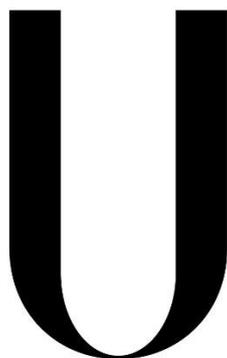


Universidade de Lisboa  
**Faculdade de Medicina Dentária**



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**Alveolar extraction socket behaviour to alloplastic  
regenerative procedures – a comparative study**

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*À minha Mãe, Irmão e Avós, o meu maior apoio e,  
Ao meu Pai, que o levo comigo no coração...*



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*“It always seems impossible until it’s done”*

Nelson Mandela

## Abstract

**Aim:** To compare clinical, and volumetric alterations of post extraction sockets with and without bone regeneration with Adbone®BCP on a socket preservation type of regeneration.

**Materials and Methods:** Participants were assigned to one of two groups, at surgery day, having 16 anterior teeth divided equally into two groups. Bone regeneration was tested by application of a biphasic calcium phosphate synthetic bone graft (Adbone®BCP) while natural healing was the control group. Clinical evaluation included intra-oral photographs and an alginate impression. 3D examination consisted in extra-oral scanning of the obtained gypsum casts to generate 3D STL files. A comparison between initial and final buccolingual dimensions was formed using CloudCompare<sup>V2</sup> (version 2.6.1 [GPL software], 2019), measuring initial and final dimensions of both groups in 5 different sites (loss at 2, 3, 4, 5, 6 mm measured from coronal to apical of the extraction socket). Follow-up appointments were performed at days 7, 14 and 3 months postoperative.

**Results:** For the t-test, there was a significantly higher ridge dimensions loss on the control group,  $p=0.029$ ,  $0.045$  and  $0.041$  for the first three measurements, respectively.

Given these p-values being  $< 0.05$ , there are significant differences regarding the loss between the 2 groups, hence confirming the H1.

**Discussion:** There were differences between the test and control groups on the first three measurements (H2, H3, H4) given that tissue modelling is a rather rapid process. However, the measurements situated apically on the alveolus, had p-values  $> 0.05$ , indicating that, given the short follow-up, the subsequent woven bone remodelling may take years to be completed and thus had not happened yet.

**Conclusion:** Sockets grafted with Adbone®BCP suffered a reduced loss of volume on the alveolar socket contour, thus being effective on preserving the alveolar ridge.

**Keywords:** synthetic bone graft, hard-tissue, bone regeneration, Biphasic Calcium Phosphate, alveolar bone.



## Resumo

As extrações dentárias são um dos procedimentos mais comuns no ramo da medicina dentária, levando a mudanças significativas no rebordo edêntulo, dificultando o correto e satisfatório posicionamento de implantes, podendo assim comprometer o resultado das reabilitações protéticas.

A extração dentária envolve um trauma mecânico nos tecidos moles, no ligamento periodontal e no osso do processo alveolar, levando a uma resposta inflamatória que recruta células hematopoiéticas e mesenquimais no local.

Após uma extração, o processo de cicatrização inicia-se com hemorragia e seguinte formação de um coágulo, sendo substituído por tecido de granulação. Em seguida, forma-se uma matriz provisória de tecido conjuntivo, dando início à fase proliferativa onde há uma incorporação de vasos e células formadoras de osso dentro da matriz provisória. Ao fim do primeiro mês após extração, verifica-se o preenchimento do alvéolo com osso imaturo que será progressivamente substituído por osso lamelar e medular. O término do processo de cicatrização é clinicamente observado pelo encerramento, primário ou secundário, do alvéolo com tecido mole epitelizado e radiográfico pelo preenchimento ósseo do alvéolo. Consequentemente, este processo levará a alterações dimensionais no rebordo edêntulo.

Embora se verifique alterações dimensionais até ao primeiro ano após extração, são durante os primeiros 3 meses que a perda óssea e tecidual é mais acentuada. Esta perda é influenciada por diversos fatores como as variações biológicas dos indivíduos, o tamanho do alvéolo pós-extracional e a extensão do trauma provocado durante a extração.

Está bem descrito na literatura que, após uma extração dentária, o rebordo edêntulo move-se em direção ao longo eixo do osso basal. A forma do maxilar parece retornar à forma em que estava antes do desenvolvimento do processo alveolar durante a erupção dentária. A falta de um estímulo funcional nas paredes ósseas e a necessidade de ajuste dos tecidos para se adaptar à geometria da crista na ausência de dentes podem explicar esta modificação.

Dadas estas alterações dimensionais, a reabilitação destes espaços edêntulos fica comprometida, influenciando tanto o resultado estético como funcional. De forma a tentar prevenir estas complicações, muitos estudos mostraram os efeitos do uso de enxerto de diferentes biomateriais e diferentes técnicas e respetivos benefícios na regeneração óssea. As primeiras investigações concentraram-se no uso apenas de membranas regenerativas.

Entretanto, pesquisas com enxertos ósseos em defeitos periodontais levaram os pesquisadores a explorar a utilidade das membranas em combinação com enxertos ósseos. Hoje em dia, a regeneração óssea guiada é geralmente realizada como um procedimento de combinação envolvendo membranas e um substituto ósseo de suporte. Alguns investigadores empregaram aloenxertos desmineralizados, maleáveis, rapidamente reabsorvidos e supostamente osteoindutores, enquanto outros utilizaram enxertos mineralizados, mais rígidos e osteocondutores. No entanto, não está claro qual material é mais eficaz para esta indicação clínica, já que estas técnicas incluem a colocação de diferentes materiais de enxerto, como autoenxertos ósseos, xenoenxertos, aloenxertos, combinados com membranas reabsorvíveis ou não reabsorvíveis e, mais recentemente, materiais bioativos, como L-PRF (leucócitos e fibrinas ricas em plaquetas).

Um autoenxerto envolve a utilização de osso obtido do mesmo indivíduo que recebe o enxerto, enquanto que um aloenxerto é derivado de seres humanos que é colhido de outro indivíduo que recebe o enxerto, como por exemplo de cadáveres. Os xenoenxertos são enxertos ósseos de uma espécie diferente da humana, como os bovinos, e são usados como uma matriz calcificada. Os aloplásticos podem ser feitos de hidroxiapatite, um mineral ósseo natural, fosfato tricálcico ou uma combinação de ambos. Os enxertos à base de fatores de crescimento são produzidos utilizando tecnologia de ADN recombinante, consistindo em fatores de crescimento humanos ou morfogénicos. Os substitutos de enxerto ósseo à base de cerâmica envolvem cerâmicas, isoladamente ou em combinação com outro material, como sulfato de cálcio, vidro bioativo e Fosfato de Cálcio. Contudo, a literatura não é clara relativamente ao material mais eficaz para as técnicas de regeneração alveolar.

Um dos materiais mais estudados, o xenoenxerto, apresenta resultados benéficos com a sua utilização. Contudo, este material tem uma taxa de reabsorção lenta, levando à presença de partículas residuais que poderão interferir com a normal cicatrização alveolar bem como influenciar a qualidade do osso regenerado.

Por outro lado, o uso de materiais aloplásticos de osteocondução também visa minimizar as alterações dimensionais que advêm após extração. Adbone®BCP é um material de enxerto ósseo totalmente bifásico feito de 75% de hidroxiapatite (HAp) e 25% de fosfato tricálcico beta-fosfato ( $\beta$ -TCP). Deste modo, parece ter todas as propriedades necessárias para minimizar as mudanças que ocorrem em alvéolos pós-extração, tanto a nível ósseo como dos tecidos moles, conduzindo a uma menor reabsorção da tábua óssea vestibular e menor colapso tecidual.

O objetivo deste estudo é comparar as alterações clínicas e volumétricas de alvéolos pós-extracionais com e sem regeneração óssea com Adbone®BCP.

**Materiais e Métodos:** 11 participantes foram inseridos de acordo com os critérios de inclusão e exclusão, sendo designados para um dos dois grupos, no dia da cirurgia, com 16 dentes anteriores divididos igualmente em ambos os grupos. A regeneração óssea foi testada pela aplicação de enxerto ósseo sintético de Fosfato de Cálcio bifásico (Adbone®BCP) comparando-a com o grupo de controlo, a cicatrização natural. A avaliação clínica incluiu fotografias intra-orais e uma impressão em alginato. O exame 3D consistiu em leitura extra-oral dos modelos em gesso obtidos para gerar arquivos 3D STL e usando o CloudCompare<sup>V2</sup> (versão 2.6.1 [GPL software], 2019), formando uma comparação entre as dimensões bucolinguais inicial e final dos tecidos duros e moles. Para tal, os ficheiros STL foram sobrepostos, escolhendo sete pontos em comum entre ambos para uma maior correspondência. Em seguida, traçou-se uma reta do ponto mais vestibular ao ponto mais palatino da raiz. Por fim, traçaram-se 5 retas, de 2 mm em 2 mm, a unir os dois ficheiros podendo avaliar as alterações dimensionais bucolinguais, em 5 regiões diferentes desde um ponto coronal e um mais apical. As consultas de acompanhamento foram realizadas nos dias 7, 14 e 3 meses de pós-operatório.

**Resultados:** Foram medidas as dimensões iniciais e finais de ambos os grupos em 5 locais diferentes (perda de 2, 3, 4, 5, 6 mm, medidos de mais coronal para mais apical no alvéolo). Para o teste *t*, houve uma perda significativamente maior no grupo controle, com valores de  $p=0,029$ ,  $0,045$  e  $0,041$  para as três primeiras medições, respectivamente. A nossa hipótese nula corresponde a que não há diferenças significativas na perda dimensional entre os dois grupos. Considerando-se que esses *p*-valores são  $< 0,05$ , existem diferenças significativas em relação à perda entre os dois grupos, confirmando, assim, a nossa hipótese testada.

**Discussão:** Dados os resultados apresentados, existem diferenças estatisticamente significativas entre os grupos teste e controle nas três primeiras medições (H2, H3, H4), dado que a modelação tecidual é um processo bastante rápido. No entanto, as duas últimas medições, sendo estas mais apicais no alvéolo, apresentaram *p*-valores  $> 0,05$ . Deste modo, especula-se que, dado o curto período de acompanhamento, o remodelamento ósseo subsequente, sendo um processo um pouco mais lento, pode levar anos para ser concluído, logo ainda não serem visíveis tais alterações.

**Conclusão:** Podemos concluir que existem diferenças estatisticamente significantes entre os alvéolos do grupo teste, regenerados com Adbone®BCP em comparação com a

cicatrização de alvéolos do grupo de controlo. No entanto, há um número limitado de estudos sobre este enxerto ósseo, expondo assim a necessidade de mais ensaios clínicos randomizados avaliando o efeito do enxerto ósseo sintético Fosfato de Cálcio bifásico na regeneração óssea. Devido ao tamanho da amostra e curto período de acompanhamento, não é possível aplicar à população em geral.

**Palavras-chave: enxerto ósseo sintético, tecido duro, regeneração óssea, Fosfato de cálcio bifásico, osso alveolar.**

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## List of abbreviations

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<b>%</b>	<b>Percentage</b>
<b>ARP</b>	<b>Alveolar ridge preservation</b>
<b>ASA</b>	<b>American society of anaesthesiologists</b>
<b>B-TCP</b>	<b>Beta-phosphate tricalcium phosphate</b>
<b>BCP</b>	<b>Biphasic calcium phosphate</b>
<b>FGFS</b>	<b>Fibroblastic growth factors</b>
<b>GBR</b>	<b>Guided bone regeneration</b>
<b>HA</b>	<b>Hydroxyapatite</b>
<i><b>i.e.</b></i>	<b>Id est</b>
<b>IGFS</b>	<b>Insulin-like growth factors</b>
<b>IL</b>	<b>Interleukins</b>
<b>L-PRF</b>	<b>Leukocyte and platelet-rich fibrin</b>
<b>mm</b>	<b>Milometers</b>
<b>MPA</b>	<b>Megapascal</b>
<b>n</b>	<b>Sample numbers</b>
<b>PA</b>	<b>Periapical radiographs</b>
<b>POST-OP</b>	<b>Postoperative</b>
<b>PDGF</b>	<b>Platelet derived growth factor</b>
<b>PRGF</b>	<b>Plasma rich in growth factors</b>
<b>RCT</b>	<b>Randomized control trial</b>
<b>STL</b>	<b>Stereolithography</b>
<b>TCP</b>	<b>Tricalcium phosphate</b>
<b>TGF-B</b>	<b>Transforming growth factor-beta</b>



## 1. Introduction

The volume and shape of the alveolar process is determined by the form of the teeth, their axis of eruption and eventual inclination. (1) Teeth extractions are one of the most common procedures in dentistry, due to multiple causes such as decay, advanced periodontal disease, trauma, and others. (2) Although dimensional changes can be observed up to 1 year after tooth extraction, it is during the first 3 months that the most statistically significant bone and tissue loss occurs. (3–5)

Following an extraction, the alveolar process will undergo resorption and the bundle bone will lose function and disappear (1), thus having a direct repercussion on the periodontal structures. Although, generally, extraction sockets heal uneventfully, the defect caused by extraction will only become partially repaired as the alveolar ridges will reabsorb. Bone loss is more pronounced on the horizontal axis. There is also loss of vertical ridge height, most pronounced on the buccal aspect. (4) This resorption results in a narrower and shorter ridge (6), placing the ridge to a more palatal/lingual position. However, in some cases, there might already exist a previous bone loss due to periodontal disease, endodontic lesions or a traumatic episode. Therefore, when there is an alveolar wall missing, there will be a more pronounced bone resorption. (1) In these cases, it will be filled with fibrous tissue which does not allow a correct healing. (2,4,7)

In 1996, Soikkonen et col. described that systemic conditions such as osteoporosis, diabetes, vascular, endocrine or renal pathology can accelerate bone loss and thus interfering with the bone's metabolism. Even the simple trauma created during an extraction creates a microtrauma on the surrounding bone which can accelerate bone loss. (8)

### 1.1 Healing Process

The healing of bone tissues includes both regenerations, where there is a complete restoration of morphology and function, and repair, which differs in morphology and function.

Teeth extraction involves a mechanical trauma in the soft tissues, periodontal ligament, bundle bone and the bone of the alveolar process (7,9), thus leading to an inflammatory response that includes both hematopoietic and mesenchymal cells in the site. (8,10) Tissue and cell proliferation are mediated at different stages by various growth factors, inflammatory cytokines, and signalling molecules. Although it is a continuous process, bone repair can be divided into three phases: inflammation, proliferative and modelling/remodelling. (7)

The inflammation phase begins immediately after tissue damage and lasts for approximately 2 weeks. The initial step in the repair process is the formation of a blood clot that effectively plugs the detached blood vessels and stops bleeding. It acts as a physical matrix that directs cellular movements and it contains substances (i.e. growth factors) that influence mesenchymal cells and enhance the activity of inflammatory cells. Such substances will thus induce and amplify the migration of various types of cells into the socket wound, as well as their proliferation, differentiation, and synthetic activity within the coagulum. (11-12)

Cytokine release from injured cells then recruits inflammatory cells into the area, where macrophages begin phagocytosis of damaged tissues and cells. The clot is comprised mainly of erythrocytes and platelets that get trapped in a network of fibrin. Isolated neutrophils are present in the central and apical compartments of the blood clot. The principal Sharpey's fibres in the bundle bone were found to be in direct contact with the coagulum in the socket. (2,13) Osteoclasts begin the process of resorbing damaged bone in the area to recycle mineral components. In addition, cells from myeloid and mesenchymal cell lineages are recruited to the area where they begin to differentiate into osteoblasts and chondroblasts. Within 2–3 days, large numbers of inflammatory cells mediated by signalling molecules (i.e. growth factors and cytokines), like platelet-derived growth factor (PDGF), insulin-like growth factors (IGFs), fibroblastic growth factors (FGFs) and transforming growth factor-beta (TGF- $\beta$ ), which are also responsible for cell differentiation and proliferation (7,14), migrate to the wound in order to “clean” the site before new tissue can start forming. The combination of inflammatory cells, vascular sprouts, mesenchymal cells from the severed periodontal ligament and immature fibroblasts forms the granulation tissue. As the site becomes sterilized, the granulation tissue is gradually replaced with a provisional connective tissue matrix that is rich in collagen fibres and cells, and the proliferative phase of the wound-healing process begins. (7,12,15)

The proliferative phase may be divided into two parts – fibroplasia and woven bone formation – and is characterized by intense and rapid tissue formation. After 4-5 days, the epithelium from the margins of the soft tissue starts to proliferate to cover the granulation tissue in the socket. (15) Fibroplasia is the rapid deposition of a provisional matrix. Subsequently, there is an incorporation of vessels and bone forming cells within the provisional matrix where projections of woven bone are arranged around the blood vessels. These projections will completely surround a vessel in order to form the primary osteon. Woven bone can be identified in the healing socket 2 weeks after tooth extraction and remains in the wound for several weeks. Such formation is ongoing in the apical portion of the socket, occurring from the periphery to

the centre of the alveolar socket. Woven bone is a provisional type of bone without any load-bearing capacity and therefore needs to be replaced with mature bone types (lamellar bone and bone marrow). In the first month, the socket is filled with woven bone. (4)

The last phase is bone modelling which is defined as a change in the shape and architecture of the bone, whereas bone remodelling is defined as a change without concomitant change in the shape and architecture of the bone. The replacement of woven bone with lamellar bone or bone marrow is bone remodelling, whereas the bone resorption that takes place on the socket walls leading to a dimensional alteration of the alveolar ridge is the result of bone modelling. This may take several months and exhibits substantial variability among individuals. (7-8,16)

The walls of the socket – the alveolar bone proper or the bundle bone – are gradually resorbed and the socket becomes filled with immature woven bone that will eventually be replaced by mature lamellar bone. (8,16-17) After 3 weeks, the socket contains connective tissue and there are signs of mineralization of the immature bone, through the process of bone remodelling, and the epithelium covers the wound. After 6 weeks of healing, bone formation in the socket is pronounced and trabeculae of newly formed bone can be seen. (10)

Adequate vitamin D and calcium are critical for proper bone repair and their levels may, in part, dictate the rate of repair. The time for the remodelling stage varies depending upon individual bone metabolism, but usually require months from the time of injury. (12)

At the same time, bone resorption takes place on the socket walls leading to dimensional changes of the alveolar ridge. A few weeks after tooth removal, osteoclasts could be found around the crest of both buccal and lingual walls and on the outer and inner (bundle bone) portions of the socket. Bone modelling takes place equally on buccal and lingual walls, but since the lingual bone is usually wider than the buccal bone wall, modelling results in greater vertical bone loss at the thin buccal plate than at the wide lingual wall. (7)

Bone modelling takes place earlier than bone remodelling, in such way that about two-thirds of the modelling process occurs in the first 3 months of healing. (3) The complete remodelling of the woven bone into lamellar and bone marrow may take several months or years and it depends on individual variability. Bone resorption is less in mesial/distal sites than in buccal/lingual sites and it may be due to the presence of adjacent teeth. In total, the mean value of vertical bone loss is 1.24 mm ( $\pm 0.11$ ) at 6 months(4,13,18). Regarding horizontal bone resorption, the mean value is 3.79 mm ( $\pm 0.23$ ) at the level of the alveolar crest in the first 6

months, with more pronounced tissue loss in the buccal aspect. The end of socket-healing process is clinically observed by the closure of the socket with firm epithelized soft tissue and radiographic by bone filling of the socket. This will be influenced by biologic individuals' variations, alveolar socket size and the extended of socket trauma during the extraction. (7)

## **1.2 Socket Preservation/regeneration techniques**

There are several types of grafts. An autograft involves utilizing bone obtained from the same individual receiving the graft. An allograft is derived from humans which is harvested from another individual of that receiving the graft. Xenografts are bone grafts from a species other than human, such as bovine and are used as a calcified matrix. Alloplastic grafts may be made from hydroxyapatite, a naturally bone mineral, tricalcium phosphate or a combination of both. Growth factors enhanced grafts are produced using recombinant DNA technology, consisting of either human growth factors or morphogens. Ceramic-based bone graft substitutes involve ceramics, either alone or in combination with another material such as calcium sulphate, bioactive glass, and calcium phosphate. (19)

It is now well established that following tooth extraction the ridge crest moves toward the long axis of the basal bone. (7,20) The shape of the jawbone appears to return to the shape that was present prior to the development of the alveolar process during tooth eruption. The lack of a functional stimulus on the bone walls and the need for tissue adjustment to meet “genetically” determined demands regarding ridge geometry in the absence of teeth may explain this modification. (4)

Clinicians often perform extractions without any planning on preserving the alveolar ridge for later implant rehabilitation or without evaluating the possibility of immediate implant placement. This may lead to consequences on the remaining bone, which in turn may threaten the entire rehabilitation. Failing to preserve the residual alveolar ridge after a tooth extraction often leads to compromising future placement of implants and further rehabilitation. Therefore, throughout the years, many studies have shown the effects of grafting different biomaterials and different techniques and their benefits on bone regeneration. Early investigations focused on using regenerative membranes alone. However, research with bone grafts in periodontal defects led investigators to explore the utility of membranes in combination with bone grafts. (8) Nowadays, guided bone regeneration (GBR) is generally performed as a combination procedure involving membranes and a supporting bone substitute. Some researchers have

employed demineralised, malleable, rapidly resorbed and reportedly osteoinductive allografts (21), while others have used mineralised, more rigid, minimally resorbing and reportedly osteoconductive grafts. (7,14) Scheyer et al., 2016, compared both. Nevertheless, it is not clear which material is most effective for this clinical indication (22), as these techniques include the placement of different grafting materials such as bone autografts, xenografts, allografts, combined with resorbable or non-resorbable membrane (23-24), and, more recently, bioactive materials, as L-PRF (leukocytes and platelet rich fibrins).

Even though the occurrence of bone loss in both buccal and lingual side is always expected, the placement of graft materials has been described as an ideal procedure to reduce the level of bone resorption. (1-2) Some studies have shown that, with these techniques, the amount of ridge reduction in height ranged from +1.3 mm to -2.64 mm and in width varied from -1.2 mm to 2.64 mm, depending on the type of materials used. (1,25) Willenbacher et al., on a meta-analysis, concluded that about 0.95 mm up to 1.12 mm of mean apico-coronal ridge height and 1.31 mm to 1.54 mm of mean bucco-oral ridge width can be preserve using alveolar ridge preservation techniques compared to natural healing with a defined 6 months of follow up. (26)

Different kinds of graft materials may influence the socket healing and may compensate for the buccal loss. (7,25) However, the presence of residual particles is a concern since they might interfere with normal healing. (2) Another fact that may be relevant is the bone quality, which is dependent on the resorption rate of the grafting material used, as well as the ability to promote bone formation. (25) A decrease in bone density is expected if the residual particles do not integrate well with bone. (25) Thus, in case of implant rehabilitations, these must be placed more apically to previous socket to achieve primary stability. (27) The greater percentages of residual graft remnants were seen in sockets treated with xenografts and allografts. The use of a xenograft or an allograft had a beneficial effect in bone preservation compared to alloplastic materials. Xenograft is one of the most studied materials. (23)

Experimental studies in a dog model (2,9) have demonstrated that placing bone substitutes in a fresh extraction socket failed to inhibit the processes of modelling and remodelling that took place in the socket walls following tooth extraction. However, it was observed that the graft supported hard-tissue formation, in particular in the cortical region of the extraction site, and the dimension and profile of the alveolar ridge was better preserved. The authors concluded that the placing a biomaterial in an extraction socket may modify modelling and compensate for the buccal bone loss. The cross-sectional area of the grafted sites exhibited

a reduction of only 3% of their initial dimensions, whilst in the non-grafted sites, the corresponding reduction was 25%.

Araújo et al. (2011), showed that applying Bio-Oss Collagen® (xenograft) in the gap during immediate implant placement modified the process of hard tissue healing, provided additional amounts of hard tissue, improved the level of marginal bone-to-implant contact and prevented soft tissue recession.

Immediate implant placement in fresh extraction sockets fails to prevent bone modelling. (7) The use of hard- or soft-tissue grafts with immediate implant placement to prevent ridge reduction has been evaluated in several clinical and experimental studies. In these studies, the hard-tissue graft, mainly a bone substitute, was placed in the space between the implant surface and the inner surface of the buccal bone wall, whilst the soft-tissue graft was adapted to the outer surface of the bone wall. These demonstrated that graft procedures, combined with implant placement, may hinder ridge alterations following tooth extraction. (7)

In 2015, Atieh et al., states that the literature is not clear about which material is the most effective for preservation and regeneration techniques.

### **1.3 Bone Quality**

The internal structure of the bone is described in terms of quality or density, which is reflected in a set of biomechanical properties - strength and modulus of elasticity. The bone quality is strongly dependent on the position in the arch - the bone with the highest density is found in the mandibular anterior region, followed by the anterior region of the maxilla, posterior region of the mandible, and finally the posterior region of the maxilla, where the bone density is lower. (28) This may be given due to the different biomechanical functions performed by these structures - the mandible is an independent structure which acts as a unit of force absorption; the maxilla acts as a force distributor. Thus, in the presence of teeth, the mandible presents a dense bone cortex and a relatively dense trabecular bone; the maxilla redirects forces through the zygomatic and palate arches, away from structures such as the brain and orbits, and it is anatomically beneficial to have a thin cortex and dense trabecular bone. (29-30) After an extraction, there is a decrease in both bone quantity and its density. This decrease is more relevant in the posterior maxilla and less in the anterior mandible. (31)

Several classifications have been made throughout these years. In 1970, Linkow and Chercheve classified bone density into 3 categories. (32)

Based on the volume of remaining mineralized bone, the edentulous sites may, according to Lekholm and Zarb (1985), be classified into five different groups (Fig. 1a). In groups A and B, substantial amounts of the ridge still remain, whereas in groups C, D, and E, only minute amounts of hard tissue remain. (33)

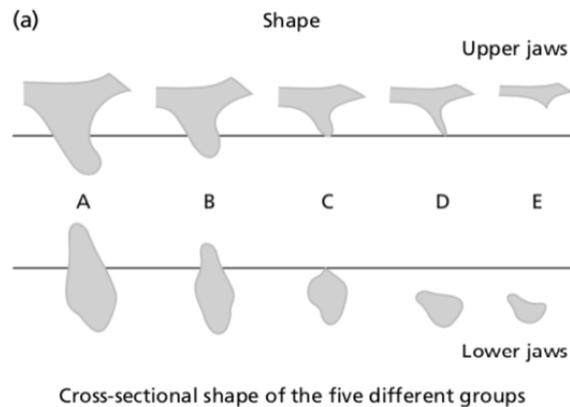


Figure 1a – Schematic drawing showing a classification of residual jaw shape. (Adapted from Lekholm & Zarb 1985. Reproduced from Quintessence. (33) )

Lekholm and Zarb (1985) also classified the bone quality in the edentulous site. Class 1 and class 2 characterized a location in which the walls – the cortical plates – of the site are thick and the volume of bone marrow is small. Sites that belong to class 3 and class 4 have relatively thin walls of cortical bone, while the amount of trabeculae of lamellar bone and marrow, is large. (33)

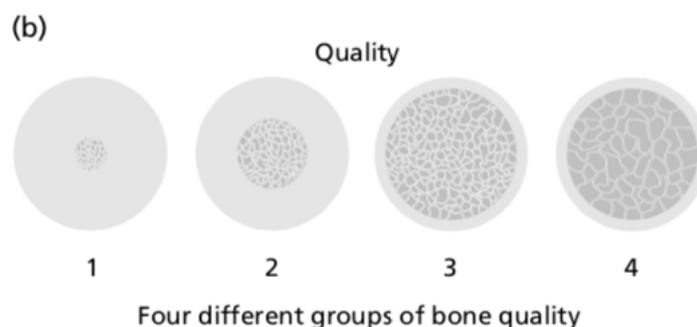


Figure 1b – Schematic drawing showing a jaw bone quality. (Source: Lekholm & Zarb 1985. Reproduced from Quintessence.)

Even though it is the most used classification, it presents a high level of bias since it depends on the quality of the radiographic examination and the clinical perception of the health professional. (34) Thus, in 2007, Misch proposed another classification, based on macroscopic density of edentulous areas of the maxilla and mandible:

Table 1 – Bone density classification by Misch. (34)

BONE	DENSITY
D1	>1250 HU Dense cortical bone
D2	850-1250 HU Thick dense to porous cortical bone on crest and coarse trabecular bone within
D3	350-850 HU Thin porous cortical bone on crest and fine trabecular bone within
D4	150-350 HU Fine trabecular bone
D5	<150 HU Immature, non-mineralized bone

The regional locations of the different densities of the cortical bone are more consistent than those of the trabecular bone. Bone density can be determined by tactile sensitivity during surgery, radiographic evaluation or anatomical location. (34)

A literature review and a post-surgical study in partially edentulous patients indicate that the location of different bone densities is strongly related to the different regions of the oral cavity (Table 1). (34)

Bone density is directly related to implant stability and, consequently, to successful rehabilitation. As a result, the region with the highest rate of osseointegration and successful implantation is the anterior mandible; the one that presents a worse rate of osseointegration and success of implant rehabilitation is the posterior maxilla. (20,35)

According to the classification of Elian et al. 2007, in situations where facial soft and hard tissues are at normal levels in relation to the cemento-enamel junction of the tooth and remain with the same levels after extraction, this alveolus is classified as type I. If the bone level is below the previous references, meaning the buccal plate is partially missing, but the soft tissues are at a normal level, it is classified as type II. The type III alveolus is the most complex to rehabilitate, with bone and tissue resorption. Type I alveoli are the easiest to treat and have the most predictable results. (34-35)

#### **1.4 Biphasic calcium phosphate synthetic bone graft (Adbone®BCP)**

Synthetic calcium phosphates are commonly used in bone substitutes. Within the group of phosphates, hydroxyapatite (HA) and tricalcium phosphate (TCP) are the most common

materials used for bone substitution. HA has excellent biocompatibility with the bony environment; however, it is mostly used for surface coating on metal implants due to its low solubility and brittle nature. TCP has the advantage of osteoconductivity, but it is limited in clinical use due to its rapid degradation rate. Therefore, biphasic calcium phosphate (BCP) has been used to overcome the disadvantages of HA and TCP. Since BCP includes HA and TCP, it provides optimal dissolution and good bioactivity, cell attachment, proliferation, and differentiation for new bone regeneration. (38)

Adbone®BCP is a fully biphasic bone graft material made from 75% HA and 25%  $\beta$ -TCP. Adbone®BCP features a multi-directional interconnected 80% porosity that guides the three-dimensional regeneration of bone, having a pore size ranging from 300-500 microns. This forms an ideal environment for vascularization. (39)

As the bone healing process occurs, Adbone®BCP is reabsorbed and replaced with new bone. Due to its composition, it has a biphasic reabsorption and was developed to achieve the highest degree of porosity without compromising mechanical strength. In average, whilst other materials have a mechanical resistance of 0.5MPa, adbone has 3.0MPa. It can be mixed with patient's blood. The hydrophilic behaviour confers a high cohesivity of the particles. It is radiopaque, allowing the monitorization of the graft osteointegration. It facilitated the formation and ingrown of new bone and blood vessels (osteoconduction) due to three dimensional, highly porous structure. The use of this allograft may be considered when autogenous bone is not indicated or as an adjunctive therapy when it is not possible to harvest a sufficient quantity of autogenous bone to fulfil the needs of the proposed surgical procedure. It is designed to regenerate bone in oral defects associated with disease, trauma and degeneration. There is no indication to use a membrane, unless there is a risk of graft exposure. (39)

Adbone®BCP is intended to be used as a bone void filler or augmentation material for bone defects that are not intrinsic to the stability of the bony structure such as maxillofacial osteotomy, sinus lift augmentation, crestal access, lateral access, implantology, alveolar regeneration, vertical augmentation, horizontal augmentation, peri-implant defects, dehiscence and fenestration.

## 2. Aim

The aim of this study is to compare clinical and volumetric alterations of post extraction sockets with and without bone regeneration with Adbone®BCP on a socket preservation type of regeneration.

## 3. Hypothesis

The null hypothesis (**H0**) of the present study is: “There is no difference between test and control groups regarding bone resorption, soft tissue healing and collapse of the alveolar socket after bone regeneration compared to non-regenerated alveolar sites.”.

It will be tested the hypothesis (**H1**) that there is a difference between test and control groups regarding bone resorption, soft tissue healing and collapse of the alveolar socket after bone regeneration compared to non-regenerated alveolar sites.

## **4. Materials and Methods**

### **4.1 Study design and Randomization**

This study is a unicentric study conducted at Faculty of Dentistry, University of Lisbon (FMDUL). Participants were assigned to one of two groups at surgery day, starting with 8 alveoli being attributed to the control group and subsequent 8 attributed to the experimental group.

Post-extraction sockets were submitted to bone regeneration, after debridement and irrigation with saline solution, by application of a biphasic calcium phosphate synthetic bone graft (Adbone®BCP) whereas control group's post-extraction sockets were just debrided and irrigated with saline solution.

The approach was a socket preservation type described by Elian in 2009. The regenerative material was placed in the intact wall socket and the graft particles were compacted.

An informed consent was made (Appendix 1) and approved by the Ethic Committee for Health from Faculty of Dentistry, University of Lisbon (Comissão de Ética para Saúde-FMDUL) (Appendix 2). Prior to surgery, each patient signed the approved informed consent (Appendix 1) agreeing to being submitted either to unassisted socket healing or grafted socket healing.

### **4.2 Sample Size calculation**

A total of 12 patients (16 samples) entered this study. Given that it is a pilot study, it was decided to use this small sample to evaluate if the data is enough for a power sample.

### **4.3 Inclusion Criteria**

The inclusion criteria in this study were as follows:

- Patients from FMDUL aged 18 or over;
- Requiring teeth extraction in the premolar region and anterior maxilla (5-5);
- Presence of intact buccal bone plate;
- ASA (Physical Status Classification System, American Society of Anaesthesiologists) I or II.

#### 4.4 Exclusion criteria

The exclusion criteria included patients with:

- Uncompensated systemic diseases;
- Metabolic and healing disorders, i.e. diabetes mellitus, hyperparathyroidism, cancer, HIV;
- Heavy smokers (>5 cigarettes/ day);
- Bone metabolic diseases;
- Severe renal dysfunction or liver disease;
- Patients who had received systemic corticosteroids or other immunosuppressive agents, radiation therapy and/or chemotherapy for the past 2 months;
- Active infections in the surgical site;
- Patients with periodontal or/and endodontic disease.

#### 4.5 Surgical technique

Each patient was submitted to local subperiosteal anaesthesia (Articaíne 4% with epinephrine 1: 200 000, Inibsa, Sintra, Portugal), both buccal and palatal, after local application of topic anaesthesia (Topigel, Benzocaine, 2%, Clarben S.A, Madrid, Spain).

Following the anaesthetic procedure, the surgeon performed tooth extraction the more atraumatic possible, to preserve the integrity of the alveolar buccal plate, without elevation of a mucoperiosteal flap. Then, followed thorough degranulation of soft tissue remnants, ensuring integrity of the buccal plate, and irrigation with sterile saline solution (0.9% NaCl, B. Braun Medical, Lisbon, Portugal).

After allocation to either test or control group, each participant on the test group was submitted to application of a biphasic calcium phosphate synthetic bone graft (Adbone®BCP) whereas control group's post-extraction sockets were just debrided and irrigated with saline solution.

##### Control group:

After tooth extraction, the alveolar socket was thoroughly debrided using a Lucas curette (Lucas CL8, Dentaleader S.A., Lisbon, Portugal). Subsequently, they were irrigated using saline solution (0.9% NaCl, B.Braun Medical, Queluz de Baixo, Portugal) and then sutures (Surgical silk suture, non-absorbable, 3/0 Silkam®, B. Braun Medical, Lisbon, Portugal) were made, when necessary.

Test group - socket treatment with biphasic calcium phosphate synthetic bone graft:

After tooth extraction, the alveolar socket was thoroughly debrided using a Lucas curette (Lucas CL8, Dentaleader S.A., Lisbon, Portugal) and irrigated using saline solution.

The alveolar socket was filled with biphasic calcium phosphate synthetic bone graft, according to the following protocol:

4.5.1 The granules of the synthetic bone graft are mixed with a few droplets of blood. Once a uniform agglomerate is formed, these are to be introduced inside the socket, compressed firmly, certifying that there are no free spaces left. Excess of blood is to be absorbed with a gauze.

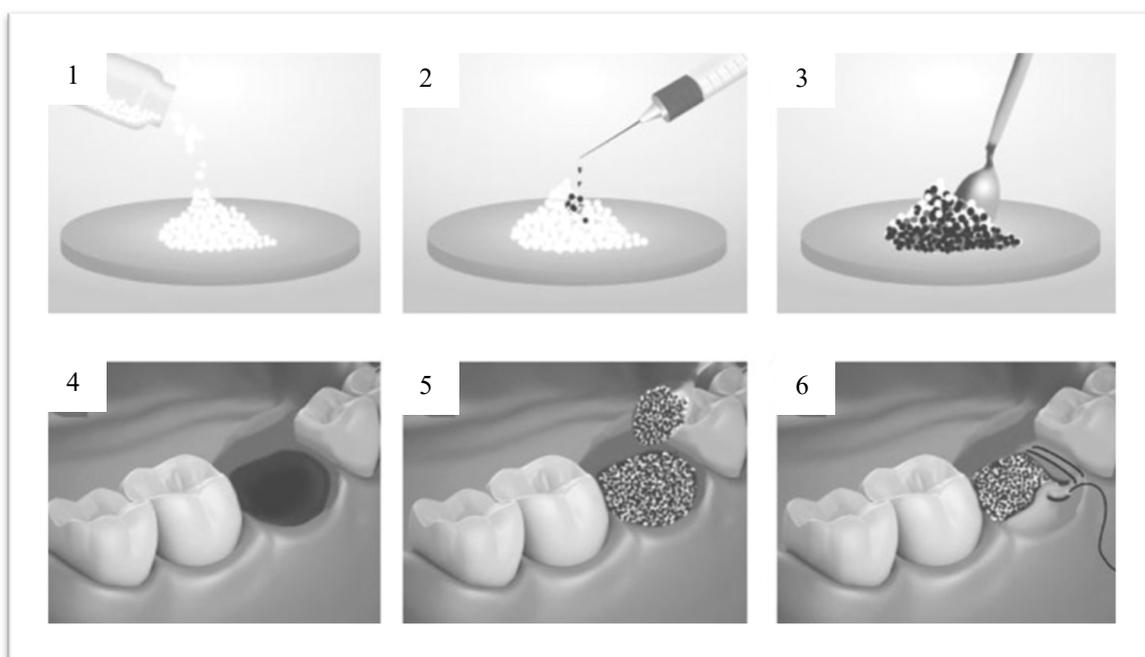


Figure 2 – Instructions on how to handle Adbone®BCP (Adapted from MedBone). (39)

5.5.1 A tension-free monofilament non-resorbable cross suture is to be placed on the socket in order to maintain the graft in place.

6.5.1 It is not required the use of membrane unless there is risk of graft exposure. When so, a Spongostan™ Dental (Ethicon Inc., Johnson & Johnson, New Jersey, United States) is to be cut into the alveolar shape and placed on top of the graft, stabilizing it with a tension-free monofilament non-resorbable cross suture.

## **4.6 Post-operative Management**

Patients, in both groups, whenever there was therapeutically indication, went through a therapeutic regimen of 1-tab Amoxicillin 1000mg Cipamox 1000 g (Atral Laboratories S.A., Santarem, Portugal) each 12H, for 8 days.

The pain medication regimen included 1 tab of paracetamol 1000mg Ben-u-ron 1000g (bene-Arzneimittel GmbH, Munich, Germany) 8/8h.

In case of extreme inflammation, Ibuprofen 600mg, 12/12h was prescribed.

Patients were also advised to use a 0.2% chlorhexidine mouth rinse (0.2% Bexident Post, Isdin, Lisbon, Portugal) to be used three times per day for a period of 7 days.

All the postoperative recommendations were explained.

## **4.7 Clinical evaluation**

Clinical evaluation began before the extraction with intraoral photographs. An alginate impression (R&S Turboprint, Dentaleader, Lisbon, Portugal) was taken of the maxilla to create stone cast models to determine the pre-extraction dimensions.

Patients were monitored postoperatively to observe healing and soft-tissue closure. Follow-ups were at days 7, 14 and 3-months post-operative. In the first follow-up appointment, sutures were removed and observed tissue healing. In the last appointment, another alginate impression was taken of the alveolar extraction socket to determine the post-extraction dimensions after 3 months suffering bone remodulation.

### 4.7.1 Intra-oral photographs

Occlusal and lateral photographs to compare the pre- and post-surgical dimensions (see Annexe 2).

### 4.7.2 Alginate Impressions

Kromopan Alginate (Lascod S.P.A., Italy) was used to take maxillary impressions of each patient of either groups prior to surgery and at the 3-month follow-up appointment. These were casted using stone cast type III and type IV, respectively (Pro-Stone® 21, Pro-Dental, Saint-Gobain Formula)

## **4.8 Radiographic Examination**

At surgery day, the patient was scheduled to do a periapical radiography, before surgery. In the test group, immediately after placing the graft, another periapical radiography was taken to evaluate if the graft was well placed, compacted and filled the alveolar socket. At 3 months post-op, the participant returned to the clinic and did another periapical X-ray to compare and evaluate the results of the treatment with Adbone®BCP and natural healing (see Annexe 3).

## **4.9 3D Examination**

Alginate impressions were taken prior to surgery in order to create stone cast models (following the precise manufacturer indication) for each patient. At 3-month post-op, another alginate impression was taken.

Once both impressions were casted, these were scanned using an extra-oral digital scanner (Scanner S600 Arti, Zirkonzahn Software, Portugal) to generate surface stereolithography (STL) files. Using CloudCompare (version 2.6.1 [GPL software], 2019), it was made a 3D analysis of the models, which thus enabled a comparison between initial and final dimensions of the soft tissue. The software can make an analysis calculating the differences between STL files and differences between areas and thus enabling an evaluation of the amount of soft tissue collapse. To do so, the STL files were overlaid, choosing seven points in common between both models for better matching. Secondly, a line was drawn from the most vestibular point to the most palatine point of the root. Finally, 5 lines were drawn, with intervals of 2 mm by 2 mm, to join the two files and evaluate the dimensional buccolingual alterations, in 5 different regions from the most coronal to the most apical point (see Annex 4).

#### **4.10 Step-by-step procedures**

Surgery appointment → Signed informed consent; Periapical radiography; Alginate maxillary impression; Intra-oral photographs; Adbone®BCP protocol for test group and natural healing for control group; sutures; PA radiograph for test group;

##### Follow-up appointments:

- 1<sup>st</sup> Appointment (7 days after surgery) – To remove sutures and evaluate soft tissue healing;
- 2<sup>nd</sup> Appointment (14 days after surgery) – evaluate soft tissue healing;
- 3<sup>th</sup> Appointment (3 months after surgery) – Periapical radiography; Alginate maxillary impression; Intra-oral photographs.

#### **4.11 Statistical Analysis**

The statistical analysis was performed using the IBM SPSS® program (Statistical Package for the Social Sciences v.21, SPSS Inc., Chicago, United states of America).

## 5. Results

Attached is a table with each patient results (see Annex 1), obtained from CloudCompare (version 2.6.1 [GPL software], 2019), referring to buccolingual alveolar ridge alterations. The initial and final volumes of both groups in 5 different sites (loss at 2, 3, 4, 5, 6 mm were from coronal to apical of the extraction socket) were measured and found the difference between them.

For each moment, the loss between experimental and control group was compared. For this, a T-test was used, because in all cases, although the samples were small, the distributions were considered normal.

For the T test, **H0** corresponds to the hypothesis that there are no significant differences in tissue loss between the 2 groups. If  $p\text{-value} < 0.05$ , thus there are significant differences in tissue loss between the 2 groups, hence confirming the **H1**.

It is further possible to observe in figures 3 - 7, representing boxplot graphs of both groups, that the observed values are linearly related to each other. This confirms, once again, the normality of the results.

- **2mm:**

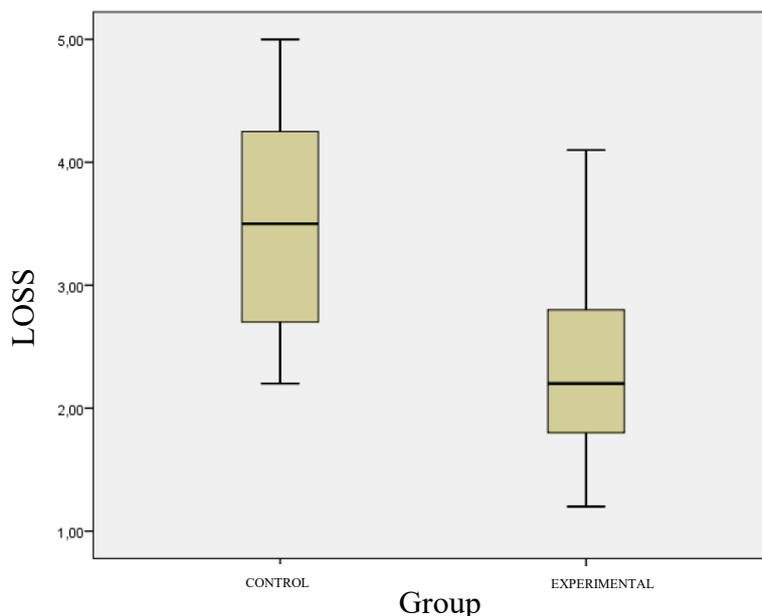


Figure 3 - Box-plot graph representing the volumetric loss on control group (natural socket healing) and experimental group (grafted socket healing). There is a greater loss on the control group.

## Alveolar extraction socket behaviour to alloplastic regenerative procedures – A comparative study

Table 2 – Group statistics for tissue loss at 2 mm.

<b>Group Statistics</b>					
Group		N	Mean	Standard Deviation	Mean Standard Error
Loss	Control	8	3.5125	.97459	.34457
	Experimental	8	2.3625	.91016	.32179

Table 3 – Testing of independent samples for tissue loss at 2 mm.

### Testing of independent samples

		Levene Test for equality of variances		T-test for Mean Equalities						
		F	Sig.	t	gl	Sig. (bilateral)	Mean difference	Standard error of difference	95% Confidence Interval of Difference	
Loss	Equal variances assumed	.248	.626	2.439	14	.029	1.15000	.47146	.13881	2.16119
	Equal variances not assumed			2.439	13.935	.029	1.15000	.47146	.13837	2.16163

p-value = 0.029 < 0.05. For 2 mm, on average, the control group had a significantly higher loss than the experimental group.

▪ **3mm:**

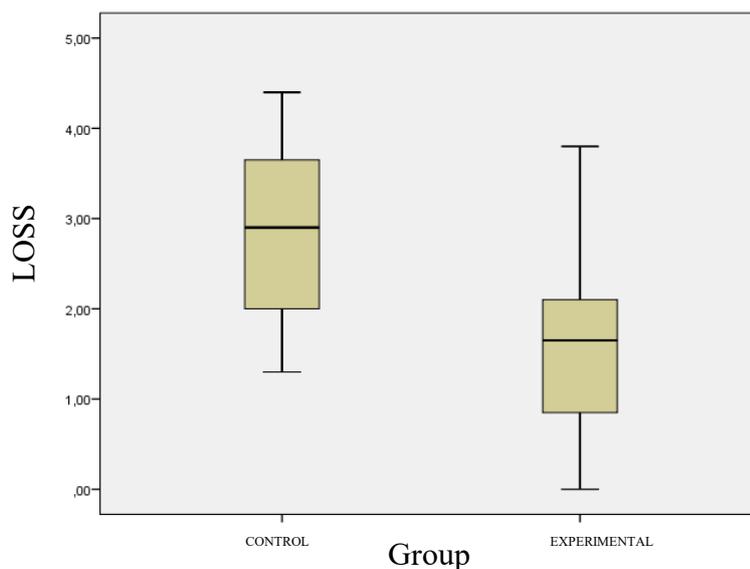


Figure 4 - Box-plot graph representing the volumetric loss on control group (natural socket healing) and experimental group (grafted socket healing). There is a greater loss on the control group.

Table 4 – Group statistics for tissue loss at 3 mm.

Group Statistics					
	Group	N	Mean	Standard Deviation	Mean Standard Error
Loss	Control	8	2.8500	1.07968	.38173
	Experimental	8	1.6250	1.14984	.40653

Table 5 – Testing of independent samples for tissue loss at 3 mm.

Testing of independent samples										
		Levene Test for equality of variances		T-test for Mean Equalities					95% Confidence Interval of Difference	
		F	Sig.	t	gl	Sig. (bilateral)	Mean difference	Standard error of difference	Inferior	Superior
Loss	Equal variances assumed	.006	.941	2.197	14	.045	1.22500	.55766	.02894	2.42106
	Equal variances not assumed			2.197	13.945	.045	1.22500	.55766	.02850	2.42150

p-value = 0.045 < 0.05. For 3 mm, on average, the control group had a significantly higher loss than the experimental group.

▪ **4mm:**

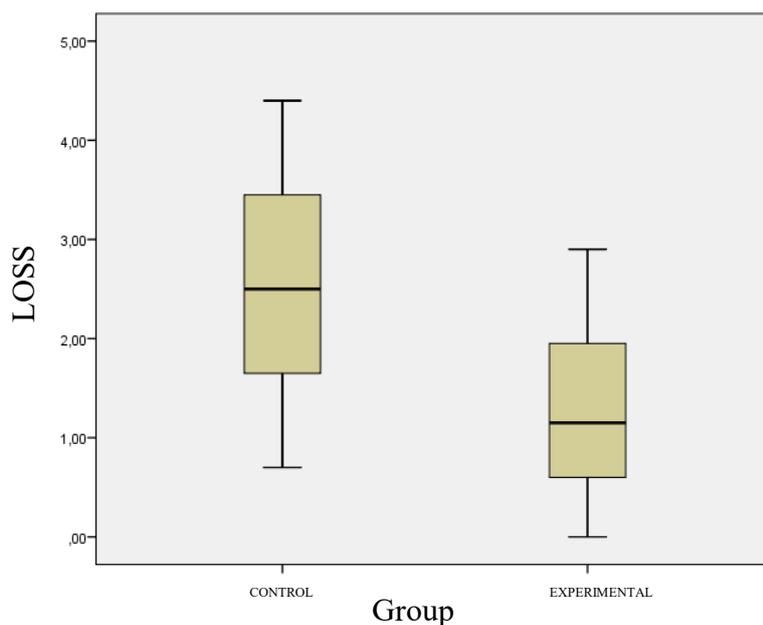


Figure 5 - Box-plot graph representing the volumetric loss on control group (natural socket healing) and experimental group (grafted socket healing). There is a greater loss on the control group.

Table 6 – Group statistics for tissue loss at 4 mm.

Group Statistics					
	Group	N	Mean	Standard Deviation	Mean Standard Error
Loss	Control	8	2.5375	1.24778	.44116
	Experimental	8	1.2875	.95833	.33882

Table 7 – Testing of independent samples for tissue loss at 4 mm.

Testing of independent samples										
		Levene Test for equality of variances		T-test for Mean Equalities				95% Confidence Interval of Difference		
		F	Sig.	t	gl	Sig. (bilateral)	Mean difference	Standard error of difference	Inferior	Superior
Loss	Equal variances assumed	.681	.423	2.247	14	.041	1.25000	.55626	.05695	2.44305
	Equal variances not assumed			2.247	13.126	.042	1.25000	.55626	.04946	2.45054

p-value = 0.041 < 0.05. For 4 mm, on average, the control group had a significantly higher loss than the experimental group.

▪ **5mm:**

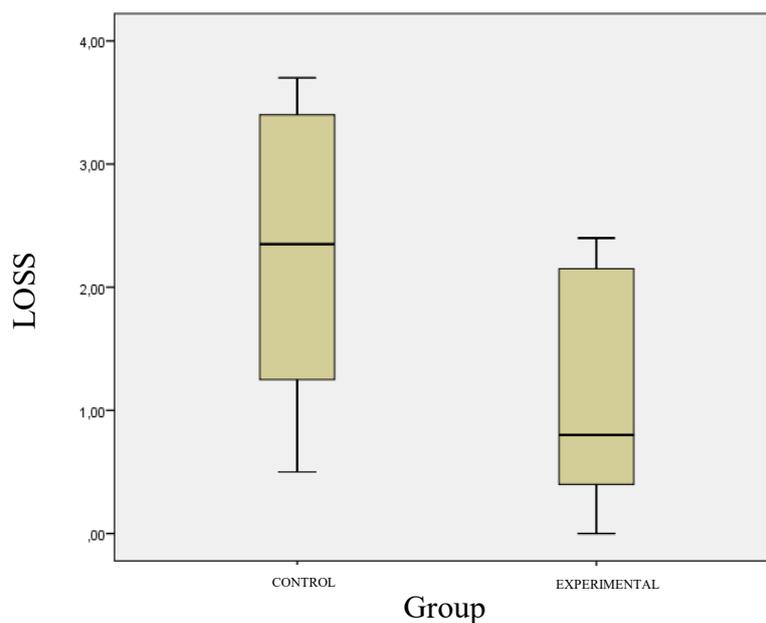


Figure 6 - Box-plot graph representing the volumetric loss on control group (natural socket healing) and experimental group (grafted socket healing). There is a greater loss on the control group but with no statistical differences.

Table 8 – Group statistics for tissue loss at 5 mm.

Group Statistics					
	Group	N	Mean	Standard Deviation	Mean Standard Error
Loss	Control	8	2.2750	1.23491	.43661
	Experimental	8	1.1375	.95310	.33697

Table 9 – Testing of independent samples for tissue loss at 5 mm.

Testing of independent samples										
		Levene Test for equality of variances		T-test for Mean Equalities						
		F	Sig.	t	gl	Sig. (bilateral)	Mean difference	Standard error of difference	95% Confidence Interval of Difference	
									Inferior	Superior
Loss	Equal variances assumed	.716	.412	2.062	14	.058	1.13750	.55152	-.04539	2.32039
	Equal variances not assumed			2.062	13.155	.059	1.13750	.55152	-.05256	2.32756

p-value = 0.058 > 0.05. For 5 mm, there are no significant differences between the loss of the control group and the loss of the experimental group.

▪ **6mm:**

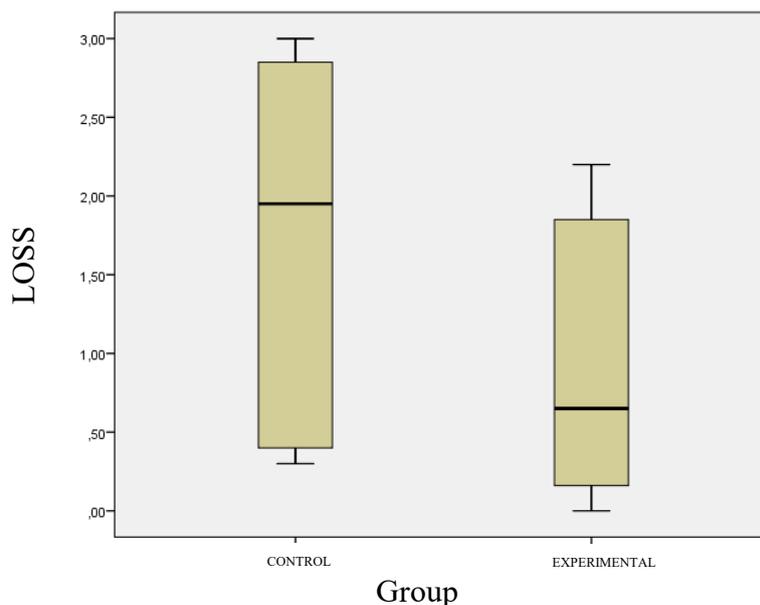


Figure 7 - Box-plot graph representing the volumetric loss on control group (natural socket healing) and experimental group (grafted socket healing). There is a greater loss on the control group but with no statistical differences.

Table 10 – Group statistics for tissue loss at 6 mm.

Group Statistics					
	Group	N	Mean	Standard Deviation	Mean Standard Error
Loss	Control	8	1.7125	1.19216	.42149
	Experimental	8	.9400	.90092	.31852

Table 11 – Testing of independent samples for tissue loss at 6 mm.

Testing of independent samples										
		Levene Test for equality of variances		T-test for Mean Equalities					95% Confidence Interval of Difference	
		F	Sig.	t	gl	Sig. (bilateral)	Mean difference	Standard error of difference	Inferior	Superior
Loss	Equal variances assumed	1.226	.287	1.462	14	.166	.77250	.52831	-.36062	1.90562
	Equal variances not assumed			1.462	13.029	.167	.77250	.52831	-.36859	1.91359

p-value = 0.166 > 0.05. For 6 mm, there are no significant differences between the loss of the control group and the loss of the experimental group.

## 6. Discussion

The findings in the present study suggest that there is a statistically significant difference between test and control groups regarding bone resorption, soft tissue healing and collapse on the alveolar socket after bone regeneration compared to non-regenerated alveolar sites. Thus, the null hypothesis (H<sub>0</sub>) of the present study is discarded.

In alloplastic grafts, HA resembles the inorganic component of human bone and is mostly used due to its osteoconductive properties, hardness and acceptability by bone. (19) TCP is gradually replaced by new bone due to its bioresorbability. BCP have a longer degradation rate than that of TCP and are stable enough to provide bone formation. The higher porosity and more suitable pore size an interconnected pore structure has, the more bone cells transform into new bone tissue. In addition, a steady and gradual dissolution of BCP can help create a rich environment in calcium and phosphorus for osteogenic precursor cell adhesion, differentiation, production of bone matrix, and finally, ossification. (38) Therefore, the use of Adbone®BCP is advantageous whenever there is indication to graft an alveolar socket, preserving the dimension of the alveolar ridge.

The present study showed that the placement of an alloplastic graft in fresh extraction sockets may prevent ridge reduction in extraction sites. This finding is supported by previous studies that showed that bone grafting in combination with collagen membrane placement significantly limited the resorption of hard tissue after tooth extraction. (38-39) Araújo et al found that, during healing of a xenograft, the particles of the graft material became integrated with the bone crest and further enhanced its dimensions. This is in agreement with findings presented by Nevins et al, who reported that sockets treated with bovine bone mineral showed a reduction of less than 20% of the buccal plate, whereas control sites, i.e. not grafted, showed a reduction of more than 20%. (41)

The results from measurements at 2 mm, 3 mm and 4 mm shown a significantly higher loss on the control group, having p-values of 0.029, 0.045 and 0.041 respectively, in comparison to those on the experimental group, thus having a statistically significant difference ( $p < 0.05$ ). On the other hand, measurements at 5 mm and 6 mm, being the two most apical measurements of the extraction socket, show no significant differences between tissue loss of the control group and that of the experimental group. This suggests that all the alveolar ridge alterations following a tooth extraction might not have happened yet due to the short follow-up on this investigation. Follow-up appointments were made at days 7, 14 and after 3 months of the tooth extraction.

In a later and long-term study, Trombelli et al. (2008) examined socket healing in biopsies sampled during a 6-month period from human volunteers. In later phases of healing, it was observed that the process by which woven bone was replaced by lamellar bone and marrow, was slow and exhibited great individual variation. At 6 months of healing, only a limited number of specimens had woven bone been replaced with bone marrow and trabeculae of lamellar bone.

In a 12-month prospective study, Schropp analysed 46 premolar and molar extraction sockets from 46 patients and found a 50% loss in ridge with an average 6.1 mm of horizontal loss. However, two thirds of this loss of bone volume occurred within the first 3 months. (15) Therefore, it can be assumed that tissue modelling following tooth extraction in humans is a rather rapid process, while the subsequent woven bone being remodelled into lamellar bone and marrow, is slow and may take years to be completed. However, it must be taken into account that this methodology was done by raising flaps which can alter the final results.

On the test group, the buccal plate resorbed until reaching the graft wall whereas the control group would have a greater resorption, given the fact that it had no stimuli. Thus, we speculate that a longer-follow up might have statistically significant differences between test and control groups in the apical portion of the socket site.

Other studies have suggested that the amount of ridge contraction varies within the socket itself. Araújo and Lindhe stated that in the apical and middle portions of the socket site, minor dimensional alterations occurred, while in the coronal portion of the ridge the reduction of the hard tissue volume was much more significant. (9,15) Hence, these findings are in accordance with those on the present study given that the more apical measurements have less statistically significant differences compared to those on the control group.

Comparing differences between jaws, mandible resorbs more than maxilla. (4) However, the direction of resorption is opposite in the maxilla, as the buccal wall of the alveolar socket tends to resorb more rapidly after dental extraction and the ridge gradually becomes represented by the previous palatal wall (centripetal resorption). (15) The amount of tissue loss that occurs in these processes varies considerably from subject to subject and from site to site (12) in the same individual.

On the following table (table 12), it is noticeable the existing differences among the amount of resorption between different sites on the maxilla and mandible.

## Alveolar extraction socket behaviour to alloplastic regenerative procedures – A comparative study

Table 12 – Average amount of resorption of tooth extraction in different tooth areas (Source: Lindhe(12))

Tooth	Average amount of resorption (mm)		Difference
	Buccal surface	Lingual/palatal surface	
<i>Mandibular teeth</i>			
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
<i>Maxillary teeth</i>			
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

In the study of Pietrokovski & Massler, in 1967, the amount of resorption was greater along the buccal surface than along the lingual or palatal surface in every specimen examined, although the absolute amounts and differences varied very widely. This caused a shift in the centre of the edentulous ridge towards the lingual or palatal side of the ridge with a concomitant decrease in arch length in the mandible as well as the maxillae. In another study, the molar teeth site had a greater value of reabsorption, but it was more critical in the anterior region due to aesthetics demands. (9,16)

In this context, it is important to acknowledge that the buccal bone plate in the frontal tooth region in humans is frequently (>80% of sites) <1 mm wide. (12) Hence, it can be anticipated that tooth loss in this part of the dentition may result in noticeable dimension alterations (horizontal as well as vertical) of the ridge and that this in turn may cause aesthetic concerns. (12)

On the present study, we included teeth on the anterior maxilla, from last premolar to the contralateral last premolar (5 to 5). On the control group, two central incisors were included, as well as 1 lateral incisor, 1 canine and four pre-molars. On the test group, we included two lateral incisors, one canine and five pre-molars. Knowing that different types of teeth may have different resorption rates, the comparison between test and control groups may have that bias since we had different clinical situations.

The extraction of single as well as multiple teeth induces a series of adaptive changes in the soft and hard tissues that result in an overall regression of the edentulous site(s). (12) The repair process results in reduced height and width of the residual ridge. The reduction in the alveolar bone ridge is much greater when multiple adjacent teeth are extracted, rather than a single tooth. (41)

As the buccal bone has been suggested to be completely composed of bundle bone, a significantly higher osteoclastic activity may occur on this surface of the extraction socket as compared with the lingual or palatal surface, given the osteoclastic activity occurring 16 weeks post-extraction. (11)

Misch et col and Araújo et col speculated that constriction of the blood clot within the alveolus may significantly contribute in bone remodelling process following tooth extraction. This comes in accordance with Al-Hezaimi et al who attributed the difference in bone loss to a reduction in the blood supply during healing of multiple adjacent extraction sites. (11) It is also hypothesized that extraction of contiguous teeth is associated with more severe alveolar bone resorption as compared with when a single tooth is extracted.

In 2012, Mansour Al-Askar showed that on a single-tooth extraction, a slightly higher remodelling on the buccal side compared with the palatal/lingual side occurred whereas on the extraction of two adjacent teeth showed an equivocal bone remodelling on buccal and lingual/palatal side. When extracting three adjacent teeth, the Micro-CT analysis demonstrated a more significantly pronounced remodelling ( $p < .001$ ) on the lingual/palatal side compared with the buccal side having more bone resorption than the other two groups. (11) The author concluded that extraction of contiguous teeth causes a more extensive bone remodelling compared with extraction of a single tooth.

In another study, ridge preservation surgery results in a similar pattern of bone remodelling in the horizontal and vertical dimensions of the edentulous ridge after single and multiple adjacent teeth extractions (41), thereby suggesting that regardless the number of teeth extracted, the socket healing with grafting regenerative procedure reduced bone resorption. However, it only had 4-months follow-up.

Our sample had both single and contiguous extractions, regardless the groups, which might have compromised the results given that we were not able to have the same amount of both types of extractions on control and test groups. However, our results show that when grafting the socket, whether it had adjacent teeth or not, there is a lower resorption of the ridge.

Given the presented results, there are statistically significant differences between the test and control groups. However, due to sample size and short follow-up, it is not possible to apply to the general population. For future studies to have statistically significant power, the G Power3 program (42) should be used to calculate the sample needed for statistical power (80%)

### **Main considerations**

The alveolar process is a tooth dependent tissue. (43) After a tooth extraction, there is loss of the periodontal ligament thus losing the stimuli on the walls. Subsequently, there will be resorption of the buccal plate, placing it to a more palatal/lingual position.

Based on the 1961 paper by Gargiulo, the mean biologic width was determined to be 2.04 mm, of which 1.07 mm is occupied by the connective tissue attachment and another approximate 0.97 mm is occupied by the junctional epithelium. However, given to the biological width, there is, on average, a 2,5 mm of soft tissue that will eventually collapse regardless the existence a bone graft or not. This regression will lead to the collapse of the soft tissues. (44)

By placing a synthetic bone graft, we intended to reduce this bone resorption. There are several grafts from different sources that could be placed, although Adbone®BCP, due to its three dimensional, highly porous interconnected structure provided a favourable environment for new bone regeneration. The slow resorption rate of such biomaterial could be considered a clinical advantage in that it helps stabilizing the contour, opposing to what has been reported with autogenous bone where a high resorption rate of the original volume was measured (45), and it still has some serious complications such as limited graft volume and donor site morbidities. (38)

Iasella and coworkers (1,46) analyzed ridge width and ridge height in non-molar extraction sockets when freeze dried bone allograft and a collagen membrane were used after tooth extraction and compared these dimensions to extraction alone. They found that the sockets that were preserved lost 1.6 mm less ridge width and 2.2 mm less ridge height. In addition, this group noticed approximately 15% more bone in the sockets that were preserved.

Lekovic and coworkers compared the use of a bioabsorbable membrane over extraction sockets to extraction sockets alone and found that the preserved sites lost 0.38 mm of ridge height and 1.3 mm of ridge width as compared to extraction sites alone, which lost 1.5 mm of ridge height and 4.56 mm of ridge width. (15) The findings from these studies indicated that a

greater amount of socket resorption can be expected if a graft is not used. Nowadays, the gold standard is the immediate placement of an implant and provisional crown so that the soft tissues modulate around the provisional, hence there being reduced soft tissue collapse.

Horváth demonstrated, in a systematic review, that different alveolar ridge preservation (ARP) techniques do not totally eliminate post-extraction alveolar ridge resorption or predictably promote new bone formation. However, the reduction in ridge width and height following ARP may be less than that following natural socket healing (2), which comes in accordance with the findings shown on the present study.

## 7. Conclusion

Over the past years, the resorption of the alveolar ridge following tooth extraction has become a significant problem, especially in the anterior region. (1) In our daily practice, aesthetics has received more emphasis in treatment planning and the dentist faces multiple challenges. Hence, thorough understanding of the three-dimensional changes of both the bone and mucosa contours after tooth extraction would enrich our ability to plan treatments and provide rehabilitations to a level of optimum function and high aesthetic results.

Although alveolar ridge resorption is an unavoidable consequence of tooth loss, it appears to be more pronounced at the buccal than at the lingual/palatal aspects of the ridge.

The present study revealed statistically significant differences between sockets which were grafted using Adbone®BCP compared to unassisted socket healing. In addition, the hypothesis **H1** is confirmed: There are significant differences between test and control groups regarding bone resorption, soft tissue healing and collapse of the alveolar socket after bone regeneration compared to non-regenerated alveolar sites. Hence, this alloplastic graft combines bicalcium phosphate with hydroxyapatite, giving effect of both, osteoconduction and resorbability, reducing the loss of volume on the alveolar socket contour.

Nevertheless, further studies need to be performed. In order to make the results more reliable, additional studies must include a longer follow-up, larger sample size and with a standardized socket extraction method where a single extraction is performed compared to multiple extractions. The literature indicates good results concerning osteoinductive allografts. However, there is a limited number of studies regarding this bone graft, thus exposing the need for further RCTs assessing the effect of a biphasic Calcium Phosphate synthetic bone graft on bone regeneration.



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## 9. Appendix

### 9.1 Appendix 1 – Informed Consent

#### Consentimento de Participante em Estudo Clínico

##### Identificação

Investigador: Mariana Guerreiro

Estudante de 5ºano do Mestrado Integrado de Medicina Dentária Contacto:

916350114

e-mail: marianaguerreiro96@gmail.com

Orientadores: Professor Doutor André Chen e Professora Doutora Helena Francisco

#### Consentimento livre e esclarecido

Este consentimento informado destina-se a todos os pacientes que preencheram os requisitos e critérios de inclusão para o estudo **“Alveolar extraction socket behaviour to alloplastic regenerative procedures – a comparative study”**

Este estudo será realizado na Faculdade de Medicina Dentária da Universidade de Lisboa (FMDUL), dirigido pelo Prof. Doutor André Chen, será coordenado pelo Investigadora Prof<sup>a</sup>. Helena Francisco e será executado pela aluna Mariana Guerreiro, do 5º ano do Mestrado Integrado em Medicina Dentária.

**Este consentimento Informado é recomendado pela WHO-World Health Organization para consentimentos informados referentes a ensaios clínicos e é compreendido por duas partes:**

**Parte I - Constituída por uma folha informativa**

**Parte II - Certificado de consenso (com assinatura, caso o doente aceite fazer parte do estudo)**

Será dada uma cópia deste consentimento informado ao doente.

## **Parte I - Parte Informativa**

### **1-Introdução**

A Faculdade de Medicina Dentária da Universidade de Lisboa tem como objetivos o ensino pré-graduado na área da cirurgia oral, através da prestação qualificada de serviços de Medicina Dentária à população, e o contributo para o desenvolvimento desta área do saber. Estamos a fazer investigação sobre a técnica de manutenção da arquitetura alveolar. Iremos fornecer informações detalhadas e convidá-lo/a a fazer parte deste estudo. Se tiver alguma questão, poderá esclarecê-la com um dos médicos participantes do estudo.

### **2- Objetivo da Investigação**

Comparar a eficácia da técnica de cicatrização do alvéolo (regeneração alveolar).

O nosso objetivo é avaliar se a técnica de regeneração alveolar com osso de origem sintética é igualmente eficaz para a extração de dentes na zona estética superior trazendo menos complicações volumétricas pós-operatórias.

### **3- Tipo de Intervenção**

Envolve dois grupos, um grupo que recebe uma técnica de manutenção do alvéolo pós-extraccional e outra em que não é colocado nenhum biomaterial.

### **4- Seleção de participantes**

Iremos convidar todos os pacientes que tenham dentes de segundo pré-molar superior direito a segundo pré-molar superior esquerdo indicados para extração.

### **5- Participação Voluntária**

A sua participação neste estudo é totalmente voluntária. É sua, a escolha em participar ou não. Se optar por não participar neste projeto de investigação, pode à mesma realizar o procedimento pois não afetará o seu atendimento nesta instituição.

### **6- Procedimento e protocolo**

Aos participantes de um grupo será dado um tipo de regeneração enquanto os participantes do outro grupo não terão nenhuma. É importante que, o paciente não tenha conhecimento sobre qual o tipo de regeneração alveolar será aplicada. Qualquer um destes procedimentos poderá ser considerado de rotina na cirurgia oral atual e/ou sem consequências nocivas para o paciente.

## **7- Descrição do Protocolo e Programa de Consultas**

A duração do estudo durará 2 visitas, que terá de obrigatoriamente comparecer se desejar entrar no estudo.

1– Exodontia de pré-molar superior direito ao pré-molar superior esquerdo - com uma técnica de regeneração dependendo do grupo ao qual foi alocado; Realização de Periapical; Preenchimento de Questionário. Tomada de impressão da arcada maxilar em alginato e realização de fotografias intra-orais

2– Consulta de pós-operatório às 7 e 14 semanas e depois aos 3 meses;

## **8- Riscos**

Os riscos que existem ao entrar nesta investigação são os mesmos a que se expõe quando vai fazer uma extração na zona do maxilar inferior/superior posterior, fora do âmbito deste estudo. Não iremos usar nada que não seja de uso corrente nos consultórios dentários em Portugal. O procedimento é igual ao procedimento que usaria em qualquer gabinete dentário ou bloco operatório onde se extraem dentes.

## **9- Confidencialidade**

A informação que recolhemos a partir deste projeto de investigação será mantida em sigilo. As informações recolhidas durante a pesquisa serão guardadas e ninguém, exceto os investigadores terão acesso às mesmas.

## **10- Resultados**

Os resultados desta investigação serão publicados em revista própria e tornados públicos para toda a comunidade científica, sendo que a sua participação será sigilosa, sendo que em nenhuma altura será identificado ou identificável.

### **11- Direito a recusar ou a desistir**

Não tem de participar nesta pesquisa, se não quiser fazê-lo. Não afetará o seu atendimento nesta instituição. Pode interromper a sua participação no estudo em qualquer momento, sem perder qualquer dos seus direitos como paciente nesta instituição. O seu tratamento na clínica não será afetado de alguma forma.

### **12- Contacto**

Caso tenha algumas perguntas pode perguntar agora ou mais tarde, mesmo depois do estudo ter sido iniciado. Se quiser fazer perguntas mais tarde, pode contactar por email, o investigador principal.

## **Parte II - Certificado de consentimento**

### **Declaração do consentimento do participante**

Eu, \_\_\_\_\_, declaro que li as informações sobre o estudo, ou foram lidas para mim. Tive a oportunidade de fazer perguntas sobre o assunto e todas as perguntas que fiz foram respondidas para minha compreensão. Concordo voluntariamente em participar neste estudo.

Assinatura do participante \_\_\_\_\_

Data \_\_\_\_\_

Dia/Mês/ano

### **Declaração do Investigador**

Eu, Mariana Guerreiro e Silva, li o consentimento informado ao participante, com o melhor da minha capacidade, expliquei ao participante os passos que irão ser realizados.

Confirmo que o participante teve a oportunidade de fazer perguntas sobre o estudo, e todas as perguntas feitas pelo mesmo foram respondidas corretamente e com o melhor das minhas capacidades. Confirmo que o participante não tenha sido coagido a dar o seu consentimento e este foi dado livre e voluntariamente. Uma cópia do consentimento foi dada ao participante.

Assinatura do investigador Principal \_\_\_\_\_

Data \_\_\_\_\_

Dia/Mês/Ano

## 9.2 Appendix 2 – Ethic Committee approval



### FACULDADE DE MEDICINA DENTÁRIA

### Comissão de Ética para a Saúde (CES-FMDUL)

#### PARECER

A Comissão de Ética para a Saúde da Faculdade de Medicina Dentária da Universidade de Lisboa (CES-FMDUL), apreciou o pedido de parecer para a realização de um estudo intitulado "***Alveolar extraction socket behavior to different regenerative procedures – a comparative study.***" submetido pela estudante Mariana de Medeiros Campos Guerreiro Silva, tendo por orientadores a Professora Doutora Helena Francisco e o Dr. André Tsou Chen, destinado ao trabalho final do curso de Mestrado Integrado em Medicina Dentária.

A CES-FMDUL deliberou e decidiu emitir **parecer favorável**.

Lisboa, 16 de janeiro de 2019

O presidente da CES-FMDUL.

(Professor Catedrático João Aquino)

## 10. Annexes

### 10.1 Annex 1 – Results

Table 13 – Results of each patient on both groups.

			Loss at 2mm	Loss at 3mm	Loss at 4mm	Loss at 5 mm	Loss at 6mm
1	<b>EXPERIMENTAL</b>	25	2.1	0,9	0.7	0.6	0.7
2		15	1,7	0.8	0,5	0.2	0.02
3		15	2,4	1,5	0.8	0,7	0,3
		14 control	2,2	1,9	1.4	1,1	0.7
4		12	1,2	0	0	0	0
5		12	1.9	1.8	1.8	2,2	1.6
6		24	3.2	2.4	2.1	2.1	2.1
7		15	4.1	3.8	2.9	2.4	2.2
8	13	2.3	1.8	1.5	0.9	0.6	
	<b>CONTROL</b>						
1		24	2,2	1,3	1,3	0.5	0.3
2		11	3.0	2,7	2.0	1,8	1.7
3		25	3.3	2.5	2.1	2.0	0.5
4		21	4.1	3.5	2.9	3.4	2.8
5		22	5.0	4.4	4.4	3.7	3
6		23	4.4	3.8	3.8	3.4	2.9
7		24	3.7	3.1	3.1	2.7	2.2
8	14	2.4	1.5	0.7	0.7	0.3	

## 10.2 Annex 2 – Intra-oral photographs

The following patients are from the experimental group, who had also suffered other extractions on the anterior maxilla, thus helping to visualize and compare the differences between grafted sites and unassisted socket healing sites.



Figure 8 – Patient 3: Pre-extraction photograph of teeth 14 and 15. The alveolar socket of tooth 15 was grafted with Adbone®BCP.



Figure 9 – Patient 3: 3-month post-extraction photograph of teeth 14 and 15. The alveolar site of tooth 15 maintains buccal contour while the socket contour of tooth 14 has a soft tissue collapse being positioned more palatal.



Figure 10 – Patient 4: 3-month post-extraction frontal view photograph of the alveolar sites of teeth 12 and 21. The alveolar socket of tooth 12 was grafted with Adbone®BCP and maintains buccal contour while the alveolar site of tooth 21 has a soft tissue collapse being positioned more palatal.



Figures 11 and 12 – Patient 4: 3-month post-extraction side view photographs of the alveolar sites of teeth 12 and 21. The alveolar socket of tooth 12 was grafted with Adbone®BCP and maintains buccal contour while the alveolar site of tooth 21 has a soft tissue collapse being positioned more palatal.

### 10.3 Annex 3 – Radiographic Examinations

#### Annex 3.1 – Control Group – Patient 3:



Figure 13– Pre-extraction periapical radiograph.



Figure 14 –3-month follow-up post-extraction periapical radiograph.

Annex 3.2 – Experimental Group – Patient 8:



Figure 15– Pre-extraction periapical radiograph of tooth 13.



Figure 16– Immediate post-extraction periapical radiograph of grafted socket.

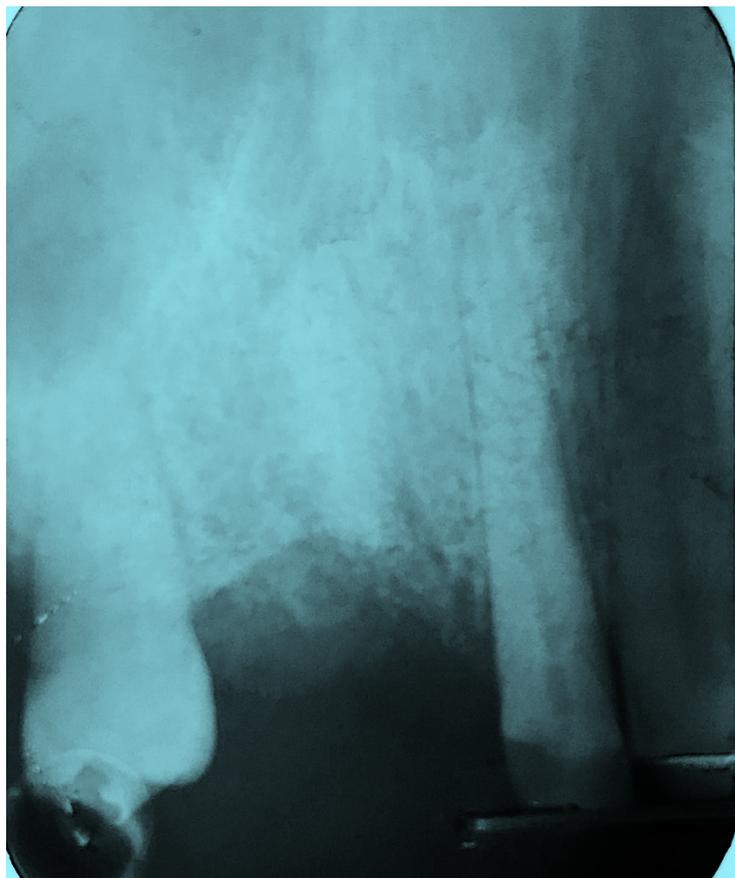


Figure 17– 3-month follow-up post-extraction periapical radiograph of grafted socket.

### 10.4 Annex 4 – 3D analysis on Control and Experimental Groups

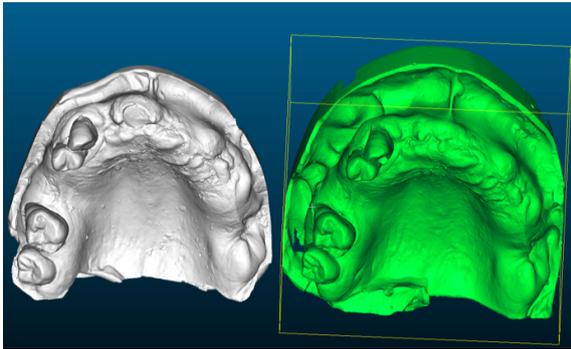


Figure 18 – 3D analysis comparing pre-extraction and 3-months post-extraction models on the Control Group

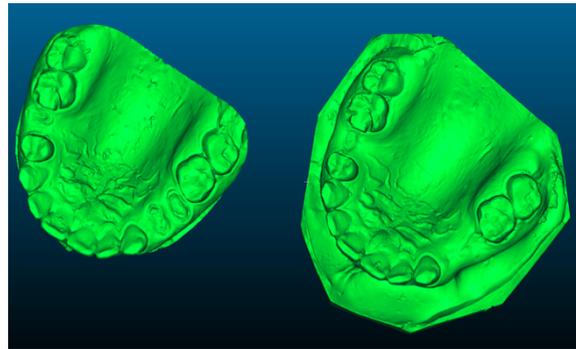


Figure 19 – 3D analysis comparing pre-extraction and 3-months post-extraction models on the Experimental Group

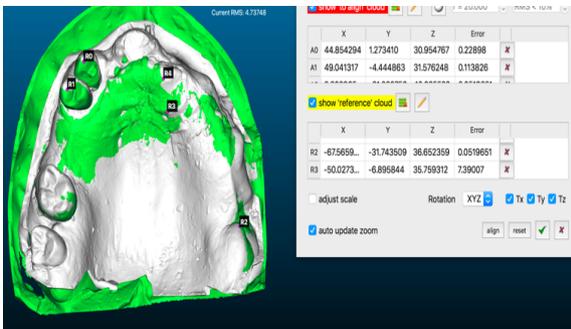


Figure 20 – 3D analysis on the Control Group

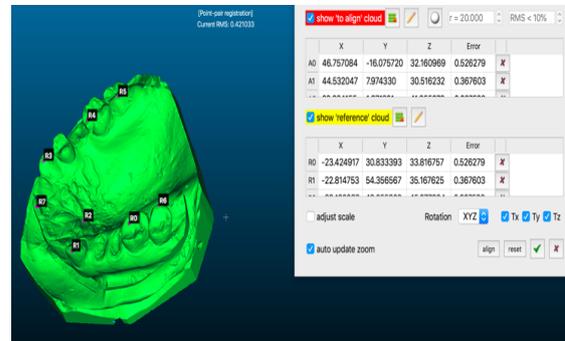


Figure 21 – 3D analysis on the Experimental Group

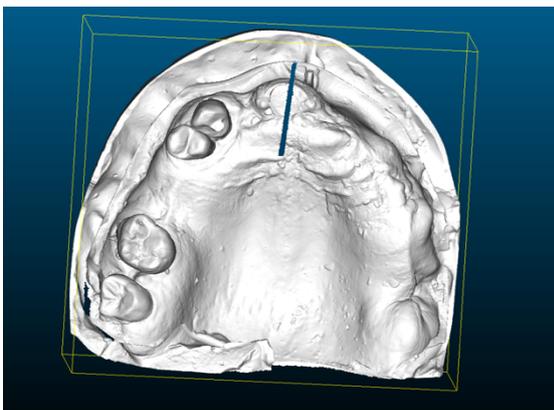


Figure 22 – 3D analysis of the buccolingual dimensions on the Control Group

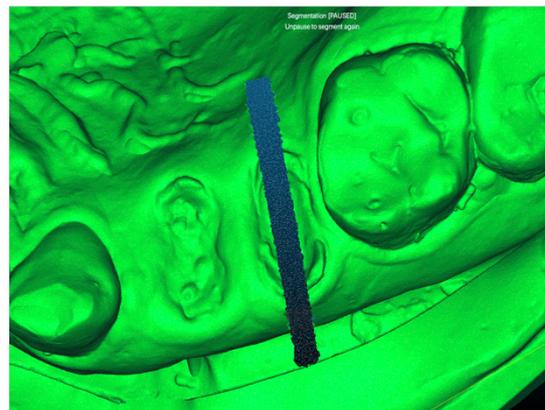


Figure 23 – 3D analysis of the buccolingual dimensions on the Experimental Group

