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FACULDADE DE MEDICINA DENTÁRIA
VISEU

COMPARISON BETWEEN TOOTH-DERIVED MATRIX AND DBBM GRANULES ON AN ENHANCED BONE HEALING: A SCOPING REVIEW

Dissertação apresentada à Universidade Católica Portuguesa para obtenção do grau de Mestre em Medicina Dentária

Por:

Victor Cirfeda

Viseu, 2024

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Orientador: **Professor Doutor Júlio César Matias de Souza**

Coorientador: **Professor Doutor Bruno Henriques, CMEMS-UMINHO**

Viseu, 2024

Epigraph

“Non smettere mai di credere nei tuoi sogni.”

Dedications

“A miei carissimi nonni, che non sono più con noi. Questo traguardo è dedicato a voi, che mi avete insegnato il valore del duro lavoro e dell'educazione. La vostra assenza ha lasciato un vuoto, ma il vostro spirito continua a guidarmi. Grazie per avermi dato la forza e l'ispirazione per completare questo lungo percorso. Spero di rendervi orgogliosi. Un giorno ci riconteremo.”

Acknoweledment

Queria exprimir a minha mais profunda gratidão ao meu orientador, Professor Julio Souza, pelo seu inestimável apoio e conselhos durante a redação da minha tese. Além disso, gostaria de agradecer calorosamente a todos os professores que tive o privilégio de conhecer ao longo dos anos. Sem a vossa orientação e sabedoria, não teria conseguido atingir este marco importante. Obrigado do fundo do meu coração.

Un ringraziamento speciale va a mio padre, la cui presenza e sostegno sono stati fondamentali per la realizzazione di questo sogno. Senza di lui, non avrei mai potuto raggiungere questo traguardo. Un sentito grazie alla mia famiglia, la cui presenza costante e l'amore incondizionato mi hanno sostenuto in ogni momento. Nei momenti di gioia e nei momenti di sfida, siete sempre stati al mio fianco, offrendomi conforto e forza. Il vostro sostegno ha reso possibile ogni mio successo e per questo vi sono eternamente grato.

Desidero esprimere un ringraziamento pieno d'amore alla mia ragazza. Nei momenti più bui, sei stata la mia luce, una fonte di conforto e di speranza. La tua presenza costante al mio fianco ha reso i momenti difficili più sopportabili. Il tuo amore e il tuo sostegno sono stati inestimabili. Grazie, dal profondo del mio cuore, per essere sempre al mio fianco. Sei un dono prezioso nella mia vita. Grazie di cuore, amore mio.

Infine, vorrei esprimere un ringraziamento che va oltre le parole al mio caro amico Matteo. In questo momento di difficoltà, la tua resilienza e il tuo coraggio sono un faro di speranza e ispirazione per me. La tua amicizia è un dono prezioso che ho avuto la fortuna di ricevere. Nonostante le sfide che stai affrontando, sei rimasto un amico straordinario. Il mio cuore si riempie di gratitudine per te. Ti auguro con tutto il cuore di ritrovare presto la salute e la pace interiore. Sei costantemente nei miei pensieri e nelle mie preghiere. Grazie, Matteo, per tutto quello che sei. Sei un vero amico.

Resumo

Objetivo: O objetivo deste projeto foi realizar uma *scoping review* sobre a comparação entre a matriz derivada do dente e os grânulos de tecido ósseo bovino desproteinizado (DBBM) para potenciar a cicatrização óssea.

Materiais e Métodos: Foi realizada uma pesquisa bibliográfica nas bases de dados eletrónicas PubMed e Scopus de estudos publicados em língua Inglesa até abril de 2024. Foram avaliadas as seguintes palavras-chave: "deproteinized bovine bone mineral" OR "DBBM" OR "Bio-Oss" AND "dentin matrix" OR "tooth-derived" OR "dentin" OR "dentin-derived" OR "ATDM" OR “ATDG” AND "bone substitute" OR “graft” OR “granule” OR “block” AND “bone” AND “healing” OR “repair” OR “augmentation” OR “regeneration” OR “growth” OR “formation” OR “osteoblast” OR “osteogenic” OR “mineralization” OR “cell culture”.

Resultados preliminares: Os grânulos da matriz derivada da dentina revelaram a presença de túbulos dentinários remanescentes que são benéficos para a absorção de proteínas e moléculas do meio. Vale enfatizar que a dentina remanescente é uma fonte intrínseca de colagénio e de factores de crescimento como o TGF-1, BMP-2, VEGF e PDGF. Já, os grânulos de DBBM apresentaram poros interconectados em macro-escala que também suportam a adesão celular e a formação de novos vasos sanguíneos. O DBBM revelou uma porosidade de aproximadamente 80% e uma menor taxa de reabsorção quando comparado a grânulos derivados do dente. Em modelos in vivo, os grânulos de matriz dentinária induziram resultados bastante semelhantes para o crescimento ósseo quando comparados com o DBBM, tal como confirmado por análises imunohistoquímicas.

Conclusões: Os grânulos de matriz derivada da dentina apresentaram aspectos morfológicos e composição química adequada para potenciar o reparo ósseo comparável ao efeito dos grânulos de tecido ósseo bovino desproteinizado. O enxerto autólogo derivado da dentina é um material alternativo eficaz para o reparo ósseo.

Palavras-chave: matriz derivada de dentina, DBBM, mineral ósseo bovino desmineralizado, cicatrização óssea, enxerto ósseo.

Abstract

Purpose: The purpose of this project was to perform a scoping review on the comparison between tooth-derived matrix and demineralized bovine bone mineral (DBBM) granules for enhanced bone healing.

Materials and Methods: A literature search was conducted on PubMed and Scopus electronic databases studies published in English until April 2024. The following keywords were assessed: "deproteinized bovine bone mineral" OR "DBBM" OR "Bio-Oss" AND "dentin matrix" OR "tooth-derived" OR "dentin" OR "dentin-derived" OR "ATDM" OR “ATDG” AND "bone substitute" OR “graft” OR “granule” OR “block” AND “bone” AND “healing” OR “repair” OR “augmentation” OR “regeneration” OR “growth” OR “formation” OR “osteoblast” OR “osteogenic” OR “mineralization” OR “cell culture”.

Preliminary results: The dentin-matrix granules revealed micro-scale pores due to the remnant dentin that promote the adsorption of proteins and bioactive molecules. It should be highlighted the remnant dentin is intrinsic source of collagen and growth factors such as TGF-1, BMP-2, VEGF, and PDGF. The DBBM showed macro-scale interconnected pores which enhances the adhesion of cells and formation of new blood vessels. DBBM also revealed a porosity of around 80% and a lower resorption rate when compared to tooth-derived granules. On in vivo models, dentin-matrix granules induced quite similar results for bone growth when compared to grafting with DBBM as confirmed by histological analyses.

Conclusions: The dentin-derived matrix granules showed morphological aspects and chemical composition suitable for enhancing bone repair comparable to the effects of deproteinized bovine bone mineral granules.The autologous dentin-derived graft is an effective alternative material for bone augmentation.

Key words: dentin-derived matrix, DBBM, demineralized bovine bone mineral, bone healing, bone graft.

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Tables and Figure Index

List of abbreviations and acronyms

DBBM: Deproteinized Bovine Bone Mineral.

ATDM: Autogenous Dentin Matrix.

PRISMA: Preferred Reporting Items for Systematic Reviews.

PICO: Population, Intervention, Comparison, Outcome

IGF-2: Insulin-like growth factor 2.

MSC: Mesenchymal stem cells.

TGF: Transforming growth factor.

BMP-2: Bone morphogenetic protein 2.

HA: Hydroxyapatite.

PDL: Periodontal ligament.

EDTA: Ethylenediaminetetraacetic acid.

NaOH: Sodium hydroxide.

PBS: Phosphate buffer.

ISQ: Implant stability quotient.

β-TCP: β-tricalcium phosphate.

PDGF: Platelet Derived Growth Factor.

TGF-b: Transforming Growth Factor-b.

FGF: Fibroblast Growth Factor.

IGF: Insulin Like Growth Factor.

VEGF: Vascular Endothelial Growth Factor.

EGF: Epidermic Growth Factor.

ECM: Extracellular Matrix.

GBR: Guided Bone and Tissue Regeneration.

PRT: platelet-rich plasma.

PRF: platelet-rich fibrin.

BMSC: Bone Marrow stromal cells.

DMP1: Dentinal matrix protein 1.

MSFA: Sinus floor in dogs.

1.INTRODUCTION

1. Introduction

After bone loss, dimensional alterations occur on alveolar bone ridge, resulting in complications for further oral rehabilitation (1–3). The use of bone grafting materials aims at supporting the bone healing after a surgical procedure. Bone grafting acts as a support for osteogenic cell differentiation and clot stabilisation decreasing the risks of soft tissue collapse in bone defects (1,4–6). Autogenous bone grafts are traditionally used although some limitations have been reports such as the need of a donor site for bone harvesting, increased surgical morbidity and high rates of bone remodelling (1,4,5,7) (2,4,5,7–9). In fact, autogenous material harvesting is often a highly invasive procedure. The use of other bone substitutes such as allografts, xenografts and alloplasts can be considered as alternative approaches for atrophic alveolar ridge treatment (1–3,9). Among xenografts, deproteinized bovine bone mineral (DBBM) has been well-reported in literature and its clinical application has widely increased in the last year (1). DBBM is gathered from bovine bone sources through an extraction processing using chemical and thermal treatment leading to a complete removal of organic matter, while preserving the hydroxyapatite integrity of the original bone architecture (1). The porous three-dimensional (3D) structure of DBBM granules stimulate growth, migration and differentiation of human cells for bone healing (1). In vivo studies have validated a faster blood vessels' formation and bone growth after bone grafting with DBBM (1,4–6). Thus, DBBM granules fulfil certain requirements for enhanced bone healing, such as: (i) interconnected macro-scale pores with size from 100 up to 400 μm to allow the integration and vascularization of bone tissue; (ii) high wettability of the surface inducing cell adsorption and proliferation; (iii) balanced bio-integration and bio-absorption; (iv) adequate compressive strength ranging from 2 up to 10 MPa (a compressive strength comparable to cancellous bone); and (v) industrial viability to be synthesized on specific shape and size (2,4,5,8,9).

Bone is a complex tissue described as a natural composite of 70% hydroxyapatite (Hap) and 30% collagen, possessing a natural functionally gradated porous structure (2,4,5,8,9). Thus, alternative bone substitutes should have a similarly porous composite structure with interpenetrating inorganic and organic phases. The chemical composition of teeth shows remarkable similarities with that of bone structures. Dentin has around 60–80% Hap, type I collagen, growth factors, non-collagenic proteins (NCPs), and the following growth factors: insulin-like growth factor

(IGF)-II, bone morphogenetic protein (BMP)-2, and transforming growth factor (TGF)-b (2–4,10). The proportion of inorganic and organic components in dentin and bone reflects distinctive biochemical affinity for adsorption of proteins and osteogenic cell behavior(2,3). It is relevant to point out that both teeth and jaw bones have a common embryological origin, both deriving from the neural crest (2–4).

Recent studies have provided evidence that autologous tooth-derived matrix (ATDM) reveals osteogenic stimuli thanks to its chemical composition and biological content. A harvested tooth can be mechanically and chemically treated providing a particulate material within 15–20 \min. Thus, the clinical feasibility of preparing ATDM granules plays a major role in the use of such material as a bone substitute. However, the amount of ATDM granules is limited, and therefore, a mixture with xenogeneic or synthetic bone substitutes has become a promising strategy for bone healing. In addition, the source of graft material can be absent in some cases that do not show indications for tooth extraction. In fact, the type, concentration, and exposure time of the chemical substances determine the morphological aspects and chemical composition of the tooth-derived matrix.

1.1. Objectives and hypothesis

The purpose of this study was to perform a scoping review on the comparison between tooth-derived matrix and demineralized bovine bone mineral granules for enhanced bone healing considering osteogenic cell behaviour, new bone formation, blood vessels' formation, residual graft material, and connective tissue. It was hypothesized that autologous tooth-derived matrix and bovine bone mineral granules reveals different pathways to stimulate osteogenic cell enhancing the bone healing.

2.STATE OF ART

2.State of art

2.1. Deproteinized bovine bone mineral (DBBM)

Deproteinized bovine bone mineral (DBBM) granules are retrieved from cattle sources and then treated by chemical and thermal treatment leading to a complete removal of organic matter, while preserving the hydroxyapatite integrity of the original bone architecture, as shown in Figure 1 (1) (8). Preferred bone sources include fragments of the femur, tibia, radius, and ulna.

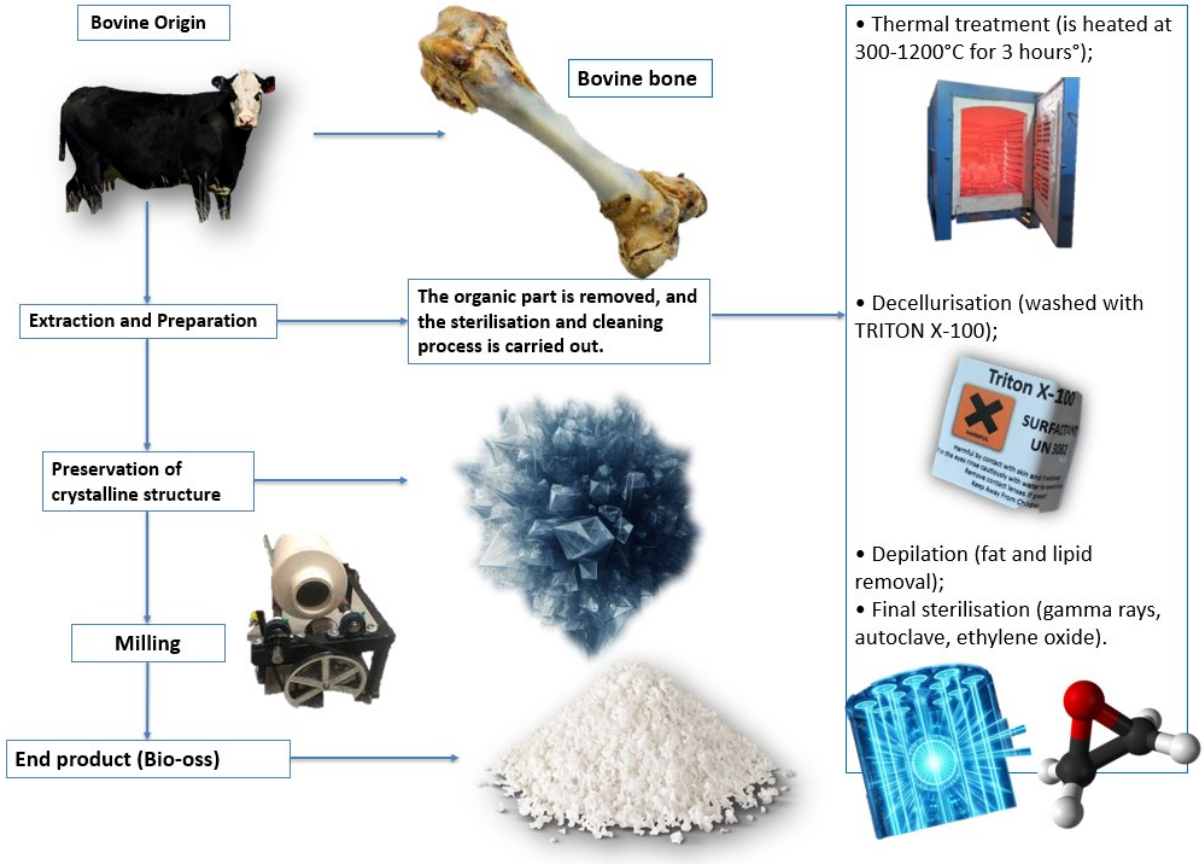

Figure 1. Bio-oss™ Manufacturing of deproteinized bovine bone mineral (DBBM, Bio-oss™ , Geistlich, Switzerland).

The manufacturing of DBBM granules starts with the rinsing of the raw bone and removal of soft tissue including periosteum and extraction of the bone marrow using a marrow scraper. Bone tissues are cut into fragments using a saggital saw and then washed several times in hot water (55-59°C) to remove the organic matter. Also, the

removal of lipids (degreasing) can be performed using organic solvents such as chloroform / methanol, 95% ethanol, 70% ethanol, diethyl ether, or liquid non-ionic surfactants. After rinsing, the bone fragments cane be stored at -80 °C before lyophilisation for 3 days in a freeze drier prior to milling and storage at -80 °C (8). After the degreasing, the bone tissue is milled using ball milling and then the granules are separated by sieve and sorted according to the size (11). A partially demineralization can be carried out using various acidic solutions such as HCl, EDTA, formic acid, citric acid, nitric acid, acetic acid and/or nitric acid under stirring (8). Next, the material undergoes a thermal treatment ranging from 300 up to 1200 °C over a period of 3h. Finally, the material is sterilised by gamma-Rays irradiation. Such steps ensure the preservation of the crystalline structure. Once all steps are completed, the material is milled using ball milling, reducing the material into granules(11).

Regarding the size of the DBBM granules, several studies have shown two types of granules for bone grafting procedures, namely: (i) Larger granules ranging from 1up to 2 mm (1000-2000 μm), as shown in Figure 2; (ii) Smaller granules ranging from 0.25 and 1 mm (250-1000 μm) (11,12). The porosity of the DBBM granules is around 75% and 80%. The size of the pores ranges from 50 up to 490 μm at micro-scale although sub-micron pores are found at around 330 and 670 nm (12,13). As seen in Figure 2, the macro-scale pores are interconnected that support the bone formation process.

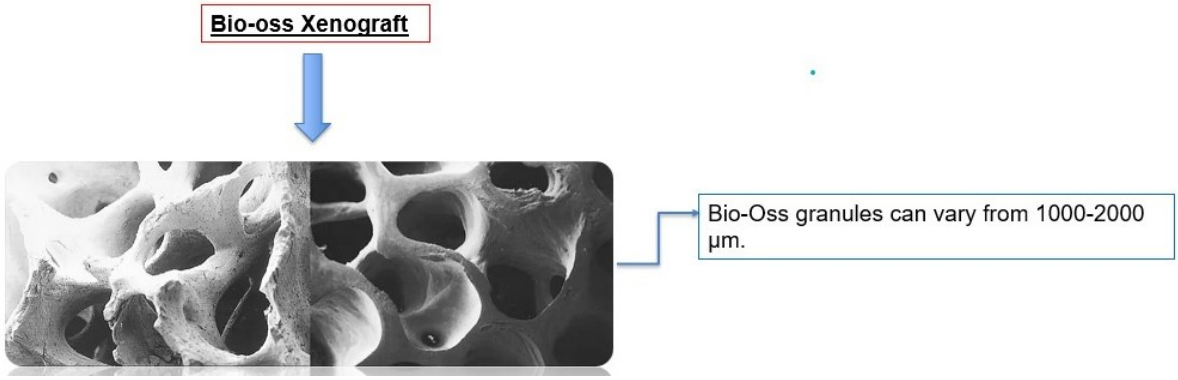

Figure 2. DBBM granules size (Bio-oss™ , Geistlich, Switzerland).

2.2. Autogenous tooth-derived matrix (ATDM)

The dentin tissue from the teeth contains approximately 70% hydroxyapatite, 20% organic matrix, and 10% water. Additionally, a network of collagen fibers is embedded in the porous structure of the dentin tissues surrounded by micro-scale dentin tubules. Dentin tubules disclose diameter ranging from 1 up to 3 μm, with an amount ranging from about 20 k to 50 k tubules/mm^2. The chemical composition and morphological aspects of the dentin has brought the attention of scientists and clinicians to manufacture autogenous tooth-derived matrix (ATDM) granules for bone healing, as shown in Figure 3(5).

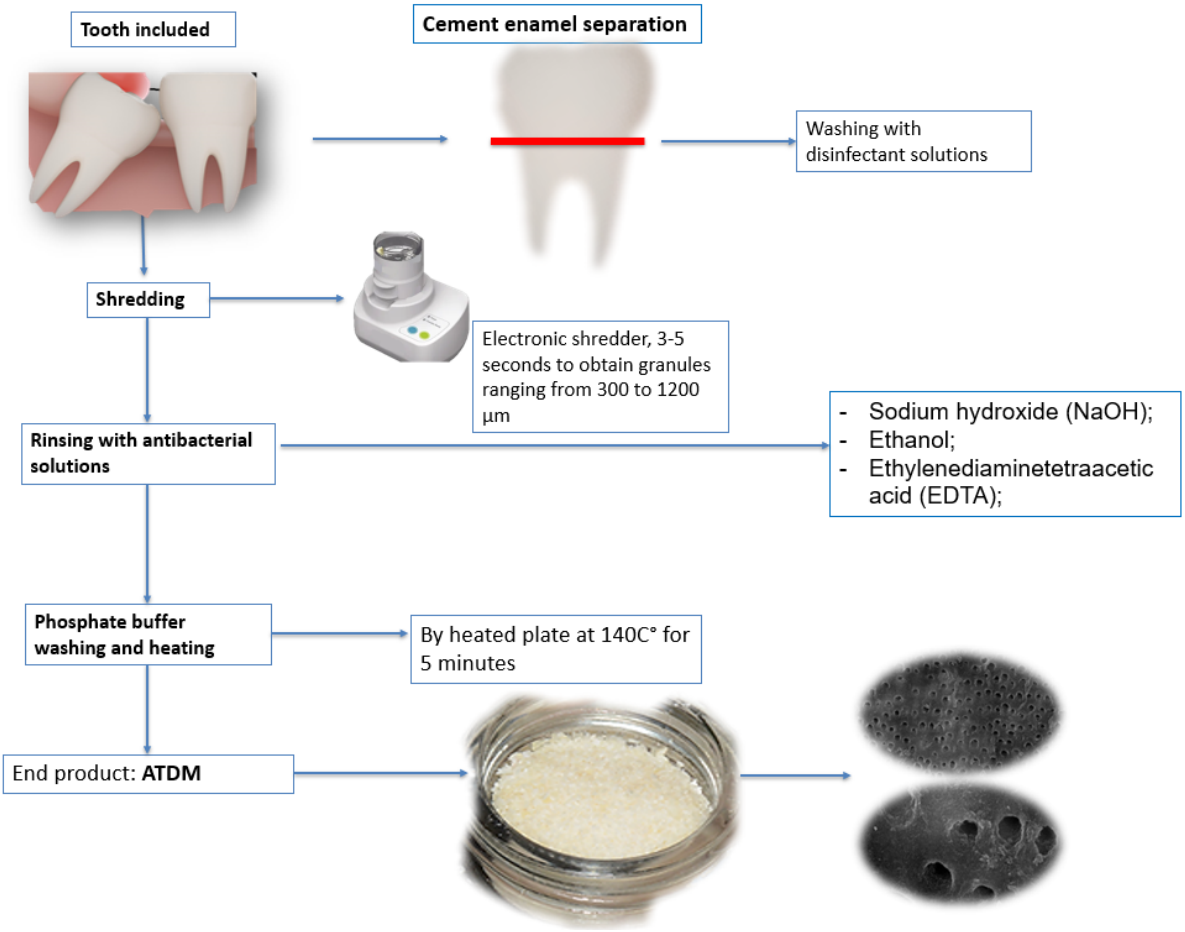

Figure 3. Manufacturing of autogenous tooth-derived matrix (ATDM) granules(5).

ATDM granules can be produced from teeth which are indicated for extraction such as third molars (i.e., insufficient space or pericoronitis) or pre-molars (i.e., orthodontic reasons). Once the tooth is extracted, the enamel and cement are mechanically removed using tungsten or diamond burs, thus exposing the dentine

tissues. Following, the remnant dentin is milled into granules. The dentin fragments are submitted to chemical disinfection in solutions such as sodium hydroxide (NaOH), ethanol, and ethylenediaminetetraacetic acid (EDTA) (Figure 1E). Once the dentine has been disinfected and dried, dentin fragments can be milled into granules for 5 s. Sieves with different mesh are used to separate the granules ranging from 300 to 1200 μm(5).

The immersion exposure can differ depending on the guidelines and chemical solutions. Thus, a standard rinsing technique has been described in NaOH and ethanol solutions for 5 min. Sodium hydroxide solution is a strong disinfection solution which has been utilized in various medical applications due to its degreasing effects. Sodium hydroxide is also efficient in denaturation of proteins and proteins and nucleic acids together with deactivating most bacteria, viruses, yeasts, fungi, and endotoxins. Ethanol is used in association with NaOH to provide the infiltration into dentin tubules uncovering the clean surface of the mineralized dentin matrix. As a second stage, the EDTA solution is to remove Gram-negative and Gram-positive bacteria and yeasts. Furthermore, EDTA can dissolve hydroxyapatite uncovering the collagen network and partially demineralizing the dentin granules. The tooth matrix can retain bone morphogenetic proteins (BMP) depending on the demineralization process(5).

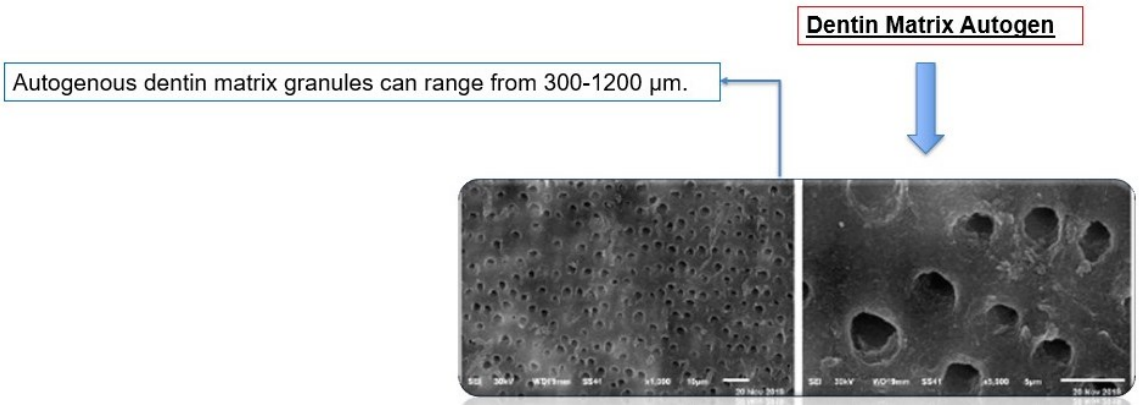

Figure 4. Size of the ATDM granulesza(7).

The structure of ATDM maintains micro-scale pores with a diameter ranging from 1 to 3 μm. Then, granules are washed twice in sterile phosphate buffered saline (PBS) after the immersion in EDTA. Dentin granules can be heated at 140C° for 5 min and cooled down at room temperature before clinical procedure (7). Thus, several guidelines for the manufacturing of ATDM granules have been described in previous

studies. Hence, several other terminologies have been used for ATDM considering the processing guidelines such as deproteinized demineralized dentin-matrix (dDDM), demineralized dentin-matrix (DDM), tooth-derived dentin-matrix (TDM), mineralized dentin-matrix (MDM), or partially mineralized dentin-matrix (PDM)(7).

2.3. Biological response

The biological interaction of DBBM and ADTM granules is mostly influenced by the size of the granules and pores, porosity itself, and their chemical composition (11) (12). The granule size and chemical composition modify the activity and rate of bioabsorption following the bone growth process. The pores stimulate adhesion and enhance the proliferation and differentiation of osteogenic cells. Macro- and micro-scale pores in the DBBM structure support the adsorption of proteins, growth factors, adhesion of osteogenic cells, and the formation of new blood vessels that are key elements for the bone formation. In the same way, micro-scale pores in ATDM granules assist the adsorption of proteins and cell attachment. However, the micro-scale pores in ATDM granules do not allow enough space for the formation of blood vessels. Actually, blood vessels can grow among the ATDM granules (11).

Once the graft material is inserted in the bone defect, the primary response takes place with the migration of macrophages, lymphocytes, and monocytes into macro-scale pores of the biomaterial to combat the bacteria. The inflammatory process also incites the infiltration of osteogenic cells and blood cells (erythrocytes and leukocytes). Micro-scale pores act as stores for the gathering and gradual distribution of molecules, minerals, and proteins, including BMPs and the following growth factors: Platelet Derived Growth Factor (PDGF), Transforming Growth Factor-b (TGF-b), Fibroblast Growth Factor (FGF), Insulin Like Growth Factor (IGF), Vascular Endothelial Growth Factor (VEGF) and Epidermal Growth Factor (EGF), as shown in Figure 5 (12).

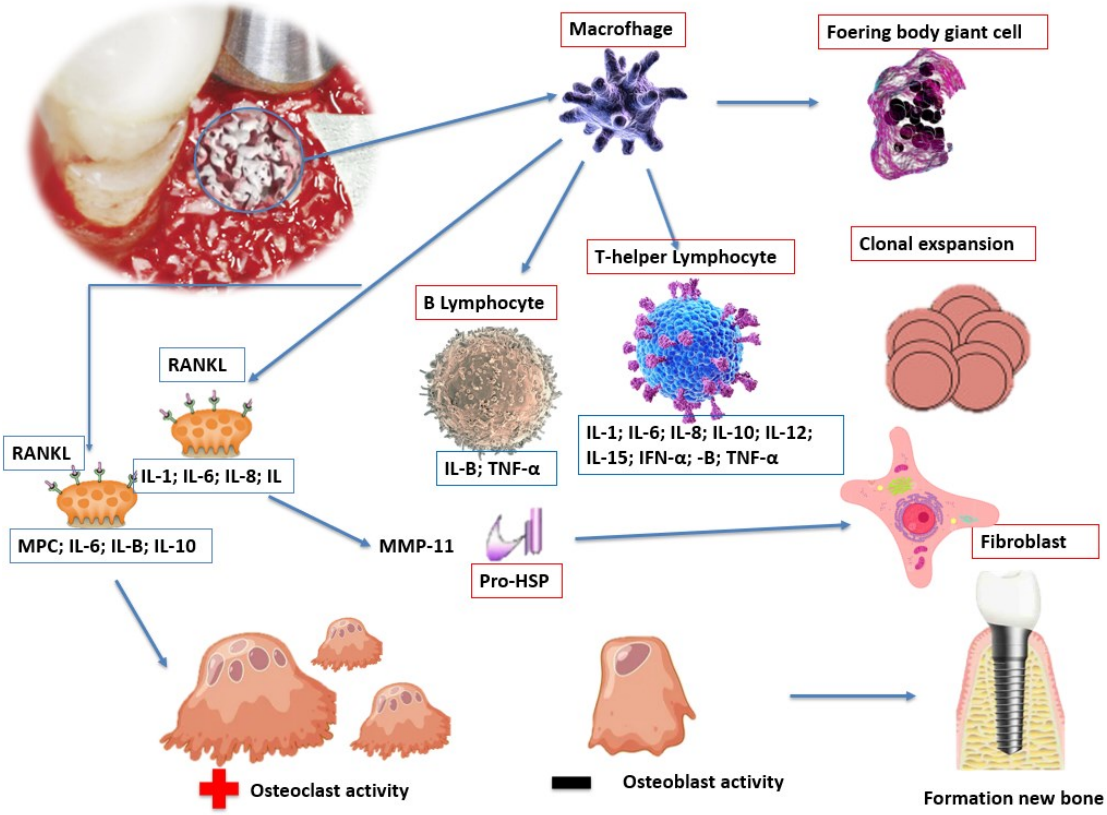

Figure 5. Cell and material interaction(12).

A previous study reported that particle sizes between 0.25 and 1.0 mm have the ability to promote osteogenesis in a 5 mm bone defect filled with DBBM (8). Growth of newly bone was recorded at 12 weeks after DBBM placement without any resorption. DBBM showed excellent osteoconductive properties and improved bone formation with partially resorption and distribution of the graft material. Furthermore, with regard to the dentin matrix (ATDM), it demonstrated the same similar osteoconductive properties were noticed for ATDM although with slower formation of new bone tissue(8). In another study in rabbits, a significant increase in thickness and density of the newly formed bone was recorded for eight weeks after ATDM grafting compared to four weeks. Plentiful osteoblasts were spotted on the surface of the newly formed bone, with the incidence of some osteoclasts on the surface and throughout the bone. The size and density of the ATDM decreased over a period of eight weeks(13). After eight weeks of DBBM placement, soft tissues and blood vessels were detected surrounding the granules. The thickness of the newly formed bone had increased although the density of the DBBM granules was similar to that observed at four weeks.

3.MATERIALS AND METHODS

3. Materials and Methods

3.1. Information sources and search strategy

A bibliographical pursuit was performed on PubMed (via National Library of Medicine) and Scopus regarding such database comprises the major studies in the field of dentistry and biomaterials. The current method was performed in accordance with the search approach utilized in previous studies on integrative, scoping or systematic reviews(2,13,14). The following combination of search terms was used in this study: "deproteinized bovine bone mineral" OR "DBBM" OR "Bio-Oss" AND "dentin matrix" OR "tooth-derived" OR "dentin" OR "dentin-derived" OR "ATDM" OR “ATDG” AND "bone substitute" OR “graft” OR “granule” OR “block” AND “bone” AND “healing” OR “repair” OR “augmentation” OR “regeneration” OR “growth” OR “formation” OR “osteoblast” OR “osteogenic” OR “mineralization” OR “cell culture”.

The inclusion criteria included studies published in the English language, up to April 2024, reporting the of comparison between autologous tooth-derived matrix (ATDM) and deproteinized bovine bone mineral (DBBM) granules on an enhanced bone healing. The eligibility inclusion criteria used for article searches also involved *in* vitro studies; meta-analyses; randomized controlled trials; and prospective cohort studies. Ongoing studies were searched in the following clinical trial registries: Current Controlled Trials, International Clinical trials registry platform, ClinicalTrials.gov, ReBEC, and EU Clinical Trials Register. Also, a hand-search was carried out on the reference lists of all main sources and eligible studies of this review for further relevant publications. The exclusion criteria were the following: papers without abstract; case reports with short follow-up period; and studies assessing only the DBBM or dentin-derived matrix granules. Studies based on publication date were not constrained during the search process.

3.2. Study selection and data collection process

The studies retrieved by the search approach were assessed in three steps. Studies were primarily examined for relevance by title and then the abstracts were evaluated. Two of the authors (JCMS, VC) independently analysed the titles and abstracts of potentially relevant studies. A third author (BH) accomplished a final

evaluation in case of disagreement. The studies were compiled for each combination of search items, and therefore, the duplicates were removed using Mendeley citation manager (Ed. Elsevier). The second step encompassed the evaluation of the abstracts and non-excluded studies, giving the eligibility criteria in the abstract revision. A preliminary evaluation of the abstracts was carried out to establish whether the articles met the purpose of the study. Selected articles were individually read and evaluated concerning the purpose of this study. At last, the eligible articles received a study identification label, combining first author and year of publication. The following factors were retrieved for this review: authors' names, publication year, journal, purpose, study design, preparation of DBBM and ATDM, analyses, and main outcomes.

The PICO (population, intervention, comparison and outcome) approach was followed as a framework to structure the following research question: Do the autologous tooth-derived matrix and bovine bone mineral granules reveal different pathways to stimulate osteogenic cell enhancing the bone healing? Regarding the PICO question, the following factors were taken into consideration: (i) population: bone substitutes, human volunteers, cells, animal models; (ii) intervention: surgical procedure, cell culture assays, histomorphometry analyses, microscopy, CBCT, X-rays, further analyses, and equipment. (iii) comparison: other bone substitutes, bone grafts, and blood clot. (iv) outcomes: major findings reported by the studies when comparing ATDM and DBBM.

4.RESULTS

4. Results

The literature search identified a total of 148 articles in PubMed and of 236 articles in Scopus, as shown in Figure 6. After reading the titles and abstracts of the studies, 250 were excluded because they did not meet the inclusion criteria. The remaining 60 potentially relevant studies were then evaluated (Figure 6). Of those studies, 48 studies were excluded because they did not contain comprehensive data related to the purpose of the present study. Thus, 12 studies were included in this review.

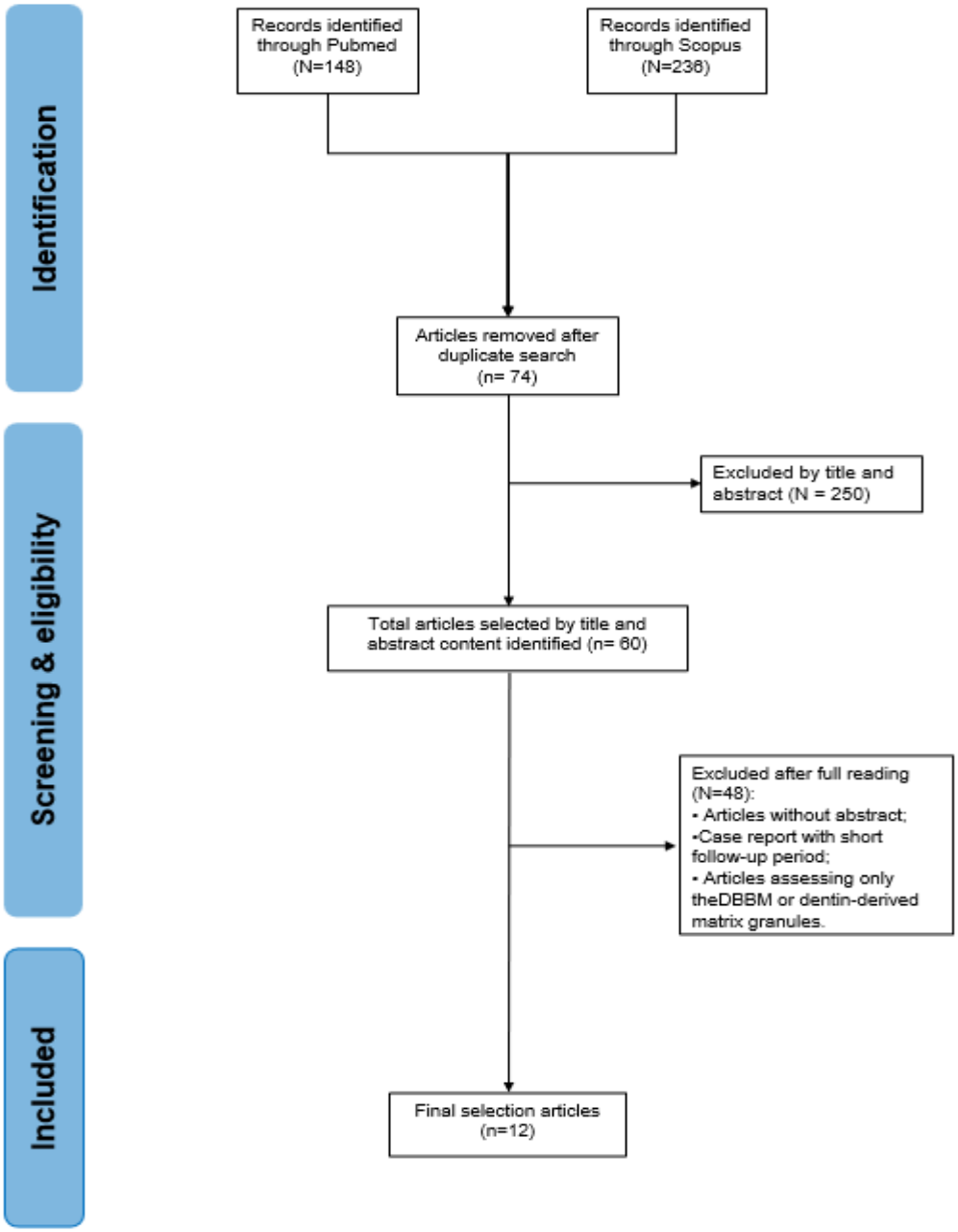

Figure 6. Flow diagram of the search strategy used in this study (PRISMA) (3–5,8–10,13–15).

The main outcomes of the selected studies are drawn as follows:

- The demineralization of dentin using chemical treatment preserve the organic content (approximately 20%), while increasing the bioavailability of Bone Morphogenetic Protein (BMP-2). Demineralised autogenous dentine (dD) showed excellent biocompatibility even surpassing DBBM. No infections of the graft material occurred, and the graft sites healed without complications (5).
- The vertical dimensions of the alveolar bone increased by 5.3 ±2.6 mm in the group treated with dentin matrix and 6.5 ±3.5 mm in the group receiving DBBM, evaluated for 6 months after extraction. A histomorphometry analysis showed that the percentage of new bone formation in the site grafted with dentin matrix was around 31.2 ±13.8% and around 35 ±19.3% for DBBM. Regarding the implant stability quotient (ISQ), implants placed in the sites grafted with dentin matrix showed a value of 72.8 ±10.8, while those placed in the sites grafted with DBBM showed an ISQ of 70 ±12.8 (3). Patients who received the autogenous dentin matrix graft showed a significant reduction in sinus height (SH) and a lower residual rate than those treated with DBBM graft material. Autogenous dentin matrix has been shown to be as effective as Bio-Oss in addressing bone augmentation for oral bone defects(9).
- The animal study involved histomorphometry analysis for bone regeneration in the maxillary sinuses of 18 adult male rabbits using blood clot grafts, DBBM, and demineralized dentin matrix (13). The percentage of newly formed bone was 8.4 ±1.8, 17.8 ±2.6 and 12.1 ±2.7%, respectively. The area of newly formed bone in group 2 was significantly higher for demineralized dentin matrix followed by DBBM and clot groups.
- The DBBM group exhibited less bone formation compared to demineralized dentin and demineralized dentin combined with mesenchymal stem cells (MSCs); no other significant differences emerged in the H&E analysis. DBBM group showed increased expression of type I collagen compared to the Dentin and Dentin/MSC-treated groups, along with increased expression of osteocalcin (4). Those results show that autogenous demineralized dentin is a viable alternative for alveolar bone grafting, with further improvements achievable through association with mesenchymal stem cells (MSCs) (4).

4.1. Table 1. Data retrieved from the selected studies.

Authors (years) Country	Purpose	Study design	DBBM	Dentin-derived preparation	Analyses	Main outcomes
Bono et al (2017) Italy.	This study aimed to investigate the effects of demineralization on the physical-chemical and biological behaviour of Dentin and Enamel.	Seven human teeth were extracted due to diseased. periodontal disease from healthy patients (aged 47 to 78 years) with informed consent. The osteoblastic cell lines MG63 and SAOS-2 were used in the in vitro cell culture experiments.	Bio-Oss® was purchased from Geistlich Pharma AG (Wolhausen, Switzerland).	Enamel and Dentin particles were subjected to demineralization and sterilization processes according to a single protocol. Briefly, particles were treated with demineralization reagent, bicinchoninic acid and sterile deionised water, at 70°C under shaking by means of a thermomixer (1,000 rpm); washed sequentially with 2 solutions for 2 minutes. Demineralized dentin and enamel particles were next collected in sterile 1.5 mL polypropylene tubes and stored until use.	AlamarBlue cell viability assay The fluorescence of the medium was recorded with a GENios Plus reader (Tecan, Monza, Italy) Scanning electron microscopy (SEM) ELISA kits to determine mineral, collagen type I and BMP-2 contents	The high mineral content of Enamel was found to inhibit cell proliferation in some way. Dentin invariably exhibited excellent biocompatibility, even greater than that of the widely used Bio-Oss®. The demineralization process of Dentin allowed preserving the organic content and increasing the BMP-2 bioavailability.
Kang et al (2016) Korea	The aim of this study was to prospectively evaluate the clinical efficacy and histological outcome of the autogenous tooth graft material (AutoBT) compared to that of	A total of 33 graft sites in 24 patients (20 years old) were included in this study. AutoBT was used in 21	(Bio-Oss, Geistlich, Switzerland)	Dentine was demineralized after the extraction of human teeth.	Histomorphometric analysis, sample specimens were dehydrated using a dehydration system with agitation and vacuum in graded ethanol dilutions, and embedded in light-cured methacrylate.	The vertical dimensions of alveolar bone increased by 5.38 ± 2.65 mm in AutoBT group and 6.56 ± 3.54 mm in Bio-Oss group at 6 months post

	anorganic bovine bone (Bio-Oss, Geistlich, Switzerland) in post-extraction alveolar bone augmentation.	sites of 15 patients and Bio-Oss was used in 12 sites of 9 patients for alveolar bone augmentation 2–4 weeks after dental extraction. In vivo study on humans.			Scanning electron microscopy (SEM). Trephine cores were harvested in the AutoBT group and from the Bio-Oss group.	extraction. Histomorphometrically, new bone formation of AutoBT-grafted site was 31.24 ± 13.87% while that of Bio-Oss was 35.00 ± 19.33%. The implant stability quotient (ISQ) of implants placed in AutoBT-grafted sites measured 72.80 ± 10.81 while those placed in Bio-Oss - grafted sites measured 70.0 ± 12.86. There were no statistically significant differences between measurements of the two groups.
Li et al (2018) China	Demineralized dentin matrix (DDM) from the patient's own extracted healthy tooth can be recycled as an autogenous biomaterial for reconstructive dentistry. The aim of the present study was to evaluate the clinical efficacy of autogenous DDM versus	From November 2015 to March 2017, 20–60-year-old patients referred to the Foshan Stomatology Hospital, who was diagnosed with localized severe	Bio-Oss® was purchased from Geistlich Pharma AG (Wolhausen, Switzerland).	Then, the pure dentine was grinded by an automatic mill at 20 000 rpm for 7-10 seconds. The crushed granules from 300 to 1200 μm were demineralized in 2% HNO3 for 20 minutes to expose the dentine's organic matrix (Demineralization) and then were immersed in 5% peracetic acid and 75% ethanol for 10 minutes to remove any bacteria and smear layer (Defatting and Sterilization).	The implant stability quotient (ISQ) was measured by Osstell Mentor and the digital periapical radiograph of the graft site The marginal bone resorption was evaluated by Dbaseline-Dpostoperative Based on the length of implant, the magnification of each	There was no statistically significant difference between the 2 groups in implant stability quotient values and marginal bone resorption. The autogenous DDM granules prepared at the chairside after extractions could act

	Bio-Oss granules in guided bone regeneration (GBR) for immediate implantation in periodontal post extraction sites.	periodontitis and agreed to dental implant treatment, were consecutively included in this study. In vivo study on humans.		Finally, the prepared DDM granules were washed twice with distilled water.	individual radiograph was calculated.	as an excellent readily available alternative to bone graft material in GBR, even for implantation of severe periodontitis cases.
Li et al (2022) China	This study aimed to evaluate the clinical efficacy and histological outcomes of autogenous demineralised dentin matrix (ADDM) as bone graft material compared with Bio-Oss® in bone augmentation for the treatment of patients with oral bone deficits.	Meta analysis of vivo studies in humans.	N/A	N/A	Statistics on histological analysis by previous studies.	The application of ADDM could significantly promote bone regeneration and was not inferior to Bio-Oss®. ADDM is as effective as Bio-Oss® in bone augmentation for oral bone defect.
Su-Gwan, et al (2001) Korea	The purpose of this study is to assess the combination of particulate dentine and plaster as bone substitute material in calvarial bone defects in rats, and to compare it with a bone xenograft (Bio-Oss1).	In vivo study on 40 rats.	Bio-Oss is a xenograft material of bovine origin consisting of sterilized cancellous particles of resorbable porous hydroxyapatite (HA). Two different particle sizes are available (0.25–0.5 mm and 0.5–1.0 mm, respectively) with a porosity of 75% to 80%. In this study, we	The particulate dentine is fabricated as follows: (1) the extracted sound teeth are cleansed, (2) heated in a furnace at 9508C (17428F) for 30 min, (3) the tooth material is pulverized by means of mortar and pestle, and (4) the dentine is filtered into particles using a 100-mesh screen. The particulate dentine and plaster are sterilized in ethylene oxide gas.	Computer-assisted histomorphometry was performed in order to measure the amount of newly formed bone in the defects. The images were captured using an Olympus BX-50 microscope. The amount of mineralized tissue present was determined by measuring the area stained green	New bone formation was highest in Group 4, followed by Group 3, then Group 2, Group 1, and finally the control group.

			used particles in the range 0.25 to 0.5 mm diameter.		based on the Goldner's technique in five microscopic fields.	
KHANIJOU et al (2021) Thailand	To analysed physicochemical such as surface structures, the crystallinity, chemical composition, calcium phosphate dissolution and osteogenic properties of tooth derived bone substitute (TDBS) processed chair-side and other grafting materials.	Human osteoblasts were co-cultured with TDBS or allograft in transwell system to examine cell migration. BMP2 released from TDBS was measured by ELISA. In vitro study.	NA	The TDBS was prepared following the Smart Dentin Grinder® protocol (SDG®, KometaBio, USA) without any modifications. Immediately after extraction, the tooth was cleaned with a high-speed bur to remove any soft tissue and debris. Completely cleaned tooth with both crown and roots was air-dried and placed in SDG®. The grinding and sorting yielded the particles between 300– 1,200 µm. The particulates were then placed in the solution provided by the manufacturer for 10 min.	Scanning electron microscopy (SEM) and energy dispersive X-ray spectroscopy (EDS) analysis. The release of BMP2 protein from each material was investigated in the same condition medium as the migrating experiment.	TDBS had high crystallinity similar to Bone Ceramic while it had a broad pattern to ramus bone, OraGRAFT, and Bio-Oss. Calcium/phosphorus dissolution of TDBS show closely related to those of mandibular ramus bone and OraGRAFT. In addition, microbial decontamination of TDBS by the chemical processing revealed a hundred percent efficacy.
Mahardawi et al (2023) Thailand	The aim of this study was to determine whether the autogenous dentin graft (ADG) shows comparable results and similar clinical performance to other graft materials when utilized for implant placement.	Meta analysis of vivo studies in humans.	N/A	N/A	Statistics on histological analysis and ISQ by previous studies.	The autogenous dentin graft is an effective option for bone augmentation around dental implants, with acceptable implant stability, marginal bone loss, and incidences of complications and failure.

Dong et al (2018) Korea	The purpose of this animal study is to evaluate, by histomorphometry analysis, bone regeneration in rabbit's maxillary sinuses with blood clots alone, Bio-Oss, β-tricalcium phosphate (β-TCP), and demineralized tooth dentin (DTD) grafting.	Bilateral sinus augmentation procedures were performed in 18 adult male rabbits. Rectangular replaceable bony windows were made with a piezoelectric thin saw insert. In vivo study.	-	After sterilization of teeth with sterilization reagent (peracetic acid ethanol solution) in a vacuum-ultrasonic, the sterilized teeth were stored at –20°C before preparing tooth bone. Teeth was crushed and into powders of 0.8–1.0 mm in size on experimental day and demineralization using 0.6 N hydrochloride was done for 15 minutes under vacuum compression and ultrasonic vibration. The DTD was then washed with phosphate buffered saline (PBS), sterilized with sterilization reagent, and consecutively washed again with PBS and distilled water.	The following histomorphometric measurements were made: total augmented area, graft material (BioOss, β-TCP, or DTD) area, newly formed bone area, mature lamella bone area, bone marrow area, and connective tissue area. The mature lamella bone was defined as a red color structure containing osteocytes in MT stain.	Dentin matrix can be effective graft materials for bone regeneration of the maxillary sinus augmentation.
Barreiro et al (2022) Germany	Considering the chemical and structural properties of dentin, this study was aimed at evaluating the effect of dentin matrix alone or combined with mesenchymal stromal cells (MSC) on post extraction alveolar bone regeneration.	In vivo animal study.	-	-	Histological analysis and image acquisition were performed using an Olympus BX-43 light microscope. Micro-computed tomography (micro-CT) was performed, and the samples were scanned in the three spatial planes. Serum analysis was performed, where serum samples were digested in 2% nitric acid for 120 minutes and analysed by plasma	The Bio-Oss group showed less bone than Gelita-Spon and Dentin/MSC; no other significant differences were seen in H&E analysis. Autogenous non demineralized dentin is an alternative for alveolar bone grafting, which can be improved by combination with MSC.

					mass spectrometry to measure calcium and phosphorus levels.	
Xin Liu et al (2016) China	The aim of the study was to evaluate the effects of the combined use of bone marrow stromal cells (BMSC) genetically modified with dentin matrix protein-1 (DMP1) and Bio-Oss1 for the placement of implants of sinus floor augmentation (MSFA) in dogs.	In vivo animal study.	Each cell suspension was gently added to the Bio-Oss scaffolds drop by drop until saturated. The BMSC/Bio-Oss constructs were incubated for an additional 4 hours to allow cell attachment prior to use. The additional BMSC/Bio-Oss constructs were incubated separately for 4 hours and 1 day in complete medium and were then fixed in 2% glutaric dialdehyde for 2 hours. Bio-Oss® was purchased from Geistlich Pharma AG.	Dentin matrix protein-1 (DMP1) is a highly phosphorylated protein that has been documented to play a crucial role in bone mineralisation. This ptotein was obtained from the extraction of the dog's first molar.	A series of histological and histomorphometric analyses were conducted.	No significant difference was found between the residual volume of bone substitute material (BSMV) in the Lenti-DMP1 group (35.86 ± 7.35) and the BMSC group (32.16 ± 9.16). According to the results of Ozyucaci versus Bio-Oss BSMV, 25% and 30% of the residual Bio-Oss graft was found at 6 months and 8 months, respectively.
Pimentel et al (2023) Portugal	This study was to evaluate the morphological aspects and distribution of granules composed of deproteinized bovine bone mineral (DBBM) and human dentin-derived bone graft (HDBG) into a putty consistency mixture.	In vitro study, are required to evaluate the morphological aspects and distribution of particulate bone graft prior to surgery. .	The deproteinized bovine bone mineral (DBBM) used in this study was provided by Biograft™. Or test group, DBBM was mixed with alginate-based hydrogel (Orthoprint™, Zhermack,Germany) at	On harvesting human dentin-derived bone graft (HDBG), extracted third molars from human donors were firstly immersed in distilled water for 10 min and then in a solution of 2% sodium hypochlorite (NaOCl) for 10 min. Afterward, teeth were immersed in 10% malin solution for 7 days. Finally, teeth were stored in 0.9% NaCl solution for hydration over a period of	Optical microscopy Scanning electron microscopy (SEM).	Microscopic analyses revealed a size of DBBM granules ranging from 750 up to 1600 µm while HDBG particles showed particle size ranging from 375 up to 1500 µm. No statistical differences were

			bone graft/hydro gel ratio of 1:1 or 1:3 vol/vol under the sterile condition at room temperatures.	7 days prior to the milling procedure. Teeth roots and enamel were removed to harvest the dentin tissue. Then, teeth were immediately milled with the Smart Dentin Grinder™ apparatus (KometaBio Inc., Cresskill, NJ, USA). The milling process resulted in dentin particles (granules) ranging from 300 up to 1200 µm. The dental particles were then immersed in an isopropyl alcohol solution in a sterile container for 10 min to dissolve all organic debris and bacteria. Then, dentin granules were placed in ethyl enediaminetetraacetic acid (EDTA) for 2 min for partial demineralization and then washed in sterile saline solution for 3 min.		identified regarding the size of granules ($p>0.5$). The mean values of pores' size of DBBM particles were noticed at around 400 µm while HDBG particles revealed micro-scale pores of around 1–3 µm promoted by the dentin tubules ($p<0.05$).
Ribes et al (2023) Spain	The main goal of this study was to assess key factors for optimal ground ATDG properties by utilizing three methods (Gouge forceps, electric grinder, and manual) within the study group (SG), and comparing them to the control group (CG) which used Bio-Oss®.	Study conducted in a laboratory setting. These properties can be explained by the similar makeup of teeth and bones, their shared origin in embryos, the ability of bones to differentiate in a lab setting, as well as the	After obtaining and categorising the samples based on their particle size, they were compared with each other and with Bio-Oss® xenograft from Geistlich Pharma AG, a biomaterial made from bovine bone that undergoes a chemical extraction process at low temperature (300 ◦C) to remove all	In order to access the optimal characteristics of the substance known as autologous tooth-derived graft (ATDG). For this reason, different studies have chosen to use three specific ATDG crushing methods found in existing literature. Helmut Zepf® offers 2 different types of gouge forceps. Automated Smart Dentin Grinder Kometa-Bio by Bioner®; 3. Hand-operated grinder made by Master Surgical SL®.	The equipment analyzed the particle size and specific surface area by measuring Gaussian bells of the sizes and surfaces.	The electric grinder produced a sample with the highest specific surface area value (2.4025 ± 0.0218 m2/g), and the particle size, indicated by the average diameter (751.9 µm), was the lowest and most uniform among the three groups. Hence, the electric grinder

		promotion of new bone growth and good compatibility with the body.	organic material while preserving the physical structure. It is made up of a porous system that is interconnected, which supports the clot's initial stability and the growth of blood vessels inside it, facilitating the movement of osteoblasts and the development of new bone.			enabled the acquisition of ATDG with increased regenerative characteristics thanks to its distinct surface-area measurement and particle size aligned with the most backed xenograft in literature (Bio-Oss®). A greater specific surface area leads to enhanced reactivity with physiological substances, resulting in quicker biological processes.

5.DISCUSSION

5. Discussion

In this study, a comparison was made between deproteinized bovine bone mineral (DBBM) and autogenous tooth-derived matrix (ATDM), referring to previous research in cells and animal models, as well as in patients. The results highlighted a marked stimulation of osteogenic cells and an improvement in bone formation, both for DBBM and ATDM. Consequently, the initial hypothesis of the study was disproved, given that both DBBM and ATDM appear to follow similar pathways to stimulate new bone formation.

The chemical composition and morphological aspects of a tooth-derived bone graft material (ATDM) have been explored and compared to DBBM. (5). In a previous study, ATDM was produced following the Smart Dentin Grinder® method without any modifications. After extraction, seven human teeth taken from healthy individuals aged between 47 and 78 years suffering from periodontal disease were cleaned, dried and ground to obtain particle sizes between 300 and 1,200 µm (6,12). These enamel and dentin particles were subjected to a demineralisation and sterilisation process following a specific protocol. The demineralised particles were then stored in sterile 1.5 ml polypropylene tubes until use(5). To study cell migration, human osteoblasts were co-cultured with ATDM or allograft. The amount of BMP2 released by ATDM was determined by ELISA (5). The results revealed that ATDM possesses a high crystallinity, similar to that of DBBM, and contains elements such as carbon, calcium, oxygen, phosphate, sodium and magnesium. The dissolution of the calcium/phosphorus ratio of ATDM was closely correlated to that of the mandibular branch bone. In addition, the chemical treatment enabled the complete microbial decontamination of ATDM(7,15). It was found that the high mineral content of enamel can somewhat inhibit cell proliferation. Regardless of demineralisation, the extracellular matrix (ECM) of dentin showed excellent biocompatibility, superior to that of commonly used Bio-Oss®(5). In addition, the dentin demineralisation method maintained the organic content and increased the bioavailability of BMP-2, resulting in an overall improvement in biocompatibility compared to untreated dentin(5).

The tooth-derived dentin matrix contains BMP proteins that are preserved after the partial demineralisation of the tooth matrix without compromising its structure. That is a key factoron the ATDM to become a promising choice for regenerative

procedures(11). For bone formation, it must be considered that the two types of materials have different porosity. DBBM has a porosity of about 75%, while ATDM has a porosity of about 45%. This aspect is very important for biological interaction(12).

Another previous study conducted an in-depth investigation into the effect of dentin matrix, both alone and in combination with mesenchymal stem cells (MSCs), on alveolar bone regeneration after extraction (9). The analysis was conducted on animals in vivo, providing a realistic model to study bone regeneration(9). In the H&E analysis, it was observed that the Bio-Oss group showed less bone than the ATDM group. Such result suggests that dentin matrix and MSCs may have a positive effect on bone regeneration. However, no other significant differences were observed between the groups, indicating that further research is needed to fully understand these results(9). Non-demineralised autologous dentin has proven to be a viable alternative to alveolar bone grafting. The results indicate that combining autologous dentin with MSC can further improve bone regeneration results. The finding opens new perspectives for improving bone grafting techniques and suggests that further research in this field could lead to important advances in regenerative medicine (9).

On an in vivo study, bone regeneration was assessed in the maxillary sinuses of rabbits, after placement of blood clots, Bio-Oss, β -tricalcium phosphate (β -TCP) and demineralised dentin matrix graft (ATDM). Sinus augmentation procedures were conducted in 18 adult male rabbits and dogs and the bone repair was analyzed by histomorphometry (6,13). As part of the in vivo research, teeth were sterilised with a solution of peracetic acid and ethanol in a vacuum ultrasound system and stored at -20°C prior to bone preparation. On the day of the experiment, the teeth were crushed and reduced to powders of size 0.8-1.0 mm and demineralisation was performed using 0.6 N hydrochloride for 15 minutes under vacuum followed by ultrasonic vibration(13). The ATDM was then washed with phosphate-buffered saline (PBS), sterilised with sterilisation reagent and washed again with PBS and distilled water. The study suggested that ATDM (dentin matrix) may be an effective graft material for sinus lift bone regeneration(13).

In another animal study, the potential of ATDM particles was assessed for bone grafts in cranial defects in rats and compared to DBBM (8). ATDM was produced through a series of steps: cleaning of the healthy extracted teeth, heating in an oven

at 950 °C (17428°F) for 30 min, grinding of the dental material with a mortar and pestle and filtration of the particle dentine through a 100-mesh sieve. ATDM particles were subsequently sterilised with ethylene oxide gas. Computer-assisted histomorphometry was performed to quantify the formation of new bone in the defects. It was noted that new bone formation was most pronounced in bone defects with ATDM when compared to those with DBBM (8).

The aim of another previous study was to compare the clinical efficacy of autologous ADTM with DBBM granules on guided bone regeneration (GBR) for immediate implantation in post-extraction periodontal sites of humans. Humans volunteers aged 20-60 years who were diagnosed with severe localised periodontitis accepted implant treatment. DBBM was supplied by Geistlich Pharma AG (Wolhausen, Switzerland) and dentine was ground by an automatic mill at 20,000 rpm for 7-10 s. The ATDM granules, which ranged in size from 300 to 1200 μm, were demineralised in 2% HNO_3 for 20 min to expose the organic matrix of dentin (demineralisation) and were then immersed in 5% peracetic acid and 75% ethanol for 10 minutes and then rinsed twice with distilled water. Forty patients (45 implants) were included in the study. Apart from 2 cases with wound infection, 43 implants did not present postoperative complications and had a satisfactory result after 1 year of prosthetic loading. No statistically significant differences were found between the two groups in implant stability quotient and marginal bone resorption values. ADTM granules prepared in the clinic after extractions can be an excellent and readily available alternative to bone grafting material in GBR, including cases of severe periodontitis(14). Another interesting previous study aimed to examine the clinical efficacy and histological results of using autogenous ADTM versus DBBM as a bone graft material in the treatment of patients with oral bone defects. In total, 220 patients were considered eligible for the study, of which 111 were assigned to the ADTM group and 109 to the DBBM group. The results showed that the use of ATDM could significantly promote bone regeneration that was not lower to DBBM (9).

Considering previous findings on the use of ATDM, future studies should focus on the following aspects:

- Relationship between porosity and angiogenesis: examining how graft porosity affects the formation of new blood vessels could provide valuable information on bone regeneration.
- Size and distribution of granules in the bone defect: analysing how granule size and distribution affect bone regeneration could help optimise graft preparation.
- Granule distribution when mixed with hydrogel or platelet-rich fibrin: investigating how mixing granules with hydrogel or platelet-rich fibrin affects granule distribution could improve graft efficacy.
- Combination of DBBM and dentin matrix granules with different percentages: exploring optimal combinations of DBBM and dentin matrix granules could lead to better bone regeneration results.
- Microscopic details of DBBM and dentin matrix granules: detailed analysis of DBBM and dentin matrix granules at the microscopic level could provide further information on their structure and function, contributing to the improvement of bone grafting techniques.

6.CONCLUSIONS

6. Conclusions

The major concluding remarks can be drawn:

- The chemical processing of ATDM maintained a partially demineralized hydroxyapatite structure with a high content of organic compounds such as collagen and bone morphogenetic protein.
- Non-demineralised autogenous dentine combined with mesenchymal cells (MSC) has proven to be a viable alternative for bone augmentation.
- In a rabbit model, the bone formation was statistically higher for surgical sites with DBBM granules when compared to the blood clot. Also, ADTM granules induced a higher bone formation in surgical sites than that reported for blood clot.
- ATDM granules proved as effective as DBBM in bone augmentation for oral bone defects in humans.

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