# INSTITUTO UNIVERSITÁRIO EGAS MONIZ

## MESTRADO INTEGRADO EM MEDICINA DENTÁRIA

# THE USE OF AUTOGENOUS TEETH FOR ALVEOLAR RIDGE PRESERVATION: A LITERATURE REVIEW

Trabalho submetido por
**João Pedro Alves Valadas de Lima Cenicante**
para a obtenção do grau de Mestre em Medicina Dentária

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Trabalho orientado por
**Mestre Alexandre Santos**


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***"With every mistake, we must surely be learning"***

*George Harrison, White Album, The Beatles*

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## Abstract

Following a tooth extraction, a cascade of biological events will lead inevitably to a decrease in the height and width of the alveolar ridge, mostly on the buccal side and horizontally. In this sense, given how often this procedure is performed in dental practice, it is pivotal that every clinician is acquainted with these dimensional changes and its possible impact on future oral rehabilitation.

Consequently, several treatment modalities, commonly known as Alveolar Ridge Preservation (ARP) are described in the literature and include: socket grafting, with the use of a bone graft material, guided tissue regeneration (GTR), with the use of a barrier membrane and finally guided bone regeneration (GBR) with the use both a bone graft material and a barrier membrane.

Currently, there are several options for bone graft materials available to the clinician, comprising autografts, allografts, xenografts and alloplasts, having each its advantages and drawbacks. The biological plausibility regarding the use of these biomaterials is that thanks to biological properties intrinsic to the grafts, the alveolar ridge resorption would decrease.

In the past decade, the use of autogenous teeth as a bone graft material has been described with encouraging results, nevertheless, describing distinct preparation protocols prior to the ARP procedure.

Therefore, this literature review aims to summarize all the evidence regarding the use of autogenous teeth as a bone graft material in ARP in post-extraction sockets, its several preparation protocols, efficacy and future perspectives.



**Keywords:** extracted teeth; autogenous tooth bone graft; demineralized dentin; bone regeneration

**Resumo**

Após qualquer exodontia, uma série de eventos biológicos conduzem inevitavelmente a uma redução ao nível da altura e largura do rebordo alveolar, principalmente na componente vestibular e horizontalmente. Desta forma, dada a frequência com que este procedimento é realizado na Medicina Dentária, é fulcral que qualquer clínico esteja informado destas alterações dimensionais e possível impacto numa futura reabilitação oral.

Consequentemente, diversas opções de tratamento, vulgarmente conhecido como Preservação da Crista Alveolar (PCA) foram descritas incluindo: regeneração óssea, através do uso de um enxerto ósseo, regeneração tecidular guiada (RTG), através do uso de uma membrana barreira e ainda regeneração óssea guida (ROG) com o uso de um enxerto ósseo associado uma membrana barreira.

Atualmente, existem diversas opções de enxertos ósseos disponíveis para o clínico, compreendendo autoenxertos, aloenxertos, xenoenxertos e aloplásticos, tendo cada um vantagens e limitações. A plausabilidade biológica destes biomateriais pode ser explicada devido a propriedades biológicas intrínsecas ao enxerto ajudando a minimizar a reabsorção óssea.

Na última década, o uso de dente autólogo como substituto ósseo tem sido descrito com resultados encorajadores, contudo, descrevendo protocolos de preparação distintos antes de realizar a PCA.

Desta forma, esta revisão de literatura procura resumir a evidência disponível relativamente ao uso de dente autólogo como substituto ósseo na PCA em alvéolos pós-extração, os diversos protocolos de preparação, eficácia e perspetivas futuras.

**Palavras-chave:** dentes extraídos; enxerto ósseo de dente autólogo; dentina desmineralizada; regeneração óssea

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## Abbreviation Index

**ARP |** Alveolar Ridge Preservation

**BC |** Blood Clot

**BM |** Bone Marrow

**BMP |** Bone Morphogenetic Protein

**CBCT |** Cone Beam Computerized Tomography

**CEJ |** Cementoenamel Junction

**DDM |** Demineralized Dentin Matrix

**DFDBA |** Demineralized Freeze-dried Bone Allograft

**d-PTFE |** High Density Polytetrafluoroethylene

**e-PTFE |** Expanded Polytetrafluoroethylene

**FDBA |** Freeze-dried Bone Allograft

**FGF |** Fibroblast Growth Factor

**FGM |** Free Gingival Margin

**GBR |** Guided Bone Regeneration

**GT |** Granulation Tissue

**GTR |** Guided Tissue Regeneration

**IGF |** Insulin-like Growth Factor

**ISQ |** Implant Stability Quotient

**KG |** Keratinized Gingiva

**LMP-1 |** Lim Mineralization Protein 1

**MB |** Mineralized Bone

**N/R |** Data not reported

**PDDM |** Partially Demineralized Dentin Matrix

**PDGF |** Platelet-derived Growth Factor

**PM |** Provisional Matrix

**PRF |** Platelet-rich Fibrin

**PRP |** Platelet-rich Plasma

**PTFE |** Polytetrafluoroethylene

**RhBMP-2 |** Recombinant human Bone Morphogenetic Protein-2

**RPPCTG |** Rotated Pedicle Palatal Connective Tissue Graft

**TGF- β |** Transforming Growth Factor β

**Ti-d-PTFE |** Titanium Reinforced High Density Polytetrafluoroethylene

**UDD |** Undemineralized Dentin Matrix

**VEGF |** Vascular Endothelial Growth Factor

**α-TCP |** Alpha-Tricalcium Phosphate

**β-TCP |** βeta-Tricalcium Phosphate

# I. INTRODUCTION

## 1. DYNAMICS OF HARD AND SOFT TISSUES FOLLOWING TOOTH EXTRACTION

### 1.1. Biological Effect of a Tooth Extraction

The primary goal of every clinician is to preserve the patient´s oral health assuring its function and/or aesthetics (Avila-Ortiz et al., 2014; Avila-Ortiz et al., 2019). When such goal is not possible, a tooth may be indicated for extraction (Horváth et al., 2013). This process generates a series of biological events that will threaten the homoeostasis of the socket, triggering a structural and dimensional shift (Avila-Ortiz et al., 2019).

With tooth extraction being a frequent procedure in dentistry, it is key that the clinician is aware of these biological events and the magnitude of these structural and dimensional changes, in order to make an informed decision and an appropriate treatment plan (Tan et al., 2012). In this sense, several studies focused on analyzing the structural and dimensional changes one may expect following tooth extraction (Amler, 1969; Araújo & Lindhe, 2005; Cardaropoli et al., 2003; Tan et al., 2012; Van Der Weijden et al., 2009).

One key aspect when studying the dynamics of alveolar bone and its relationship with the tooth is that these entities are interdependent (Marks & Schroeder, 1996). Therefore, the volume and shape of the alveolar bone will be determined by the tooth´s form and axis of eruption (Araújo & Lindhe, 2005; Tan et al., 2012; Van Der Weijden et al., 2009).

Already in 1969, Amler investigated the time sequence of tissue regeneration in human extraction wounds, reaching conclusions that to this day are still a reference when addressing this subject (Amler, 1969). Amler (1969) described several stages of the post-extraction healing period that marked important changes in the socket composition such as: formation of the blood clot, replacement of the clot with granulation tissue, replacement of the granulation tissue with connective tissue, epithelization and finally bone tissue formation (Amler, 1969).

More recent investigations allowed to have a more concise and accurate perspective regarding these stages (Araújo & Lindhe, 2005; Cardaropoli et al., 2003).

Within the first 24 hours following a tooth extraction, a blood clot is formed, composed mainly of erythrocytes and platelets placed in a network of fibrin (Cardaropoli et al.,

2003). The Periodontal ligament cells alongside the bundle bone of the socket will progressively disappear, as bone tissue is formed (Cardaropoli et al., 2003).

Within the first week of healing, this blood cloot will gradually be replaced with provisional matrix in the medium and apical thirds of the socket (Araújo & Lindhe, 2005; Cardaropoli et al., 2003). This provisional matrix is comprised of fibroblasts, newly formed vessels, collagen fibers, immature mesenchymal cells as well as leukocytes (Araújo & Lindhe, 2005; Cardaropoli et al., 2003). Interestingly, in the coronal third, both Cardaropoli et al. (2003) and Araújo & Lindhe (2005) reported the formation of a granulation tissue, containing vessels and inflammatory cells. This mechanism can be seen as a protective barrier to the oral cavity, in order to prevent the contamination of the socket, allowing its healing (Cardaropoli et al., 2003). This granulation tissue formation is corroborated by the animal studies by Araújo, et al. (1997) who reported the appearance of this tissue within two weeks of healing (Araújo et al., 1997). As the healing period progresses, the granulation tissue will eventually disappear due to the formation of a keratinized epithelium (Cardaropoli et al., 2003).

After two weeks of healing, it was found newly formed bone in the medium and apical thirds of the socket (Araújo & Lindhe, 2005; Cardaropoli et al., 2003). Cardaropoli et al. (2003) reported that while 50% of medium and apical thirds were comprised of woven bone, in the coronal third only 15% of woven bone was found (Cardaropoli et al., 2003). This difference can be explained by the direct contact initially with the oral cavity (Cardaropoli et al., 2003).

It is a consensus that both the periodontal ligament cells and bundle bone will gradually disappear (Araújo & Lindhe, 2005; Cardaropoli et al., 2003), nonetheless, one particular study by Lin et al. (1994) highlighted the importance that the periodontal ligament cells have in bone tissue formation. Through cell labelling technique, Lin et al. (1994) discovered that periodontal ligament cells, following tooth extraction, proliferate and migrate to the blood clot and differentiate into osteoblasts, thus becoming involved in bone tissue formation (Lin et al., 1994).

At four weeks of healing, the provisional matrix is located in the most center regions of the socket, with bone marrow and woven bone occupying the more peripheral sites (Araújo & Lindhe, 2005). At this time, approximately, the process of corticalization reaches a decisive stage (Ohnishi et al., 2000). This process includes not only the

formation of woven bone, but also its removal and replacement with lamellar bone, granting the socket with an enhanced mechanical stability (Cardaropoli et al., 2003; Ohnishi et al., 2000). This process will lead to the formation of a stable periosteum, allowing an attachment between the mucosa and the cortical bone (Cardaropoli et al., 2003).

As the healing period advances, the percentage of woven bone decreases as it is replaced by lamellar and bone marrow (Araújo & Lindhe, 2005). Cardaropoli et al. (2003) reports that while at day 30 the mineralized bone occupies 80%, at day 180 the percentage decreases to 15%. On the other hand, the bone marrow reaches 75% at day 60 and 85% on day 180 (Cardaropoli et al., 2003).

A summarize of these structural changes in the alveolar socket composition can be found in table 1.

| Healing Period | Alveolar Socket Composition |
|---|---|
| 24 hours | BC + GT |
| 1 week | BC + GT + PM |
| 2 weeks | GT + PM + BM |
| 4 weeks | MB + BM |
| 30 days to 180 days | Decrease of MB and Increase of BM |

**Table 1 | Alveolar socket composition following tooth extraction**

Alveolar socket composition throughout the healing period (BC: blood clot; GT: granulation tissue; PM: provisional matrix; MB: mineralized bone (woven bone, parallel fibered bone and lamellar bone); BM: bone marrow) (Araújo & Lindhe, 2005; Cardaropoli et al., 2003).

## 1.2. Alveolar Bone Dimensional Changes

The alveolar bone dimensional changes following a tooth extraction is reported in literature accordantly. Although the dimensional percentages may vary from study to study, a tooth extraction inevitably causes alveolar bone loss both in the horizontal and vertical widths (Botticelli et al., 2004; Tan et al., 2012; Van Der Weijden et al., 2009).

Regardless of the treatment plan, alveolar bone loss after tooth surgery is inevitable, with a reduction in height and width, mainly on the buccal side and horizontally (Tan et al., 2012; Van Der Weijden et al., 2009). One possible reason, accordingly to Araújo & Lindhe (2005), is that the crestal of the buccal bone has a larger percentage of bundle

bone, a tooth-dependent tissue, which will necessarily lose its function and disappear (Araújo & Lindhe, 2005).

These dimensional changes can be seen mainly in the first 3 months, nonetheless, they last until one year after the surgery (Schropp et al., 2003). This process will generate a narrower and shorter ridge, shifting it to a more palatal/lingual position (Botticelli et al., 2004; Pinho et al., 2006).

The assessment of alveolar bone loss in a patient can gain a more complex approach when, associated with a tooth indicated for extraction, there is already periodontal, endodontic and/or traumatic lesion (Van Der Weijden et al., 2009).

Notwithstanding, the repercussions of a tooth extraction also affects the soft tissues (Tan et al., 2012; Van Der Weijden et al., 2009). After a tooth extraction, the socket is left to heal by secondary intention, which will result in a cell proliferation, leading to an increase in soft tissue thickness (Tan et al., 2012; Van Der Weijden et al., 2009). One particular study assessed a soft tissue thickness increase of 0.4 to 0.5 mm, 6 months following tooth extraction (Iasella et al., 2003). When compared to the test group, where alveolar ridge preservation was performed using a freeze-dried bone allograft and a collagen membrane, the soft tissue thickness presented a decrease of 0.1 to 0.6 mm (Iasella et al., 2003). According to the authors, such results can be explained due to the interposition of the membrane between the bone surface and the soft tissue, affecting the vascular supply (Iasella et al., 2003).

Regarding vertical dimensional change, Barone et al. (2008) reported, with a 7 month follow up after tooth extraction, a height loss of 3.0 and 3.6 mm lingual/buccal, 0.4 and 0.5 mm mesial/distal, respectively (Barone et al., 2008). Such difference can be explained by the presence of adjacent teeth, which as previously stated, thanks to the interdependent relationship between alveolar bone and teeth, causes a more pronounced bone loss in the lingual/buccal walls than in the mesial/distal walls (Barone et al., 2008; Marks & Schroeder, 1996). Nevertheless, a systematic review performed by Tan et al. (2012), with a follow up period of up to 12 months, reported a bone loss of 1.24 ± 0.11 mm in buccal sites, 0.84 ± 0.62 mm on mesial sites and 0.80 ± 0.71 mm on distal sites. In terms of percentage of vertical dimensional change in the buccal plate the values ranged from 11% to 22% at 6 months follow-up (Tan et al., 2012).

Concerning horizontal dimensional change, two systematic reviews, Tan et al. (2012) and Van Der Weijden et al. (2011) reached similar results, reporting a horizontal hard tissue loss of 3.79 ± 0.23 mm and 3.87 mm, respectively, with follow-up periods varying from 3 to 12 months (Tan et al., 2012; Van Der Weijden et al., 2009). Hence, it can be expected to have a horizontal loss that may range from 29 to 63% at 6 to 7 months (Tan et al., 2012).

Due to the devastating consequences that a simple tooth extraction can have in the soft and hard tissues, the clinician should be not only mindful of the magnitude of these repercussions, but also able to develop a strategy to help minimize the consequences of this procedure, aiming to restore the health, function and/or aesthetics of the patient (Avila-Ortiz et al., 2014; Avila-Ortiz et al., 2019; Bassir et al., 2018; Ten Heggeler et al., 2011; Vignoletti et al., 2012).

### 1.3. Surgical Approach during Tooth Extraction and Role-playing Factors

Several factors can play a decisive role in terms of dimensional loss that hard and soft tissues suffer following a tooth extraction (Tan et al., 2012; Van Der Weijden et al., 2009). One particular aspect that is not usually the focus of studies is the surgical approach during the tooth extraction, prior to alveolar ridge procedures (Barone et al., 2013).

A key aspect to the clinician when dealing with a tooth extraction is trying to be as conservative and atraumatic as possible (Jambhekar et al., 2015). This approach can be useful in minimizing the inherent alveolar dimensional loss, specially in cases where there is also endodontic or periodontal lesions (Van Der Weijden et al., 2009) or an absence of alveolar walls (Iasella et al., 2003). The surgical trauma during tooth extraction as well as the length of the surgery also plays a role, being able to accentuate the bone loss (Adeyemo et al., 2007; Bartee, 2001a). All of these factors should be considered in the treatment plan of the clinician and informed to the patient providing a meticulous prognostic (Iasella et al., 2003).

Before starting the surgery, it is important to complete a strict and comprehensive clinical and radiographic examination (Kubilius et al., 2012). Aspects such as proximity to important anatomic structures (e.g., mandibular canal, sinus floor), complex root anatomy, alterations in the periodontal ligament space as well as other tooth related

features (e.g., filling materials and carious lesions) are essential when planning any surgery (Kubilius et al., 2012).

The results of one prospective study performed by Adeyemo et al. (2007) emphasizes the need for this prior assessment (Adeyemo et al., 2007). These authors assessed the most common trans-operative complications during tooth extraction (Adeyemo et al., 2007). As demonstrated in figure 1, the main complications were: root fractures (44.76%), crown fractures (34.21%) and alveolar bone fractures (2.63%) (Adeyemo et al., 2007).

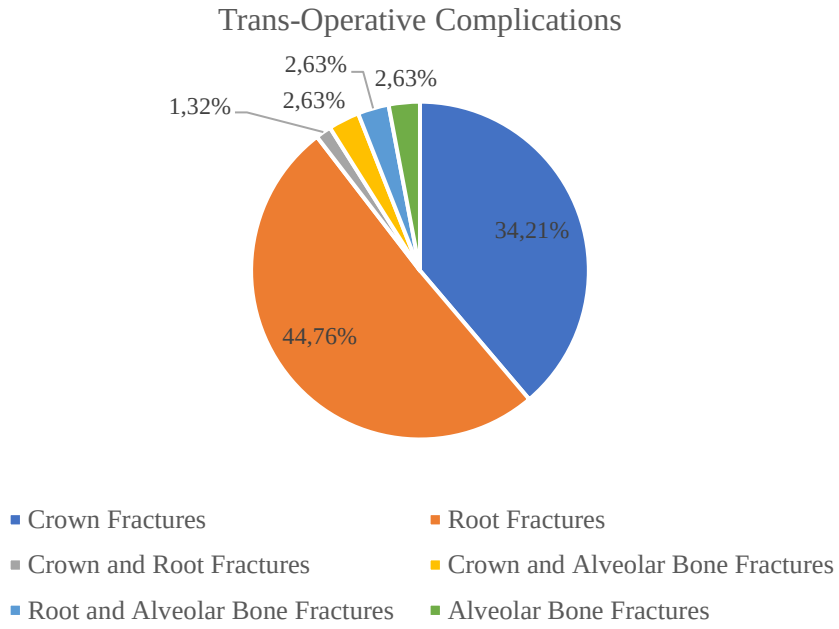


**Figure 1 | Most common trans-operative complications during tooth extraction**

Distribution of the most common trans-operative complications reported in Adeyemo et al.´s study (2007). The prospective study included 301 teeth indicated for extraction of which 73 (24,25 %) presented trans-operative complications (adapted from Adeyemo et al., 2007).

Regarding the surgical approach, the process begins with the loosening of the soft tissue around the tooth (Kubilius et al., 2012). Such step can be done using a scalpel or a periotome, through push-pull movements, in order to reduce the damage on the soft tissues (Belle De Oliveira et al., 2005). Finally, the tooth luxation and extraction can be performed using forceps or elevators (Kubilius et al., 2012). In this phase it is important to bear in mind that we should protect the alveolar bone as much as possible (Kubilius et al., 2012). After the removal of the tooth, the removal of the remaining periodontal ligament and infected soft tissues can be performed with a carefully selected periapical curette (Bartee, 2001b; Kubilius et al., 2012). If not performed correctly, the presence of

infected tissue may lead to post-operative complications, which will compromise the desirable outcome (Bartee, 2001b).

One frequent question to which a definitive conclusion can not still be drawn is whether to perform a muco-periosteal flap versus a flapless technique after the alveolar ridge preservation procedure (Barone et al., 2013, 2015).

The flap technique was designed to allow the socket to heal through primary intention, and in this way covering the membrane, when used (Barone et al., 2015). Although it was reported initially that wound dehiscence and membrane exposure could lead to a decrease in bone formation and infection, recent studies, reported that the exposure of membranes did not affected the outcome of guided bone regeneration procedures (Barone et al., 2015; Cardaropoli & Cardaropoli, 2008).

Nonetheless, the choice between flap versus flapless technique is controversial, with the literature being divided. On one hand, one particular study referred that the approach used (flap versus flapless) did not influence the dimensional changes in a 6 months observation experimental study (Araújo & Lindhe, 2009). On the other hand, several studies point to the opposite conclusion (Araújo et al., 2015; Barone et al., 2013, 2015; Engler-Hamm et al., 2011; Fickl et al., 2009).

The premise behind the worse results of the flap approach is that through a muco-periosteal flap, the bone loses the vascular supply, thus leading to a more marked resorption in the buccal plate (Barone et al., 2015). Furthermore, the preservation of more keratinized tissue as well as the less post-operative discomfort in the flapless technique was also reported as advantages towards the flapless technique (Barone et al., 2013; Engler-Hamm et al., 2011). One interesting result was found in a randomized clinical trial where after an histological and histomorphometric analysis, there were no differences in terms of quality of bone regeneration when comparing the flap group versus the flapless group in alveolar ridge preservation procedures (Barone et al., 2015).

Additionally, there are other possible factors that may affect the dimensional change following tooth extraction and deserve the clinician´s attention (Tan et al., 2012; Van Der Weijden et al., 2009). Systemic factors which include the patient´s health can increase alveolar bone loss (e.g., osteoporosis, renal disease, vascular and endocrine disorders) (Bartee, 2001a). General habits such as smoking can have a devastating impact on the dimensional changes of the alveolar bone (Saldanha et al., 2006). Although the specific

mechanism through which tobacco affects healing is not fully understood so far, the main component of tobacco, nicotine, is known to be a cytotoxic and vasoconstrictive substance (Saldanha et al., 2006). In this sense, it can be expected that smokers show a 0.5 mm loss in alveolar bone reduction when compared to non-smokers (Van Der Weijden et al., 2009).

Notwithstanding, local factors such as the reasons behind the extraction indication, integrity of the alveolar socket and tissue phenotype have been described as important aspects that can compromise the final architecture of the alveolar bone and soft tissues (Chen et al., 2004). One interesting aspect was studied by Moya-Villaescusa & Sánchez-Pérez (2010) who compared the dimensional changes between single-rooted versus multiple-rooted teeth (Moya-Villaescusa & Sánchez-Pérez, 2010). After 3 months following tooth extraction, there was no significant difference when comparing the height of bone loss (single-rooted: 4.16 mm, multiple-rooted: 4.48 mm) (Moya-Villaescusa & Sánchez-Pérez, 2010). Another local factor which might be of help during the post-operative period is a regular rinsing with a chlorhexidine solution, as reported by two systematic reviews (Horváth et al., 2013; Van Der Weijden et al., 2009).

Functional factors are also worthy of mention since forces due to bruxism, complete denture wear and heavy bite forces were reported as able to influence bone resorption (Bartee, 2001a).

### 1.4.Classification and Clinical Management of Extraction Sockets

Following a tooth extraction, there are several treatment options in order to perform an implant-supported restoration (El Chaar et al., 2016). The clinical management can vary from case to case, ranging from a simple protocol to a more complex staged approach (Caplanis et al., 2005).

In this sense, in order to easily communicate, gather information, and apply the evidence in order to better reach a comprehensive treatment plan that fulfills both the patient and clinician´s goal, an extraction socket classification can be essential (Caplanis et al., 2005; El Chaar et al., 2016; Juodzbalys et al., 2019). In the literature, there can be found several classifications that although vary in terms of parameters assessed, have the intention of serving as a clinical guide in assisting the clinician upon choosing the most adequate

treatment modality (Caplanis et al., 2005; Chu et al., 2015; El Chaar et al., 2016; Elian et al., 2007; Juodzbalys et al., 2008; Smith & Tarnow, 2013).

In general, there seems to be a consensus between the several alveolar socket classifications that both the quality and quantity of soft tissues and the buccal hard tissues are key factors when assessing the long-term healing (Elian et al., 2007; Juodzbalys et al., 2019).

In 2005, Caplanis et al. presented the Extraction Defect Sounding Classification (Caplanis et al., 2005). This classification assessed visually the amount of socket walls affected and the amount of hard tissue lost, using as a guide for the future restoration a surgical template (Caplanis et al., 2005). The distance between the soft tissue and the crestal bone seems to be essencial in the sense that the risk of soft tissue recession is proportional to the distance between these two entities (Caplanis et al., 2005; Juodzbalys et al., 2008). Regarding soft tissues, this classification also divides the periodontal phenotype into two categories: thick and thin (Caplanis et al., 2005). The thick phenotype is usually associated with wide and short teeth, showing a higher resistance to resorption and therefore, having a better prognostic in this type of procedure (Caplanis et al., 2005). On the other hand, the thin phenotype, more associated with long and narrow teeth, are more prone to suffer recession when exposed to surgical procedures and tissue manipulation (Caplanis et al., 2005; El Chaar et al., 2016). The difference between these two phenotypes is not purely mechanical, since the thick phenotype shows less discoloration due to the implant-body show-through (El Chaar et al., 2016). Consequently, a soft tissue assessment is fundamental and can affect the outcome of the restoration due to mechanical and aesthetic reasons (Caplanis et al., 2005; El Chaar et al., 2016).

In 2007, Elian et al. proposed a simplified classification for the aesthetic region (Elian et al., 2007). In this classification, the alveolar sockets are divided into three categories according to the buccal bone level and the facial soft tissue level (Elian et al., 2007).While type I sockets present both the buccal plate and facial soft tissue at standard levels as regards to the cementoenamel junction, in type II sockets, the buccal plate is partially absent (Elian et al., 2007). Moreover, type III sockets presents both the buccal plate and the facial soft tissue partially missing (Elian et al., 2007). Regarding this particular classification, Chu et al. (2015) suggested a subclassification of the type II sockets (facial soft tissue present but partial absence of the buccal bone plate). This subclassification distinguishes the amount of buccal bone plate loss into coronal third, coronal and middle

third and finally the absence of coronal, middle and apical third (Chu et al., 2015). The reason for this subclassification, according to the authors, is that the type II sockets, as presented by Elian et al. (2007), incorporated several clinical scenarios with different prognosis and possible estethic outcomes depending of the size, extent and shape of the bony defect (Chu et al., 2015).

In 2008, a comprehensive classification performed by Juodzbalys et al. was presented (Juodzbalys et al., 2008). This classification included quantitative and qualitive measurements of both soft and hard tissues (Juodzbalys et al., 2008). Regarding soft tissues, it is included not only the periodontal phenotype, but also the soft tissue contour variations, vertical deficiency, keratinized gingival width, papilla appearance according to the classification reported by Nordland & Tarnow (1998) as well as the color, consistency and contour of the tissue (Juodzbalys et al., 2008; Nordland & Tarnow, 1998). In terms of hard tissue evaluation, a comprehensive assessment is also made. Parameters such as the alveolar process height, bone available beyond the apex, labial bone vertical position, buccal bone thickness, presence of socket bone lesions, intradental bone peak height, mesiodistal distance and palatal angulation are included (Juodzbalys et al., 2008).

A classification for posterior sockets was presented in 2013 by Smith & Tarnow (Smith & Tarnow, 2013). This classification presents three types of socket according to the morphology of the septal bone and its role in implant stability (Smith & Tarnow, 2013). This classification does not specify any soft tissue parameters (Smith & Tarnow, 2013).

Finally, Chaar et al. (2016) proposed a classification based essentially on three hard tissue parmeters: buccal plate loss, apical topography and interproximal bone loss (El Chaar et al., 2016). As previously stated, the thickness and quality of the buccal plate is critical to the success of any future restoration, since a thin buccal plate is more prone to resorb and cause pronounced dimensional changes (Caplanis et al., 2005; El Chaar et al., 2016; Elian et al., 2007). In terms of the apical topography, this factor will determine the shape and contour of the alveolar socket, limiting the treatment modalities accordingly (El Chaar et al., 2016). Finally, the level of the interproximal bone is key in dictating the presence or absence of the papilla and therefore have a pivotal role in the aesthetic outcome (El Chaar et al., 2016). Nonetheless, this classification also includes a periodontal phenotype (thick or thin) assessment (El Chaar et al., 2016).

A detailed description concerning the several parameters of each classification, types of alveolar socket and the treatment modality suggested by the authors can be found in table 2 and table 3.

| Study | Year | Hard Tissue Evaluation | Soft Tissue Evaluation |
|---|---|---|---|
| Caplanis et al. | 2005 | • Affected socket walls<br>• Amount of bone loss<br>• Distance from the alveolar bone to restorative margin of the surgical template | • Periodontal phenotype (Thick or Thin) |
| Elian et al. | 2007 | • Buccal bone plate | • Facial soft tissue level |
| Juodzbalys et al. | 2008 | (Parameters were graded adequate, compromised or deficient)<br>• Alveolar process height (≥10 mm, 8 to 10 mm, ≤8 mm)<br>• Bone beyond the apex (≥4 mm, 3 to 4 mm <3mm)<br>• Labial bone vertical position (≤ 3 mm, 3 to 7 mm, ≥7 mm)<br>• Buccal bone thickness (≥2 mm, ≥1 to <2mm, <1mm)<br>• Presence of socket bone lesions<br>• Intradental bone peak height (3 to 4 mm, ≥1 mm to <3 mm, <1 mm)<br>• Mesiodistal distance ( ≥7 mm, >5 to <7 mm, ≥5 mm) | (Parameters were graded adequate, compromised or deficient)<br>• Soft tissue contour (no gap, <2 mm, ≥2 mm)<br>• Vertical soft tissue deficiency (0, 1 to 2 mm, >2 mm)<br>• KG width on the mid-buccal side of the socket (≥2 mm, 1 to 2 mm, <1 mm)<br>• Mesial and distal papilla (Class I, Class II, Class III) (Nordland & Tarnow, 1998)<br>• Gingival tissue phenotype (≥2 mm, 1 to 2 mm, <1 mm)<br>• Soft tissue quality |

| | | | |
|---|---|---|---|
| | | • Palatal Angulation (<5º, 5º to 30º, >30º) | |
| Smith & Tarnow | 2013 | • Coverage of the immediately placed dental implant by the septal bone | N/R |
| Chu et al. | 2015 | (Subclassification of Elian et al.´s study)<br>• Buccal bone plate | (Subclassification of Elian et al.´s study)<br>• Facial soft tissue level |
| El Chaar et al. | 2016 | • Buccal plate loss<br>• Apical topography<br>• Interproximal bone level | • Periodontal phenotype (Thick or Thin) |

**Table 2 | Parameters assessed by the several post-extraction sockets classifications**

A summarized description of the parameters used by each author to elaborate their alveolar socket classification (KG: keratinized gingiva; N/R: data not reported) (Caplanis et al., 2005; Chu et al., 2015; El Chaar et al., 2016; Elian et al., 2007; Juodzbalys et al., 2008; Smith & Tarnow, 2013).

| Study | Year | Classification | Treatment Recommendation |
|---|---|---|---|
| Caplanis et al. | 2005 | **EDS-1:**<br>• 0 socket walls affected<br>• 0 mm of hard tissue loss<br>• Distance from the alveolar bone to restorative margin of the surgical template: 0 to 3 mm<br>• Phenotype: Thick<br>**EDS-2:**<br>• 0 to 1 socket wall affected<br>• 0 to 2 mm hard tissue loss<br>• Distance from the alveolar bone to restorative margin of the surgical template: 3 to 5 mm<br>• Phenotype: Thick or Thin | **EDS-1:** Immediate implant (one-stage)<br>**EDS-2:** Site preservation or immediate implant (one or two-stage) |

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| | | **EDS-3:**<br>• 1 to 2 socket walls affected<br>• 3 to 5 mm hard tissue loss<br>• Distance from the alveolar bone to restorative margin of the surgical template: 6 to 8 mm<br>• Phenotype: Thick or Thin<br>**EDS-4:**<br>• 2 to 3 socket walls affected<br>• ≥6 mm hard tissue loss<br>• Distance from the alveolar bone to restorative margin of the surgical template: ≥6 mm<br>• Phenotype: Thick or Thin | **EDS-3:** Site preservation then implant placement (two-stage)<br>**EDS-4:** Site preservation, site development and finally implant placement (three-stage) |
| Elian et al. | 2007 | **Type I:**<br>• The buccal bone plate and facial soft tissue level are at normal levels regarding the CEJ before and after extraction<br>**Type II:**<br>• The facial soft tissue is present, however the buccal bone plate is partially missing after tooth extraction<br>**Type III:**<br>• Both the facial soft tissue and buccal bone plate are clearly reduced | **Type I:** N/R<br>**Type II:** GBR using a collagen membrane and mineralized cancellous freeze-dried bone allograft<br>**Type III:** N/R |

| | | | |
|---|---|---|---|
| | | following tooth extraction | |
| Juodzbalys et al. | 2008 | **Type 1:**<br>• All parameters were graded adequate<br>**Type 2:**<br>• At least one parameter was graded compromised<br>**Type 3:**<br>• At least one parameter was graded deficient | **Type 1:** immediate implant placement<br><br>**Type 2:** immediate or delayed implant placement with soft and hard tissue augmentation suggested<br><br>**Type 3:** Delayed implant placement after soft and hard tissue augmentation. Orthodontic treatment might be indicated |
| Smith & Tarnow | 2015 | **Type A:**<br>• There is an adequate amount of septal bone capable of covering the coronal portion of the implant<br>**Type B:**<br>• There is an adequate amount of septal bone capable of stabilizing the implant, but not fully contain the coronal portion of the implant<br><br>**Type C:**<br>• There is not enough septal bone to stabilize the implant without engaging the outer walls of the socket | **Type A:** Immediate implant placement. Bone grafting might be indicated in specific cases<br><br>**Type B:** Immediate or delayed implant placement with bone grafting procedures<br><br>**Type C:** Implant placement might not be indicated. In cases where possible, implants with increased width are necessary, in order to achieve implant stability |
| Chu et al. | 2015 | (Subclassification of Elian et al.´s study)<br>**Type 2A:**<br>• Absence of the coronal third of the buccal bone | (Subclassification of Elian et al.´s study)<br>Immediate implant placement and GBR procedure using a resorbable membrane, bone graft with a custom-healing abutment |

| | | | |
|---|---|---|---|
| | | plate (5 to 6 mm from the FGM)<br>**Type 2B:**<br>• Absence of the coronal and middle thirds of the buccal bone plate (7 to 9 mm from the FGM)<br>**Type 2C:**<br>• Absence of the coronal, middle and apical thirds of the buccal bone plate (≥10 mm) | |
| El Chaar et al. | 2016 | **Grade I:**<br>• <25% buccal plate loss<br>• Adequate interproximal bone (0 to 2 mm periodontal bone loss on the adjacent teeth)<br>• Adequate apical topography (enough bone apically to allow an engagement of 3 to 4 mm of a correctly positioned immediate implant placement)<br>**Grade II:**<br>• 25% to 50% of buccal plate loss<br>• Adequate interproximal bone (0 to 2 mm periodontal bone loss on the adjacent teeth)<br>• Adequate apical topography (enough bone apically to allow an engagement of 3 to 4 mm of a correctly positioned immediate implant placement)<br>• Thick/Thin phenotype | **Grade I:** Immediate implant placement with possible provisionalization as well as bone grafting procedure<br><br>**Grade II:**<br>**Thick phenotype:** Immediate implant placement. A bone grafting procedure using a bone graft and a membrane is indicated.<br>**Thin phenotype: Maxilla:** ARP procedure with bone graft using RPPCTG; **Mandible:** ARP procedure with bone graft<br><br>**Grade III:**<br>**Proximal bone loss with or without buccal plate loss:**<br>**Maxilla:** ARP procedure with bone graft using RPPCTG; **Mandible:** ARP procedure with bone graft<br>Delayed implant placement<br>**Or**<br>Forced eruption (reevaluation of the socket´s classification after orthodontic treatment) |

| | | | |
|---|---|---|---|
| | | **Grade III:**<br>• >50% of buccal plate loss<br>• Inadequate interproximal bone<br>• Inadequate apical topography | **Inadequate apical topography:** Ridge Augmentation and delayed implant placement |

**Table 3 | Types of post-extraction sockets according to each classification and respective treatment recommendation**

A summarized description of the classification and suggested treatments by each author (EDS: extraction defect sounding; CEJ: cementoenamel junction; GBR: guided bone regeneration; N/R: data not reported; FGM: free gingival margin; ARP: alveolar ridge preservation; RPPCTG: rotated pedicle palatal connective tissue graft) (Caplanis et al., 2005; Chu et al., 2015; El Chaar et al., 2016; Elian et al., 2007; Juodzbalys et al., 2008; Smith & Tarnow, 2013).

## 2. ALVEOLAR RIDGE PRESERVATION

### 2.1. Concept and Current Evidence

With the constant development of modern dentistry, it is important to every clinician to understand the biology behind every procedure performed to develop progressively more predictable and successful results (Avila-Ortiz et al., 2014).

As previously stated, a tooth extraction causes a series of biological events that can lead to pronounced alveolar dimensional changes (Avila-Ortiz et al., 2014; Horváth et al., 2013; Troiano et al., 2017). These changes, more prominent horizontally and on the buccal side (Tan et al., 2012; Van Der Weijden et al., 2009), can pose a challenge to the clinician regarding rehabilitation, since both soft and hard tissues are affected following a tooth extraction (Bassir et al., 2018; Stumbras et al., 2019; Vignoletti et al., 2012).

With bone quantity and quality being the paramount of implant therapy, this dimensional loss can have an impact on the final outcome, since the placement of a dental implant should be placed in an ideal three-dimensional position (Chan et al., 2013; Iocca et al., 2017; Troiano et al., 2017). This led the investigators to try and find a possible solution to overcome this obstacle.

In this sense, in order to attempt to arrest these alveolar dimensional changes, several treatment modalities have emerged in the last 20 years with the purpose of preserving or, in some cases, even increase the alveolar ridge dimensions and soft tissues contours, with

the intention of obtaining a functional and aesthetic outcome (De Risi et al., 2015; Ten Heggeler et al., 2011; Vittorini Orgeas et al., 2013).

The commonly used term alveolar ridge preservation is usually used for procedures who prevent and maintain the alveolar socket dimensions adequately in order to allow a dental implant placement in its ideal position (Horváth et al., 2013). Nonethelless, the term itself, according to some authors, is a misnomer and broad (Bassir et al., 2018; Jambhekar et al., 2015). The reason for this claim is that the term preservation implies the maintenance of the socket in its original state, which is not desirable (Jambhekar et al., 2015). This term is also vague in the sense that it includes several possible interventions, which consequently difficult the systematic review of all the available evidence (Bassir et al., 2018).

Every alveolar ridge preservation procedure comprises essentially three goals: (1) the preservation of the existing soft and hard tissues, (2) the maintenance of a stable ridge volume in order to achieve an aesthetic and functional outcome, and (3) the simplification of the procedures following the alveolar ridge preservation (De Risi et al., 2015).

According to a systematic review performed by Stumbras et al. (2019), the literature available does not have a clear answer when it comes to indications for this sort of procedure (Stumbras et al., 2019). Notwithstanding, Juodzbalys et al. (2019) in a systematic review published in the same year proposed a clinical decision tree based on three reasons: aesthetic, functional and risk related (Juodzbalys et al., 2019). The first group indicates cases where it is impossible to reach a satisfying aesthetic result (Juodzbalys et al., 2019). The functional indication is when the implant primary stability is not achieved (Juodzbalys et al., 2019). Finally, the risk related group refers to risks such as: marked alveolar ridge resorption, maxillary sinus perforation and need for elevation of the sinus floor, nasal floor perforation and need for elevation of the nasal floor (Juodzbalys et al., 2019).

Several treatment modalities have appeared with the purpose of preserving the architecture of the alveolar ridge (Troiano et al., 2017). In this sense, possible interventions include: socket grafting, through the use of a biomaterial, guided tissue regeneration (GTR), through the use of a barrier membrane, and finally guided bone regeneration (GBR) wich involves the use of both a bone graft material associated with a barrier membrane (Avila-Ortiz et al., 2014; Avila-Ortiz et al., 2019; Barallat et al., 2014;

Chan et al., 2013; De Risi et al., 2015; Horváth et al., 2013; Jambhekar et al., 2015; Ten Heggeler et al., 2011; Troiano et al., 2017; Vittorini Orgeas et al., 2013).

Regarding the various bone substitutes available for the clinician, materials such as autogenous grafts (e.g. autogenous bone), allografts, xenografts, alloplasts as well as other materials (e.g. bone morphogenetic proteins, platelet-rich plasma) are described in the literature (Avila-Ortiz et al., 2014; Avila-Ortiz et al., 2019; Barallat et al., 2014; Chan et al., 2013; De Risi et al., 2015; Horváth et al., 2013; Jambhekar et al., 2015; Kim et al., 2017; Li et al., 2018; Ten Heggeler et al., 2011; Troiano et al., 2017; Vittorini Orgeas et al., 2013). The hypothesis behind the use of these biomaterials is that due to certain biological properties inherent to the grafts, the alveolar ridge dimensional loss that occurs in natural healing would decrease (Horváth et al., 2013).

In terms of the use of a barrier membrane, the premise behind their use is to selectively exclude a specific type of cells, such as epithelial and connective tissue in order to enhance bone formation (Chan et al., 2013; Horváth et al., 2013). Despite the type of barrier membrane used in Alveolar Ridge Preservation (ARP), several criteria must be met such as: biocompability, cell-occlusivity, space making function in order to allow tissue ingrowth, clinical handling properties and tissue integration (Hämmerle & Jung, 2003; Rakhmatia et al., 2013; Sheikh et al., 2017). The barrier membranes used for this procedure comprises resorbable and nonresorbable (Troiano et al., 2017).

Nonresorbable membranes are extensively described in the literature, with the most commonly used being polytetrafluoroethylene (PTFE) which can be divided into expanded PTFE (e-PTFE), high density PTFE (d-PTFE) and titanium reinforced high density PTFE (Ti-d-PTFE) and also titanium mesh (Hämmerle & Jung, 2003; Rakhmatia et al., 2013; Sheikh et al., 2017). These barrier membranes preserve their structure after placement and require a second surgical procedure in order to remove it, which increases patient morbidity and risk of tissue damage and infection (Hämmerle & Jung, 2003; Sheikh et al., 2017). Initially, the first non resorbable membranes available were e-PTFE, presenting besides the previously mentioned drawbacks, a significant limitation in terms of possible early membrane exposure which can lead to bacterial contamination (Barboza et al., 2010). Such contamination can cause tissue inflammation and graft disintegration, demanding the early removal of the barrier membrane before complete bone formation (Windisch et al., 2020). Nonetheless, this procedure was simplified with the use of d-PTFE (Barboza et al., 2010). When in comparison with the e-PTFE, d-PTFE display

lower porosity (<0.2 µm) which increases the membrane resistance to bacterial contamination, lowering the risk of infection upon early membrane exposure (Bartee, 2001b). Such aspect of the d-PTFE membrane grants several advantages in ARP procedures, as it allows the clinician to perform a minimally invasive flap, preserving the soft tissue architecture (Bartee, 2001b). Several previously published studies have already described good results with the use of intentionally exposed d-PTFE membranes upon ARP procedures (Barber et al., 2007; Barboza et al., 2010).

Overall, these membranes allow a greater control for the clinician and in this sense, assure a proper healing and hard tissue growth, since they are more effective in space maintaining, when compared to resorbable membranes (Rakhmatia et al., 2013; Sheikh et al., 2017).

The drawbacks related to nonresorbable membranes led the investigators to the use of resorbable membranes, which can overcome some limitations previously mentioned such as the need for a second surgical period, patient morbidity and risk of tissue damage and infection (Rakhmatia et al., 2013; Sheikh et al., 2017). Nonetheless, these membranes have limitations as well such as their limited mechanical strength, which reduces the space maintaining property of the biomaterial, and their uncontrolled resorption rate which will consequently affect the bone growth (Hämmerle & Jung, 2003; Sheikh et al., 2017). The most frequently used resorbable membranes are obtained through natural and synthetic polymers such as collagen, polyglycolide or polylactide (Hämmerle & Jung, 2003; Rakhmatia et al., 2013; Sheikh et al., 2017).

A detailed definition of each of these biomaterials can be found in table 4.

| **Biomaterials most used in Alveolar Ridge Preservation** | |
|---|---|
| Autogenous bone graft | Bone graft taken from an intraoral or extraoral site and placed in the same individual. Origin of the graft will determine whether it is cortical, corticocancellous, or cancellous in nature. |
| Allogeneic bone graft | Graft between genetically dissimilar members of the same species. Iliac cancellous bone and marrow, freeze-dried bone allograft (FDBA) and demineralized freeze-dried bone allograft (DFDBA) are available commercially from tissue banks. |

| | |
|---|---|
| Xenogeneic bone graft | Graft taken from a donor of another species. Called also heterograft. |
| Alloplastic bone graft | Graft material such as hydroxyapatite (HA), tricalcium phosphate (TCP), polymethylmethacrylate (PMMA) and hydroxyethylmethacrylate (HEMA) polymer, or bioactive glass that is derived either synthetically or from a foreign, inert source. |
| Resorbable membrane | Membrane made of absorbable natural or synthetic materials used to avoid a second surgery for its removal. After implantation in the body, membranes are degraded by enzymatic activity (collagen membranes) or by hydrolyses (polylactic acid and copolymers of polylactic and polyglycolic acids membranes). |
| Nonresorbable membrane | Membrane made of nonresorbable biomaterial, most often of expanded polytetrafluoroethylene (e-PTFE). Use of a nonresorbable requires a second surgery to remove it from the site. |

**Table 4 | Definition of the several biomaterials used for Alveolar Ridge Preservation**

Summarized definitions of several biomaterials for alveolar ridge regeneration described in the literature, according to the Glossary of Oral and Maxillofacial Implants (Laney, 2007)

As all these treatment modalities became available to the clinician, investigators tried to answer the question as to which biomaterial provides a better outcome in alveolar ridge preservation. Several systematic reviews addressed this thematic, nonetheless, the authors point out to a rather scarce and sometimes conflicting evidence.

While one systematic review reported no major histological and histomorphometric statistical significant differences between alveolar ridge procedures and natural healing following tooth extraction (De Risi et al., 2015), a considerable number of other systematic reviews seems to indicate otherwise (Avila-Ortiz et al., 2014; Avila-Ortiz et al., 2019; Barallat et al., 2014; Bassir et al., 2018; Chan et al., 2013; Horváth et al., 2013; Iocca et al., 2017; Jambhekar et al., 2015; Stumbras et al., 2019; Ten Heggeler et al., 2011; Troiano et al., 2017; Vignoletti et al., 2012; Vittorini Orgeas et al., 2013).

There seems to be a general consensus that according to the available literature, although a dimensional loss following tooth extraction is inevitable, alveolar ridge preservation can reduce the percentage of hard and soft tissue lost (Avila-Ortiz et al., 2014; Avila-

Ortiz et al., 2019; Barallat et al., 2014; Bassir et al., 2018; Chan et al., 2013; Horváth et al., 2013; Iocca et al., 2017; Jambhekar et al., 2015; Stumbras et al., 2019; Ten Heggeler et al., 2011; Troiano et al., 2017; Vignoletti et al., 2012; Vittorini Orgeas et al., 2013). In this sense, in situations where decrease of the alveolar ridge reduction is essential, alveolar ridge preservation is indicated (Avila-Ortiz et al., 2019).

Furthermore, when assessing which sort of biomaterial is the absolute gold standard in minimizing the inevitable changes due to tooth extraction, no definitive conclusions can be drawn.

On the one hand, some studies advocate the use of barrier membranes alone, in the sense that this membrane will function as a shield, protecting the blood clot and enhancing the healing process (Bassir et al., 2018; Vittorini Orgeas et al., 2013). On the other hand, other studies suggest the treatment modality via socket grafting (Avila-Ortiz et al., 2019), reporting success with xenografts (Avila-Ortiz et al., 2014; Barallat et al., 2014; Jambhekar et al., 2015), allografts (Avila-Ortiz et al., 2014; Iocca et al., 2017; Jambhekar et al., 2015; Stumbras et al., 2019), alloplasts (Chavda & Levin, 2018) and autogenous bone (Iocca et al., 2017). Other systematic reviews recommend the use of both a bone graft as well as the use of a barrier membrane (Avila-Ortiz et al., 2014; Troiano et al., 2017). In terms of the use of other materials such as platelet-rich plasma and recombinant human bone-morphogenetic proteins, two systematic reviews highlight the scarce evidence available regarding this subject (Avila-Ortiz et al., 2019; Jambhekar et al., 2015).

Consequently, the literature available to this day does not indicate an absolute gold standard biomaterial when performing alveolar ridge preservation, having each its drawbacks and advantages (Stumbras et al., 2019). It is up to the clinician to make a clinical choice based on the diverse studies already published.

The reason behind these conflicting evidence can be partially explained by the high heterogeneity present in the included studies (Avila-Ortiz et al., 2014; Avila-Ortiz et al., 2019; Barallat et al., 2014; Bassir et al., 2018; De Risi et al., 2015; Horváth et al., 2013; Jambhekar et al., 2015; Stumbras et al., 2019; Ten Heggeler et al., 2011; Troiano et al., 2017; Vignoletti et al., 2012; Vittorini Orgeas et al., 2013). Factors such as: the socket morphology (single rooted and multirooted, number of walls remaining, number of adjacent teeth), periodontal phenotype, systemic factors patient-related (smoking status,

systemic diseases), patient compliance, surgical approach, healing periods, treatment modality (bone graft alone, barrier membrane alone, combination of bone graft and barrier membrane), adjunctive use of bone morphogenetic proteins and platelet derivatives, can make a comparative assessment between all the treatment modalities difficult to perform (Avila-Ortiz et al., 2014; Barallat et al., 2014; Bassir et al., 2018; Horváth et al., 2013; Jambhekar et al., 2015; Vignoletti et al., 2012).

With this in mind, several systematic reviews mention the need for well-designed randomized controlled clinical trials, with precise protocols in order to truly understand the weight of each of the variables addressed previously, in order to reach a more definitive conclusion regarding this matter (Avila-Ortiz et al., 2014; Avila-Ortiz et al., 2019; Bassir et al., 2018; Vignoletti et al., 2012; Vittorini Orgeas et al., 2013).

## 2.2. Bone Grafts used in Alveolar Ridge Preservation

The bone tissue is a dynamic organ capable of regenerating itself (Fillingham & Jacobs, 2016; Oryan et al., 2014). For this process to be possible, bone homeostasis must be achieved, and consequently, some conditions must be met (Fillingham & Jacobs, 2016; Oryan et al., 2014).

The presence of viable cells, appropriate vascularity, adequate stability, presence of a matrix and growth factors are essential in assuring a proper bone healing (Fillingham & Jacobs, 2016; Khan et al., 2005). In cases where there is an insufficient blood supply, the presence of infection in the bone tissue and/or the surrounding tissues as well as systemic diseases, the healing process can be affected (Oryan et al., 2014).

In this sense, the use of bone grafts is indicated to assist and promote an adequate bone healing, thanks to their biological properties (Fillingham & Jacobs, 2016). A bone graft can be defined as an inserted material that fosters bone repair, alone or adjunctively with other material, through key processes such as osteogenesis, osteoinduction and osteoconduction (Elsalanty & Genecov, 2009).

Osteogenesis is defined by the ability to produce new bone from living cells transplanted within the graft (Fillingham & Jacobs, 2016; Gutierres et al., 2006; Khan et al., 2005; Morjaria et al., 2014; Oryan et al., 2014). Therefore, in order for a graft to have such

property, it must comprise viable cells such as mesenchymal stem cells, osteoblasts and osteocytes (Fillingham & Jacobs, 2016; Morjaria et al., 2014).

The concept of osteoinduction had his first breakthrough in 1965 thanks to Marshall R. Urist, with the discovery of the latter known bone morphogenetic proteins (BMP) (Urist, 1965). This term refers to the graft´s capacity to induce the differentiation of the host´s multipotent mesenchymal stem cells into bone-forming cells such as osteoblasts (Albrektsson & Johansson, 2001; Fillingham & Jacobs, 2016; Khan et al., 2005; Morjaria et al., 2014; Oryan et al., 2014). This recruitment and differentiation are regulated by growth factors which are present in the graft´s matrix (Khan et al., 2005). Some examples of these growth factors are BMP´s, transforming growth factor-β (TGF- β), platelet-derived growth factor (PDGF), vascular endothelial-derived growth factor (VEGF) and insulin-like growth factor (IGF) (Albrektsson & Johansson, 2001; Khan et al., 2005; Li et al., 2018; Oryan et al., 2014).

Another important biological property to any bone graft is osteoconduction (Albrektsson & Johansson, 2001). Osteoconduction is a characteristic that grants the graft with the capacity to act as a scaffold, which allows the growth of newly formed bone and vessels (Albrektsson & Johansson, 2001; Fillingham & Jacobs, 2016; Khan et al., 2005; Morjaria et al., 2014; Oryan et al., 2014) This ability is essential since this scaffold will allow a predictable bone formation according to the biology of the graft and the host/graft interface (Khan et al., 2005).

When using a bone graft, several key factors can play a role and affect the final outcome (Khan et al., 2005; Oryan et al., 2014). The clinician must consider aspects such as the type, size and shape of bone graft, the vascularity, size and shape of the site of the implantation, the host/graft interface, ethical issues as well as other local and systemic associated complications patient-related (Khan et al., 2005; Oryan et al., 2014). The aspect of vascularity is particularly decisive since it can allow a faster incorporation of the graft granting an adequate revascularization and thus a briefer healing period (Oryan et al., 2014).

When considering the ideal bone graft the choice should rely on a biomaterial that presents biocompatibility, low donor morbidity, no restriction regarding quantity available, long shelf life, efficient cost and demonstrates osteogenic, osteoinductive and osteoconductive properties (Oryan et al., 2014). In spite of that, when selecting a bone

graft, we must bear in mind that none of the bone graft available in the market have all the characteristics listed previously (Fillingham & Jacobs, 2016; Morjaria et al., 2014; Oryan et al., 2014).

As previously stated, bone grafts can be divided into: autografts, allografts, xenografts and alloplastic grafts (Fillingham & Jacobs, 2016; Morjaria et al., 2014; Oryan et al., 2014).

Of all the options available in the literature, autogenous bone differentiates from the rest of the options since it is the only biomaterial who shows osteogenic (e.g. presence of marrow-derived osteoblastic cells and preosteoblastic precursor cells), osteoinductive (e.g. noncollagenous proteins) and osteoconductive (e.g. hydroxyapatite and collagen) properties (Gual-Vaqués et al., 2018; Khan et al., 2005). Autogenous bone falls in the autograft category, which as mentioned before, is defined by the transplantation of the bone graft from one site into another site in the same individual (Khan et al., 2005; Oryan et al., 2014). In terms of donor sites, many locations are described in the literature. Depending on the case at hand, bone grafts can be harvested from an intraoral site, such as the mentonian region, retromolar area and maxillary tuberosity, or extraoral site, for instance, iliac crest, tibia, radius, humerus, ulna, ribs, calcaneus and olecranon (Jakoi et al., 2015; Khan et al., 2005; Oryan et al., 2014; Santos et al., 2013).

Regarding autogenous bone grafts, they can be divided in cancellous, cortical or cortico-cancellous grafts (Jakoi et al., 2015; Oryan et al., 2014). Cancellous bone presents a trabecular structure which allows an easier revascularization and incorporation of the graft (Pape et al., 2010). One of the main advantages of this type of graft is the enhanced biologic response, which leads to an earlier bone ingrowth (Khan et al., 2005). Nonetheless, one limitation inherent to cancellous bone is the initial lack of mechanical stability, when in comparison with cortical bone (Khan et al., 2005; Oryan et al., 2014; Pape et al., 2010). Cancellous bone grafts are usually used in maxillofacial defects, dental defects and other small bone defects (Oryan et al., 2014).

Other possible type of autogenous bone is a cortical bone graft, which comprises the same biologic advantages as the cancellous bone, but to a more constrained extent (Sutherland & Bostrom, 2005). This type of graft retains less viable cells after transplantation, resulting in a reduced number of osteoblasts, osteocytes and growth factors and consequently a minimized biologic response, when compared to the cancellous bone

(Oryan et al., 2014; Pape et al., 2010; Sutherland & Bostrom, 2005). On the other hand, in contrast with the first type of graft mentioned, cortical bone offers a good initial mechanical stability (Oryan et al., 2014; Pape et al., 2010; Sutherland & Bostrom, 2005). Cortical grafts can be indicated for cases where there is a need to augment bone volume outside the anatomical boundaries defined by the bone itself (Oryan et al., 2014).

Finally, there is also a corticancellous bone graft, which combines the mechanical stability of the cortical graft with the biologic response of the cancellous graft (Jakoi et al., 2015).

When confronting cancellous versus cortical bone, two essential differences arise: the cellular diversity and activity, which is increased in the cancellous bone, and the mechanical strength, which is an advantage of the cortical bone (Pape et al., 2010). However, in both of these grafts, complete bone remodeling can take several months, with some literature reporting changes up to 1 year (Jakoi et al., 2015; Pape et al., 2010).

According to the literature, autogenous bone, which can be presented in the form of block or particles, shows a great clinical performance (Gual-Vaqués et al., 2018; Oryan et al., 2014; Ramanauskaite et al., 2019; Santos et al., 2013). Such outcome can be explained due to the osteogenic, osteoinductive and osteoconductive properties, the absolute histocompatibility which consequently assures a lack of immunogenicity, proving to be, from a biological perspective, the first choice in bone grafting (Gual-Vaqués et al., 2018; Oryan et al., 2014; Ramanauskaite et al., 2019; Sutherland & Bostrom, 2005).

Notwithstanding, there are some limitations in using this graft, since it is associated with limited material supply, which in cases of extensive grafting this graft might not be an option, donor morbidity, due to the prolonged surgical time and postoperative complications, and high resorption rates (Figueiredo et al., 2010; Gual-Vaqués et al., 2018; Jakoi et al., 2015; Khan et al., 2005; Oryan et al., 2014; Ramanauskaite et al., 2019; Santos et al., 2013; Sutherland & Bostrom, 2005). Although values may alter depending on the donor site, it can be expected a bone resorption rate of around 12% to 60% for iliac crest grafts and up to 15% for intra-oral grafts (Chiapasco et al., 2006).

With these limitations in mind, investigators tried to find other alternatives that could surpass some of these drawbacks inherent to autogenous bone (Gual-Vaqués et al., 2018).

As mentioned in table 4, allograft refers to the process transferring the bone from one individual to another from the same species (Khan et al., 2005; Oryan et al., 2014). Allografts can be acquired from cadavers and living donors, with the first form being available in Tissue Banks (Jambhekar et al., 2015; Khan et al., 2005; Oryan et al., 2014; Ten Heggeler et al., 2011).

Similarly to autogenous graft, allografts can be presented in the form of cancellous, cortical or cortico-cancellous grafts (Fillingham & Jacobs, 2016; Jakoi et al., 2015; Oryan et al., 2014). Regarding processing, this type of graft can be demineralized or mineralized, fresh, freezed or freeze-dried, which will have an impact in the biological properties and clinical performance of the graft (Fillingham & Jacobs, 2016; Khan et al., 2005; Oryan et al., 2014; Sutherland & Bostrom, 2005). In terms of preserving the allograft (fresh, freezed or freeze-dried), the literature available highlights the decrease of antigenicity and the enhanced osteoconduction and osteoinduction with preserved grafts in comparison with fresh allografts (Khan et al., 2005; Ten Heggeler et al., 2011).

Other important aspect that can have an impact in bone grafting is the demineralization process (Barallat et al., 2014; Stumbras et al., 2019). The demineralization of the bone matrix can expose growth factors and other noncollagenous proteins which will grant the graft with osteoinductive property (Chan et al., 2013; Figueiredo et al., 2010; Fillingham & Jacobs, 2016; Khan et al., 2005; Stumbras et al., 2019). During this process, aspects such as the demineralizing agent and time of demineralization are worthy mentioning, since it can alter the graft properties (Khan et al., 2005). Several systematic reviews report demineralized freeze-dried bone allograft (DFDBA) being the most used allograft (Barallat et al., 2014; Jambhekar et al., 2015; Ten Heggeler et al., 2011). When comparing with the mineralized graft, which only present osteoconductive capacity (Stumbras et al., 2019), the demineralized allografts (e.g. DFDBA) appear to have more promising results (Wood & Mealey, 2012). However, we must keep in mind that there is a variability in the quantity of bone morphogenetic proteins in DFDBA, where factors such as donor´s age and different Tissue Banks can affect the osteoinductivity of the graft (Chan et al., 2013; Jambhekar et al., 2015).

The use of allografts requires a very strict and methodical process in order to assure the safety throughout the bone grafting procedure, including an adequate screening of the medical history of the cadavers and living donors (Khan et al., 2005; Sutherland & Bostrom, 2005). When in comparison with autogenous bone, it overcomes some of its

limitations such as donor site morbidity and limited availability, since it is possible to obtain allografts in various shapes, forms and sizes (Figueiredo et al., 2010; Fillingham & Jacobs, 2016; Oryan et al., 2014; Sutherland & Bostrom, 2005). Nevertheless, allografts poses some limitations that can restrain its use (Jambhekar et al., 2015). Besides social, religious and political reasons (Jambhekar et al., 2015), risk of disease transmission, variable osteoinductive capacity, lack of osteogenic properties and mechanical strength reduction due to the processing necessary are still obstacles to the use of this type of graft (Figueiredo et al., 2010; Fillingham & Jacobs, 2016; Gual-Vaqués et al., 2018; Khan et al., 2005; Oryan et al., 2014; Sutherland & Bostrom, 2005).

Another possible alternative are Xenografts (Avila-Ortiz et al., 2014; Barallat et al., 2014; Jambhekar et al., 2015). This type of graft has been used and reported in the literature with promising results (Avila-Ortiz et al., 2014; Barallat et al., 2014; Jambhekar et al., 2015). It differs from the previously mentioned grafts because it is harvested from animal sources comprising bovine, equine and porcine substitutes (Figueiredo et al., 2010; Gashtasbi et al., 2020; Oryan et al., 2014). The reason behind its use is due to the similarity of the xenogeneic bone to human bone regarding its structure and morphology (Amid et al., 2020; Figueiredo et al., 2010). However, one important aspect concerning the use of xenograft is the processing method, which can have serious implications in the final outcome (Amid et al., 2020; Figueiredo et al., 2010; Gashtasbi et al., 2020; Haugen et al., 2019; Jambhekar et al., 2015; Schroeder & Mosheiff, 2011; Yamada & Egusa, 2017).

Several processing methods are described in the literature, with the most commonly used being a heat and a chemical treatment (Amid et al., 2020; Yamada & Egusa, 2017). The main goal of these methods is to remove the organic components, specially xenogenic antigens, in order to prevent an immune response (Amid et al., 2020; Jambhekar et al., 2015; Ten Heggeler et al., 2011; Yamada & Egusa, 2017). In this sense, an adequate and meticulous sterilization is required in order to assure the safety and biocompatibility of the biomaterial (Gashtasbi et al., 2020). On the other hand, this strict processing method is capable of reducing some of the biological properties inherent to the graft, in order to prevent disease transmission (Haugen et al., 2019; Oryan et al., 2014; Schroeder & Mosheiff, 2011). A recent systematic review reported that the literature available does not allow a definitive response as to which processing method is preferable (Amid et al., 2020).

Xenografts presents a porous structure, which helps in acting as a scaffold, allowing the growth of newly formed bone and vessels, an adequate calcium/phosphorus ratio, biocompability and mechanical properties which makes this biomaterial a viable candidate for bone grafting procedures (Amid et al., 2020; Haugen et al., 2019). Of all the available options for the clinician, bovine substitutes are frequently the choice in terms of bone regeneration, being used not only in alveolar ridge preservation but also in sinus lift procedures (Amid et al., 2020; Haugen et al., 2019).

In comparison with the autografts and allografts, it has unlimited supply and can be useful in reducing donor site morbidity (Amid et al., 2020; Figueiredo et al., 2010; Oryan et al., 2014). In addition, xenografts display a human-like physicochemical structure, presenting predictable outcomes already reported in the literature (Amid et al., 2020; Haugen et al., 2019).

Nonetheless, with the use of these type of grafts there is always a risk of immunogenicity and zoonotic disease transmission (Figueiredo et al., 2010; Oryan et al., 2014). Moreover, the lack of viable cells and decrease of a biological response is inevitable due to the sterilization necessary (Amid et al., 2020; Haugen et al., 2019). These grafts are reported to present only osteoconduction (Gashtasbi et al., 2020; Gual-Vaqués et al., 2018).

Another possible type of bone substitute used in alveolar ridge preservation is the alloplastic graft. These biomaterials are synthetic and synthesized from non-organic sources (Chavda & Levin, 2018; Moussa & Dym, 2020; Sheikh et al., 2017). In the current market, several examples of alloplasts have been presented, showing different properties according to their composition (Fukuba et al., 2021; Sheikh et al., 2017). This type of graft has been the target of several investigations, and although it only presents osteoconductivity, the combined use with growth factors or other bone grafts has been reported in the literature in order to optimize the biological response of the graft (Chavda & Levin, 2018; Fukuba et al., 2021).

These synthetic materials are fabricated with the purpose of reproducing the bone tissue, regarding its chemical composition and structural properties (Figueiredo et al., 2010). The most frequently used alloplasts are bioceramics and polymers, which have intrinsic characteristics that can make an impact in the clinician´s decision and outcome (Chavda & Levin, 2018; Eppley et al., 2005; Fukuba et al., 2021; Haugen et al., 2019; Sheikh et al., 2017). Besides the composition of the alloplast, one must also consider the procedure

that requires the alloplast grafting in order to choose an adequate alloplast according to its ineherent characteristics (Eppley et al., 2005; Fukuba et al., 2021).

The most commonly used alloplast in the literature are the bioceramics, which include calcium phosphates, bioactive glass and calcium sulfate (Chavda & Levin, 2018; Sheikh et al., 2017). The biologic plausibility behind the use of bioceramics is the similarity to the mineral phase of the bone, since this tissue is mainly composed by hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$) (Chavda & Levin, 2018; Eppley et al., 2005). Bioceramics comprise a variety of biomaterials which differ in terms of mechanical strength, resorption rate and handling properties (Eppley et al., 2005; Moussa & Dym, 2020). The degradation of these bioceramics can occur due to a physicochemical dissolution or due to osteoclastic action (Eppley et al., 2005). Key factors such as particle size, porosity, calcium/phosphate ratio, surface area, local pH and temperature can affect the resorption rate of the alloplast, and therefore must be considered by the clinician (Chavda & Levin, 2018; Eppley et al., 2005; Moussa & Dym, 2020).

The calcium phosphates more frequently used in the literature are hydroxyapatite, beta-tricalcium phosphate (β-TCP) and a combination of both, designated as biphasic calcium phosphate (Haugen et al., 2019). Synthetic hidroxyapatite has the advantage of being similar to the mineral content of the bone, nonetheless, it presents a slow resorption rate which in cases of early re-entry for implant placement, such property might be a limitation (Fukuba et al., 2021). However, as previously stated, factors such as processing temperature methods, porosity, calcium/phosphate ratio, and mineral structure can modify the resorption rate (Sheikh et al., 2017). On the other hand, tricalcium phosphate (TCP) can be used in two forms: α-TCP and β-TCP, with the latter one being more frequently used (Fukuba et al., 2021; Sheikh et al., 2017). β-TCP, in contrast with hydroxyapatite, which presents greater stability, shows a rapid resorption rate (Eppley et al., 2005; Fukuba et al., 2021) with literature pointing out to variable results using this biomaterial (Joshi et al., 2016; Nakajima et al., 2007). In order to combine the features of both biomaterials, biphasic calcium phosphate (BCP) has been reported in the literature (Fukuba et al., 2021). An interesting randomized clinical trial compared the use of BCP versus a xenograft in maxillary sinus floor elevation, reporting no statistical significant difference in terms of newly formed bone (Cordaro et al., 2008).

Bioactive glass are also included in the bioceramics category, and comprise amorphous materials containing acid oxides, silica and alkaline oxides (Fukuba et al., 2021; Sheikh

et al., 2017). Notwithstanding, bioactive glass still has limited evidence regarding regenerative procedures (Sheikh et al., 2017). Lastly, literature also refers the use of calcium sulfate, which is usually used bone filler, being used concomitantly with other bone grafts (Moussa & Dym, 2020; Sheikh et al., 2017).

Another group of alloplasts are the synthetic polymers (e.g. polyglycolic acid, polycaprolactone, polylactic acid), which also show promising results, due to their adaptable biomechanical properties (Haugen et al., 2019; Kretlow & Mikos, 2007). Notwithstanding, there are still some limitations regarding the use of these polymers, such as low cell attachment and local alterations due to the release of acidic products (Haugen et al., 2019).

Comprehensively, alloplasts display advantages in comparison to allografts and xenografts such as no risk of disease transmission and a standardization of product quality (Fukuba et al., 2021). However, similarly to allografts and xenografts, only shows osteoconduction, which can be seen as a limitation (Fukuba et al., 2021; Gual-Vaqués et al., 2018).

Although no definitive conclusions can be drawn, the evidence regarding the use of alloplasts shows scarce and sometimes conflicting results (Barallat et al., 2014; Haugen et al., 2019; Jambhekar et al., 2015).

Overall, the main complications associated with the various grafts are the persistence of residual graft, inefficiency in restoring the alveolar ridge dimensions in height and width, delayed healing periods as well as the possible risk of disease transmission (Morjaria et al., 2014).

Consequently, more studies in this field are required to assist the clinician when choosing a bone substitute to perform alveolar ridge preservation procedures.

## 3. THE USE OF AUTOGENOUS TEETH AS A BONE GRAFT MATERIAL

Research on the use of teeth as a bone graft material dates back to 1967. After establishing bone formation by autoinduction in 1965 (Urist, 1965), Bang & Urist and Yeomans & Urist first mentioned the potential osteoinductive capacity of demineralized dentin (Bang & Urist, 1967; Yeomans & Urist, 1967).

Firstly, Bang & Urist (1967) performed an investigation where they gathered 520 samples of dentin from humans, rats and rabbits and after a demineralizing process, placed in the anterior chamber of the eye and the abdominal wall of rats and rabbits (Bang & Urist, 1967). They concluded that the demineralized dentin matrix was able to induce bone formation, although the mechanism of this bone induction was not known at that time (Bang & Urist, 1967).

In the same year, Yeomans & Urist (1967) investigated alongside other samples, the use of demineralized dentin placed in the abdominal muscle, in a drill-hole bone defect in the mandible and in an empty alveolar socket (Yeomans & Urist, 1967). Interestingly, already in 1967, the authors concluded that although the best results were achieved with autogenous bone, demineralized dentin might be a potential alternative (Yeomans & Urist, 1967). Regarding the use of demineralized dentin, the authors reported bone induction in 75% of the cases after a period of 8 to 12 weeks (Yeomans & Urist, 1967).

Even though the use of demineralized dentin dates back to 1967, the development of a bone substitute using autogenous teeth, commonly known as AutoBT, in South Korea by the Korea Tooth Bank in 2008 caused a paradigm shift in this subject, which led to a significant increase in investigations in order to trully understand the potential this biomaterial could have (Gual-Vaqués et al., 2018; Kim, et al., 2013b).

The biological plausibility of the use of autogenous teeth as a bone graft material can be explained due to the chemical similarity between the tooth, specially dentin, and the alveolar bone (Kim, 2012; Kim, et al., 2013b; Ramanauskaite et al., 2019; Tabatabaei et al., 2016; Um et al., 2017). Firstly, both the tooth and the alveolar bone derive from neural crest cells and when analysing the inorganic/organic/water ratio of each component of the tooth and alveolar bone, similarities arise (Kim, et al., 2013b). While the alveolar bone has a ratio of 65%/25%/10%, enamel has 95%/0.6%/4%, dentin has 70-75%/20%/10% and finally cementum has a inorganic content of 45 to 50% and an organic content of 50 to 55% (Gual-Vaqués et al., 2018; Kim, 2012; Kim et al., 2013c).

Concerning the inorganic portion of dentin, there are essentially four types of calcium phosphate who play a decisive role in bone remodelling: hidroxyapatite, tricalcium phosphate, octacalcium phosphate and amorphous calcium phosphate (Gual-Vaqués et al., 2018; Kim, 2012; Kim, et al., 2013b; Kim et al., 2013c; Um et al., 2017). The

inorganic component of dentin grants the autogenous graft with an osteoconductive capacity (Gual-Vaqués et al., 2018; Kim et al., 2013c).

In this sense, characteristics such as the calcium phosphate crystallinity, particle size and calcium/phosphate ratio can affect the potential osteoconductivity of the graft (Kim, 2012; Um et al., 2017). One study by Kim et al. in 2011 performed a dispersive X-ray spectroscopy and an X-ray diffraction analysis in order to assess some of the characteristics previously mentioned. Regarding the several components of a tooth, while the enamel presented a calcium/phosphate ratio of 1.54, dentin and cementum showed a ratio of 1.02 and 0.96, respectively (Kim et al., 2011). A similar comparison was also done between the crown and root portion of the tooth, obtaining ratios of 1.72 and 1.32, respectively (Kim et al., 2011). This ratio is an aspect to consider, since a lower ratio is associated with an easier resorption of the biomaterial, allowing it to be replaced by newly formed bone (Eppley et al., 2005). One also essential factor is the crystallinity of the calcium phosphate, since it is known that as the crystallinity increases, the resorption rate decreases, since the osteoclasts do not disintegrate as easily the calcium phosphate minerals (Kim et al., 2013c). X-ray diffraction analysis reported that while the enamel´s hidroxyapatite was associated with high-crystalline calcium phosphate, dentin´s hydroxyapatite was linked to low-crystalline calcium phosphate, similarly to that of the alveolar bone and in this sense allowing an easier resorption and enhancing the osteoconductive capacity (Kim, et al., 2013b; Kim et al., 2013c).

Regarding the organic component of dentin, type I collagen fibrils represents about 90% of its content (Gual-Vaqués et al., 2018; Kim et al., 2013c). However, the remaining 10% are mainly occupied by the so called noncollagenous proteins, which are known to be an important factor in osteoinduction (Gual-Vaqués et al., 2018; Kim, 2012; Kim et al., 2013c; Linde, 1989). Some examples of these noncollagenous proteins are phosphoryn, sialoprotein, glycoprotein, proteoglycan, osteopontin and osteocalcin. (Gual-Vaqués et al., 2018; Kim, 2012; Kim et al., 2013c; Murata, 2012; Tabatabaei et al., 2016; Um et al., 2017).

Also present in the organic dentin composition are several growth factors who are key in enhancing the osteoinductive properties of the autogenous tooth graft (Gual-Vaqués et al., 2018; Kim, 2012; Tabatabaei et al., 2016; Um et al., 2017). These growth factors, which are present both in dentin and bone, are signalling proteins that stimulate cell proliferation and differentiation from mesenchymal stem cells into bone and cartilage

tissues (Kim et al., 2013c; Um et al., 2017). Some examples of these growth factors are IGF, PDGF, fibroblast growth factor (FGF), TGF-β, Lim mineralization protein 1 (LMP-1), BMP, as well as angiogenic growth factors such as the VEGF (Boden et al., 1998; Cassidy et al., 1997; Finkelman et al., 1990; Gual-Vaqués et al., 2018; Kim et al., 2013c; Reis-Filho et al., 2012; Roberts-Clark & Smith, 2000). Regardind the resemblance between dentin and the alveolar bone in terms of growth factors, a frequently cited investigation performed by Bessho et al. (1991) reported interesting conclusions (Bessho et al., 1991). After comparing bone-derived bone morphogenetic proteins with dentin-derived bone morphogenetic proteins, the authors concluded that although chemically different, both growth factors have a similar function since both induced bone formation (Bessho et al., 1991).

A schematic overview of the main organic and inorganic composition of dentin can be seen in figure 2.

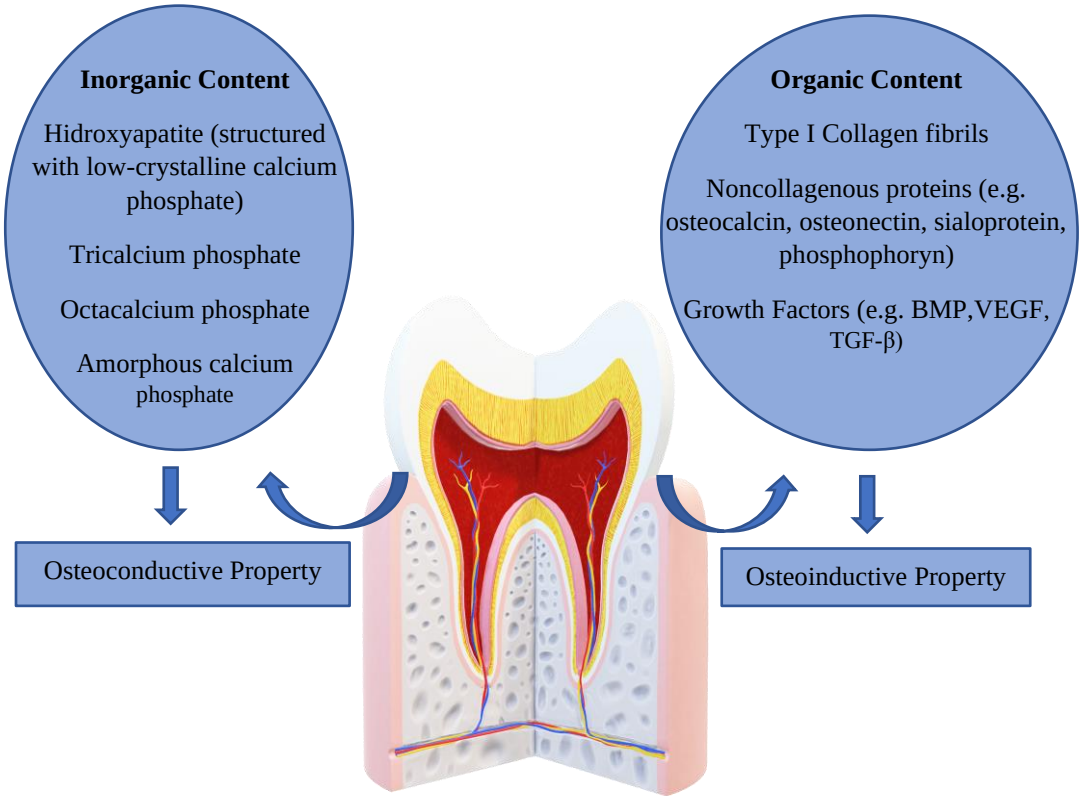


**Figure 2 | Autogenous teeth as a bone graft material**

When analyzing the inorganic/organic content between Dentin (70-75%, 20%) and alveolar bone (65%, 25%), the similarity becomes clear. Dentin hydroxyapatite is structured with low-crystalline calcium phosphate which allows the osteoclasts to easily decompose this mineral, promoting an effective bone remodelling, granting the graft with osteoconductivity. Additionally, the role of noncollagenous proteins and growth factors are key in providing this material with osteoinductive properties (BMP: bone morphogenetic protein; VEGF: vascular endothelial growth factor; TGF-β: transforming growth factor β) (Gual-Vaqués et al., 2018; Kim, 2012; Kim et al., 2013b; Kim et al., 2013c; Tabatabaei et al., 2016; Um et al., 2017).

Given the osteoconductive and osteoinductive potential associated with autogenous teeth, several authors assessed its clinical efficacy in alveolar ridge preservation and augmentation procedures, sinus floor elevation and in the treatment of furcation defects (Jun et al., 2014; Kim, 2013a; Kim, et al., 2013b; Ramanauskaite et al., 2019; Reddy et al., 2019; Schwarz et al., 2019; Um et al., 2017).

Several processing methods prior to the application of this biomaterial have been reported (Tabatabaei et al., 2016). However, the degree of demineralization stands as the most used one (Gual-Vaqués et al., 2018; Kim, 2012; Kim et al., 2013c). Upon this rationale, the demineralization releases several growth factors and noncollagenous proteins reducing the inorganic portion of the biomaterial, fostering new bone formation (Gual-Vaqués et al., 2018; Kim, 2012; Kim et al., 2013c; Park et al., 2015; Tabatabaei et al., 2016). Using the degree of demineralization classification, we may have demineralized dentin matrix (DDM), partially demineralized dentin matrix (PDDM) and undemineralized dentin matrix (UDD) (Gual-Vaqués et al., 2018). Several success rates have been reported in the literature using either UDD (Andrade et al., 2019; Binderman et al., 2014; Calvo-Guirado et al., 2018a; Calvo-Guirado et al., 2018b; Del Canto-Díaz et al., 2019; Dwivedi & Kour, 2020; Nadershah & Zahid, 2019), PDDM (Joshi et al., 2016; Minamizato et al., 2017) or DDM (Chung & Lee, 2011; Kim, 2015; Kim et al., 2017; Li et al., 2018; Minetti et al., 2020; Pang et al., 2016; Park et al., 2012; Wu et al., 2019), though the optimal choice for processing method is still not consensual.

Three systematic reviews on autogenous tooth as a bone graft material in alveolar ridge preservation have been published, reporting limited evidence due to the considered heterogeneity present in the included studies (Gharpure & Bhatavadekar, 2017; Gual-Vaqués et al., 2018; Ramanauskaite et al., 2019). The substantial variability among processing protocols alongside the several role-playing factors above mentioned (for more details please see section 2.1) make a definitive conclusion hard to reach (Gharpure & Bhatavadekar, 2017; Gual-Vaqués et al., 2018; Ramanauskaite et al., 2019; Tabatabaei et al., 2016).

In spite of that, the clinical benefit of autogenous tooth as a bone graft material is considerable, still, high quality evidence is required to establish consistent and robust

guidelines (Gharpure & Bhatavadekar, 2017; Gual-Vaqués et al., 2018; Kim, 2012; Kim, et al., 2013b; Kim et al., 2013c; Ramanauskaite et al., 2019).

## 4. AIMS

The present literature review aimed to summarize all evidence on autogenous teeth as a bone graft material in alveolar ridge preservation in post-extraction sockets. We have structured this review according to the dentin processing method: DDM, PDDM and UDD.

## II. THE USE OF AUTOGENOUS TEETH FOR ALVEOLAR RIDGE PRESERVATION: A LITERATURE REVIEW

Adapted from:

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*Review*

# The Use of Autogenous Teeth for Alveolar Ridge Preservation: A Literature Review

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**Abstract:** Alveolar ridge resorption is a natural consequence of teeth extraction, with unpleasant aesthetic and functional consequences that might compromise a future oral rehabilitation. To minimize the biological consequences of alveolar ridge resorption, several surgical procedures have been designed, the so-called alveolar ridge preservation (ARP) techniques. One important characteristic is the concomitant use of biomaterial in ARP. In the past decade, autogenous teeth as a bone graft material in post-extraction sockets have been proposed with very interesting outcomes, yet with different protocols of preparation. Here we summarize the available evidence on autogenous teeth as a biomaterial in ARP, its different protocols and future directions.

**Keywords:** extracted teeth; bone regeneration; bone graft; autogenous graft; autogenous tooth bone graft; human dentin; demineralized dentin

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## 1. Introduction

A tooth is indicated for extraction when it is no longer possible to restore or maintain in acceptable conditions considering its health, function and/or aesthetics [1]. The extraction of a tooth triggers a series of events that further result in the decrease of height and width of the alveolar process, particularly on the buccal side and horizontally [2–7]. After extraction, this resorptive event occurs during the first three months of healing until one year, with potential aesthetic and functional consequences for prosthetic rehabilitation [2,8].

Due to the fallouts of alveolar ridge resorption after tooth extraction, a socket-filling procedure is frequently required when dental implants are planned to rehabilitate function, aesthetics and comfort [9].

To this end, alveolar ridge preservation (ARP) in post-extraction sockets is a well described surgical technique able to prevent bone resorption partially but not completely [10,11].

Several graft materials have been advocated in ARP including bone substitutes, such as allografts, xenografts, alloplasts and autografts (i.e., autogenous bone) [4]. Bone graft materials must have three main properties: osteoconduction (the ability to provide scaffold for bone regeneration), osteoinduction (the capacity to recruit primitive, undifferentiated and pluripotent cells that are developed into having a bone-forming capacity) and osteogenesis (presence of cells that promote bone regeneration) [12,13]. Autogenous bone

is widely accepted as the gold standard bone graft material as it contemplates all three characteristics [9]. Nonetheless, autogenous bone has limited intra-oral availability, causes high donor site morbidity and presents elevated resorption rates [9,12].

A recently proposed material was autogenous teeth, commonly seen as dental waste after dental extractions [14]. Chemically, dentin is very similar to bone, with an osteoconductive and osteoinductive matrix, and therefore is a viable candidate for bone grafting [15,16]. Autogenous teeth have fair intra-oral availability and may be obtained through standard procedures with low morbidity [17]. Nonetheless, it is important to bear in mind that the amount of dentin graft is dependent on the condition of the discarded teeth [12].

Ever since, several protocols have been proposed for ARP using autogenous teeth as a graft material and, so far, three different methods of dentin processing have been developed: demineralized dentin matrix (DDM), partially demineralized dentin matrix (PDDM) and undemineralized dentin (UDD) (Figure 1) [12,14]. However, these different methods present clinical pros and cons that deserve attention. For this reason, this review summarizes the available evidence on autogenous teeth as graft material, its different types and its applicability in ARP.

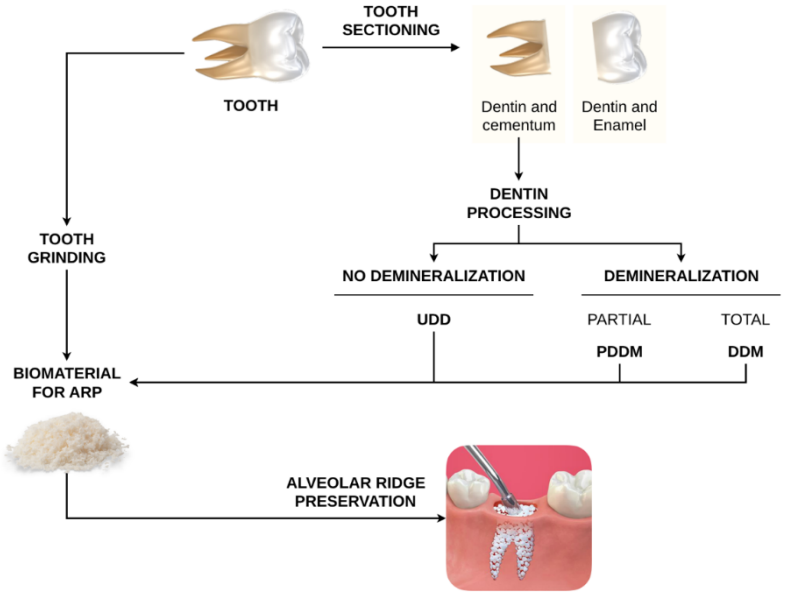


**Figure 1.** Schematic diagram explaining different dentin processing approaches. UDD—undemineralized dentin matrix; PDDM—partially demineralized dentin matrix; DDM—demineralized dentin matrix).

## 2. Alveolar Ridge Preservation in Extraction Sockets

### *2.1. Biological effect of a Tooth Extraction*

Tooth extraction sets off a series of biological events, with a local inflammatory response and an irreversible structural transformation of the periodontium [3]. In terms of hard tissues, as previously stated, it can be expected a bone resorption, mainly in the first three months, causing both vertical and horizontal changes in the alveolar process [5,10].

These anatomical changes are more buccally and horizontally pronounced [3–7], with an average horizontal reduction of 3.79–3.87 mm and an average vertical reduction on the buccal side of 1.24–1.67 mm [5,7].

Concerning the soft tissues, the socket defect will determine the healing process through secondary intention resulting in cell proliferation, whereas the gingival form mostly depends on the external shape of the alveolar bone [5].

In order to diminish the biological effect of a tooth extraction, an appropriate treatment plan and technique are central [3]. As for the surgical technique, a flapless approach is considered a simple, atraumatic and conservative method, being the usual choice to reduce post-surgery healing period, discomfort and inflammation [4]. This surgical approach is characterized by the nondetachment of the periosteum, preserving the blood supply to the buccal bone, which, as mentioned before, suffers a more pronounced resorption [18].

*2.2. Alveolar Ridge Preservation: Concept and Bone Graft Materials Used*

The biological effect subsequent to a tooth extraction might have a devastating impact on the rehabilitation treatment, affecting both hard and soft tissues [3]. While bone availability might decrease, which is a key factor in the implant placement, the aesthetic result may also be compromised, by damaging the soft tissue [8,19].

Under the rationale of ARP, filling a socket with grafting materials might reduce alveolar ridge resorption comparing to natural healing via blood clot [19]. Overall, ARP comprises three essential goals: 1) the maintenance of the existing soft and hard tissue envelope; 2) the preservation of a stable alveolar ridge in order to maximize the functional and aesthetic outcome; and 3) the simplification of the treatment procedures following the alveolar ridge regeneration [20].

When considering ridge resorption in this procedure, one must not only analyze the socket graft material and the surgical protocol but also the systemic and local characteristics that can play a role in this clinical procedure [1]. Among the factors that might affect ARP are number of adjacent teeth to be extracted, socket morphology (single versus multirooted teeth), integrity of the socket walls, periodontal phenotype (assessing its thickness), smoking status, systemic factors (e.g., bone metabolic disorders, uncontrolled diabetes) and patient compliance [1,3,8].

Regarding the numerous biomaterials used for socket grafting, many approaches have been described in the literature [2,6,21]. Examples of these approaches are: using only bone grafting alone, including autografts (e.g., autogenous bone), allografts (including cortical mineralized freeze-dried bone and cortical demineralized freeze-dried bone) xenografts (derived from bovine bone), alloplasts (including medical-grade calcium sulfate, hydroxyapatite and beta-tricalcium phosphate (β-TCP)) [2,6,21].

Finally, it has been also described the application of a membrane alone (resorbable or non-resorbable), or combined with a grafting material [2,6,21].

Several systematic reviews have addressed ARP effectiveness. While some of these reviews points out to a rather scarce evidence with no significant conclusions [2,19,20], more recent systematic reviews showed more promising results [1,3,4,6,8,10,11,21–23]. Comprehensively, there is general consensus that ARP does not avoid completely the inevitable dimensional loss that exists [1,3,4].

While xenogenic or allogenic materials have been associated with better results when compared with alloplastic grafts [1,3,4], others highlight the positive influence of the use of barrier membranes, resorbable and non-resorbable [8,10,21] or the combined use of a bone graft with a resorbable membrane [6]. Nonetheless, other studies advocate that although the benefit of this procedure exists, the evidence available is insufficient to state which method is best in reducing the dimensional changes addressed before [8,11,23].

The reason behind this limited evidence can be explained by the high heterogeneity present in the existing systematic reviews [1–4,6,8,10,11,19–23]. This heterogeneity is dependent on the broad definition of alveolar ridge regeneration, where many aspects enter

the equation. Some examples are: type of graft material used, with or without resorbable or non-resorbable membrane, use of growth factors, with or without raising a flap when extracting the tooth, achieving primary or secondary intention closure, with damaged or intact sockets, multi rooted teeth or single rooted teeth, mandible or maxilla, among other patient related factors mentioned before [3,10,19,21,22].

Another technique that has also been described with promising results is the socket-shield [24]. The hypothesis behind this technique is that by retaining a section of the buccal side of the root during implant placement the extensive bone loss that occurs on the buccal side of the bone will be reduced [24–26]. Regarding this technique, some modifications have appeared since it was first presented, showing promising results [25]. However, more high level evidence studies are required to better assess this approach [25,26].

## 3. Autogenous Teeth as a Bone Graft Material

### *3.1. Biological Plausibility*

In order to understand the use of human teeth as a bone graft material, we must bear in mind the chemical composition of human teeth and alveolar bone. The ratio inorganic/organic/water of the various components of the teeth goes as follows: enamel (95%/0.6%/4%), dentin (70–75%/20%/10%) and cementum (45–50%/50–55%) [12,16]. When comparing with the alveolar bone ratio, (65%/25%/10%), the similarity between bone and especially dentin becomes clear [16].

Considering this potential, researches started looking for the different hard tissues present in teeth. Yeomans and Urist pioneer study on the potential bone-inducing properties of dentin opened up new boundaries on graft materials [27]. Yeomans and Urist firstly reported the bone induction capacity of autogenous demineralized dentin matrix [27]. In the same year, Bang and Urist also referred the similarity between dentin collagenous matrix and bone matrix in terms of osteoinductive capacity [28]. Only in 2008, the Korean Tooth Bank, in Seoul, Korea, developed an autogenous tooth bone graft material, which lead to a significant increase of studies in this field regarding the clinical performance of this material [29].

Given the role and highly percentage of dentin in autogenous tooth [30], several studies have focused on different methods of treating dentin matrix towards the optimization of the procedure clinical effectiveness [14].

In the inorganic component of dentin, X-ray diffraction analysis showed that, unlike enamel hydroxyapatite, dentin hydroxyapatite (which consists of 70% of the dentin in its weight volume) is structured with low-crystalline calcium phosphate, which in turn, allows the osteoclasts to easily decompose this mineral, promoting an effective bone remodeling [15,30]. This property is not only similar to bone tissue, also mainly composed by low-crystalline calcium phosphate, but also essential in alveolar ridge regeneration, ensuring osteoconductive capacity [12,16,29]. Besides hydroxyapatite, there are other three biological calcium phosphates such as: tricalcium phosphate, octacalcium phosphate and amorphous calcium phosphate [31]. All these forms interact with each other, playing a positive role in bone remodeling [15].

In the organic component of the dentin matrix, a dense network of type 1 collagen fibrils represents 90% of its content [12]. The other 10% is formed by the so-called noncollagenous proteins such as: osteocalcin, osteonectin, sialoprotein and phosphoprotein, which are known to be involved in bone calcification [15]. Additionally, growth factors are also present, including bone morphogenetic proteins (BMP), LIM mineralization protein 1, transforming growth factor-β among others [12,14]. Bessho et al. compared the dentin-matrix derived BMP with the bone-matrix derived BMP, concluding that although they are not identical, both induce bone formation [32]. Similarly, Boden et al. demonstrated that LIM mineralization protein 1 is a positive regulator of the osteoblast differentiation [33]. These growth factors, alongside other noncollagenous proteins have a proven osteoinductive capacity [12,15,16,29,32–35].

One important aspect that can be beneficial in terms of implant placement is the healing period. In the literature, this period usually varies from 4 to 6 months [36,37], although in some cases, dental implants may be placed 2 to 3 months after alveolar ridge preservation [38]. Several authors compared the use of autogenous tooth graft versus a xenograft [17,39,40]. While some studies assess the performance of the implants immediately placed after graft [17,40], one study compared the two grafts after a healing period of 6 months [39]. Regarding this matter, thanks to the reduced resorption rate of the autogenous tooth graft (4 to 6 months) an earlier placement of the implant can be done, reducing the healing period [38,41].

*3.2. Dentin Processing*

As aforementioned, autogenous teeth can be used as bone graft material with osteoconductive and osteoinductive potential [9,12]. However, several concerns have been addressed regarding the need for any dentin processing prior to bone grafting for the purpose of clinical optimization. Some examples are the extraction of noncollagenous proteins [42], elimination of the organic matrix [14] and finally, one of the most commonly used, dentin preparation by demineralization [12].

The hypothesis of demineralization is that through this procedure, the organic substances (type 1 collagen fibrils, noncollagenous proteins and growth factors) will be more exposed, decreasing the graft crystallinity and increasing its porosity and surface area [16,35,43]. This process releases growth factors and noncollagenous proteins, which in turn, results in an enhanced osteoinductive activity [14].

Although protocols vary from study to study, a general protocol includes tooth extraction, removal of soft tissue, carious lesions and filling materials of any nature [17,44–46], sectioning into blocks or particles and finally choosing the degree of demineralization [47]. Among the demineralization agent are ethylenediaminetetraacetic acid (EDTA), phosphoric acid, chloridric acid, nitric acid, hydrogen oxide, ethyl ether and ethyl alcohol [14]. Hence, dentin materials were categorized into 3 categories: demineralized dentin matrix (DDM), partially demineralized dentin matrix (PDDM) and undemineralized dentin (UDD) [12].

While some investigators have reported success when using DDM (or PDDM) [17,37,39,40,44,48–50] others prefer using in its undemineralized form [38,51–57].

Mineralized dentin particles offer a mechanical stability, creating a solid site for implant placement [38,52]. With the use of a mineralized graft, although the osteoinductive properties of dentin may be delayed, the low crystallinity of dentin hydroxyapatite allows the progressive bone remodeling [15,30].

Due to a lack of uniformity and standardization in the literature, it is difficult to determine with certainty which form of graft is advantageous for which clinical indication. Regarding ARP procedures, several authors have reported success when using DDM, PDDM and UDD, indicating that each form can be a viable option [38,40,41]. Nonetheless, some authors suggest an approach patient-based. DDM and PDDM can be indicated when the socket walls have already been resorbed or destroyed due to pathological causes [58]. The exposure of growth factors and noncollagenous proteins, as previously stated, will allow an earlier regeneration [14,38]. The UDM on the other hand, thanks to the mechanical stability inherent to the graft, may allow an earlier placement of dental implants [38].

As previously stated, the amount of biomaterial that the clinician can gather is dependent on the extension of carious lesions and filling materials [17,44–46], nonetheless, one possible approach that can overcome this limitation is the extraction of impacted third molars, when it is required a larger amount of biomaterial [51,59].

In order to obtain a demineralized graft, the Korea Tooth Bank, established in Seoul, was one of the first to be available for clinicians [60]. However, due to this time-consuming option, several devices appeared on the market for this purpose.

The VacuaSonic® (Cosmobiomedicare, Seoul, Korea) produces a demineralized graft. This system comes with a powder reagent (DecalSi® DM Powder reagent) and a block

reagent (DecalSi® DM Block reagent), giving the clinician a choice, on which form of graft he prefers. According to the manufacturer, the process takes 30 min for powder graft and 2 h for block graft [50].

Another system that can be used is the Smart Dentin Grinder™ (Kometa Bio ltd., Holon, Israel) which is a device that grinds the tooth to particles of 250–1200 μm, according to the manufacturer. Alongside this grinder, comes a disposable griding chamber (single-use) as well as a dentin cleanser (0.5 M NaOH and 30% ethanol (V/V)) which is applied for 5 min and a phosphate buffer saline (PBS) solution with calcium and magnesium with an application time of 1 min, repeating this last step. This device can be used in order to produce a mineralized or partially demineralized graft, which in this last case, a 10% solution of EDTA during 2 min is added [38].

Finally, another system commonly used to produce a demineralized graft is the Tooth Transformer device (TT Tooth Transformer srl. Milan, Italy). This device comes with a tooth grinder and a series of disposable accessories that contacts with the resulting autologous material and liquid responsible for the demineralization. According to Minetti, this process takes approximately 25 min [61]. Regarding prices, while the VacuaSonic® (Cosmobiomedicare, Seoul, Korea) costs around 12365 €, the Smart Dentin Grinder™ (Kometa Bio ltd., Holon, Israel) costs around 1277 € and finally the Tooth Transformer (TT Tooth Transformer srl. Milan, Italy) device has a price of around 2000 €.

Due to the potential of the autogenous tooth as a bone substitute, several clinical applications have appeared in the literature besides ARP procedures [9,12,35].

One study performed lateral alveolar ridge augmentation comparing the use of autogenous tooth roots versus the use of autogenous bone blocks [62]. In this particular study, after 26 weeks of healing, the implants were placed with no significant difference between groups ($p > 0.05$) in terms of primary implant stability quotient [62].

The use of autogenous tooth graft was also associated with the treatment of grade II and III furcation defects by one study, which compared the clinical and radiologic performance of this graft material with the use of freeze-dried bone allograft [63]. The results of this study point out the potential benefit that autogenous tooth can have as a bone graft material, demonstrating a significant reduction in vertical bone depth, horizontal bone depth as well as radiographically bony defect [63].

Another possible application for autogenous tooth is in sinus floor elevation procedures [64,65]. One particular study compared the use of autogenous tooth versus the bovine-derived xenograft Bio-Oss (Geistlich Pharma AG, Wolhusen, Switzerland) [64]. With a follow up period of 4 months, there was no significant difference between the two groups after a clinical, radiologic and histomorphometry assessment [64]. In another study, Kim et al. performed a micromorphometry and histological evaluation 9 months after sinus bone graft using autogenous tooth [65]. This evaluation concluded that autogenous tooth showed excellent bone healing, proving to be a viable option for this kind of procedure [65].

## 4. Demineralized Dentin Matrix (DDM)

### *4.1. Preclinical Studies*

Two preclinical studies have confirmed the potential of human DDM placed in extraction sockets as well as the influence that this biomaterial has on proteins and growth factors such as BMP-2, BMP-4 and vascular endothelial growth factor (VEGF) [45,46]. In both studies, there was a common protocol: after the removal of caries lesions, pulp tissues and periodontal ligament, the agent responsible for the demineralization was a 10% EDTA solution with a pH varying from 7.2 to 7.3 [45,46]. After cutting with a cryostat, one study stored the material in a sterile phosphate buffered saline (PBS) with penicillin and streptomycin for decontamination [46].

4.1.1. Histologic and Histomorphometric Outcomes

A histologic and morphometric analysis showed that human DDM integrated newly formed bone after 14 days showing histological features of mature bone, proving its osteoconductivity [45,46].

4.1.2. Immunohistochemistry Outcomes

One interesting aspect regarding these studies results from the immunohistochemistry evaluation. Oliveira et al. found that with the degradation of the human DDM, the number of BMP-2 and BMP-4 immunostained cells increased at day 10, suggesting that this event is key in stimulating cellular differentiation and consequently bone formation [46]. A similar result can be seen in Reis-Filho et al.'s study after a period of 14 and 21 days, where with the human DDM resorption, the expression of VEGF increased, indicating angiogenesis, which in turn accelerates the healing process [45]. Both these results support the evidence of the osteoinductive capacity of the DDM [45,46].

*4.2. Clinical Studies*

Furthermore, several clinical studies have been published endorsing the use of DDM in ARP despite diverging in terms of the protocol used for dentin processing [17,37,39,40,44,48–50,66,67].

The removal of carious lesions, fillings and soft tissues seems shoes an apparent unanimity [17,37,39,44,66], however, while most authors use dentin, enamel and cementum, some eliminate these last two [40], or simply use the root portion of the tooth [37]. Some investigators defend the use of dentin alone due to its osteoconductive and osteoinductive properties being similar to alveolar bone [35,43] and in this way enamel shall be removed because it has high-crystalline calcium phosphate and therefore might complicate the absorption process [15,30]. On the other hand, it is described in some protocols the use of the whole tooth as a bone graft material, combining the chemical properties of dentin with the mechanical advantage that enamel brings, allowing an earlier placement of dental implants [38,52,57].

In the majority of these studies, the demineralization agent was not specified [17,39,44,48–50,66], but rather the explanation that the autogenous graft went through a dehydration, defatting, demineralized and lyophilized course [39,66]. Nonetheless, studies often report the use of 70% ethyl alcohol, 0.6 N chloridric acid and 2% nitric acid [37,40,67]. The size of the graft particles varies from 200 to 1000 μm [37,39,40,66].

These studies evaluated the efficacy of this biomaterial in the clinical, radiologic, histologic and morphometric scenario.

4.2.1. Clinical Outcomes

Overall, grafted sites healed without any clinical manifestation of infection, wound dehiscence, or implant failure, in the cases where dental implants were placed [17,44,50]. In these studies, the primary stabilization ranged from 71.8 to 74 implant stability quotient (ISQ) [37,39,49].

Several intervention studies performed an interesting evaluation comparing the clinical, radiologic and histologic efficacy between DDM and a standard xenograft (Bio-Oss (Geistlich Pharma AG, Wolhusen, Switzerland) with excellent and proven efficacy [17,39,40]. Both groups, showed comparable healing process, implant stability and bone formation ration, proving that this biomaterial can be a viable alternative to the xenograft, with the advantage of being autogenous [17,39,40]. Furthermore, from the patient's perspective, autogenous teeth were associated with low levels of pain and swelling [17].

4.2.2. Radiologic Outcomes

Regarding radiologic outcomes, the studies presented favorable results. The mean density of the graft decreased with time, with the architecture of the DDM becoming

increasingly more similar to that of the surrounding bone, suggesting a satisfactory bone healing [40,50,67].

4.2.3. Histologic and Histomorphometric Outcomes

Histologic and histomorphometric analysis showed a good tissue integration with a direct union between the new bone and the graft material, evidencing osteoconductive and osteoinductive properties [39,66]. It was reported a dense lamellar bone formation [48–50] associated with connective tissue rich in angiogenesis [37], fulfilling the goal of minimizing the alveolar bone loss in extraction sockets [44]. The follow-up period on which these results were found varied from 3.5 to 6 months [39,44,48,66].

The most important limitations when comparing these studies are the variety of protocols and adjuvant materials used, for instance absorbable [44,50] or non-absorbable membranes [67], or the use of platelet-rich fibrin (PRF) [40].

**5. Partially Demineralized Dentin Matrix (PDDM)**

Regarding PDDM, only two interventional studies have studied its clinical potential for ARP, one pilot on PDDM associated with platelet-rich plasma [36], and another randomized trial concerning PDDM alone [41].

In terms of protocol for dentin processing, both studies present slight changes. In both studies, the soft tissues, caries and calculus were removed with the teeth being crushed with the auxiliary of different grinders, who generated graft particles varying between 300 and 800 μm [36,41]. The main difference in terms of protocol is the agent used for partial demineralization. On the one side, Minamizato et al. used a 2% $HNO_3$ solution (pH 1.0) for 10 min, followed by an extensive 10 min rinse with 0.1 M Tris-HCl (pH 7.4) [36]. On the other side, Joshi et al. used lactic acid (1N) for a 15–20 min period and later a sterile normal saline solution [41]. The reason behind the choice of an organic acid was, according to Joshi et al., the contact between the residues with human tissues [41].

*5.1. Clinical Outcomes*

Clinically speaking, the postoperative follow-up occurred uneventfully [36,41]. In the Minamizato trial, dental implants were placed at 4–6 months postoperative with primary stability and insertion torque varying from 25 to 40 N cm [36]. At the time of the second surgery, the implant stability quotient (ISQ) was over 60 in all cases, suggesting a positive osteointegration [36]. One factor that could help the healing process is the demineralization the occurred, enhancing the antimicrobial activity of some dentin components [36]. In the Joshi Trial, although no implants were placed, after a period of 4 months, the authors reported that the sockets grafted with PDDM showed visually less width shrinkage when compared with the sites grafted with β-TCP and non-grafted sites [41].

*5.2. Radiologic Outcomes*

Radiographic assessment was made by X-ray panoramic and cone beam computed tomography (CBCT). This analysis showed that the radiopacity of the PDDM decreased gradually with the lamina dura around the graft becoming progressively indistinguishable [36]. Comparing the dimensional changes of the alveolar ridge between PDDM and β-TCP, the width and height loss was lower in the PDDM group, with these values being statistically significant [41]. In terms of ridge height, while in the PDDM group there was a reduction of 0.28 ± 0.13 mm, in the β-TCP group there was a reduction of 1.72 ± 0.56 mm and in the control group it was reported a reduction of 2.60 ± 0.88 mm ($p < 0.05$) [41]. In terms of width, a similar result was achieved, with the control group showing an increased reduction (2.29 ± 0.40 mm), followed by the β-TCP group (1.45 ± 0.40 mm) and finally the PDDM group (0.15 ± 0.08 mm) ($p < 0.05$) [41].

*5.3. Histologic Outcomes*

Finally, histologic analysis showed a positive integration of the PDDM at 4 to 6 months postoperative [36,41]. Histologic specimens of the PDDM group showed newly formed bone in both studies [36,41], with a higher percentage of osteoid formation, when comparing to the β-TCP group [41].

These two studies point out the use of PDDM as a viable option in alveolar ridge regeneration, displaying good clinical, radiologic and histologic outcomes.

**6. Undemineralized Dentin Matrix (UDD)**

In terms of UDD, a solid number of preclinical and clinical studies have been performed evaluating its efficacy [38,51–57,68].

*6.1. Preclinical Studies*

The protocol used for the preparation of this biomaterial was very similar in all of the preclinical studies. The crown portion of the tooth was removed, as well as pulp tissues and periodontal ligament still attached [52,53,68]. This was made by using curettes, ultrasonic devices, hand instruments and specific burs [52,53,68]. In all studies, the preparation was rinsed with a saline solution along with a basic alcohol cleanser [52,53,68]. Finally, either using the Smart Dentin Grinder™ (Kometa Bio ltd., Holon, Israel) [52,53] or a specific grinder [68], the teeth were grinded into particles with diameters over 300 μm and less than 1200 μm [52,53], or between 350 and 500 μm [68].

6.1.1. Histologic and Histomorphometric Outcomes

After assessing the viability of UDD under radiologic, histologic and histomorphometry analysis, some preclinical studies reached opposite conclusions. In 2015, one study, after histologic and histomorphometry analysis, reported that the use of UDD, after 8 weeks did not offered any improvement in bone regeneration, showing in terms of ratio of bone to total area of each probe 170 ± 16 $\mu m^3$ for the control group (no bone graft material used) and 71 ± 14 $\mu m^3$ for the UDD group, with a significant difference ($p < 0.05$) [68].

The opposite was concluded in two other preclinical studies [52,53]. When compared to a healing without any bone graft material, after a 90 days observation period, the added benefit of the UDD was proven [52,53]. In one study, the percentage of newly bone formation was 91.32 ± 0.8% in the UDD group and 65.89 ± 0.6% in the control group ($p < 0.05$) [52]. In the other study, the percentage of immature bone was 14.2 ± 0.66% in the UDD group and 35.17 ± 0.74% in the control group ($p < 0.05$) [53].

*6.2. Clinical Studies*

Equivalently to the studies mentioned before, these clinical studies applied a similar protocol when preparing UDD. Generally speaking, after the teeth extraction, removal of crowns, fillings of any nature, pulp tissues and periodontal ligament, the biomaterial was grinded in order to generate particles with a diameter varying from 300 to 1200 μm [38,51,54–57,59]. In most of the studies, a basic alcohol cleanser consisting of 0.5 M of NaOH and 30%/20% alcohol as well as a sterile phosphate buffered saline were applied to the samples gathered [38,55,56]. This step is important in order to remove organic debris and also possible bacteria and toxins found in dentine [38,55,56].

When assessing the efficacy of the UDD in these studies, one aspect that is worthy of mention is that in some studies a combination of UDD was used either with platelet-rich fibrin [54] or with leukocyte-platelet-rich fibrin and fibrinogen [57], which can be seen as a drawback when analyzing this biomaterial due to lack of standardization as well as understanding the real influence of the UDD.

6.2.1. Clinical Outcomes

Clinically, the healing process was satisfactory, with no major post-operative complications, with less inflammation and rejection response, one potential limitation of other types of bone grafts [38,57].

One particular split-mouth randomized double-blind study deviated from the usual analysis of this subject. This study used UDD from lower third molar extractions and evaluated clinical outcomes such as: pocket depth, recession, clinical attachment level regarding the lower second molar, as well as patient-related outcomes: pain, healing and swelling [51]. After a 3-month observation period, in terms of pocket depth (control group: 3.43 ± 0.79, UDD group: 2.86 ± 0.9), gingival recession (control group: –2.29 ± 1.25, UDD group: -2.86 ± 0.9) and clinical attachment level (control group: 1.14 ± 1.57, UDD group: 0 ± 0), the differences found were not statistically significant ($p > 0.05$) [51]. Finally, regarding patient-related outcomes (pain, healing and swelling), similar results were found, with no statistically significant differences found between groups ($p > 0.05$) [51]. A similar result was found in a split-mouth clinical trial where the use of the lower third molar as a bone substitute resulted in a significant reduction of the pocket depth, mainly in the first 3 months [59]. After a 6-month-period, the bone density found in the test group was greater, with statistically significant difference ($p < 0.001$) [59].

#### 6.2.2. Radiologic Outcomes

Radiologically, CBCT images showed that alveolar ridge dimensions were preserved in most cases [54,55,57]. In the study by Andrade et al. the vertical and horizontal dimensions of the sockets grafted were preserved, and in some cases increased [57]. One particular study by Pohl et al. performed a retrospective radiographic cone-beam computed tomography in order to better assess the efficacy of this graft in terms of volume stability [54]. Comparing the preoperative and the postoperative (4 months after ARP procedure) dimensions, the reduction in the buccal bone plate thickness at 1 mm, 3 mm and 5 mm bellow the buccal crest was, respectively: –0.87 ± 0.84 mm; –0.60 ± 0.70 mm and –0.41 ± 0.55 mm [54]. Following the same level measurements, the mean ridge width changes were, respectively: 1.38 ± 1.24 mm, 0.82 ± 1.13 mm, and 0.43 ± 0.89 mm [54]. Finally, the authors concluded that the average mid-buccal bone height gain was 1.1 % and the mid-lingual height gain was 5.6 % [54]. Another study that evaluated through CBCT analysis the alveolar ridge dimensions before and 4 months after the ARP procedure reported a loss of 0.76 mm in the vertical dimension and a loss of 1.1 mm in the horizontal dimension [69].

#### 6.2.3. Histologic and Histomorphometry Outcomes

Regarding histologic and histomorphometry analyses, UDD generated moderate osteoblastic activity, presenting some dentin fragments as well as connective tissue, suggesting a gradual increase in the graft resorption and consequently bone formation [54,56,57]. Additionally, Andrade et al. reported a consecutive increase of the bone percentage (26.3% at 4 months and 66.5% at 6 months), and a decrease on dentin (10.4 % at 4 months and 0.9% at 6 months) and connective tissue (63.3% at 4 months and 32.6% at 6 months) in the socket, substantiating a gradual bone formation along with graft resorption [57].

## 7. Conclusions

Autogenous teeth as a biomaterial for ARP present osteoconductive and osteoinductive properties, which suggests that they can be an equally effective bone substitute. In some cases, autogenous teeth have superior clinical performance when compared with other grafts. According to this literature review, autogenous teeth, in every form of processing, present potential within the clinical, radiologic and histologic outcomes.

Nonetheless, further research, with standardized protocols in terms of patient selection, dentin processing, surgery procedure and comparison with other grafts are essential in order to reach a definitive conclusion about this graft efficacy. Particularly, there is a scarcity of studies comparing the different dentin processing protocols with each other, though the difference between each method may only rely on the advantages and fallouts of the method itself (demineralization vs. non-demineralization) and not in the clinical potential per se.

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## III. GENERAL DISCUSSION

To the best of our knowledge, this literature review is the first to summarize the main evidence regarding the use of autogenous teeth in alveolar ridge preservation, according to the degree of demineralization: DDM, PDDM and UDD.

Although it was not the focus of this literature review, there were other processing methods described in the literature, such as the elimination of the organic matrix (Elkayar et al., 2009; Moharamzadeh et al., 2008) or the extraction of noncollagenous proteins (Martin De Las-Heras et al., 2000; Tomson et al., 2007). Notwithstanding, the development of an autogenous tooth bone graft material by the Korea Tooth Bank in 2008 led to a significant increase of investigations in this field, dividing the tooth processing according to the degree of demineralization (Kim et al., 2013b).

Regarding the elimination of the organic matrix, the protocol included the soft tissues removal as well as carious lesions followed by the placement of the teeth samples in boiled distilled water (Elkayar et al., 2009; Moharamzadeh et al., 2008). Both Elkayar et al. (2009) and Moharamzadeh et al. (2008) used this method when using bovine teeth (Elkayar et al., 2009; Moharamzadeh et al., 2008). The boiling distilled water allows the elimination of the organic matrix which decreases the risk of disease transmission (Elkayar et al., 2009; Moharamzadeh et al., 2008). Moharamzadeh et al. (2008), after the implantation in rats´s femurs reported a positive biocompability of the processed dentin with the formation of newly formed bone (Moharamzadeh et al., 2008).

Another possible processing method is through the extraction of noncollagenous proteins (Martin De La-Heras et al., 2000; Tomson et al., 2007). The biological plausibility of this method can be explained due to the dentin´s chemical composition (Tomson et al., 2007). Thanks to agents such as guanidium chloride, mineral trioxide aggregate (MTA) or EDTA, there is a release of noncollagenous proteins, which, according to this method, can enhance bone tissue engineering (Martin De Las-Heras et al., 2000; Tabatabaei et al., 2016; Tomson et al., 2007).

As aforementioned, dentin processing through demineralization is the frequently chose method in order to process autogenous teeth prior to its clinical use, in order to enhance the osteoinductive capacity of the biomaterial acting as a scaffold were noncollagenous proteins and growth factors are present and able to induce bone formation (Kim et al., 2013c; Um et al., 2017).

When assessing the available evidence regarding the efficacy of the use of autogenous teeth as a bone graft material, one obstacle to every investigator is the considerable diversity when it comes to the protocol used, where several differences can be found when comparing the studies already published in the literature.

One common step among the different protocols used involves the removal of soft tissues attached to the tooth, such as the periodontal ligament or granulation tissue, elimination of any carious lesions, calculus and filling materials of any nature (Andrade et al., 2019; Binderman et al., 2014; Calvo-Guirado et al., 2018a; Dwivedi & Kour, 2020; Gomes et al., 2006; Joshi et al., 2016; Kim et al., 2010; Nadershah & Zahid, 2019; Pang et al., 2016; Wu et al., 2019). This biomaterial can be used either in particles, after grinding (Andrade et al., 2019; Binderman et al., 2014; Calvo-Guirado et al., 2018a; Dwivedi & Kour, 2020; Gomes et al., 2006; Joshi et al., 2016; Kim, 2015; Kim et al., 2010; Nadershah & Zahid, 2019; Pang et al., 2016; Wu et al., 2019) or as a block (Dwivedi & Kour, 2020; Kim, 2015; Park et al., 2012). It is also described in the literature the use of autogenous tooth roots for staged lateral alveolar ridge augmentation (Schwarz et al., 2019).

One of the aspects where the protocols diverge is the components of the tooth used for the processing. While most studies use the whole tooth (enamel, dentin and cementum) (Andrade et al., 2019; Binderman et al., 2014; Dwivedi & Kour, 2020; Gomes et al., 2006; Joshi et al., 2016; Kim, 2015; Kim et al., 2010; Nadershah & Zahid, 2019; Pang et al., 2016; Wu et al., 2019), other authors chose to only use the root portion (dentin and cementum) (De Oliveira et al., 2013; Del Canto-Díaz et al., 2019; Kadkhodazadeh et al., 2015; Kim et al., 2017; Park et al., 2012; Pohl et al., 2020; Reis-Filho et al., 2012), the crown portion (Park et al., 2012) or the use solely of dentin, removing both the enamel and cementum (Li et al., 2018). Interestingly, two studies reported the use of endodontically treated teeth, after thorough removal of filling materials such as gutta percha (Minamizato et al., 2017; Minetti et al., 2020).

Another step of the protocol where the studies deviate is the agent responsible for the demineralization. Some frequently used agents include EDTA ($C_{10}H_{16}N_2O_8$) (2-10% for 3 months), lactic acid ($C_3H_6O_3$) (1N for 15 to 20 minutes), chloridric acid (HCl) (0.6N for 30 minutes) and nitric acid ($HNO_3$) (2% for 10 to 20 minutes) (De Oliveira et al., 2013; Elfana et al., 2021; Gharpure & Bhatavadekar, 2017; Joshi et al., 2016; Kim et al., 2017; Li et al., 2018; Minamizato et al., 2017; Reis-Filho et al., 2012). Factors such as chemical composition, concentration and time of demineralization also varies between

studies, representing an obstacle when assessing the potential of this biomaterial. Although the choice regarding the degree of demineralization as well as the agent responsible for such step is controversial with no conclusive answer, some studies addressed this topic (Erfan et al., 2020; Um et al., 2021). Um et al. (2020) reported that, when in comparison with EDTA, HCl demineralization led to a more pronounced osteoinductive activity, which in turn allowed a significant release of growth factors and noncollagenous proteins (Um et al., 2021). However, Erfan et al. (2020) after comparing a complete demineralization with HCl versus partial demineralization with EDTA, concluded that the mechanical properties of the graft demineralized with HCl decreased, with this difference being statistically significant ($p < 0.001$) in terms of microhardness (Erfan et al., 2020). In this sense, it is clear that the choice regarding the agent responsible for demineralization of the graft can have an impact on its osteoinductivity and mechanical properties, thus, it is up to the clinician to decide which agent is best for the case at hand (Erfan et al., 2020; Kim et al., 2016).

Additionally, one factor which complicates the real assessment of this biomaterial´s efficacy is that several studies adopt different treatment modalities when using autogenous tooth as a bone substitute in ARP. While some of the studies solely used autogenous tooth as a bone graft, closing the wound through secondary intention with sutures (Calvo-Guirado et al., 2018a; Calvo-Guirado et al., 2018b; De Oliveira et al., 2013; Nadershah & Zahid, 2019) or through primary intention with coronally repositioned flaps (Pang et al., 2016), several authors used alongside autogenous tooth grafts, non resorbable membranes such as PTFE (Gomes et al., 2006) or titatinium mesh (Kim, 2015) or even resorbable membranes (Kim, 2015; Minetti et al., 2020; Wu et al., 2019) with the collagen membrane being frequently used (Del Canto-Díaz et al., 2019; Minamizato et al., 2017). Moreover, several authors used concomitantly platelet-rich fibrin (PRF), platelet-rich plasma (PRP) and recombinant human bone morphogenetic protein-2 (rhBMP-2) with the purpose of enhancing the healing process (Andrade et al., 2019; Binderman et al., 2014; Kim et al., 2017; Li et al., 2018; Minamizato et al., 2017; Pohl et al., 2020).

Overall, the application of DDM presented a clinical, radiologic, histologic and histomorphometric potential in ARP (Chung & Lee, 2011; De Oliveira et al., 2013; Gomes et al., 2006; Kim, 2015; Kim et al., 2017; Kim et al., 2010; Li et al., 2018; Minetti

et al., 2020; Pang et al., 2016; Park et al., 2012; Radoczy-Drajko et al., 2021; Reis-Filho et al., 2012; Wu et al., 2019).

Clinically speaking, wound healing occurred uneventfully with no major post-operative complications such as wound dehiscence, local infection, graft exposure, or implant failure, being able to reduce the inevitable loss after tooth extraction (Kim, 2015; Li et al., 2018; Minetti et al., 2020; Pang et al., 2016; Radoczy-Drajko et al., 2021; Wu et al., 2019). A systematic review published by Gual-Vaqués et al. (2018) described as the main post-operative complications infection (9.1%) wound dehiscence (29.1%) and hematoma (3.64%) (Gual-Vaqués et al., 2018). As regards the dental implants, either they were placed immediately after tooth extraction, combined with the DDM graft (Kim, 2015; Li et al., 2018; Park et al., 2012; Wu et al., 2019), with a primary stabilization ranging from 53 ± 11.9 to 74 (ISQ) (Li et al., 2018; Park et al., 2012) or after a period varying from 4 to 6 months (Kim, 2015; Kim et al., 2017; Minetti et al., 2020; Pang et al., 2016; Radoczy-Drajko et al., 2021) with a primary stabilization from 71.8 to 72.80 ± 10.81 (ISQ) (Kim et al., 2017; Pang et al., 2016).

DDM presented a satisfactory clinical outcome in terms of soft tissue response, infection resistance and ISQ values, proving to be a viable option as a bone graft material (Kim, 2015; Li et al., 2018; Minetti et al., 2020; Pang et al., 2016; Radoczy-Drajko et al., 2021; Wu et al., 2019).

About the radiologic outcomes, several studies reported favorable results (Chung & Lee, 2011; Gomes et al., 2006; Kim, 2015; Li et al., 2018; Radoczy-Drajko et al., 2021; Wu et al., 2019). One recent study has described after a follow-up period of 6 months, an horizontal dimensional loss of 20.7% at the crest level of the alveolar socket, 15.9% 2 mm below the crest and 13.1% 4 mm below the crest (Radoczy-Drajko et al., 2021). In terms of vertical dimensional changes, a gain of 18.3% was observed (Radoczy-Drajko et al., 2021).

After the bone grafting procedure, it is expected to observe a radiopacity of the graft inside the alveolar socket, corresponding to the DDM particles (Gomes et al., 2006; Li et al., 2018). However, as bone healing occurs, this clear radiopacity of the graft decreases, with the alveolar socket presenting a more organized and homogeneous structure, similar to that of the surrounding alveolar bone (Gomes et al., 2006; Li et al., 2018). Such process

can be expected to be achieved in approximately 6 months (Kim, 2015; Li et al., 2018; Radoczy-Drajko et al., 2021; Wu et al., 2019).

The literature available also reports positive results after histologic and histomorphometric evaluation (Chung & Lee, 2011; Kim, 2015; Kim et al., 2017; Kim et al., 2010; Minetti et al., 2020; Pang et al., 2016; Park et al., 2012; Radoczy-Drajko et al., 2021). Following a follow-up period of 4 months, histologic analysis by Kim et al. (2017) described an average of 14.98 ± 10.09% newly formed bone, 6.22 ± 5.5% residual DDM, and 60.86 ± 18.66% soft tissue components (Kim et al., 2017). Additionally, Minetti et al. (2020), in the same follow-up period, reported an average of 36.68 ± 8.90% of bone volume, 19.70 ± 13.75% of residual DDM and finally 20.78 ± 13.29% of vital bone (Minetti et al., 2020). After a follow-up period of 6 months, Radczy-Drajko et al. (2021) revealed, following histologic analysis, a mean of 56% newly formed bone, 7% residual DDM and 37% connective tissue (Radoczy-Drajko et al., 2021). These results are in line with the previously assessment made by Kim et al. (2010), who revealed a mean of 46% to 87% after a follow-up period of 3 to 6 months (Kim et al., 2010).

It was confirmed a gradual resorption of the bone graft, allowing new bone formation with the presence of osteoblasts and matured osteocytes (Kim, 2015; Pang et al., 2016; Park et al., 2012; Radoczy-Drajko et al., 2021). Overall, in the samples collected in the studies, it was described the presence of newly formed bone in a trabecular structure, connective tissue and residual graft particles, surrounded by osteoid, with a direct union between the biomaterial and the new bone, ensuring a satisfying integration of the bone graft (Kim, 2015; Kim et al., 2017; Kim et al., 2010; Pang et al., 2016; Park et al., 2012; Radoczy-Drajko et al., 2021). An important aspect reported in the histological assessments made is the absence of chronic inflammation and filling materials of any nature (e.g. composite, gutta-percha) (Kim, 2015; Kim et al., 2017; Minetti et al., 2020).

Several studies seem to endorse the osteoconductive and osteoinductive properties of DDM, describing the previously mentioned histological outcomes after a follow-up period ranging from 3 to 6 months (Chung & Lee, 2011; Kim, 2015; Kim et al., 2017; Kim et al., 2010; Minetti et al., 2020; Pang et al., 2016; Park et al., 2012; Radoczy-Drajko et al., 2021).

Regarding the osteoinductive properties of this graft, two interesting animal studies were performed in order to assess the expression of specific growth factors in DDM particles

placed in rats´s alveolar sockets (De Oliveira et al., 2013; Reis-Filho et al., 2012). Through immunohistochemical analysis, it was concluded that as the DDM particles are resorbed, growth factors such as VEGF, BMP-2 and BMP-4 are released, within a period of 5 to 10 days, granting this biomaterial with an osteoinductive capacity (De Oliveira et al., 2013; Reis-Filho et al., 2012). These growth factors may have a pivotal role in bone healing, since VEGF can stimulate angiogenesis and consequently osteogenesis, and BMP´s also stimulate cell differentiation (De Oliveira et al., 2013; Reis-Filho et al., 2012).

Regarding the use of DDM as a bone graft material, several investigations assessed its clinical performance in comparison with a frequently used xenograft with a high level of evidence (Bio-Oss, Geistlich Pharma AG, Wolhusen, Switzerland) (Li et al., 2018; Pang et al., 2016; Wu et al., 2019).

Pang et al. (2016), 6 months following ARP procedure, performed an histologic analysis where an average of 31.24 ± 13.87% newly formed bone was found in the DDM group and 35.00 ± 19.33% was seen in the Bio-Oss group (Pang et al., 2016). In terms of ISQ, while the DDM group showed a quotient of 72.80 ± 10.81, the Bio-Oss group presented a ISQ of 70.0 ± 12.86 ($p = 0.755$) (Pang et al., 2016). In terms of vertical dimensional changes, the DDM group reported an increase of 5.38 ± 2.65 mm while the Bio-Oss group led to an increase of 6.56 ± 3.54 ($p = 0.337$) (Pang et al., 2016).

Moreover, Li et al. (2018), 18 months after immediate implant placement along with either DDM or Bio-oss as a bone graft material described similar results (Li et al., 2018). Regarding ISQ, while the DDM group showed a quotient of 79.5 ± 6.0, the Bio-Oss group reported a quotient of 80.2 ± 4.3 ($p = 0.09$) (Li et al., 2018). In terms of marginal bone resorption, while the DDM group showed a resorption of 1.9 ± 0.6 mm, the Bio-oss group had a resorption of 2.0 ± 0.5 mm ($p = 0.18$) (Li et al., 2018).

Wu et al. (2019) assessed radiographically the horizontal dimensional changes of the alveolar ridge at level 0 mm, 3 mm and 6 mm following an immediate implant placement associated with DDM or Bio-Oss (Wu et al., 2019). After a follow-up period of 12 months, the DDM group reported a dimensional change of respectively, 7.99 ± 5.29% , 6.94 ± 2.70% and 4.58 ± 1.91% while the Bio-Oss group showed a change of 7.18 ± 2.62% , 6.31 ± 2.76% and 5.15 ± 2.36% ($p > 0.05$) (Wu et al., 2019). During this period,

the marginal bone resorption of the DDM group was around 0.38 ± 0.1 mm and 0.31 ± 0.12 mm in the Bio-Oss group ($p > 0.05$) (Wu et al., 2019).

In these studies, no statistically significant differences were found between the two groups in regard to new bone formation, ISQ and marginal bone resorption, advocating that the use of DDM can be a viable option in addressing ARP procedures (Li et al., 2018; Pang et al., 2016; Wu et al., 2019). Moreover, one relevant factor is the patient´s perception, which can have an impact in the procedure itself (Wu et al., 2019). In one particular study, after answering a questionnaire, the group of patients which received DDM as a bone graft material reported less pain and swelling, in comparison with the xenograft group, describing a higher level of satisfaction (Wu et al., 2019).

Furthermore, in two studies where PDDM were used as a bone graft material in ARP, similar positive results were achieved in terms of clinical, radiologic and histologic outcomes (Joshi et al., 2016; Minamizato et al., 2017).

After ARP procedure using PDDM, no significant post-operative complications were described, with bone healing occurring as expected (Joshi et al., 2016; Minamizato et al., 2017). After a follow period ranging from 4 to 6 months (Joshi et al., 2016; Minamizato et al., 2017), implants were successfully placed, with insertion torque of 25 to 40 N cm (Minamizato et al., 2017). ISQ values at the time of the second surgery, 3 months after implant placement, varied from 65 to 80, with no implant loss during a period of 1 year (Minamizato et al., 2017).

In terms of radiologic assessment, in line with the radiologic outcomes of DDM, a gradual decrease of PDDM´s radiopacity was observed, as bone formation occurred (Minamizato et al., 2017). Through cone beam computerized tomography (CBCT), such radiologic analysis was able to be performed, indicating that the use of such biomaterial was essential in reducing the alveolar ridge loss that naturally occurs after a tooth extraction (Joshi et al., 2016).

In both studies, histologic evaluation was made at 4 to 6 months after the ARP procedure, having reached similar results (Joshi et al., 2016; Minamizato et al., 2017). In both studies it was reported PDDM particles surrounded with newly formed bone, connective tissue as well as osteoid, an indicator of new bone formation (Joshi et al., 2016; Minamizato et al., 2017).

The comparison of PDDM versus an alloplast, β-TCP, was conducted by one randomized, controlled, prospective, clinical pilot study where PDDM presented better clinical, radiologic and histologic outcomes (Joshi et al., 2016). Not only PDDM showed, visually, less alveolar ridge reduction, but it was also reported a statistically significant difference in terms of alveolar ridge dimensions after ARP between the two groups (Joshi et al., 2016). While the PDDM group reported, 4 months after the ARP procedure, a vertical dimensional decrease of 0.28 ± 0.13 mm, the β-TCP group revealed a decrease of 1.72 ± 0.56 mm, with the control group (no bone graft) having a decrease of 2.60 ± 0.88 mm ($p < 0.05$) (Joshi et al., 2016). Regarding horizontal dimensional changes, the changes were less pronounced in the PDDM group, with a reduction around 0.15 ± 0.08 mm, followed by the β-TCP group with a reduction of 1.45 ± 0,40 mm and finally the control group presenting a reduction of 2.29 ± 0.40 mm ($p < 0.05$) (Joshi et al., 2016).

Finally, after histologic evaluation, there were less newly formed bone and osteoid formation in the β-TCP specimens, endorsing the results previously mentioned (Joshi et al., 2016).

Finally, several studies evaluated the efficacy of UDD in ARP procedures, having reached equally positive results (Andrade et al., 2019; Binderman et al., 2014; Calvo-Guirado et al., 2018a; Calvo-Guirado et al., 2018b; Del Canto-Díaz et al., 2019; Dwivedi & Kour, 2020; Kadkhodazadeh et al., 2015; Nadershah & Zahid, 2019; Pohl et al., 2020; Sánchez-Labrador et al., 2020).

As regards to clinical outcomes, equivalently to DDM and PDDM studies, the healing process after ARP procedure occurred without any sign of a rejection response by the host or post-operative complications (Andrade et al., 2019; Binderman et al., 2014; Nadershah & Zahid, 2019). The time between the ARP procedure with UDD and implant placement varied from 4 to 6 months (Andrade et al., 2019; Dwivedi & Kour, 2020; Pohl et al., 2020), with one study reporting an insertion torque over 40 N cm in approximately 90 % of the patients (Dwivedi & Kour, 2020). UDD was also used for ARP after lower third molar extraction, in order to assess its efficacy in minimizing periodontal defects commonly seen after such procedure (Nadershah & Zahid, 2019; Sánchez-Labrador et al., 2020). While Nadershah & Zahid (2019) reported no differences statistically significant between the UDD group and the control group (natural healing without a bone graft material), a more recent study performed by Sanchéz-Labrador et al. (2020) reported statistically significant differences in terms of probing depth, bone density (assessed

radiographically), and alveolar bone crest maintenance between the two groups (Nadershah & Zahid, 2019; Sánchez-Labrador et al., 2020). In both studies, UDD was considered a viable option in ARP procedure, with the potential of minimizing the hard and soft tissue loss inherent to lower third molar extractions (Nadershah & Zahid, 2019; Sánchez-Labrador et al., 2020).

UDD also reported satisfying results in terms of radiologic assessment (Andrade et al., 2019; Binderman et al., 2014; Del Canto-Díaz et al., 2019; Dwivedi & Kour, 2020; Pohl et al., 2020). Canto-Díaz et al. (2019) assessed throughout 16 weeks the dimensional as well as the densitometric changes between post-extraction sockets grafted with UDD (UDD group) and the post-extraction sockets who healed without the use of any bone graft material (control group) (Del Canto-Díaz et al., 2019). Following 16 weeks, after measurements between the bottom of the sockets to the crestal area of the lingual cortical bone, while the UDD group presented a reduction of 4.2%, the control group decreased 16.87% (Del Canto-Díaz et al., 2019). In terms of socket width, with radiographic references at 1 mm, 3 mm and 5 mm, the UDD group revealed a reduction of 14.9%, 6.66% and 0.3% while the control group showed a reduction of 59.4%, 39,5% and 10.2%, respectively (Del Canto-Díaz et al., 2019). The difference between these two groups was statistically significant at 1 mm and 3 mm ($p = 0.098$) (Del Canto-Díaz et al., 2019). Del Canto-Díaz et al. (2019) also performed a densitometric analysis in order to assess the bone density of the regenerated bone in the coronal, medial and apical portion of the post-extraction sockets obtaining the following results: UDD group (922.68 ± 250.82 HU, 840.74 ± 392.35 HU, 817.22 ± 260.79 HU) control group (564.35 ± 288.73 HU, 708.33 ± 148.35 HU, 876.30 ± 256.87 HU), respectively (Del Canto-Díaz et al., 2019). The results published by Dwivedi & Kour (2020) are in agreement with the previously mentioned study as both point out the potential and benefit of UDD as a bone substitute (Del Canto-Díaz et al., 2019; Dwivedi & Kour, 2020). After comparing the average dimensional values before ARP procedure (height: 26.962 ± 0.7129 mm, width: 11.652 ± 1.1073 mm) and 4 months following such procedure (height: 27.562 ± 0.7626 mm, width: 12.330 ± 0.8795 mm) statistical differences were found in terms of height ($p = 0.009$) and width ($p = 0.001$) (Dwivedi & Kour, 2020).

Comprehensively, ARP procedure using UDD was able to decrease the alveolar bone loss, allowing a positive osteointegration of dental implants (Andrade et al., 2019; Binderman et al., 2014). In this sense, in comparison with natural healing, the use of UDD

allows a better preservation of the alveolar socket dimensions, which is key in future oral rehabilitation (Del Canto-Díaz et al., 2019).

Histological and histomorphometric analysis displayed that the use of UDD promoted mature bone formation as the graft particles were resorbed (Andrade et al., 2019; Binderman et al., 2014; Dwivedi & Kour, 2020; Pohl et al., 2020). Several studies reported an intimate contact between the dentin particles and the newly formed bone, allowing an adequate dentin-bone interface and the placement of dental implants (Andrade et al., 2019; Binderman et al., 2014; Dwivedi & Kour, 2020; Pohl et al., 2020). Dwivedi & Kour (2020) reported 4 months after ARP procedure 34 to 66% of newly formed bone in 40% of the patients and 67 to 100% in 60% of the patients (Dwivedi & Kour, 2020). Through histological and histomorphometric analysis, two animal studies concluded that UDD revealed statistically significant differences in terms of newly formed bone versus natural healing after 90 days, favouring the UDD group, which endorses its potencial as a bone graft material (Calvo-Guirado et al., 2018a; Calvo-Guirado et al., 2018b). While one study revealed an average of 77.18 ± 0.76 % newly formed bone in the UDD group versus 59.92 ± 0.32 in the control group ($p < 0.017$) (Calvo-Guirado et al., 2018b), another similar study reported an average of 91.32 ± 0.8 % in the UDD group and 65.89 ± 0.6 % in the control group ($p < 0.05$) (Calvo-Guirado et al., 2018a).

Santos et al. (2021) performed a randomized controlled clinical trial where they compared the use of UDD (test group) versus a xenograft (Bio-Oss, Geistlich Pharma AG, Wolhusen, Suíça) (control group) in ARP procedures with implant placement 24 weeks later, with a follow-up period of 18 months (Santos et al., 2021). No statistically significant differences were found in terms of clinical outcomes, such as ISQ, radiologic and patient-related (Santos et al., 2021). Notwithstanding, following histologic analysis, the authors reported a higher percentage of newly formed bone in the UDD group (47.3%) when in comparison with the Bio-Oss group (34.9%), with this difference being statistically significant ($p < 0.001$) (Santos et al., 2021). Consequently, the percentage of residual graft was significantly lower in the UDD group (12.2%) than in the Bio-Oss group (22.1%) ($p < 0.001$) (Santos et al., 2021).

Recently, Elfana et al. (2021) performed a randomized controlled clinical trial where UDD and DDM were compared in terms of clinical, radiologic and histological outcomes (Elfana et al., 2021). In line with other publications, the healing occurred uneventfully

and no statistically significant differences were found following radiologic assessment ($p > 0.05$) (Elfana et al., 2021). Regarding histologic analysis, higher percentages of newly formed bone and lesser residual graft particles were associated with the DDM group at 6 months follow-up, suggesting that the demineralization process could have expedite the degradation of the mineral content of the graft and allowed an earlier release of the growth factors, thus enhancing the osteoinductive potential (Elfana et al., 2021).

Overall, the use of autogenous teeth as a bone graft material presents several advantages when in comparison with other bone grafts such as allografts, xenografts or alloplasts (Elfana et al., 2021). When using autogenous teeth, there is no risk of disease transmission or immunogenicity, which are limitations of allografts and xenografts, showing simpler processing and storage methods (Elfana et al., 2021; Figueiredo et al., 2010; Gual-Vaqués et al., 2018; Oryan et al., 2014). Moreover, autogenous teeth presents both osteoconductive and osteoinductive properties, unlike xenografts, alloplasts and most of allografts (Fukuba et al., 2021; Gual-Vaqués et al., 2018; Kim, 2012; Kim, et al., 2013b; Kim et al., 2013c; Tabatabaei et al., 2016; Um et al., 2017). When in comparison with autogenous bone, although it does not have osteogenic properties, it reduces the patient morbidity, surgical time and resorption rates, which are drawbacks of autogenous bone grafts (Elfana et al., 2021; Figueiredo et al., 2010; Gual-Vaqués et al., 2018; Jakoi et al., 2015; Khan et al., 2005; Oryan et al., 2014; Ramanauskaite et al., 2019; Santos et al., 2013; Sutherland & Bostrom, 2005).

Nevertheless, autogenous teeth show some inherent limitations that clinicians must bear in mind (Elfana et al., 2021). Not only the amount of biomaterial is dependent of the extent of carious lesions and filling materials but also its use is only possible when the patient has a tooth indicated for extraction, being used as a bone graft material the tooth located in the socket where ARP will be performed (De Oliveira et al., 2013; Elfana et al., 2021; Minetti et al., 2020; Reis-Filho et al., 2012; Wu et al., 2019) or another tooth with the same indication, such as third molars (Nadershah & Zahid, 2019; Sánchez-Labrador et al., 2020).

## IV. CONCLUSIONS AND FUTURE PERSPECTIVES

When choosing a bone graft material for ARP procedure, each biomaterial available has advantages and limitations, which can pose a challenge to the clinician upon deciding which biomaterial to operate.

The use of autogenous teeth as a bone substitute for ARP procedure can be justified due to its osteoconductive and osteoinductive properties, presenting potential within clinical, radiologic and histologic outcomes.

Our literature review summarized the existing evidence regarding the use of autogenous teeth according to the dentin processing used (DDM, PDDM and UDD). Each dentin processing reported satisfactory results, indicating to be equally effective as other bone grafts and in some cases, more efficient. As to the clinical indication for each type of dentin processing (DDM, PDDM and UDD), in light of the current evidence, DDM is indicated for clinical situations where it is necessary a more pronounced influence of growth factors and noncollagenous proteins, enhancing the osteoinductivity of the bone substitute. On the other hand, UDD, despite having a late osteoinductivity, presents a good osteoconductive capacity. Finally, PDDM presents mainly an osteoconductive capacity as well as a moderate osteoinductive property.

Nevertheless, sample size, follow-up periods and the concomitant use of autogenous teeth with other materials difficults the real assessment of this bone substitute. In this sense, more randomized controlled clinical trials are needed with standardized protocols in terms of patient selection, surgical approach and comparison with other grafts in order to reach a more definitive conclusion.

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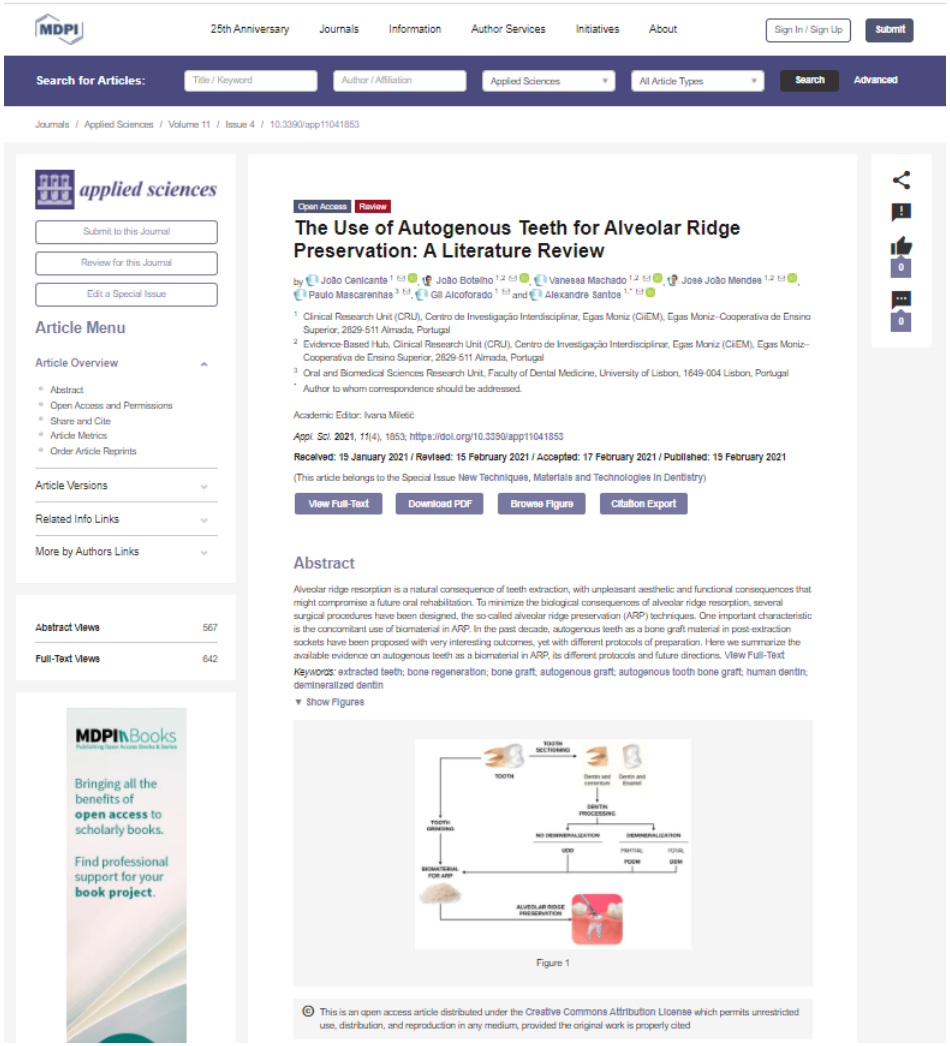
# VI. APPENDICES



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# The Use of Autogenous Teeth for Alveolar Ridge Preservation: A Literature Review

by João Caricante [1], João Botelho [1,2], Vanessa Machado [1,2], José João Mendes [1,2], Paulo Mascarenhas [3], Gil Alcoforado [1] and Alexandre Santos [1,*]

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## Abstract

Alveolar ridge resorption is a natural consequence of teeth extraction, with unpleasant aesthetic and functional consequences that might compromise a future oral rehabilitation. To minimize the biological consequences of alveolar ridge resorption, several surgical procedures have been designed, the so-called alveolar ridge preservation (ARP) techniques. One important characteristic is the concomitant use of biomaterial in ARP. In the past decade, autogenous teeth as a bone graft material in post-extraction sockets have been proposed with very interesting outcomes, yet with different protocols of preparation. Here we summarize the available evidence on autogenous teeth as a biomaterial in ARP, its different protocols and future directions. View Full-Text

*Keywords:* extracted teeth; bone regeneration; bone graft; autogenous graft; autogenous tooth bone graft; human dentin; demineralized dentin

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Figure 1

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Face ao resultado meritório deste projeto, este grupo de trabalho (João Cenicante, João Botelho, Vanessa Machado, José João Mendes, Paulo Mascarenhas, Gil Alcoforado, Alexandre Santos) viu ser premiado o seu esforço com a publicação do seguinte artigo científico:

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Cordialmente,

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Estimado aluno,

Congratulo-o pelo trabalho de mérito publicado, bem como a toda a equipa de investigação que a acompanha, agradecendo o empenho de todos.

Neste sentido, e também ouvido o Regente de Orientação Tutorial, a Presidente da Comissão Científica e a Coordenadora de ciclo de estudo, não vimos nenhum impedimento à forma como pretende organizar e adequar o seu trabalho escrito, permitindo a sua execução.

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