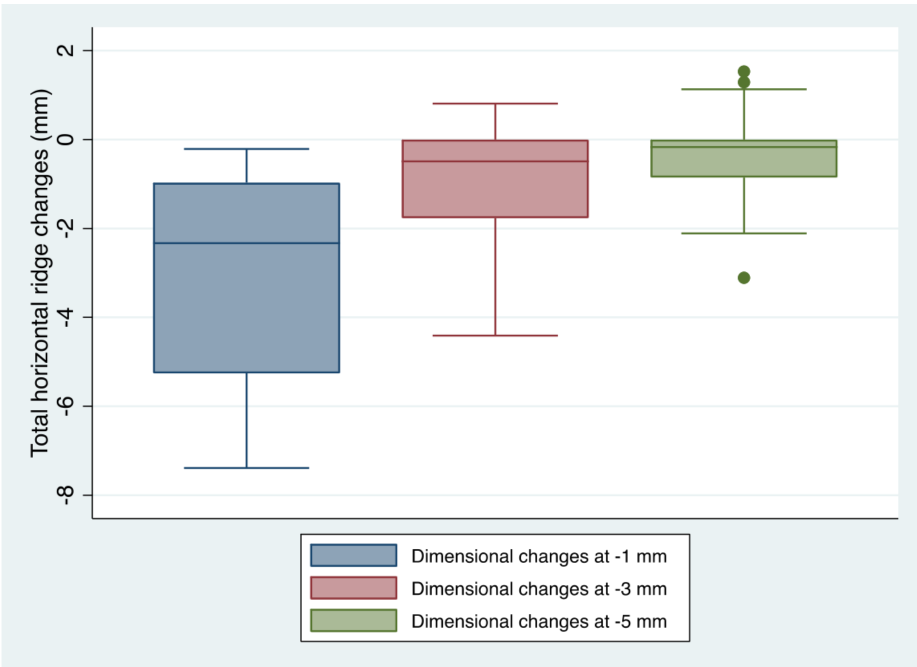

Figure 13. Horizontal changes. Ridge width (RW) at 1 mm (RW-1), 3mm (RW-3), and 5 mm (RW-5), after 5 months.

Both FDBA and DBBM groups exhibited a reduction in width at all levels from baseline to 5 months. These changes were statistically significant with the use of DBBM at RW-1 and RW-3mm and with the use of FDBA at RW-1mm. A tendency of less reduction in width with the use of FDBA was observed at RW-1 and RW-3. However, no statistically significant differences in horizontal mean ridge alterations between both biomaterials at RW-1 *(p = 0.66)*, RW-3 *(p = 0.67)* and RW-5 *(p = 0.91)* were observed (table 4) (figure 14).

		DBBM (mm) N= 11	**FDBA (mm)** N=10	**DBBM versus FDBA *P* value**
RW-1	**Baseline**	13.32 ± 1.22	12.89 ± 1.39	0.27
	5 months	9.91 ± 3.05	9.60 ± 2.93	
	Difference	-3.20 ± 2.39 -24.63 ± 20.14 %	-2.73 ± 2.29 -21.81 ± 18.66	0.66
	***P* value**	0.01*	0.01*	
RW-3	**Baseline**	13.74 ± 1.23	13.92 ± 1.71	0.89
	5 months	12.54 ± 2.42	13.11 ± 2.25	
	Difference	-1.20 ± 1.60 -9.18 ± 12.33 %	-0.81 ± 1.43 -5.89 ± 10.90 %	0.67
	***P* value**	0.04*	0.07	
RW-5	**Baseline**	14.04 ± 1.27	14.78 ± 1.82	0.29
	5 months	13.76 ± 1.48	14.28 ± 2.34	
	Difference	-0.27 ± 1.03 -1.83 ± 7.01 %	-0.49 ± 1.23 -3.51 ± 7.96 %	0.91
	***P* value**	0.18	0.16	

Table 4. Horizontal ridge width (RW), expressed in millimetres (mm) and percentages (%), at baseline and after 5 months in DBBM and FDBA groups, at 1 mm (RW-1), 3 mm (RW-3) and 5 mm (RW-5) from the bone crest. Intra-group volumetric changes were analyzed with Wilcoxon test, while U-Mann Whitney test was used to evaluate differences between treatment groups. *Statistically significant ($p<0.05$).

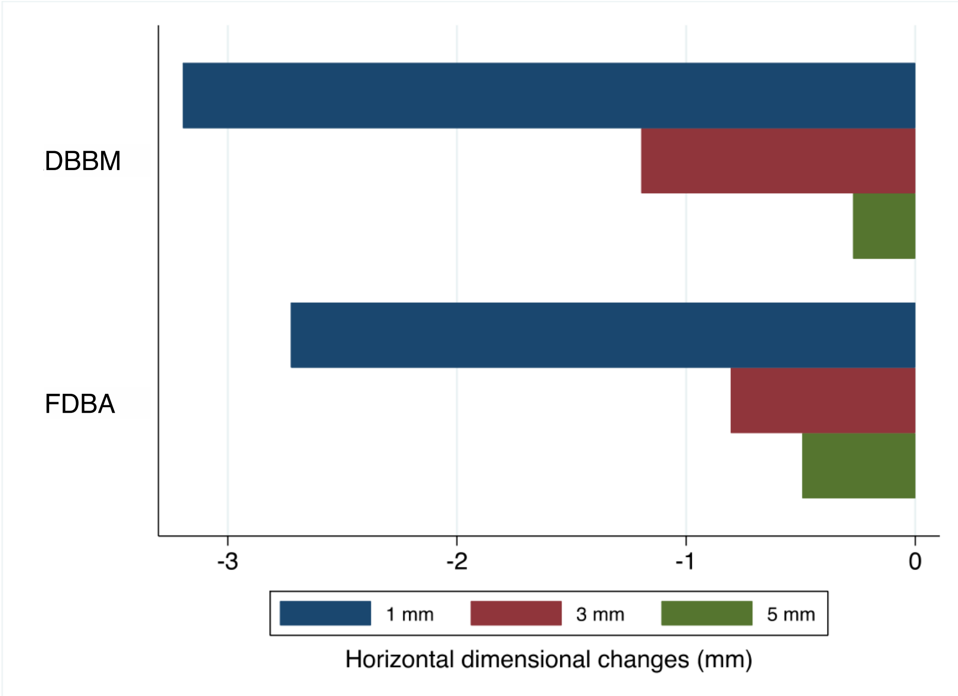

Figure 14. Comparison of horizontal changes at 1mm (RW-1), 3mm (RW-3), and 5mm (RW-5), with the use of DBBM or FDBA after 5 months.

Baseline mean BP was 1.64 ± 0.55 mm, 2.21 ± 1.06 mm, 2.52 ± 1.31 mm at BP-1, BP-3 and BP-5, while the corresponding values for LP were 2.04 ± 1.29 mm, 3.09 ± 1.81 mm, and 3.75 ± 2.10 mm at LP-1, LP-3, LP-5, respectively (table 5). A positive correlation between initial BP at BP-1 (figure 15), BP-3, BP-5 and ridge reduction in width at RW-1, RW-3 and RW-5 was found at 5 months. However, no significant correlation was found between initial LP, at any level, and bone changes in width (table 6). Thinner bone plates (< 1.5 mm) displayed a reduction in RW-1 of 3.91 ± 2.41 mm, while thicker bone plates (≥ 1.5 mm) accounted for a reduction of 1.95 ± 1.75 mm at 1 mm from the bone crest *(p = 0.046)* (table 7).

	-1 mm	**-3 mm**	**-5 mm**
BP (baseline) (N= 21)	1.64 ± 0.55	2.21 ± 1.06	2.52 ± 1.31
LP (baseline) (N=21)	2.04 ± 1.29	3.09 ± 1.81	3.75 ± 2.10

Table 5. Baseline thickness of buccal plate (BP) and lingual plate (LP).

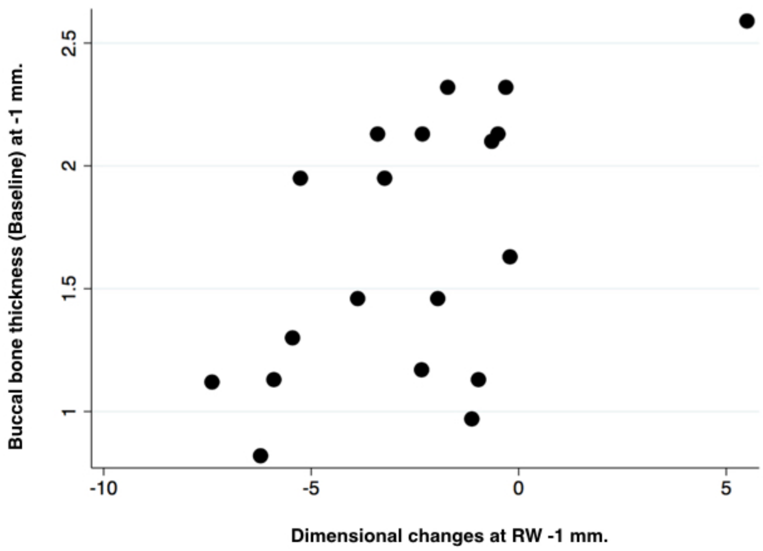

Figure 15. Spearman rho (correlation coefficient) of buccal bone plate thickness (BP) and width ridge changes at 1 mm (RW-1) below the bone crest.

		RW -1	**RW -3**	**RW -5**
BP (baseline) (N = 21)	BP-1	r = 0.490, (IC 95% 0.076 to 0.905) *p =0.020**		
	BP-3		r = 0.515 (IC 95% 0.150 to 0.879) *p =0.006**	
	BP-5			r = 0.463 (IC 95% 0.036 to 0.890) *p = 0.034**
LP (baseline) (N = 21)	LP-1	r = -0.0005 (IC 95% -0.510 to 0.450) *p = 0.984*		
	LP-3		r = 0.116 (IC 95% -0.436 to 0.667) *p = 0.681*	
	LP-4			r = 0.109 (IC 95% -0.374 to 0.591) *p = 0.660*

Table 6. Correlation between buccal (BP) and lingual (LP) bone plate thickness at 1 mm (BP-1, LP-1), 3 mm (BP-3, LP-3) and 5 mm (BP-5, LP-5) and ridge width changes at 1 mm (RW-1), 3 mm (RW-3) and 5 mm (RW-5) after 5 months.

	RW -1 mm	BH
BP < 1.5 mm (n=10)	-3.91 ± 2.41	-3.20 ± 2.26
BP ≥ 1.5mm (n=11)	-1.95 ± 1.75	-0.86 ± 1.53
***P* value**	0.046*	0.01*

Table 7. Correlation between buccal plate thickness (BP) (≥ 1.5 mm or < 1.5 mm) and horizontal ridge dimensional changes at 1 mm from the bone crest (RW-1) and vertical ridge reduction at the buccal bone plate (BH) with dimensional changes after 5 months.

Vertical dimensional changes

At baseline, no statistically significant differences in ridge height measurements were found between both groups (table 8). In order to provide a general understanding of vertical ridge dimensional changes, a volumetric analysis was performed without differentiating the type of material used.

		DBBM (mm) N= 11	FDBA (mm) N=10	DBBM versus FDBA *P* value
BH	**Baseline**	9.07 ± 2.35	8.18 ± 2.74	0.83
	5 months	7.31 ± 2.65	5.97 ± 3.14	
	Difference	-1.76 ± 1.72	-2.21 ± 2.74	0.89
	***P* value**	0.02*	0.01*	
CH	**Baseline**	7.31 ± 3.25	7.30 ± 4.00	0.96
	5 months	7.06 ± 3.73	6.49 ± 3.67	
	Difference	-0.24 ± 1.43	-0.82 ± 1.42	0.57
	***P* value**	0.55	0.11	
LH	**Baseline**	8.75 ± 2.56	8.25 ± 3.76	0.86
	5 months	7.62 ± 2.50	6.93 ± 3.94	
	Difference	-1.13 ± 1.13	-1.33 ± 0.52	0.57
	***P* value**	0.01*	0.01*	

Table 8. Vertical ridge dimensions, expressed in millimetres (mm), at baseline and after 5 months in DBBM and FDBA groups. Measurements of buccal bone height (BH), central height (CH), and lingual height (LH). *(Statistically significant). Intra-group volumetric changes were analyzed with Wilcoxon test, while U-Mann Whitney test was used to evaluate differences between treatment groups. *Statistically significant (p<0.05).

Both BH and LH bone crests showed a significant mean reduction at 5 months (BH: -1.97 ± 2.21 mm, *p = 0.0006*; LH: -1.22 ± 0.88 mm, *p = 0.0001*), although these alterations were more pronounced in the buccal plate. Nonetheless, the CH was the area that experienced the lowest mean reduction at 5 months (-0.53 ± 1.42 mm, *p = 0.157*). Although a tendency of less reduction in vertical bone changes was observed with the use of DBBM, these changes were not statistically significant in the BH *(p = 0.89),* CH *(p = 0.57)* and LH *(p = 0.57)* between groups (table 8) (figure 16).

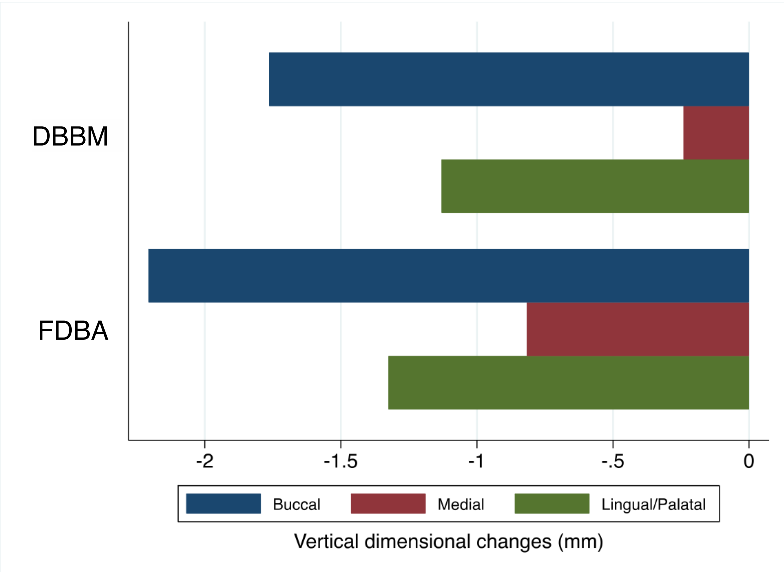

Figure 16. Comparison of vertical changes at buccal bone height (BH), central height (CH), and lingual height (LH) with the use of DBBM or FDBA after 5 months.

Similarly, the BP thickness at BP-1 (figure 17), BP-3 and BP-5 had a significant impact on the vertical dimensional changes, while no correlation was found regarding the thickness of the LP and vertical bone changes (table 9). Indeed, bone plates of < 1.5 mm exhibited a mean height reduction at the BH of -3.20 ± 2.26 mm, while plates of ≥ 1.5 mm evidence a mean vertical reduction of -0.86 ± 1.53 mm *(p = 0.01)* (table 7).

		Vertical ridge changes
BP (baseline) **(N = 21)**	BP-1	r = 0.612, (IC 95% 0.264 to 0.960) *p = 0.001**
	BP-3	r = 0.474, (IC 95% 0.091 to 0.857) *p = 0.015**
	BP-5	r = 0.438, (IC 95% 0.042 to 0.834) *p = 0.030**
LP (baseline) **(N = 21)**	LP-1	r = 0.328, (IC 95% -0.118 to 0.773) *p = 0.149*
	LP-3	r = 0.299, (IC 95% -0.122 to 0.720) *p = 0.164*
	LP-5	r = 0.227, (IC 95% -0.219 to 0.672) *p = 0.319*

Table 9. Correlation between buccal (BP) and lingual (LP) bone plate thickness at 1 mm (BP-1, LP-1), 3 mm (BP-3, LP-3) and 5 mm (BP-5, LP-5) and vertical ridge changes.

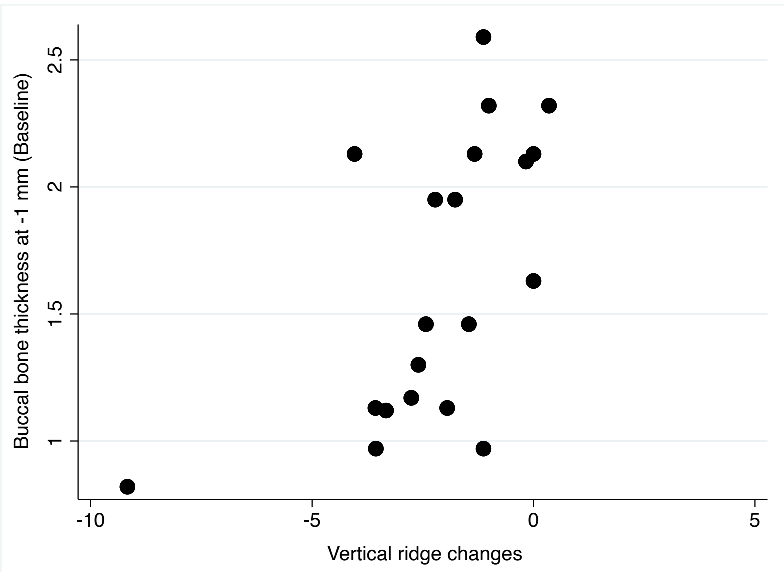

Figure 17. Spearman rho (correlation coefficient) of buccal bone plate thickness (BP) at BP-1 and vertical ridge changes.

Histologic analysis

DBBM particles were observed as light eosin stained bone fragments while FDBA particles presented an intensity of eosin staining similar to newly formed bone. Both GP contained empty lacunae and were found either in direct contact with VB or surrounded by connective tissue. Newly formed bone was observed as an osseous tissue presenting an intense eosin staining, osteocytes in the lacunae and osteoblasts in areas of new bone formation and in proximity to GP. The remaining areas were comprised of NMCT containing fibroblasts, bone marrow, collagen fibers and blood vessels. Three samples showed signs of fibrosis and chronic inflammatory infiltrate surrounding some GP (figures 18a, 18b).

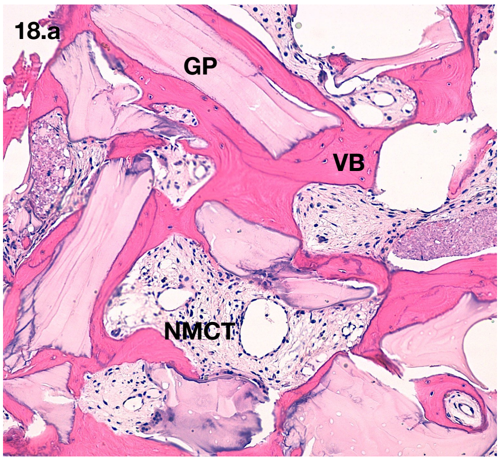

Figure 18a. Histological section of a DBBM sample at 100x. New vital bone (VB), and graft particles (GP) of DBBM in direct contact with VB and non-mineralized connective tissue (NMCT) .

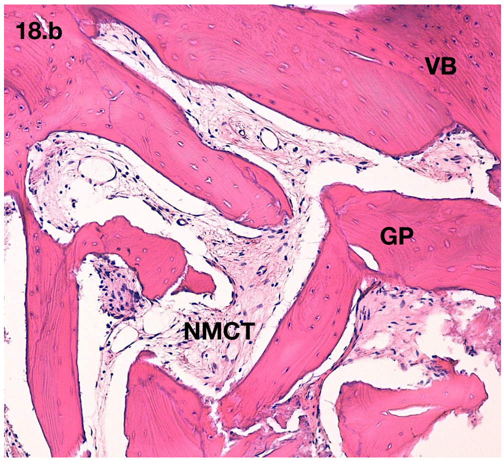

Figure 18b. Histological section of a FDBA sample at 100x. Graft particles (GP) of FDBA with empty lacunae, vital bone (VB) with presence of osteocytes and non-mineralized connective tissue (NMCT) surrounding VB and GP.

Histomorphometric analysis

From the initial three dropouts, seven more participants did not accept final implant placement and yet, histological analysis in those cases was not performed. Therefore, a total of 14 samples were included in the final histomorphometric analysis. Histological evaluation of both graft materials showed similar amounts of residual GP after 5 months of healing. The FDBA group, showed a mean percentage of VB, GP and NMCT of 48.54 ± 18.78%, 13.99 ± 10.46% and 37.38 ± 15.71%, respectively. While in the DBBM group, 46.44 ± 16.49% of VB, 15.10 ± 15.11% of GP and 38.43 ± 10.12% of NMCT was observed. No statistically significant differences in the amount of VB ($p = 0.85$), NMCT ($p = 0.75$) and residual GP ($p = 0.65$) were observed between groups (table 10). The ICC for intra-examiner reliability was 0.95 (95% CI 0.48 to 0.99; $p < 0.05$).

	VB (%)	GP (%)	NMCT (%)
DBBM N =7	46.44 ± 16.49	15.10 ± 15.11%	38.43 ± 10.12%
FDBA N=7	48.54 ± 18.78 %	13.99 ± 10.46 %	37.38 ± 15.71 %
***P* value**	0.85	0.65	0.75

Table 10. Histomorphometric results in terms of vital bone (VB), graft particle (GP) and non-mineralized connective tissue (NMCT) in percentages (%).

<u>Clinical need of regeneration or sinus lift at the time of implant placement after socket preservation procedures.</u>

A total of 9 subjects received an implant in the preserved ridges in the upper maxilla. The most commonly used implant length was 8 mm, which was placed in five cases (55.56%) (table 11). CH was 7.30 ± 3.53 mm at baseline, and 6.78 ± 3.61 mm after the healing period.

As it could be expected due to the baseline CH (7.30 mm), five (55.56%) of the preserved sites, additionally needed transcrestal sinus lift at the time of implant placement. From these sites, four cases were treated with DBBM and one with FDBA, but none of the cases needed a lateral approach. In the remaining four cases (44.44%), implants could be installed without further augmentation in ridge height. Furthermore, only one case in the DBBM group needed further horizontal ridge augmentation at the time of implant placement.

Implant Length	Crestal sinus lift (frequency)		
	No	**Yes**	**Total**
6	0	1	1 (11.11%)
8	2	3	5 (55.56%)
10	1	1	2 (22.22%)
11	1	0	1 (11.11%)
Total	4	5	9

Table 11. Distribution of implant length and frequency of transcrestal sinus lift.

Hence, establishing a threshold of 8 mm in bone height it can be suggested that residual ridge heights of < 8 mm had an OR of 1.5 *(p = 0.78)* of need for transcrestal sinus elevation after ridge preservation procedures (table 12).

CH	Crestal sinus lift (frequency)		
(baseline)	No	Yes	OR
≥ 8 mm	2	2	1
< 8 mm	2	3	1.5 (0.10-21.21)
Total	4	5	9

Table 12. Central height (CH) at baseline and need, in frequency, of transcrestal sinus lift.

DISCUSSION

1. Dimensional changes following ridge preservation in molar sites

To date, scientific evidence regarding ridge preservation in molar sites remains scarce. The present study has evaluated and compared the use of DBBM or FDBA in ridge preservation procedures in molar areas.

A previous research has demonstrated that, molar and premolar extraction, results in a clinical reduction of 50% of the bone ridge after 12 months of healing (Schropp, et al., 2003). In terms of clinical reduction, these changes have reported a ridge resorption in width and height at the buccal aspect, after molar or premolar extraction, of -3.60 ± 0.72 mm and -2.10 ± 0.66 mm (Barone, et al., 2017), and 4.04 ± 0.69 mm and 1.67 ± 0.43 mm (Cardaropoli, et al., 2014), after 3 and 4 months of healing, respectively.
Radiographically, molar extraction has shown a horizontal and vertical reduction of -2.27 ± 1.15 mm and -1.33 ± 1.11 mm, at 3 mm from the bone crest, after 4 months (Lim, et al., 2019). Moreover, studies evaluating dimensional changes following molar or premolar extraction, have concluded that, bone ridge reduction seems to be more pronounced in the coronal aspect of the ridge than in the middle and apical areas (Araújo, et al., 2008; Lim, et al., 2019).

Consequently, we can assume that following molar or premolar extraction a horizontal ridge reduction between 3 - 4 mm and a vertical loss of around 2 mm can be expected.

Ridge preservation in molar areas has demonstrated to be effective in minimizing ridge dimensional changes facilitating implant therapy (Lim, et al., 2019). The beneficial effects of this procedure in the posterior sites have been previously demonstrated (Cardaropoli, et al., 2014; Sbordone, et al., 2017; Barone, et al., 2017). However, heterogeneity among studies with regard to defect morphology, surgical technique, biomaterials used and measurement methodology employed should be of greater consideration.

The findings of the present study demonstrated that the use of both DBBM or FDBA resulted in a markedly reduction in bone height and width after alveolar ridge preservation, being unable to completely prevent dimensional changes following molar extraction. Thus, although some studies performed in molar sites have reported a significant reduced ridge resorption in vertical and horizontal dimension (Lim, et al., 2019), others have only reported significant benefits in reduced loss in height (Walker, et al., 2017; Al Harthi, et al., 2019).

In general, this investigation found that the greatest reduction in width occurred at RW-1 with a reduction of -2.93 ± 2.28 mm *(p = 0.0002)* and that the bone resorption pattern showed a tendency to decrease from coronal to apical, which is in line with previous investigations (Araújo, et al., 2008; Lim, et al., 2019). Moreover, both groups revealed a statistically significant decrease in bone height independently of the graft material used, being the major changes at BH and LH, while CH experienced the less variation. However, no statistically significant differences were observed between the two groups in bone height and width changes at any level.

1.1 Horizontal changes

Mainly, previous investigations performed in posterior segments regarding ridge preservation with xenografts have been performed with the use of DBBM with 10% collagen (DBBM-c) in combination with a collagen membrane. Thus, although the present investigation has been performed with the use of DBBM, a previous study, performed in anterior and premolar areas, has proved that differences in ridge contraction between the use of DBBM or DBBM-c evaluated by CBCT superimposition after 5 months, are negligible (Nart, et al., 2016).

Results from the present investigation have demonstrated that the use of DBBM or FDBA in ridge preservation procedures, results in a reduction in width from baseline to 5 months, with no statistically significant differences between groups, showing that, independently of the graft material used, ridge preservation in molar sites is unable to completely prevent bone dimensional changes. This horizontal resorption is greater in the coronal aspect of the ridge, which is in line with previous investigations (Lim, et al., 2019). Thus, as mayor changes in width have been determined to occur at 1 mm from the bone crest (Choi, et al., 2017), dimensional analysis at various levels may be interesting in evaluating differences in bone remodelling behavior.

In this investigation, the use of DBBM, showed a reduction in width of -3.20 ± 2.39 mm (-24.63 ± 20.14%), -1.20 ± 1.60 mm (-9.18 ± 12.33%) and -0.27 ± 1.03 mm (-1.83 ± 7.01%) at RW-1, RW-3, and RW-5, respectively, after 5 months of healing.

Studies performing clinical evaluations, have demonstrated that the use of a DBBM-c plus a collagen membrane, after molar or premolar extraction, results in 0.71 ± 0.91 mm (7.23 ± 9.24 %) of horizontal ridge reduction, at 3 mm from the bone crest after 4 months (Cardaropoli, et al., 2014). Moreover, the use of a xenograft plus a collagen membrane, in molar and premolar sites have demonstrated a reduction of 15% of ridge volume, corresponding to a bone resorption of 1.85 mm after 4 months of healing (Cardaropoli & Cardaropoli, 2008). However, the methodology employed in this study, which performed measurements with a hand caliper at the most prominent site of the alveolar crest and without a stent, may lead to less reproducibility and accuracy in the results.

The evaluation of dimensional changes in model casts, has shown a reduction in width of 1.04 ± 1.08 mm (7.70%) after the use of DBBM-C plus a collagen membrane in molar and premolar sites, at 4 months (Cardaropoli, et al., 2012). Otherwise, the use of bovine bone mineral (DBBM) plus a collagen membrane in molar sites has shown a loss of volume of -19,1% ± 6.5%, after 5 months (Sbordone, et al., 2017). Besides, assuming that model cast evaluating methods may include both hard and soft tissue components in ridge reduction analysis, it is not possible to attribute these dimensional changes only to bone remodelling.

Analysis of ridge width reduction by CBCT analysis has demonstrated that, after the use of DBBM-C plus a double collagen membrane in molar sites, a horizontal bone loss of -1.02 ± 0.88 mm and -0.31 ± 1.51 mm at 1 mm and 3 mm from the bone crest, respectively, can be expected after 4 months of healing (Lim, et al., 2019).

Furthermore, a pilot study has reported that after the use of DBBM-c plus a resorbable collagen membrane in molar sites, a horizontal loss of -1.7 ± 0.5 mm, -1.0 ± 0.5 mm, and -0.5 ± 0.2 mm at -1mm, -3mm, and -5mm respectively from the bone crest, was observed after 4 months (Choi, et al., 2017). However, this study considered, as a reference, volumetric changes after socket filling taking as a guide the center of the already regenerated socket, obtaining less bone remodelling compared to the results observed in the current investigation. Thus, this differences in methodology compared to our study could explain the differences in the results.

In the present research, the use of cortical and cancellous FDBA showed a reduction in width of -2.73 ± 2.29 mm (-21.81 ± 18.66%), -0.81 ± 1.43 mm (-5.89 ± 10.90%) and -0.49 ± 1.23 mm (-3.51 ± 7.96%), at RW-1, RW-3, and RW-5, respectively, after 5 months of healing.

Clinical evaluation of ridge changes has shown that, after the use of FDBA plus a collagen membrane in molar and premolar sites, ridge width at 1 mm from the bone crest, is significantly reduced between 2-2.5 mm, after 4 months of healing (Leblebicioglu, et al., 2013).

Evaluation by CBCT analysis has shown that, after 3 months, the use of cortical FDBA plus a non-resorbable membrane in molar sites led to a loss in width of -2.48 ± 2.86 mm and -1.16 ± 1.97 mm, at 3 and 5 mm from the bone crest respectively (Walker, et al., 2017). Besides, the combination cortical FDBA plus a collagen sponge seems to result in less horizontal ridge reduction with a decrease of -1.64 ± 1.10 mm and -0.79 ± 0.57 mm, respectively, at 3 and 5 mm from the bone crest, following 3 months of healing (Al Harthi, et al., 2019).

Yet, results from the previously mentioned studies, are inferior to our research. However, differences in evaluation methods and lack of integrity of the socket walls may explain these differences.

In general, mayor width changes in width have been found to occur in the medial area of the socket (Walker, et al., 2017). This finding is in line with the methodology employed in our study which took as a reference the middle area of the socket for performing measurements in the mid-buccal, mid-lingual and central area of the ridge. Furthermore, although the thinnest amount of alveolar bone is found in the medial areas of the mesial and distal buccal bone, bone loss was similar in all the areas of the socket, even the central which involves the furcation with a thickest part of buccal bone (Walker, et al., 2017).

One of the major limitations of the present investigation is the absence of a negative control group to compare the benefits of ridge preservation over extraction alone in molar sites, which have prevented from performing comparisons between extraction and preserved sites. Thus, the majority of the studies performed in posterior sites have reported a beneficial effect with the use of ridge preservation over spontaneous healing.

In that way, studies performed in molar and premolar areas have concluded that the use of DBBM-c plus a collagen membrane, when evaluated clinically, results in less reduction in width when compared to extraction alone, showing a loss of 0.71 ± 0.91 mm (7.23 ± 9.24 %) and 4.04 ± 0.69mm (40.15 ± 8.29%), respectively, at 3 mm from the bone crest after 4 months (Cardaropoli, et al., 2014).

Moreover, a study evaluating dimensional changes in model casts comparing the use of DBBM-c plus a collagen membrane versus extraction plus a fibrin sponge in molar and premolar sites, has shown a significant beneficial effect in favor of ridge preservation procedures with a reduction in width of 1.04 ± 1.08 mm (7.70%) and 4.48 ± 0.65 mm (33.48%), respectively, after 4 months (Cardaropoli, et al., 2012). Similarly, after 5 months, the use of DBBM plus a collagen membrane in molar sites seems to provide a better horizontal preservation of the bone crest compared to natural healing sites with a loss of volume of -19,1% ± 6.5% and -35.6% ± 7.6%, respectively (Sbordone, et al., 2017).

Besides, when evaluated by CBCT, the combination of DBBM-c plus a double collagen membrane in molar area, has also demonstrated significantly less horizontal bone loss with a reduction of -1.02 ± 0.88 mm and -0.31 ± 1.51 mm after ridge preservation compared to a bone loss of -4.44 ± 3.71 mm and -2.27 ± 1.15 mm at extraction sites, measured at 1 mm and 3 mm from the bone crest, each, after 4 months (Lim, et al., 2019).

In brief, the use of a xenograft plus a collagen membrane, in molar and premolar sites, seems to be effective in maintaining ridge contour and minimizing bone loss after tooth loss. Thus, using DBBM plus a collagen membrane in ridge preservation procedures can preserve 80% of the alveolar ridge contour 5 months following tooth extraction (Sbordone, et al., 2017).

Otherwise, the use of cortical FDBA plus a non-resorbable membrane has been compared to molar extraction plus a collagen sponge in molar sites after 3 months. In this study, CBCT evaluation showed a reduction in width of -2.48 ± 2.86 mm and -1.16 ± 1.97 mm in preserved sites compared to a loss of -3.11 ± 3.83 mm and -1.59 ± 2.23 mm after molar extraction, at 3 and 5 mm from the bone crest, each. Still, although there is a tendency of less bone loss when ridge preservation is performed, this investigation showed no statistically significant differences between groups. However, the authors concluded that, after molar extraction, 66% of the total ridge width reduction is located in the buccal aspect while after ridge preservation, horizontal ridge loss is distributed between the buccal and lingual aspects with a decrease of 49% and 51%, respectively (Walker, et al., 2017).

Furthermore, a recent study, comparing the use of cortical FDBA plus a collagen sponge versus extraction plus a collagen sponge, have shown a horizontal ridge reduction of

-1.64 ± 1.10 mm and -0.79 ± 0.57 mm, respectively, at 3 and 5 mm from the bone crest, compared to a reduction in width of -3.11 ± 3.83 mm and -1.59 ± 2.23 mm in control sites, with no statistically significant differences between groups, after 3 months. Thus, although no significant, the use of cortical FDBA plus a collagen sponge showed a tendency for less bone remodelling when compared to extraction plus a collagen sponge (Al Harthi, et al., 2019).

These results evidence the benefits of ridge preservation after molar or premolar extraction with a considerable reduction of horizontal ridge resorption. However, to date the is no evidence of a superior approach in ridge preservation procedures (Tonetti, et al., 2019; Avila-Ortiz, et al., 2019).

Thus, according to the existing literature, we may conclude that the use of DBBM (Sbordone, et al., 2017), or DBBM-c (Cardaropoli, et al., 2012) plus a single or a double collagen membrane (Lim, et al., 2019) in molar sites is effective in reducing horizontal bone loss after 4 - 5 months.

1.2 Vertical changes

Vertically, results from the present investigation have demonstrated no statistically significant differences between the use of DBBM or FDBA in BH, CH, and LH, although a tendency of less vertical reduction was observed with the use of DBBM. Hence, the use of DBBM and FDBA resulted in a vertical buccal bone loss of -1.76 ± 1.72 mm and -2.21 ± 2.74 mm, each. On the other hand, when evaluated without differentiating the type of material used, the greatest reduction was observed in BH while CH experienced the lowest mean reduction after 5 months.

In our study, the use of DBBM showed a vertical reduction of -1.76 ± 1.72 mm, -0.24 ± 1.43 mm, and -1.13 ± 1.13 mm at BH, CH and LH, respectively, after 5 months of healing. Previous research has shown that, clinically, the use of DBBM-c plus a collagen membrane in molar and premolar sites, results in a vertical mid-buccal bone loss of 0.56 ± 0.45 mm after 4 months, showing -1.11 ± 0.38 mm less vertical bone loss when compared to extraction sites (Cardaropoli, et al., 2014). In molar areas, a -9.6 ± 12.3% of vertical bone reduction has been observed after using BBM plus a collagen membrane at 5 months (Sbordone, et al., 2017). Furthermore, a previous study has reported that after the use of DBBM-c plus a resorbable collagen membrane a vertical loss of -0.8 ± 0.7 mm, -0.7 ± 0.3 mm and -0.7 ± 0.4 mm at the buccal, central area of the ridge and lingual plate, after 4 months can be expected (Choi, et al., 2017). However, as these outcomes are from a pilot study, data should be interpreted with caution.

The combination of xenograft and a collagen membrane has shown better results in ridge preservation than the use of a xenograft alone. In this regard, the use of a DBBM-c plus a double collagen membrane resulted in less vertical buccal bone loss compared to the use of DBBM-c alone, with a reduction of -0.58 ± 0.53 mm and -1.06 ± 1.57 mm, respectively. Also, the lingual bone plate was better maintained than the buccal, with a remodelling of -0.12 ± 1.10 mm and -0.33 ± 0.38 mm, each. Moreover, the center of the alveolar ridge experienced greater vertical bone resorption when using DBBM-c alone compared to DBBM-c plus a double collagen membrane, with a reduction of -1.15 ± 1.63 mm and -0.25 ± 0.95 mm each, after 4 months. Nevertheless, this study included periodontally affected molars with bone loss at 2-3 walls, which can lead to more apical and thicker walls, and affect the results (Lim, et al., 2019).

These better results in the combination of a graft plus a collagen membrane, is in line with the latest european workshop recommendations (Tonetti, et al., 2019). However, the use of single or double layer of resorbable non cross-linked collagen membranes seems to provide similar results in terms of volumetric changes and healing outcomes following ridge preservation after 4 months (Choi, et al., 2017).

Regarding FDBA, results from the present investigation showed that, the use of FDBA plus a collagen membrane resulted in a vertical bone resorption of -2.21 ± 2.74 mm, -0.82 ± 1.42 mm and -1.33 ± 0.52 mm in the BH, CH and LH, respectively, after 5 months of healing.

In previous studies, evaluation of ridge alterations by CBCT analysis have demonstrated that, the use of cortical FDBA plus a non-resorbable membrane in molar sites results in a vertical reduction of -1.12 ± 1.60 mm (Walker, et al., 2017), while areas preserved with the use of cortical FDBA plus a collagen sponge, exhibit a vertical bone loss of -1.55 ± 0.93 mm (Al Harthi, et al., 2019), in the mid-buccal area, after 3 months of healing.

Additionally, although an investigation has reported greater lingual bone loss after the use of cancellous FDBA (Eskow, et al., 2014), the use of cortical or cancellous FDBA provides similar results in terms of vertical and horizontal changes (Demetter, et al., 2017). Thus, although not the aim of the present investigation, neither differences, in terms of ridge reduction, have been observed either when compared to DFDBA (Wood & Mealey, 2012), or combinations of FDBA plus DFDBA (Borg & Mealey, 2015).

In general, results from the above mentioned studies are slightly inferior to the observed in our research. However, differences in the evaluation method employed as well as socket integrity, which may have led to an over correction of the ridge contour, may imply some differences in the outcomes.

In this regard, when clinically compared to extraction sites, previous research has shown that the use of DBBM-c plus a collagen membrane in molar and premolar sites, results in significantly less vertical mid-buccal bone loss with a decrease of 0.56 ± 0.45 mm compared to a vertical ridge reduction of 1.67 ± 0.43 mm in unassisted healing, after 4 months (Cardaropoli, et al., 2014). Likewise, the use of DBBM plus a collagen membrane in molar sites exhibited significantly less volume ridge reduction when compared to extraction alone with a loss in height of -9.6 ± 12.3% and -27.6% ± 8.4%, respectively, after 5 months of healing (Sbordone, et al., 2017).

In addition, studies evaluating dimensional changes by CBCT images have concluded that, vertical bone remodelling of the buccal and lingual plates after use of DBBM-c plus a double collagen membrane, compared to DBBM-c or extraction alone did not differ significantly. Thus, the use of a DBBM-c plus a double collagen membrane resulted in less vertical buccal bone loss compared to the use of DBBM-c or extraction alone, with a reduction of -0.58 ± 0.53 mm, -1.06 ± 1.57 mm, 1.33 ± 1.11 mm, separately. Besides, the lingual bone plate experienced less bone loss than the buccal, with a remodelling of -0.12 ± 1.10 mm, -0.33 ± 0.38 mm and -1.20 ± 0.96 mm, each (Lim, et al., 2019).

Regarding FDBA, evaluation of ridge alterations by CBCT analysis have demonstrated that, the use of cortical FDBA plus a non-resorbable membrane in molar sites or the use of cortical FDBA plus a collagen sponge, results in significantly less reduction of the buccal bone height in preserved sites with a loss of -1.12 ± 1.60 mm (Walker, et al., 2017), and -1.55 ± 0.93 mm (Al Harthi, et al., 2019), each, compared to extraction plus a collagen sponge, which presented a reduction of 2.60 ± 2.06 mm in the mid-buccal area, after 3 months of healing.

Thus, the randomized clinical trials performed by Walker et al. (2017) and Al Harthi et al. (2019), were included in a three-arm analysis which found that vertical dimensional changes were statistically significant between treated and non-treated areas, but not between different treatment sites.

Therefore, according to the literature, we may conclude that the use of DBBM-c plus a collagen membrane, (Cardaropoli, et al., 2014; Sbordone, et al., 2017), FDBA plus a non-resorbable membrane (Walker, et al., 2017) or FDBA in combination with a collagen sponge (Al Harthi, et al., 2019), is effective in minimizing ridge dimensional changes compared to extraction alone in molar sites, after 3-5 months.

2. Factors influencing ridge dimensional changes

2.1 Effect of buccal bone plate thickness on ridge dimensional changes

Findings from the present investigation have shown that thinner bone plates (< 1.5 mm) experienced more reduction with a horizontal and vertical shrinkage of -3.91 ± 2.41 mm and -3.20 ± 2.26 mm respectively, while thicker bone plates (≥ 1.5 mm) lead to 1.95 ± 1.75 mm and 0.86 ± 1.53 mm of horizontal and vertical bone loss. This threshold of 1.5 mm to evaluate the influence of bone walls thickness on ridge dimensional changes has been previously used in studies performed in molars and premolar sites (Barone, et al., 2017). Accordingly, results from the present investigation are in line with a previous study which determined that horizontal bone loss was greater in thinner buccal bone plates (< 1.5 mm) than in thicker buccal bone plates (≥ 1.5 mm) for grafted sites in molar and premolar areas (Barone, et al., 2017).

The initial thickness of the buccal bone plate has been correlated with greater bone loss in non-preserved sites. Therefore, thinner baseline buccal bone plates have shown to experienced greater alveolar bone loss after 4 months of healing compared to thicker buccal plates which exhibited less bone remodelling. However, it has been suggested that ridge preservation is able to compensate alveolar bone resorption even in presence of thinner or thicker plates, with no correlation between them when socket preservation is performed (Cardaropoli, et al., 2014). Yet, recent studies performed in molar sites have failed to find any correlation between the buccal plate thickness and bone loss after extraction plus a collagen sponge or ridge preservation procedures (Walker, et al., 2017; Al Harthi, et al., 2019).

Conversely, other investigation has determined that a thicker buccal bone wall has been associated with greater horizontal bone loss, after 4 months. However, this study also found a correlation between initial ridge width and horizontal bone loss, demonstrating that wider crests exhibit more bone loss in width (Leblebicioglu, et al., 2013). Thus, it seems confusing if loss in width in posterior sites is only attributable to the thickness of the buccal bone plate or if those sites present a wide crest dimension to which major width changes are attributable.

This is in accordance to a recent systematic review and european consensus report, as apparently, sites with a thickness of the buccal bone plate > 1.0-1.5 mm present less bone remodelling following tooth extraction, so sites with thinner buccal plates can benefit more from ridge preservation with socket fill (Avila-Ortiz, et al., 2019, Tonetti, et al., 2019).

2.2 Flap elevation

Concerning the surgical technique, minimal flaps were raised to facilitate the membrane adaptation and no attempts were made to achieve primary closure. It is well stablished that full-thickness flap elevation may cause loss of attachment and bone resorption. Apparently, the amount of bone loss is related to the thickness of the underlying bone with thinner bone experiencing greater bone resorption (Pfeifer, 1965; Araújo, et al., 2008). Human studies have concluded that the elevation of a full thickness flap entail a bone resorption of 0.62 mm (Wood, 1972). However, tooth extraction without flap elevation does not prevent ridge bone loss. Thus, it has been suggested that surgical trauma caused by tooth extraction may overlap with surgical trauma created by flap elevation (Araújo, et al., 2015).

Findings from a clinical study performed in humans, have concluded that flapless technique with secondary soft tissue healing in ridge preservation procedures result in a significant increased width of keratinized gingiva and less ridge width reduction compared to flapped procedures with primary closure. However, according to this investigation vertical changes in the buccal aspect may be benefit by a flapped technique (Barone, et al., 2014). These findings are in agreement with a recent randomized controlled trial performed in non-molar sites, which found an increased width in keratinized gingiva of 0.43 ± 0.42 mm after flapless procedures, compared to a loss of -1.57 ± 0.51 mm after elevation of a flap, moreover significantly less horizontal bone resorption was observed in flapless procedures although no differences in vertical changes with minimal bone resorption was observed (Hong, et al., 2019).

Although previous results from a systematic review have suggested that flapped surgery and primary closure may reduce horizontal ridge shrinkage (Vignoletti, et al., 2012), results from a recent systematic review have determined that primary closure doesn't provide an additional benefit in ridge preservation procedures (Avila-Ortiz, et al., 2019). Thus, the effect of flapped or flapless approach in ridge preservation procedures remains controversial. Nonetheless, differences between flapped and flapless procedures seem to be negligible after 6 months of healing (Araújo & Lindhe, 2009).

Moreover, considering a failure in ridge preservation an excessive amount of bone loss preventing from implant placement without further bone regeneration, some investigations have considered that the elevation of a flap in these procedures seems to lower the success compared to flapless technique with rates of 90.7% and 93.8%, respectively (Barone, et al., 2014).

In ridge preservation procedures, flap elevation has been generally used in combination with primary closure while flapless procedures are most commonly associated with membrane exposure and secondary soft tissue healing.

Intentional collagen membrane exposure has shown no complications in ridge preservation procedures, showing a better preservation of the hard tissue horizontal dimension and an increase in keratinized gingiva (Barone, et al., 2014). These results are in agreement with a recent research showing no adverse effects after the use of this technique (Lim, et al., 2019).

Thus, the use of single or double layer of resorbable non cross-linked collagen membranes has been investigated, providing similar results in terms of volumetric changes and healing outcomes following ridge preservation after 4 months (Choi, et al., 2017).

Besides, according to a randomized controlled clinical trial performed in molar and premolar sites, ridge preservation without primary closure resulted in similar amount of bone formation and horizontal ridge reduction with less post-operative discomfort, less displacement of mucogingival junction and superior results in width of keratinized tissue when compared to primary closure (Engler-Hamm, et al., 2011). Similarly, a recent study performed in non-molar sites has concluded that the use of a cross-linked collagen membrane plus an allograft in combination with a non-submerged protocol results in a better preservation of keratinized gingiva in width and thickness with less horizontal ridge resorption after 6 months. Moreover, membrane exposure has shown a tendency to increase soft tissue thickness in 0.46 ± 0.22 mm compared to a loss of 0.15 ± 0.23 mm when submerged (Hong, et al., 2019). Additionally, when compared to extraction sockets, membrane exposure in ridge preservation procedures results in less lingual sift of the mucogingival junction with a displacement of 1.80 ± 1.81 mm compared to extraction alone 4.01 ± 2.83 mm (Lim, et al., 2019).

With regard to tissue quality, a study comparing both techniques from a histological and histomorphometrical point of view, no differences have been observed between flapped or flapless procedures with secondary soft tissue healing (Barone, et al., 2014). Similarly, other investigation found that the absence of primary closure did not affect the amount of vital bone regeneration (Engler-Hamm, et al., 2011).

Thus, ridge preservation without primary closure seem not to affect tissue quality and may improve tissue amount and thickness of the future implant area.

2.3 Biomaterials

Based on current scientific evidence, a superior approach in ridge preservation procedures cannot be determined (Tonetti, et al., 2019; Avila-Ortiz, et al., 2019). This data is in accordance with results from previous systematics reviews (Willembacher, et al., 2016; MacBeth, et al., 2016). However, this does not mean that any material will provide good results, as few of them have been properly documented (Tonetti, et al., 2019). In addition, no conclusions can be made with regard to the use of cell therapy, rhBMP-2 and autologous blood-derived products in ridge preservation. Still, the use of xenograft or allograft in combination with a collagen membrane or a collagen sponge has been associated to a better horizontal preservation of the bone crest (Avila-Ortiz, et al., 2019).

2.4 Other factors

As bone reduction seems to be greater in the molar areas (Pietrovsky & Massler, 1967; Schropp, et al., 2003), some investigations have focused on evaluating the effects of tooth position in the posterior segment. In that way, ridge preservation with the use of DBBM plus a collagen membrane, have shown a reduction in width and height of -26.9 ± 7.2% and -22.9 ± 13.0%, respectively, in premolar areas, while molar sites exhibited less bone reduction with a loss of -19.1 ± 6.5% and -9.6 ± 12.3% in width and height, respectively, after 5 months. Thus, although results from this investigation show a greater reduction in premolar areas data from this study should be interpreted with caution as sample size of premolars was limited and only the outcomes regarding molars were statistically significant (Sbordone, et al., 2017). Other studies comparing molar and premolar areas have demonstrated that tooth site does not influence vertical dimensional changes (Barone, et al., 2017) and tooth type is not a confusion factor in the clinical analysis (Leblebicioglu, et al., 2013). Thus, no correlation has been found between tooth position and type of procedure when flapped and flapless approach was compared (Barone, et al., 2014).

Still, initial ridge width (Leblebicioglu, et al., 2013) may play a role in bone dimensional changes as wider sockets need more time to form a bony bridge over the defect which may result in a greater bone resorption (Engler-Hamm, et al., 2011). However, RCTs regarding this factor are needed to establish clear conclusions.

In the present investigation, the distribution of the procedures showed a major frequency of the sites treated with DBBM to be located in the maxilla while FDBA were most commonly treated in the mandible. Yet, tooth location whether in maxilla or mandible does not seem to influence ridge reduction after the use of FDBA plus a collagen membrane in molar and premolar sites (Leblebicioglu, et al., 2013). Although a statistically significant difference has been observed with a gain in height at the disto-buccal area of the extraction sites in the mandible, no significant differences have been observed between jaws with regard to bone loss in width. Moreover, root diameter has not demonstrated a statistically significant effect on dimensional changes in height, and root length is not significantly associated with changes in width (Leblebicioglu, et al., 2013).

On the other hand, the particle size used in this investigation was 0.60-1.25 mm for FDBA and 0.25-1 mm for DBBM. Thus, the use of small size of graft particle (125-710 µm) or a combination of small plus a greater graft size particle (2-4 mm) has demonstrated no differences with regard to dimensional changes (Hoang & Mealey, 2012).

In addition, the use of a “hidden X” suture technique has shown significantly less vertical and horizontal ridge reduction at 1mm from the bone crest and in the medial buccal area when compared to conventional X technique. Furthermore, the use of conventional X suture technique in ridge preservation procedures results in a lingual shift of the mucogingival junction of 1.56 ± 0.90 mm while the “X hidden” suture entails a buccal shift of 0.25 ± 0.66 mm. It seems that the use of conventional X suture technique may create a bucco-lingual pressure vector reducing de width of keratinized tissue. Therefore, the hidden X technique may minimize tension in the bucco-lingual area preventing horizontal ridge reduction (Park, et al., 2016). Similarly, the use of a hidden mattress technique in the present investigation may have reduced the tension in the horizontal dimension decreasing bone reduction in width.

Although many investigations have requested further research in the relation of local and systemic factors such as; systemic condition that may influence both soft and hard tissue healing, previous history of periodontitis, smoking and width of keratinized tissue on ridge preservation procedures, the effect of these parameters on ridge preservation techniques have not been analyzed yet (Avila-Ortiz, et al., 2019; Tonetti, et al., 2019).

3. Histology

Results from a systematic review have suggested that the histological beneficial effects of ridge preservation with regard to new bone formation is controversial. In fact, when comparing spontaneous healed sockets and ridge preservation with the use of DBBM, DBBM-c, FDBA or autologous bone marrow, regenerated sockets did not result in a greater amount of newly formed bone. Moreover, among alloplastic materials, calcium sulfate and hydroxiapatite are among the most commonly used, being calcium sulfate the most adequate in terms of vital bone formation while the use of xenografts and allografts resulted in a greater percentage or residual graft particles. Thus, the lack of homogeneity between studies prevents from determining definitive conclusions (Barallat, et al., 2014). Therefore, according to a posterior systematic review, the use of allografts seems to provide the highest percentage of vital bone at 3 months, while the lowest was observed at 5 months using xenografts. However, no statistically significant differences have been observed between the use of different biomaterials (De Risi, et al., 2015).

According to the literature, the most commonly used xenografts have a bovine origin (DBBM) although some investigations have employed a porcine xenograft (Barone, et al., 2014; Barone, et al., 2017). Thus, recent research has determined no statistically significant differences between them in terms of tissue composition (Lai, et al., 2020).

In the present investigation, the use of DBBM resulted in 46.44 ± 16.49%, 15.10 ±15.11% and 38.43 ±10.12% of VB, GP and NMCT, after 5 months.

Histomorphometrically, previous research have found that the application of DBBM in ridge preservation procedures sites resulted in 27,35 ± 12,39 % (Gholami, et al., 2012) and 31,4 ± 18,1% (Barone, et al., 2013) of VB, after and 6 months, respectively.

With regard to tissue composition, a 32,4 ± 20,4% of VB, 51,8 ± 12,7% of NMCT and 15,8 ± 14,5% of GP, has been observed after the use of DBBM in molar and premolar sites, at 4 months (Sivolella, et al., 2020). Thus, data from our investigation show slightly superior results in terms of VB, with less amount of GP and NMCT, after 5 months of healing. This superiority in the results may be explained as tissue biopsy was obtained without a surgical stent which may have include septal bone.

Otherwise, the employment of FDBA in the present research has showed a histomorphometric composition of 48.54 ± 18.78%, 13.99 ± 10.46% and 37.38 ± 15.71% of VB, GP and NMCT, respectively, after 5 months of healing.

Regarding allografts, the use of demineralized freezed-dried bone allograft (DFDBA) and FDBA has been widely investigated in the literature. In this regard, when compared to FDBA, the application of DFDBA in ridge preservation procedures results in a greater bone formation and less residual GP, after 18-20 weeks (Wood & Mealey, 2012).

However, it is unknown how variations in osteoinductivity affect new bone formation and whether, in the future, areas grafted with FDBA will present or not greater percentage of VB. In that sense, a combination of 70% cortical FDBA plus 30% cortical DFDBA has been investigated, showing no differences in terms of NMCT but a greater amount of VB and less GP when compared to cortical FDBA alone (Borg & Mealey, 2015).

Additionally, when comparing cortical versus cancellous FDBA no significant differences have been observed with regard to the amount of VB, with rates of 16.08% and 12.98%, respectively. However, it seems that the use of cortical FDBA results in greater amount of GP and less NMCT tissue with 28.38% and 52.90% of GP and NMCT, respectively, compared to cancellous bone which exhibited 19.94% and 62.82%, after 17-21 weeks (Eskow, et al., 2014). Consequently, combinations of cortical and cancellous FDBA have also been investigated. The use of 50% of cortical FDBA plus 50% of cancellous FDBA, when compared to cortical or cancellous FDBA alone, demonstrated no differences with regard to VB or NMCT, however a greater percentage of GP was observed with the use of cortical FDBA. Thus, the use of cortico-cancellous FDBA have shown 26.40 ± 13,18%, 23.37 ± 12.49% and 50.23 ± 11.52% of VB, GP and NMCT, respectively, after 18-20 weeks (Demetter, et al., 2017).

Although results from the present investigation are superior to the previously published, one limitation when performing biopsies in molar sites is that a certain amount of pristine bone might from the interradicular septum might be included in the biopsies, thereby altering the histomorphometric outcomes.

Even though, the majority of the cases treated with FDBA in this investigation were located in the mandible, a previous investigation has shown no histological differences after the use of FDBA plus a collagen membrane in maxilla or mandible after 4 months. However, the mandible seemed to present more areas of mineralization than resorption while in the maxilla no differences were found (Leblebicioglu, et al., 2013).

Additionally, small size particle of both grafting materials was used in the present study. However, the use of a particle size of 125-710 µm or a combination of 125-710 µm plus 2-4 mm of demineralized bone matrix (DBM) does not seem to offer a benefit histologically (Hoang & Mealey, 2012).

With regard to healing time, the present investigation evaluated the use of DBBM and FDBA after 5 months with no other comparison in time. However, this factor seems not to affect tissue quality as a previous investigation comparing the use of non-freezed-dried cancellous mineralized human bone allograft at 3 and 6 months has shown similar results in terms of tissue composition (Beck & Mealey, 2010).

Likewise, histomorphometric results from a recent systematic review and meta-analysis have concluded that, to date, there is no evidence of a superior graft material able to improve bone formation between 3 and 6 months. Thus, in terms of socket grafting, platelet rich growth factors (PRGF) seems to be the best option in terms of VB. However, these results are only from an histological point of view as a comparison of dimensional changes were not evaluated in this investigation (Canellas, et al., 2020).

4. Implant placement in preserved sites

Implant placement in previously preserved ridges has shown 100% of implant survival rate in the long term (Apostolopoulos & Darbi, 2017; Lim, et al., 2019; Cardaropoli, et al., 2015; Marconcini, et al., 2018).

In terms of success rates, the placement of implants in previously preserved ridges in premolars and molars area results in 95.83% of success rate compared to a 91,66% in naturally healed sockets with no statistically significant differences between groups (Cardaropoli, et al., 2015). Thus, more recent research have reported 100% after 4 years (Marconcini, et al., 2018).

While the majority of the studies have reported high rates of implant success following ridge preservation, a study conducted by Apostopoulos & Darby (2017) found a 51% of success rate in preserved sites compared to 58% in non-grafted areas after 2-102 months of function, with no statistically significant differences between them. Although results from this investigation are considerably inferior to the previously ones found in literature, these differences may be explained as this study followed a classification evaluation that assess peri-implant condition including both soft tissue and radiographic assessment (Karoussis, et al., 2004) while the majority of the studies followed Albrekttson criteria (Albrekttson, et al., 1986).

Still, according to a recent european workshop and systematic review, preserved sites show no differences with regard to implant loss or success rates after 12 months of implant loading (Tonetti, et al., 2019) or when comparing different ridge preservation techniques (Avila-Ortiz, et al., 2019). Additionally, with regard to implant stability quoficient (ISQ) and marginal bone levels (MBL), ISQ values seem to be similar in preserved and non-preserved areas in molar and premolar sites with values of 69,96 ± 3.24 and 70,21 ± 4.83, respectively, after 4 months (Cardaropoli, et al., 2015).

Regarding MBL changes around implants, some studies have found no differences between preserved and non-preserved sites (Apostolopoulos & Darbi, 2017; Cardaropoli, et al., 2015; Park, et al., 2020). However, one year after the placement of implant prosthesis, a recent study has reported a MBL of 0.03 ± 0.03 mm, 0.00 ± 0.04 mm and 0.00 ± 0.04 mm, after the use of DBBM-c plus a double collagen membrane, DBBM-c or extraction alone, respectively, (Lim, et al., 2019), while other has observed even a better preservation of the MBL in the preserved areas (Marconcini, et al., 2018).

5. Need of horizontal ridge regeneration at the time of implant placement

In the present investigation only one site in the DBBM treatment group needed additional horizontal ridge augmentation at the time of implant placement.

This finding is in agreement with previous investigations, where the use of DBBM-c plus a collagen membrane or a double collagen membrane in ridge preservation at molar sites resulted in no need of additional regeneration (Choi, et al., 2017; Lim, et al., 2019). However, in non-preserved sockets, four out of eight cases were in need of further bone augmentation at the time of implant placement (Lim, et al., 2019).

Regarding FDBA, Walker et al. (2017) observed that, two out of 20 cases were in need of additional regeneration at the time of implant placement after ridge preservation with cortical FDBA plus a non-resorbable membrane in molar sites, while five out of 20 cases in non-preserved sockets needed horizontal ridge augmentation. Similarly, Leblebicioglu et al. (2013) found that only two out of 25 cases required simultaneous bone regeneration at the time of implant placement after ridge preservation with FDBA and a collagen membrane.

These results are in line with our investigation, which observed a low frequency of horizontal ridge augmentation following ridge preservation, suggesting that this procedure may reduce the need of simultaneous horizontal bone regeneration at the time of implant placement.

Recently, results from systematic reviews concluded that ridge preservation is strongly associated to less bone regeneration, prior or at the time of implant placement independently of the type of technique used (Avila-Ortiz, et al., 2019). Thus, the probability of implant placement without the need of additional bone regeneration is greater in preserved sites, although this procedure could be necessary in both preserved and non-preserved sites (Tonetti, et al., 2019).

6. Sinus lift following ridge preservation in maxillary molars

The rationale for applying ridge preservation techniques in posterior sites has been related to limit bone loss in areas of reduced height and/or avoiding proximity to anatomic structures such as maxillary sinus or the inferior alveolar nerve.

In the present investigation, 55% of the maxillary preserved areas had a need of crestal sinus lift from which four cases were treated with DBBM and one with FDBA. Accordingly, initial residual ridge heights of < 8 mm had an OR of 1.5 of need for sinus lift after ridge preservation. Thus, it can be suggested that preserved ridges with a baseline height of less than 8 mm, may result in a greater need of sinus lift compared to those of a greater length.

Moreover, the residual alveolar height showed an initial and final height at CH of 7.30 ± 3.53 mm and 6.8 ± 3.61 mm, respectively, after 5 months of healing which allowed implant placement without the need of external sinus lift in all cases.

Although no significant, bone height in the center of the ridge has been found to be higher when socket preservation is performed in comparison to spontaneous healing with values of 8.55 ± 2.53 mm and 7.02 ± 3.18 mm, respectively, after 6 months. (Zhao, et. al., 2018). Moreover, after ridge preservation in the posterior maxilla with DBBM-c and a collagen membrane, statistically significant less changes of the sinus floor level have been observed (-0.14 mm [-0.31, -0.02] when compared to naturally healed sockets which experimented a change of -1.16 mm [-1.73, -0.61] (Cha, et al., 2019).

In general, when compared to unassisted healing, ridge preservation in maxillary molars has been associated to less frequency of sinus lift (Rasperini, et al., 2010). Similarly, recent research has found that, six months following ridge preservation with DBBM-c plus a collagen membrane in the posterior maxilla, 42.9% of implants could be placed without sinus lift, while 50% were in need of crestal sinus floor elevation, and 7.1% needed lateral window approach. Still, 100% of naturally healed sockets required sinus floor elevation, from which 71.4% were performed with crestal approach and 28.6% with lateral window (Cha, et al., 2019). In addition, although 69.2% of the preserved sites and 68.3% of unassisted sockets may need sinus augmentation, lateral approach has been applied significantly more frequently at spontaneous healing sockets (37.2%) than at preserved sites (8.3%). Therefore, alveolar ridge preservation may reduce the invasiveness of the procedure (Park, et al., 2020).

7. Limitations

The main limitation of this investigation was the lack of a negative control group which precluded the evaluation of the possible benefits effects of alveolar ridge preservation over spontaneous healing in molars. Secondly, the absence of a surgical stent and the presence of the alveolar septum might have hindered in some cases a precise obtaining of the bone biopsy. In third place, the absence of a control group also prevented from confirming the benefits of ridge preservation over extraction alone in limiting the need of lateral sinus lift prior to implant placement. Thus, more RCTs including a negative control group and comparing preserved versus extraction sites with larger sample sizes are needed.

CONCLUSIONS

1. The use of both DBBM or FDBA, in combination with a resorbable membrane, are similarly effective in limiting alveolar ridge reduction in ridge preservation procedures after 5 months of healing.

2. The initial thickness of the buccal bone plate correlates with the amount of ridge alterations after ridge preservation, with thinner bone plates (< 1.5 mm) exhibiting greater resorption in width and height.

3. The use of DBBM or FDBA in combination with a resorbable membrane result in similar tissue composition in terms of VB, NMCT and GP after 5 months of healing.

4. Ridge preservation may limit the need of lateral sinus lift previous to implant placement minimizing the need to perform more invasive bone augmentation techniques .

FUTURE PERSPECTIVES

Ridge preservation has demonstrated to be a predictable technique in limiting the amount of horizontal and vertical bone resorption following tooth loss. However, to date there is no evidence of superiority of any technique, and thus, answers to questions such as: "which is technique is superior in limiting bone resorption?" or "which is the influence of local and systemic patient-related factors on ridge preservation outcomes?" remain still not clear.

Furthermore, the high heterogeneity in methodology among studies with regard to defect morphology, surgical technique, biomaterials used and measurement methodology employed should be of greater consideration. Some investigations include severely affected sockets due to periodontal disease while other include sockets with absence up to 50% of the buccal bone plate which may lead to more apical and wider bone walls, with less bone reduction. Moreover, an overcorrection of the defect during the grafting procedure has also been reported in some studies. Additionally, differences regarding evaluating methods are also considerable, since CBCT measurements seems to provide an accurate visualization of both hard and soft tissues, while clinical measurements, employed in many investigations, may include both hard and soft tissue components in ridge reduction analysis, preventing from attributing these dimensional changes only to bone remodelling.

Still, although dimensionally the use of xenograft or allograft in combination with a collagen membrane or a collagen sponge seems to provide a better horizontal preservation of the bone crest, a superior approach cannot be determined yet. Moreover, from an histological point of view the use of different biomaterials has not provided a clear benefit over others. Thus, although the use of cell therapy, rhBMP-2 and autologous blood-derived products in ridge preservation procedures still lacks of sufficient evidence, they may be a promising result in terms of tissue composition in the future.

Notwithstanding, although immediate implant therapy is a predictable and alternative approach to ridge preservation procedures in molar sites, demonstrating high survival and success rates, minimal bone loss and reduced treatment time and number of interventions, many cases may be not suitable for this type of approach. Yet, evidence comparing immediate implants and ridge preservation in molar sites is scarce.

Hence, future research of well-designed RCTs including different situations (e.g. intact versus affected sockets, comparison of anterior versus molar sites), as well as the impact of local and systemic factors on the outcomes of ridge preservation procedures are needed.

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ANNEXES

Universitat Internacional
de Catalunya

Comitè d'Ètica
d'Investigació
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ACCEPTACIÓ INFORME FINAL PEL CEIm / ACCEPTACIÓ INFORME FINAL POR EL CEIm

Data informe / Fecha informe: 26/02/20
Codi de l'estudi / Código del estudio / Study Code: PER-ECL-2013-04
Versió del protocol/ Versión del protocolo / Study version: 1.1
Data de la versió/ Fecha de la versión/ Version date: 09/04/13
Títol/ Título / Title: Xenograft versus mineralized freeze-dried bone allograft in ridge preservation techniques. A randomized clinical trial and histological study in humans
Investigadores principales/ Main researchers: Dr. José Nart, Dra. Cristina Vallés
Tutor/a / Monitor/a: Lucía Barallat
Investigadoras Secundarias / Second researchers: Desiré Abellán

Sant Cugat del Vallès, 12 de març de 2020

Benvolgut Doctor/a,

Els membres del CEIm de la Clínica Universitària d'Odontologia, l'hi agraeixen l'aportació científica en el camp de la investigació i la presentació de l'informe final en aquest Comitè per a la seva avaluació.

Valorat l'informe final de l'estudi pel nostre CEIm, el 5 de març de 2020, li comuniquem que ha sigut acceptat.

Atentament,

Apreciado Doctor/a,

Los miembros del CEIm de la Clínica Universitària d'Odontologia, le agradecen su aportación científica en el campo de la investigación y la presentación del informe final a este Comité para su evaluación.

Valorado el informe final del estudio por nuestro CEIm, el 5 de marzo de 2020, le comunicamos que ha sido aceptado.

Atentamente,

Dr. J.Manuel Ribera
President CEIm

Universitat Internacional de Catalunya

Comitè d'Ètica de Recerca

APROVACIÓ PROJECTE PEL CER/ APROBACIÓN PROYECTO POR EL CER

Codi de l'estudi / *Código del estudio*: PER-ECL-2020-04
Versió del protocol / *Versión del protocolo*: 1.0
Data de la versió / *Fecha de la versión*: 08/04/19

Sant Cugat del Vallès, 12 de març de 2020

Doctoranda: Desire Abellán Iñiguez
Directors de Tesi: José Nart, Cristina Vallès, Lucía Barallat
Títol de l'estudi / *Título del estudio*: Evaluation of bone regeneration techniques using different biomaterials

Benvolgut/da,

Valorat el projecte presentat, el CER de la Universitat Internacional de Catalunya, considera que, el contingut de la investigació, no implica cap inconvenient relacionat amb la dignitat humana, tracte ètic per als animals ni atempta contra el medi ambient, ni té implicacions econòmiques ni conflicte d'interessos, però no s'han valorat els aspectes metodològics sense implicacions ètiques del projecte de recerca degut a que tal anàlisis correspon a d'altres instàncies.

Per aquests motius, el Comitè d'Ètica de Recerca, RESOLT FAVORABLEMENT, emetre aquest CERTIFICAT D'APROVACIÓ, per que pugui ser presentat a les instàncies que així ho requereixin.

Em permeto recordar-li que, si en el procés d'execució es produís algun canvi significatiu en els seus plantejaments, hauria de ser sotmès novament a la revisió i aprovació del CER.

Atentament,

Apreciado/a,

Valorado el proyecto presentado, el CER de la Universidad Internacional de Catalunya, considera que, el contenido de la investigación, no implica ningún inconveniente relacionado con la dignidad humana, trato ético para los animales, ni atenta contra el medio ambiente, ni tiene implicaciones económicas ni conflicto de intereses, pero no se han valorado aspectos metodológicos sin implicaciones éticas del proyecto de investigación debido a que tal análisis corresponde a otras instancias.

Por estos motivos, el Comitè d'Ètica de Recerca, RESUELVE FAVORABLEMENTE, emitir este CERTIFICADO DE APROBACIÓN, para que pueda ser presentado a las instancias que así lo requieran.

Me permito recordarle que, si el proceso de ejecución se produjera algún cambio significativo en sus planteamientos, debería ser sometido nuevamente a la revisión y aprobación del CER.

Atentamente,

NOGALES GADEA NOELIA - 53288914F

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Fecha: 2020.12.10 15:59:38 +01'00'

Secretaria CER-UIC

Universitat Internacional de Catalunya
COMUNICAT INTERN

Dr. José Nart
Investigador Principal

CEIC
Ref.110/2013

Comitè Ètic d'Investigació Clínica

El Comitè Ètic d'Investigació Clínica en sessió del dia 26 de juny de 2013 va adoptar, entre d'altres, el següent acord:

S'aprova l'estudi número PER-ECL-2013-04 "Xenograft versus alloplastic material in Ridge preservation techniques. A Randomized Clinical Trial and Histological study in humans" de l'àrea de Periodòncia (Investigador Principal: Dr. José Nart/Investigador Secundari: Manuel Cabezas).

Atentament,

Deborah Violant
09 de juliol de 2013

A/c.: Dr. Lluís Giner, Dra.Montse Mercadé, Manuel Cabezas.