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THE USE OF CALCIUM SULPHATE VS. DEPROTEINIZED BOVINE BONE MATRIX AS BONE SUBSTITUTES IN PERIODONTAL BONY DEFECT REGENERATION: A SYSTEMATIC REVIEW.

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ABBREVIATIONS

1. Bone morphogenic proteins: BMP
2. Calcium sulfate: CS
3. Deproteinized Bovine Bone Matrix: DBBM
4. Interleukin: IL
5. Platelet-derived growth Factor: PDGD
6. Tumor growth Factor: TGF
7. Tumor necrosis Factor: TNF
8. Open flap surgery: OFS
9. Minimally invasive surgical technique: MIST
10. Concentrated growth factors: CGF

ABSTRACT

TITLE: The use of Calcium sulphate vs. deproteinized bovine bone matrix as bone substitutes in periodontal defect reparation: a systematic review

BACKGROUND: Periodontal bone defects are a type of lesion that affects the bone and periodontal tissue, in the field of dentistry many techniques and materials can be implemented to resolve this condition. This systematic review is focused on the comparison of 2 Materials: Calcium sulphate (CS) and deproteinized bovine bone matrix (DBBM), which are materials of different natures and origins.

The aim of this systematic review is to analyze and compare the efficacy of the 2 materials in regenerating the periodontal bony defects and see which surgery types combined with these 2 materials work best.

METHOS: A systematic search of the literature was conducted to obtain the relevant studies to be included. Only randomized control clinical trials that fitted the inclusion criteria were selected and those which could not pass the exclusion criteria have been discarded, inclusion comprehended randomized clinical trials with a minimum of 8 patients, which have been published between 2008 and January 2022. Studies that were conducted on animals, where the material was mixed with other substances, and in vitro studies. The search was performed throughout 3 databases: Medline on 09/02/2022, Cochrane on 12/02/2022, and Scopus on 31/01/2022). Risk assessment was analyzed using the CASP guide. To find an answer to our research question variables shared between all the final articles were selected to carry out the comparison, in the case of this study Clinical attachment level (CAL) and Periodontal probing depth (PPD). Al the data was sorted into a table and averaged to obtain the final values presented and then into tables and graphs.

RESULTS: From a starting point of 243 articles after the removal of the duplicates and screening, 14 articles have been reputed suitable for this review. and CAL and PPD were analyzed and increment in CAL of 3.7mm and 4.04 mm was found for CS and DBBM respectively and a reduction of 4.61mm (CS) and 3.83mm (DBBM) in PPD. When analyzing the surgeries, it can be deduced that in order of effectiveness is esteemed that the best one is Open flap surgery (OFS)+ DBBM+ collagen membrane followed by OFS+CS, DBBM + OFS, CS BARRIER+OFS, and finally Minimally invasive surgery technique (MIST)+DBBM.

DISCUSSION AND CONCLUSION: In the analysis of the limitation encountered it is sassed that since a standardized surgical protocol and measurement standard were not followed in between studies a degree of imprecision may have arisen during the obtention of the final values. Still, the data obtained shows that both materials are capable of archiving regeneration of the defect and share a similar biological potential. Regarding the surgeries, the use of a collagen membrane and DBBM together in A OFS showed the best outcome possible followed by the use of CS alone in an OFS.

KEYWORDS

Periodontal Defect; Intrabony Defects; Calcium sulfate; Bovine Derived Bone matrix;

Periodontal regeneration

1. INTRODUCTION

1.1.BONE PHYSIOLOGY

Bone is a hard tissue that constitutes the skeleton. It provides protection for the various organs of the body, produces red and white blood cells, stores minerals contributing to homeostasis, provides structure and support for the body, and enables mobility (1).

Bone lesions usually comes from traumas, surgeries, congenital malformations, tumors, and/or infections. When one is produced into the bone, this activates certain mechanisms able to lead to its reparation but when the loss of integrity is beyond physiological repair, techniques, and material for guided bone regeneration can be applied to aid the process.

The first event that occurs when a tiny bone lesion, such as a fracture develops, is the release of proinflammatory cytokines in the first 24 hours. Many molecules such as TNF-alpha, Interleukin I, IL-6, IL-11, and IL-18 are released on the site. This will cause polymorphonucleated cells to migrate, including polymorphonuclear leukocytes, which will endocytose micro-bone debriefs and clean the region (1). Blood extravasation and cloth creation are determined by injured blood vessels; during this process, platelets and tumor growth factors are produced, while macrophages create tumor-derived growth factor-beta and insulin-like bone factors. Finally, bone morphogenic proteins will be synthesized by osteogenic cells (BMPs) (2).

All this chemical signaling will give a start to the renewal phase of the bone. In this phase, mesenchymal cells will proliferate and differentiate into osteoblasts and will start forming bone through intramembranous ossification. Upon completion of this process, a shifting is produced towards endochondral bone formation induced by BMPs, TGF-B2, and B3. Here chondrogenesis starts, and inflammatory mediators disappear (3).

The newly formed cartilaginous callus then is calcified being replaced by newly formed woven bone, entering so in the bone remodeling phase where osteoblast and osteoclast will replace the woven bone with lamellar bone. This stage is regulated by IL-1, 6, 11, 12, TNFa, interferon-gamma, and some hormones such as growth hormone and parathyroid

hormone (4). Some lesions although such as periodontal intrabony defects may need special procedures and materials to achieve the correct healing of a lesion.

1.2. PERIODONTAL BONE DEFECTS

A periodontal intrabony defect is a type of lesion with a particular morphology and location in the alveolar bone. It's a crater surrounded by bone walls on the sides and 1 one of them is a tooth root. They are caused by the presence of infectious foci and consequent inflammation which leads to bone resorption on the site and proliferation of granulomatous tissue. Depending on the bone type and thickness, bone resorption may start in different locations, a thin cortical wall will start a marginal defect while a thicker cortical may result in resorption starting in the trabecular bone (5). Intrabony defects are classified depending on the number of bony walls surrounding the defect. As explained in table 1.

Table 1. ***Morphological classification of bony defects***

TYPE OF DEFECT	**1 WALL**	**2 WALLS**	**3 WALLS**
MORPHOLOGICAL DESCRIPTION	*It's the most severe type of defect with the presence of only the vestibular or palatal margin* (6,7).	*When not only a vertical pattern is present but also an angular component is added to the resorption trajectory. This results in the presence of one proximal bone wall and either a vestibular or palatal wall* (6,7).	*Are narrow and deep defects close to the root surface? Can be resolved by just the debridement of the site* (6,7).

Many factors can influence the outcome of regenerative surgery. They could be dependent on the technique, the operator or being influenced by the patient's habits.

Smoking, poor hygiene, or the presence of any systemic disease that could alter the healing process, such as diabetes, are associated with poorer prognosis.

Moreover, evidence has been found that tooth mobility and complex morphology of the defects could influence the prognosis negatively.(8)

The procedure to achieve regeneration and healing of this kind of defect is called Periodontal regeneration and it aims to the recovery and new formation of the surrounding tissues around the tooth such as cementum, periodontal ligament, and bone(9)

1.3. GRAFTING MATERIALS AND THEIR PROPERTIES

Here different techniques and materials can come to our help to aid the regenerative processes.

A bone graft is placed into the lesion and covered with a membrane inducing bone repair through processes of osteogenesis, osteoinduction, and osteoconduction, depending on the materials being used. The choice of the material will depend on the type of lesion, its severity, and the quality of surrounding healthy tissue.

5 Main types of graft material exist Xenografts, Alloplastic grafts, Autologous bone Grafts, and Allografts (10).

Grafts provide the surrounding bone with a scaffold, and some even with live cells and/or chemicals, for the underlying hard tissue to grow into the lesion and effectively restore it, while the material is reabsorbed and converted into newly formed bone. usually, these materials are reabsorbed completely or sometimes partially (11).

Many factors may aid in this process thanks to the properties and type of the grafts. The 3 main properties of grafts are osteoinduction, osteoconduction, and osteogenic properties. Each type of graft may present one or more of these properties.

Osteoinduction refers to the ability of the material to induce mesenchymal cells into differentiating into osteoblast and osteoclast. Osteoconduction is the property of creating a scaffold for the cell to start the regeneration process. Osteogenic properties are proper of autologous bone since it already contains the Cells (12).

Different types of grafts exist and each different one bears different properties here explained in table 2.

Table 2. Different types of graft material

TYPE	SOURCE	EXAMPLE	PROPERTIES
AUTOGRAFT	*Patients own bone*	*Ramus, Torus, tuberosity*	*Osteogenic, osteoinductive, osteoconductive no cross infections,*
ALLOGRAFT	*Other human*	*Freeze-dried human bone, Living Donors*	*Osteoinductive, Osteoconductive Risk of infection*
XENOGRAFT	*Other species*	*Bovine bone matrix, porcine derivates, horse derivates*	Osteoconductive, Good volume stability
ALLOPLAST	*synthetic*	*Calcium sulfate Hydroxyapatite Calcium phosphates Bioactive glasses*	*Osteoconductive. Different reabsorption times. Can stimulate bone formation.*

(13)

Simply implanting a graft into a lesion may not be enough to ensure a successful surgery if the defect is extended, most of the time we'll have to cover the graft with a special membrane or barrier to avoid fibroblast migration into the site and also to protect the graft from infection (14).

1.4. CALCIUM SULPHATE

This work is focused on the properties and techniques that implement CS and DBBM as bone substitutes for the reparation of intrabony defects.

CS ($CaSO_4$) is an inorganic substance naturally found in the earth's crust or produced industrially by reacting calcium salts with sulfuric acid.

When reacting with water an exothermic reaction is produced, and a solid compact compound is obtained:

$CaSO4+2\ H2O=CaSO4.2\ H2O+heat$ (15)

It is an extremely versatile material, that has been used countless times both in the field of medicine and dentistry. It can be used in 2 crystalline forms: alpha and beta and 3 states of hydration anhydrous, hydrate, and dihydrate. The alpha form is very compact and is usually used as a dental casting material while the beta or a mix of the 2 can be used as a bone void filler.

The beta form of CS is characterized by lattice imperfections and irregular crystals conferring an innate porosity and solubility to the material, making it ideal for bodily resorption and cell proliferation.

Although if used alone in this phase can present some challenges during handling due to the beta form taking a lot of time to harden and saliva and blood causes it to dissolve too quickly; Therefore, a mixture of alpha and beta forms is preferred for surgical procedures since the alpha form confers faster setting and better handling but still retaining the right amount of porosity and solubility (11,16).

The main property of interest for CS it's biocompatibility, it is reabsorbed for dissolution in about 8 weeks with slight variations depending on the amount that is implanted.

Due to its chemical composition can provide calcium ions essential for the mineralization and formation of new bone. As well as the stimulation for the production of BMP-2, BMP-7

and TGF-b, and PDGF-BB, this is due to a local diminution of ph. in the area of implantation, winch causes a temporary demineralization of the surrounding bone walls (17).

In medical and dental literature, the indications for which CS may be used are various. It has been used and has shown efficacy in the treatment of infrabony periodontal defect, unicameral cists bone regeneration, surgical defects repair from bone tumors removal, sinus elevation, socket preservation, lateral ridge preservation, pharmacological delivery, and even used as a membrane in guided bone regeneration (11,16,17).

Right now, in the market different formulations and brands are available for dental use depending on the type of surgery is going to be performed, between these, the ones indicated for bone defects reparation are DentoGen™, NanoGen™, and Augma 3d bond™. To use this material in its pure form the technique consists in opening a flap to expose the bone defect, removal of the granulomatous tissue, and planning the exposed root, the area is then irrigated whit saline and if no marrow is exposed, the wall of the defect are perforated with a bur, then the CS powder is mixed with sterile saline droplets until a putty consistency is obtained, and subsequentially insert and modeled with a spatula in the area of interest, finally, the flap is sutured back in place covering the graft material (18). Some authors also describe injection techniques where the putty is inserted using a syringe (19).

1.5. DEPROTEINAZIDE BOVINE BONE MATRIX

One other material that can be utilized for the purpose of repairing periodontal bony defects is the deproteinized bovine bone matrix (DBBM). It's an animal bone derivate that has been shown to work with or without a membrane and possibly to achieve periodontal regeneration and not only new bone formation (20).

It is a Xenograft, obtained by the bone of oxeas, which is treated to remove any possible irritant and biological substance such as proteins, cells, etc. So that only an inorganic matrix is left behind. Due to the absence of organic components the main property of this grafting material is osteoconduction, permitting cell migration and proliferation through the scaffold, it provides but lacks any type of cell stimulation (21).

Depending on the temperatures at which is processed, some changes in the crystal structure may appear yielding 2 different versions of this material: sintered or unsintered as shown in table 3. No significant difference in performance is reported between the 2.

Table 3. Different types of the bovine bone matrix for dental use

PROCESS	COMMERCIAL NAME	MANUFACTURING TEMPERATURE	PROPERTIES
SINTERED	*OsteoGraf®/N, Endobon®, Cerabone®*	*400-900 Cº*	*18% phosphorus, Alteration in the crystalline structure*
UNSINTERED	*Bio-Oss®, Lubboc®/Laddec®*	*300-400 Cº*	*37% phosphorus Maintains the bovine bone architecture (similar to the human one)*

(22)

Commercially it`s possible find DBBM in granules of different sizes which could influence the resorption time and rate of the material and consequential amount of newly formed osteoid tissue, being the smaller size the better reabsorbed one and leading to a greater amount of new bone tissue (23). The technique for its manipulation is the following: Starting with opening a flap and debriding the area, the bone substitute is mixed with either saline solution or blood from the patient, the material is applied into the defect using a spatula and condenser, usually, the defect is covered with a collagen membrane (or another type) and tightened with sutures and finally the flap is closed and sutured (24).

2. JUSTIFICATION, HYPOTHESIS, AND OBJECTIVES:

2.1. JUSTIFICATION

Bone defect regeneration is quite a common procedure in dentistry, the most common material being used currently is a bovine-derived substitute which bears the disadvantage to be very expensive.

Calcium sulfate is one of the cheapest materials that can be used as a bone substitute in a variety of surgery where bone loss has occurred. This work wants to analyze its performance in the treatment of bone defects of 1, 2, 3 walls and analyze its validity as a material through the findings of this systemic review, compared to other more expensive material such as bovine substitute.

2.2 HYPOTHESIS:

Null hypothesis: there is not going to be a statistical difference between the performances of CS and DBBM.

Work hypothesis: The DBBM is going to perform Better than CS in repairing periodontal bone defects.

2.3. MAIN OBJECTIVE:

1) Demonstrate which material between CS AND DBBM produces better results in terms of bone regeneration

2.4. SUB OBJECTIVES

1) Evaluate which type of surgery using CS achieve better results in term of bone regeneration

2) Assess which type of surgery using DBBM achieve better results in term of bone regeneration

3. MATERIALS AND METHODS

3.1. PRISMA STATEMENT

The Prisma guide was followed to develop this systematic review (25).

3.2.PICO

P: Adult population with bone defects

I: the use of calcium sulfate in bony defect repair surgery

C: bovine bone matrix in bony defect repair surgery

O: To compare the effectiveness of calcium sulfate and bovine bone matrix in bony defect surgery

3.3. ELEGIBILITY CRITERIA:

Studies that met the following requirements were included

- Randomized control trials where calcium sulfate and/or bovine bone matrix were used in regeneration processes

- Studies with a minimum sample size of 8 patients.

- Only studies published between Jan 2008 to Jan 2022.

Exclusion criteria:

- Studies conducted on animals.

- Studies which only included data were secondary products were combined with calcium sulfate or bovine bone matrix into a composite graft.

-Studies performed in vitro

3.4. DATA SOURCE AND RESEARCH STRATEGY

Research on the databases has been carried out on Medline complete, Scopus, and Cochrane. Using the following keywords: Calcium sulfate, calcium sulfate, Bone Defect, Dentistry, Bovine Bone Matrix, Periodontal defects, bony defect.

And Boolean operators: AND, OR, NOT, Being the last search carried out the 12/02/2022.

The strategies employed throughout the databases are here shown in table 4.

Table.4. Sourcing and search strategy

DATABASE	SEARCH	FILTERS	DATE	Nº ARTICLES
Scopus	*"Calcium sulfate" OR "Calcium Sulfate" OR "bovine bone matrix" OR " deproteinized bone matrix" OR "bio-oss" OR " dentogen" OR "nanogen" OR "Augma" AND "Bony Defect*" OR "Periodontal Defect*" OR " Wall* defect*" OR "Intra bony defects" AND " Dentistry"*	*Limit to: Subject area "DENT" Articles from 2008 to 2022, humans, human Exclude extrakey: animal, animals, rats, dogs, rabbits, enamel matrix protein, nonhuman, Wistar rat, animal model, platelet-rich plasma.*	*31/01/2022*	142
Medline Complete	*(("Calcium Sulfate" OR "calcium sulphate" OR "dentogen" OR "augma" OR "nanogen" OR"bovine bone matrix" OR*	*Articles from 2008 to 2022*	*9/02/2022*	33

	"Bovine bone") AND ("periodontal defect" OR "periodontal intra bony defect" OR "infra bony defect")*			
Cochrane	"*periodontal defect*" OR "infra bony defect*" OR "intrabony defect*" OR "periodontal intrabony defect*" OR "bony defect"* *AND* *"bovine matrix" OR " bio-oss" OR "bovine bone" OR "bovine bone matrix" OR "calcium sulfate" OR "calcium sulfate" OR "dentogen" OR "nanogen" OR "AUGMA"*	*Articles from 2008 to 2022*	*12/02/2022*	66

3.5.STUDY SELECTION:

Literature was reviewed independently by 1 revisor to be selected by Appling the inclusion and exclusion criteria. This first stage was the research by Appling the filters. The second stage was done by reading the titles and abstracts and the last stage of selection was reading the full articles and application of CASP. The research was carried out by DF and asses by CRP

3.6.DATA EXTRACTION

The Data of the eligible articles was summarized into tables, taking into account: the number of patients, the number of bony defects, test intervention performed, control type of material, Variables analyzed, Probing depth, and clinical attachment level.

3.7.QUALITY CONTROL

Quality control has been carried out using the CASP guide, by subjecting each of them to 11 questions and answering with an affirmative, negative, or uncertainty supposition. Being the first 3 questions a way to assess the validity of the articles in the present study, and the following questions a further assessment of the quality of methodology, results, and application (26).

4.RESULTS

4.1 PRISMA FLOWCHART

Here follows the flowchart that leads to the selection of the studies for this systematic review. From an initial search, a total of 243 articles were found from 3 different databases (Medline, Scopus, and Cochrane). The title and doi of each article were then scanned for duplicates through an excel calculation sheet and tool for duplicate values, which lead to the finding of 20 duplicate values which were removed yielding 223 articles for scanning. From the reading of the abstract and title already 176 articles were removed since they were not relevant to our research or because not pertinent to the discipline of dentistry. Of The remaining 47 articles, only 39 were able to be retrieved due to the fact that some trials from the Cochrane database were still not completed and results not yet published.

An assessment of the remaining 39 articles is carried by applying the inclusion and exclusion criteria. Which lead to the removal of 24 articles being the main cause that they were studies on animals, or the material was only part of a composite and no control with the pure substance was performed, providing a total yield of 14 articles. 5 assessing CS and 9 DBBM. The Flow diagram showing this process is visually represented in diagram 1.

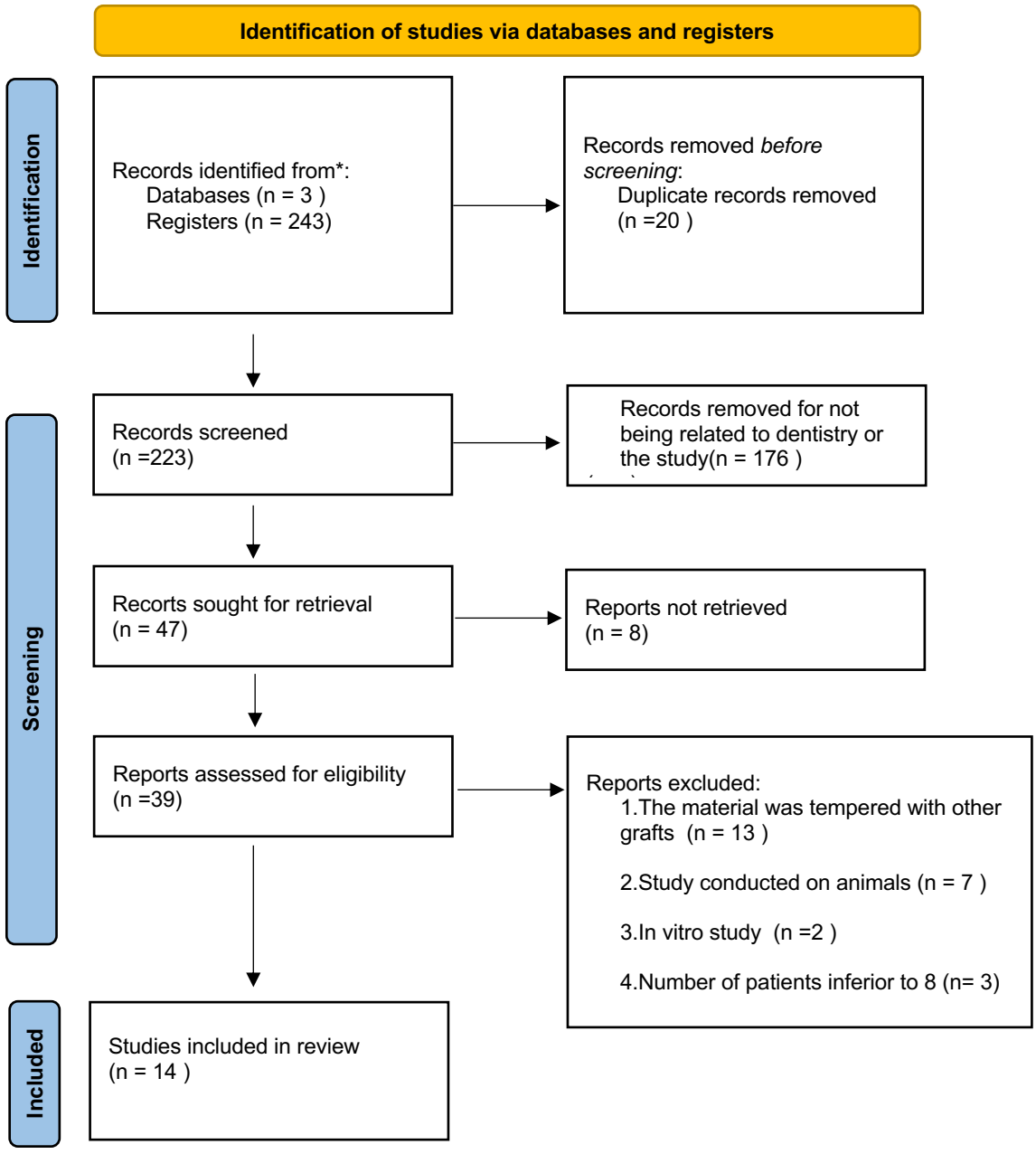

Diagram 1. Prisma flowchart

4.2. ANALYSIS OF THE CHARACTERISTIC OF THE STUDIES

4.2.1. CALCIUM SULPHATE STUDIES

Studies included spanned from 2008 to 2012 lead to the finding of 5 studies providing data about the implantation of CS graft being used in 2 different forms of application, 3 of them as bone filler, and 2 of them as a barrier to avoid soft tissue migration but using a different material as filler. A total of 142 patients which the main age for the CS group spanned from 20 years old up to 62 years old was taken into consideration, for a totality of 202 periodontal defects, half of which were subjected to CS and the remaining half to a different filling material or debridement alone. All these studies about CS recurred all to an initial OFS in order to clean the defects from any granulomatous tissue and had an overall sample size of 101 defects that have been treated this way. A multitude of variables was analyzed but not all of them were the same in each study, throughout the studies CAL and PPD are the ones that are common to all including not only CS but also, as we'll see further, DBBM studies, therefore they were selected as a mean of assessment for quality of the regeneration and comparison between the studies. Regarding the other variables analyzed by some studies Col V., Silpha B., and Farina R., included gingival indexes and plaque indexes as a means of assessing the hygiene of the participants. Follow-up was carried out in different stages depending on the study, being the majority had a follow-up between 9 months and 1 year and one article at 6 months from baseline. The description of all the variables and follow-up intervals is described in Table 6.

4.2.2. DEPROTEINAZED BOVINE BONE MATRIX

Final selection led to the inclusion of 9 studies studying and compering DBBM spanning from 2009 to 2021. The patient pool amounted to a total of 287 patients whose ages spanned from 18 to 65 years old being the main age of 41.5 years old. The total amount of defect periodontal bony defects treated reached an overall 671 sites of intervention, to which different procedures and materials were used, an extraction of procedures in which DBBM was used as graft material was performed yielding an overall of 222 defects

treated this way and analyzed, between them 3 different types of surgery and usage of the graft was assessed. 5 of the studies analyze DBBM as a filling material after a OFS without any other material involved this accounted for the majority of the defects treated, 3 of them analyzed DBBM as filler but covered with a collagen membrane and finally one of them analyzed the MIST technique with a filling of DBBM. As in CS, the common line between them was the CAL and PPD. Some of the studies also analyzed variables of the gingival index, plaque index, and radiological defect fill but since those variables were not always consistent with the other studies therefore a proper comparison could not be carried out regarding those particular variables. Regarding the follow-up, some of the studies proceeded to assess their variable at different intervals, spanning from 1 week to 6 years, in this systematic review a selection of the control time was established at approximately 1 year and our period between the articles resulted being between 6 months and 1 year. the majority of the articles included had the one-year checkpoint, 3 articles at 9 months, and 2 at 6 months.

TABLE 6. Studies included

AUTHORS	*YEAR*	*SAMPLE SIZE*	*AGE SPAN*	*EXPERIMENTAL GROUP/S*	*CONTROL GROUP*	*CLINICAL PARAMETERS*	*FOLLOW UP*
Bei Liu et al(27)	*2021*	*36 patients*	*18-65*	*MISTms + DMMB*	*MISTms alon*	*Probing depth, CAL, gingival recession, Cej-defect base, Radiografical defect dept*	*1,2,3,6 weeks and one year*
Yan Xu et al(28)	*2019*	*54 patients 120 one Wall intrabony defects*	*55.2±8.3*	*OFS+bio-oss: 30 OFS+ concentrated growth factors(CGF) OFS+bio-oss+ CGF*	*Open Flap surgery alone: 30 defects*	*Probing Depth, CAL, PD, Gingival margin level*	*6 and 12 months*
Daniela guimaraes de melo et al(29)	*2015*	*20 patients x 40 defects*	*21-27*	*Bovine bone matrix 20 defects*	*Blood cloth 20 defects*	*Probing depth, CAL, bone density*	*30 and 60 days and 1 year*
Vikram Blaggana et al(30)	*2014*	*15 patients x 30 defects*	*25-50*	*OFS+DFDBA 15 defects*	*OFS+DBBM 15 defects*	*Probing depth, CAL, linear bone fill*	*At 12 and 24 weeks*
Vincenzo Lorio siciliano et al(31)	*2014*	*40 patients one defect per patient was treated*	*33-57*	*Enamel matrix derivate+ DBBM*	*OFS+DBBM+ collagen membrane*	*Probing depth, gingival recession, cej-defect base. Width of defects at base level*	*1 year*

Deepthi Palachur et al(32)	*2013*	*14 patients with 28 bone defects*	*20-60*	*BIO-OSS+ fibrin fibronectin sistema(tissel)*	*BIO-OSS(DBBM)+ collagen type 1 membrane*	*Probing depth, CAL, gingival recession, Cej-alveolar crest,*	*6 and 9 months*
Sanjay Gupta et all(33)	*2012*	*8 patient 16 defects*	*26-58*	*CS membrane+peri obone G as filling*	*Periobone g*	*Plaque index, CAL, gingival margin positioning, percentage of bone filling.*	*9 month*
Col VB Mandlik et all(34)	*2012*	*50 patients x 100 defects*	*30-50*	*Bioactive glass (periobone g) graft*	*CS graft*	*Osseous gain, probing depth, CAL, gingival recession, plaque index, gingival index.*	*9 months*
Silpha budhiraja et all(35)	*2012*	*12 patient*	*20-50*	*CS membrane+DFD BA*	*Collagen membrane +DFDBA*	*Pocket depth, relative attachment level, gingival margin level, percentage of change of defect filled*	*6 month*
Christer Slotte et al(36)	*2012*	*32 patients each one presenting 1 defect*	*55-61*	*OFS+ DBBM*	*OFS alone*	*Probing depth, Cal, plaque index, gingival index, bleeding on probing, radiographic defect depth, and width*	*6 and 12 month*
R. Farina et al(37)	*2009*	*21 patients with one defect each*	*42-61*	*OFS+CS*	*OFS alone*	*Pocket probing depth, CAL, gingival recession, local bleeding score, plaque index,*	*1 year*
Andreas Stavropoulos et al(38)	*2009*	*45 patients x 45 defects*	*26-62*	*OFS+ Deproteinized bovine matrix + gentamicina sulphato 15 defects, OFS+DBBM + saline :15 defects*	*OFS alone 15 defects*	*Probing depth, CAL, plaque index, bleeding on probing, radiographic bone level, intrabony component.*	*At 1 and 6 years*
Ferenc Döri et al(39)	*2009*	*30 patients each one presenting 1 defect*	*28-65*	*OFS+Prp+ DBBM 15 defects*	*OFS+DBBM+ OFS 15 defects*	*Probing depth, CAL, gingival recession, plaque index, bleeding on probing, defect location*	*1 year*
Michele Paloantonio et al(40)	*2008*	*51 patients 51 defects divided into 3 groups*	*41-62*	*OFS+ CS(17 defects), OFS +collagen membrane*	*OFS alone*	*Probing depth, CAL, DBL*	*1 year*

Table 6. includes the studies selected by the screening process and their chracteristicsñ

4.3. EVALUATION OF THE METHODOLOGY AND RISK BIAS ASSESSMENT

Risk of bias assessment was carried out using the CASP guide each article was subjected to scrutiny and passed through a set of 11 questions in order to evaluate its biases. The first 3 questions were eliminatory followed by a quality assessment. All questions could be answered by an assertive, negative, or not assessable register. The precision of each study was not included since only groups where the material of interest was extracted, as well as the economical assessment of benefits of the treatment. All the proceedings of each study are illustrated in Fig.1.

Fig.1. biases control through CASP assessment.

4.4. SYNTHESIS OF THE RESULTS

4.4.1. CALCIUM SULPHATE VS DBBM COMPARISON OF BONE REGENERATION

In order to obtain a unified measurement of the outcome of the studies analyzed, the data from CAL and PPD from each study are shown in table8. And table 9. Have been combined and weighted averaged to obtain linear measurements expressed in mm. for each one of the materials. The description here obtained took into consideration the values obtained for all the types of surgery performed to have a general view of which material can deliver generally better performances, here is shown in table.7 and graphically in fig2.

Table7. Added Measurement of all the articles included Categorized by DBBM and CS

MATERIAL	Nº DEFECTS	BASELINE PPD+SD	POST PPD +SD	STARTIN CAL+SD	POST CAL+SD	CAL INCREASE	PPD reduction
CS	101	7.35-1.12	2.25-0.64	7.76-1.19	4.01-0.89	3.77	4.61
DBBM	222	7.94-1.23	4.11-1.13	9.33-1.77	5.29-1.71	4.04	3.83

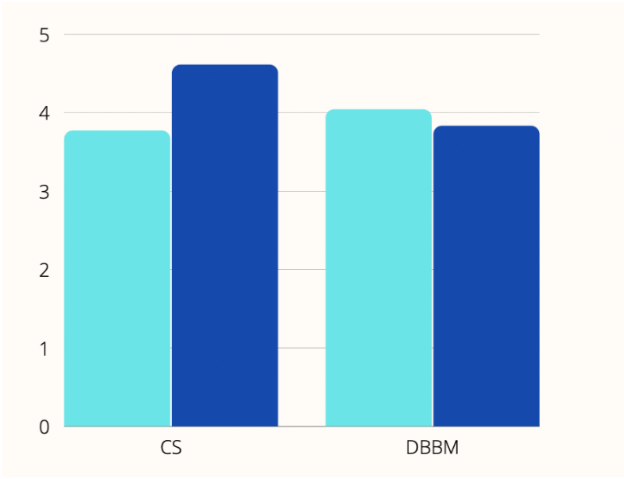

Fig2. Visual representation of the increment in CAL Increase (dark blue) and PPD reduction (light blue)

It is determined that if it is not taken into consideration the type of surgery performed, CS seems to perform better in improving the PPD compared to DBBM and has very similar results regarding the increase in CAL, although slightly worse when compared to DBBM.

4.4.2. TYPE OF SURGERY PERFORMANCES BETWEEN DDBM AND CS

To assess the linear measurements of increase of CAL and PPD the weighted average was performed between the articles sharing the same type of surgery for each material and was then combined. The gross data to obtain the final table of surgeries is a combination of the relevant articles between the 2 materials, CS work process is shown in table 8 and DBBM table 9. All the data were combined and weightily averaged using the following formula:

$$\bar{x} = \frac{\sum_{i=1}^{n} w_i x_i}{\sum_{i=1}^{n} w_i}$$

Data was then analyzed to obtain the linear measures for each surgery to corresponding material and is expressed in table 10. Together with their graphical representation in fig3.

Table 8. Measurements extracted from articles that included CS categorized by type of surgery

AUTHOR	Intervention	Nº defects	baseline CAL+SD	Baseline PD	CAL+SD at control	Pd+SD at control
Col Vb Mandlik et al(34)	CS graft+OFS	50	7.20 -1.06	7.2-1.06	2.32-0.47	2.14-0.35
Michaele Pantolino et al.(40)	CS graft+OFS	17	8.5 – 1.1	7.8 – 1.3	5.8 – 1.0	3.4 – 0.7
R. Farina et al(37)	CS graft+OFS	10	8.6-1.7	7.4-1.03	5.8- 1,8	3.5-0.9
Sanjay Gupta et al.(33)	OFS+CS as barrier	8	7.13±1.46	7.63±1.69	4.38±1.30	4.13±1.36
Shilpa Budhiraja Et al(35)	OFS+ CS Barrier	6	9.42 ± 1.08	6.92 ± 0.90	6.25 ± 1.35	3.25 ± 0.75

Table 9. Extraction of measurements in the articles that used DMMB divided by surgery type

Authors	intervention	Nº of defects	Baseline CAL +SD	Baseline PD+SD	CAL+SD at control	Pd+SD at control
Yan Xu et al.(28)	DBBM +OFS	30	8.82-2.18	7.91-1.14	4.64±1.57 1y	4.18±0.75
Vikram Blaggana et al(30)	DBBM +OFS	15	6.93-0.46	6.86-0.45	4.67±0.44	4.60±0.36
Andreas Stavropoulos et al(38)	DBBM +OFS	15	9.6 -1.6	8.5 – 1.1	5.0 – 2.0	4.6 -1.0
Ferenc Dö ri et al(39)	DBBM+OFS	15	9.6 – 1.9	8.5 – 2.0	4.9 – 1.5	3.2 – 1.3
Christer Slotte et al.(36)	DBBM +OFS	18	10.4 – 0.8	7.9 – 0.7	8.3-0.8	4.7-0.7
Daniela Guimaraes de Melo et al.(29)	DBBM + collagen membrane	20	9.6 – 1.6	8.5 – 1.1	2.5 -2.5	4.6 -1.0
Vincenzo Iorio-Siciliano et al.(31)	DBBM+ collagen membrane	20	9.3 – 2.5	8.1 – 2.1	5.6 – 2.3	3.7 – 1.3
Deepthi Palachur et al.(32)	DBBM+ collagen membrane	14	11.74-1.97	7.14-1.35	7.52±1.19	2.71-0.47
Bei liu et al (27)	DBBM + mist tecniquie	18	7.50 – 1.61	6.63 -1.06	5.50 -2.08	4.31 -1.50

Table 10. A report of the linear measurements of CAL and PPD and their corresponding increase subdivided by type of surge and material

MATERIAL	INTERVENTION	Nº of Defect	STARTING PPD+SD	POST PPD + SD	STARTING CAL +SD	POST-CAL+ SD	PPD reduction	CAL increase
CS	GRAFT +OFS	77	7.36-1.15	2.59-0.52	7.67-1.15	3.64-0.76	4.77	4.03
CS	AS BARRIER+ OFS	24	7.33-1.42	3.25-1.03	8.11-1.30	5.18-1.32	4.08	2,93
DBBM	GRAFT	93	8.15-1.08	4.26-0.81	9.07-1.50	5.45-1.30	3.89	3.62
DBBM	GRAFT+ COLLAGEN MEMBRANE	54	8.00-1.54	3.78-1.55	10.4-2.03	4.95-2.29	4.22	5.45
DBBM	MIST+GRAFT	18	6.63 ± 1.06	4.31 ± 1.50	7.50 ± 1.61	5.50 ± 2.08	2.32	2

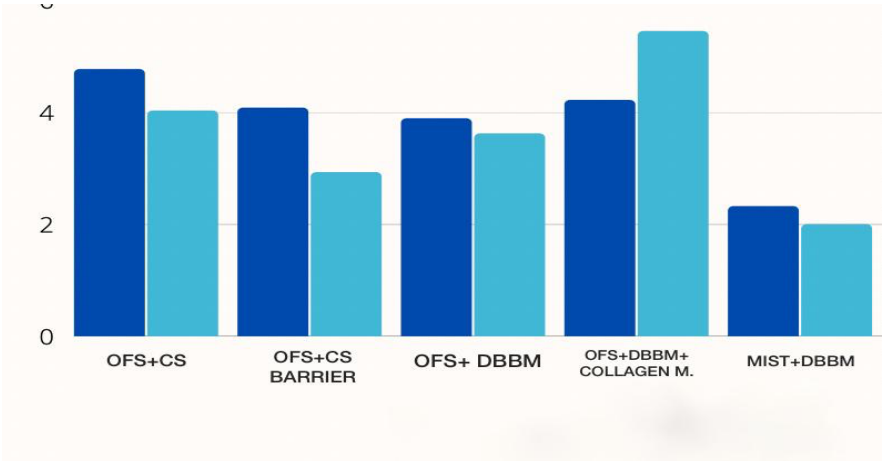

Fig.2 Visual representation of CAL increase (light blue) and PPD Reduction (dark blue) increase depending on the type of surgery

As it is shown from the values obtained in table10. And comparison chart in fig2. CS and DBBM obtain very similar results in terms of increase of CAL and PPD reduction with the slightly better result obtained by OFS+CS graft when compared to the same procedure performed with DBBM. Using a collagen membrane combined with DBBM produced the highest increase in CAL between all the surgeries and a similar PPD reduction compared to DBBM+OFS and OFS+CS barrier, being second to OFS+CS. CS barrier produced the 3rd lowest results regarding CAL increasing. The worst performance is evidenced to be the one produces by the MIST technique + DBBM filling with the lowest increase in CAL and PPD reduction.

5.DISCUSSION

From an overall analysis of the performances of the two materials, it can be valued that both materials have very similar prognosis in terms of regeneration, with a slight advantage in the improvement of PPD for CS compared to DBBM, if each value from every surgery type is combined, both materials show similar levels of regeneration power. Still, things change when comparing them through the surgery type lens.

This first general analysis shows that inherently both materials show the regenerative power to accomplish the healing and bone regeneration in periodontal defects and that the success of the therapy may be purely technique dependent.

When analyzing the surgical techniques applied, the worst outcome between the different techniques was given by the MIST using DBBM, this may be due to the fact that MIST is a difficult technique to be performed and needs special training and equipment also when comparing the values obtained with other studies it is observed that Dannan et al. (41) obtained better results with the technique compared to those found in our systematic review although theirs would implement the used of enamel Matrix derivates which could aid in the regeneration process (41).

The use of a Collagen membrane together with DBBM, gave the best results in CAL improvement, thanks to the membrane impeding the migration of epithelial tissue, therefore allowing more bone to be regenerated, when comparing this to the use of a CS barrier, it is shown a considerable difference in in the CAL augmentation, being CS the one showing lesser improvement (42).

A possible explanation is that since the use of a reduced amount of material when Appling CS as barrier, the reabsorption time of the material differs compared to its normal resorption time. Normally CS reabsorbs faster than bone deposition and if in conjunction with its reduced thickness and volumetric amount, it may be reabsorbing too quickly, not fulfilling is purpose to stop soft tissue migration and yielding lesser amount of supporting bone for the gums (43).

A good way to improve the data regarding this aspect would be the implementation of bone probing to the cement enamel junction in the defect area to get a more precise estimation since with conventional radiographic analysis only vertical, mesial, and distal measurement can be obtained but not in a palatal and buccal sense. With a Cone beam computer tomography, the precise volumetric changes of pre- and post- regeneration could be measured with more accuracy (44).

The comparison of both graft materials without membrane generates slightly better results for CS in both of the analyzed parameters, this may be justified due to the fact that calcium sulphate thanks to its molecular structure and crystallization properties beside acting as a filling material may act also as a membrane by itself stopping soft tissue migration, and a total resorption and bone substitution of the material (42).

This outcome still doesn't reach the levels obtained by the DBBM+ Collagen membrane group which produced the best results overall, revealing that the use of a collagen membrane still is one of the best ways to stabilize soft tissue, although from a clinical point of view the use of a membrane if not well executed may be followed by complication such as bacterial filtration and consequential failure of the treatment (45).

Assessing the weakness of these studies, different instruments brands were used to obtain the measurements Sanjay G. (33), Yan X. (28) and Liu et al. (27) used a "hu-Friday PCP unc 15" periodontal probe while De Melo D. (29) used a "marquis" periodontal probe, Stavropoulos A. (38) used a "Hu.Friday LL 20" which shows 1mm increments and has a 0.5 mm ball-tip and finally Palachur D. et al. (32) which used a Williams probe the other authors didn't specified which type of probe has been used . Moreover, some authors used an acrylic or silicone occlusal stent with vertical grooves to record the site of probing for reproducibility (32,33,35), step not considered in the majority of the other studies (27–31,34,36–40), the sum of this differences could have produced inconsistencies and some degree of imprecisions in the comparisons of the final measurements.

Another significative value that could be implemented for the better evaluation and reduction of errors is the inclusion of the morphology of the defect, for example in the defects presenting 3 walls are generally easier to regenerate compared to defects

presenting just one or two walls (46). Also defects that are not deep usually seem to be affected more by the microbiological presence and epithelial infiltration when compared to defects that are deeper (42).

This translate in the fact that when a defect is not too wide, a better vertical component is achieved at the evaluation during control. Nevertheless, in wide defects similar values of regeneration in between different morphologies are achieved, if instead of evaluating linear values, a volumetric analysis of the regeneration is applied (47). Therefore, the Data obtained about the amount of regeneration could be influenced by the implementation of morphological and volumetric analysis of the defects, leading to variations in results.

Unfortunately, many articles included in this systematic review didn't specify the morphology of the defects that were treated(27–30,32–35,38,39), only some of them registered the data about its 3-dimensional characteristics by classification(31,37,40), and between those even less authors recorded the exact measurements to implement a volumetric analysis.(36)

Regarding the data retrieved about the materials implanted only Sanjay G. et al (33) specified the brand of CS used in their study while the others just referred generically to the material, because of this it has been assumed that the material has been used in its pure form, although a specification of granules sizes and excipients could have improved the results obtained. On the other hand, when peeking through DBBMs studies is shown that almost all the authors specified that they used Bio-Oss® while Iorio V. et al.(31) and Slotte C. et al. (36)only indicated that they used DBBM whiteout indicating the brand.

Other factor that could have improved the precision of data obtained would have been the recording of amount and thickness of keratinized gingiva, which is fundamental for the outcome of the surgery since, if a full coverage of the defect is not obtained by the correct repositioning of the flap and its correct pressure and tension not applied over the graft, it could lead to the failing of the procedure or not reaching anyway its true regenerative potential (48).

When comparing this work with other studies it is found that our results are in accordance with the amount of regeneration obtained by Sculean A. et al(49) which analyzed in his systematic review different types of materials, including DBBM, obtaining similar results when analyzing xenografts reaching a percentage of 70% of obtained regeneration comprehensive of bone and junctional epithelium together. This is in concordance with our study since if the linear measurements of total regeneration are converted in percentage it would correspond to 65%, and the difference in between the two could be explain by the inclusion of the MIST technique,(27) which if applied to our reduced sample size could have lowered our general percentage of regeneration for the material. When looking for other systematic reviews abording regeneration of periodontal defect with CS no other studies have been found, if not only the trials included in this review.

Based on the analysis of the data obtained in our systematic review it is observed that the answer to our research question is that both materials are equally effective in the regeneration of periodontal bony defects, and the final level of regeneration could be influenced by the surgery technique used.

On the base of this findings can say that the null hypostasis is accepted therefore no statistical difference was found when comparing the 2 materials.

Regarding the clinical implication of our findings, it is an important reminder to consider the accessibility of the 2 materials. DBBM is generally very expensive therefore limiting its accessibility to patients which could refuse treatment in case of not being able to sustain the cost of the treatment, meanwhile medical-grade CS is relatively cheaper and produces satisfactory results. Therefore, while the use of OFS+DBBM combined with a collagen membrane would be the first choice of treatment, still it bears the disadvantage of needing a major economic investment for both the patient and the clinician, which for some may be a limiting factor at the time of accepting the treatment. At the light of our findings, it's recommendable to offer an alternative option like the use of a CS graft which can proportion very similar results at a lower cost. Moreover, the fact that the technique analyzed in this

systematic review doesn't involve the use of a membrane it also simplifies the overall clinical procedure. Regarding the use of CS as barrier, acceptable results are still obtained, although since the cost increase of using an underlining graft material and the need of increasing the clinical steps its recommended to simply use CS directly as a graft in the whole bony cavity.

The use of DBBM alone can bears acceptable results still it would be recommended the use in conjunction with a collagen membrane to obtain the best possible result. While the MIST technique with a filling of DBBM may not be suggested to due to its complexity of execution and the probable level of regeneration obtained. Still, more research is needed to further evaluate the effectiveness of the technique. Still due to the lack of sufficient scientific literature more research is needed to be carried on, especially in the use of CS, to which only a few clinical randomized control trials could be retrieved. Also, to better focus on the differences between CS and DBBM more clinical research is needed that would compare the 2 directly between them, following a standardized surgical protocol of application and control.

The Limitations regarding the methodologies implemented in this systematic review are tied of course to the language barrier since only articles in English, Spanish and Italian have been used. Furthermore, the limited number of databases used, is considered another limiting factor, since only 3 databases have been implemented for the search. With a broader spectrum of databases used and languages for the search, the possibility of a greater variety of articles increases. This leads to the assumption that some conducted studies which were published in other databases or other languages than English, Spanish, and Italian, have not been included in this systematic review. Another limitation is the time spans applied in the search filters, since the limit was 10 years, articles published before 2008 where not included, Nevertheless, this allows us to have a more contemporary vision of the properties of the latest versions of the materials. Also, a very different sample size was between the 2 materials compared which could also have influenced the statistical precision of the data obtained. Since not much literature regarding CS could be retrieved the sample size was half the one of DBBM. Moreover, the absence of an experimental standardized protocol in each of the studies may also introduce some degree of differences in the final results. Also, the size sample probably should be higher to increase the precision of this work.

6.CONCLUSION

1) According to the general objective, it is reasonable to assume that the use CS offers a similar grade of regenerative potential when compared to DBBM, which proportioned only a slightly less yielding of total regeneration of bone and junctional epithelium. Therefore, it justifies the use of CS into the clinical practice of treating periodontal bone defects.

2) According to our first subobjective, the type of surgery that bore the best results: Staring DBBM, an OFS together with a collagen membrane proportioned highest amount of regeneration, followed by the performance of only OFS and DBBM graft and finally the MIST technique which presented the worst outcome.

3) According to our second subobjective, the best way to implement CS for the regeneration of periodontal bone defects seemed to be the performance of an OFS with a CS graft, secondly its use as a barrier.

4) Nevertheless, more studies have to be performed in order to obtain a better grade of validation and precision.

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8.ANNEX

Prisma checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title page
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3-9
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	10
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	11
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	12-13
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	12-13
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	13
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	13
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	13
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	13
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	13
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	13
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	-
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	-
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	-
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	-
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	-
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	-
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	13
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	13

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	14-15
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	15
Study characteristics	17	Cite each included study and present its characteristics.	16-18
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	19
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	-
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	19
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	-
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	-
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	-
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	19
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	20-23
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	24-25
	23b	Discuss any limitations of the evidence included in the review.	25-26
	23c	Discuss any limitations of the review processes used.	27-28
	23d	Discuss implications of the results for practice, policy, and future research.	28
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	-
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	-
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	-
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	-
Competing interests	26	Declare any competing interests of review authors.	-
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	-

The use of Calcium sulphate vs deproteinized bovine bone matrix as bone substitutes in periodontal defect regeneration: a systematic review

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KEYWORDS: Periodontal Defect; Intrabony Defects; Calcium sulfate; Bovine Derived Bone matrix; Periodontal regeneration

ABSTRACT

BACKGROUND: This systematic review, is focused on the comparison of 2 Materials: Calcium sulphate (CS) and deproteinized bovine bone matrix (DBBM). The aim is to analyze and compare the efficacy of the 2 materials and see which surgery types combined with these 2 materials work best.

METHOS: A systematic search of the literature was conducted to obtain the relevant studies to be included. Randomized control clinical trials that fitted the inclusion criteria were selected and those which could not pass the exclusion criteria have been discarded. The search was performed throughout 3 databases: Medline on 09/02/2022, Cochrane on 12/02/2022, and Scopus on 31/01/2022). Risk assessment was analyzed using the CASP guide. All the data was sorted into a table and averaged getting the final values presented and then into tables and graphs.

RESULTS: Starting from 243 articles after the removal of the duplicates and screening, 14 articles have been reputed suitable for this review. Risk of bias was assessed and variables of clinical attachment and pocket probing dept were analyzed and averaged between studies to obtain general material performances and surgery + material performance.

DISCUSSION AND COCLUSION: About surgeries Open flap surgery (OFS)+ DBBM+ collagen membrane shown the best results followed by OFS+CS, DBBM + OFS, CS BARRIER+OFS, and finally Minimally invasive surgery technique (MIST)+DBBM.

About limitations encountered it is assessed that since a standardized surgical protocol and standardized measurement were not followed in between studies a degree of imprecision may have arisen during the obtention of the final values. Still, the data obtained shows that both materials are capable of archiving regeneration of the defect and share a similar biological potential. The use of a collagen membrane and DBBM together in an OFS showed the best outcome possible followed by using CS alone in an OFS.

INTRODUCTION

A periodontal intrabony defect is a type of bone lesion with a particular morphology and location in the alveolar bone. It's a crater surrounded by bony walls on the sides and 1 one of them is a tooth root. They are caused by the presence of infectious foci and consequent inflammation which leads to bone resorption on the site and proliferation of granulomatous tissue. Depending on the bone type and thickness, bone resorption may start in different locations, a thin cortical wall will start a marginal defect while a thicker cortical may result in resorption starting in the trabecular bone (1).

Intrabony defects are classified depending on the number of bony walls surrounding the defect and can be defined as 1, 2 or 3 wall defects (2,3).

Many factors can influence the outcome of regenerative surgery. They could be dependent on the technique the operator is using or being influenced by the patient's habits.

Smoking, poor hygiene, or the presence of any systemic disease that could alter the healing process such as diabetes are associated with a poorer prognosis. Moreover, evidence has been found that tooth mobility and complex morphology of the defects could influence the prognosis negatively (4).

This work is focused on the properties and techniques that implement CS and DBBM as bone substitutes for the reparation of intrabony defects

CS is an extremely versatile material, that has been used countless times both in the field of medicine and dentistry. It can be used in 2 crystalline forms: alpha and beta and 3 states of hydration anhydrous, hydrate, and dihydrate. The alpha form is very compact and is usually

used as a dental casting material while the beta or a mix of the 2 can be used as a bone void filler (5,6).

One other material that can be utilized for the purpose of repairing periodontal bony defects is the deproteinized bovine bone matrix (DBBM). It's an animal bone derivate that has been shown to work with or without a membrane and possibly to achieve periodontal regeneration and not only new bone formation (7).

It is a Xenograft, obtained by the bone of oxeas, which is treated to remove any possible irritant and biological substance such as proteins, cells, etc. So that only an inorganic matrix is left behind. Due to the absence of organic components the main property of this grafting material is osteoconduction, permitting cell migration and proliferation through the scaffold, it provides but lacks any type of cell stimulation (8).

JUSTIFICATION

Bone defect reparation is quite a common procedure in dentistry, the most common material being used currently is a bovine-derived substitute which bears the disadvantage to be very expensive.

Calcium sulfate is one of the cheapest materials that can be used as a bone substitute in a variety of surgery where bone loss has occurred, this work wants to analyze its performance in the regeneration of bone defects of 1, 2, 3 walls and analyze its validity as a material through the findings of this systemic review, compared to other more expensive material such as bovine substitute.

HYPOTHESIS:

Null hypothesis: there is not going to be a statistical difference between the performances of CS and DBBM.

Work hypothesis: The DBBM is going to perform Better than CS in repairing periodontal bone defects.

OBJECTIVE:

1) Demonstrate which material between CS AND DBBM produces better results in terms of bone regeneration

SUB OBJECTIVES

1) Assess which type of surgery using calcium sulfate achieve better results in term of bone regeneration

2) Assess which type of surgery using DBBM achieve better results in term of bone regeneration

MATERIALS AND METHODS

PRISMA STATEMENT

The Prisma guide was followed to develop this systematic review. (9)

PICO

P: Adult population with bone defects

I: the use of calcium sulfate in bony defect repair surgery

C: bovine bone matrix in bony defect repair surgery

O: To compare the effectiveness of calcium sulfate and bovine bone matrix in bony defect surgery

Eligibility Criteria:

Studies that met the following requirements were included

- Randomized control trials where calcium sulfate and/or bovine bone matrix were used in regeneration processes
- Studies with a minimum sample size of 8 patients
- Only studies published between Jan 2008 to Jan 2022

Exclusion criteria

- Studies conducted on animals
- studies where the only data available was about products which were combined with calcium sulfate or bovine bone matrix into a composite graft
-studies performed in vitro

Data source and Research strategy

Research on the databases has been carried out on Medline complete, Scopus, and Cochrane. Using the following keywords: Calcium sulfate, calcium sulfate, Bone Defect, Dentistry, Bovine Bone Matrix, Periodontal defects, bony defect.

And Boolean operators: AND, OR, NOT, Being the last search carried out the 12/02/2022

The strategies employed throughout the databases are shown in table 4.

Study Selection:

Literature was reviewed independently by 1 revisor to be selected by Appling the inclusion and exclusion criteria. This first stage was the research by application of filters. The second stage was done by reading the titles and abstracts and the last stage of selection was reading the full articles and application of CASP. The research was carried out by DF and assessed by CRP

DATA EXTRACTION

The Data of the eligible articles was summarized into tables considering the number of patients, the number of bony defects, test intervention performed, control type of material, Variables analyzed, Probing depth, and clinical attachment level.

QUALITY CONTROL

Quality control has been carried out using the CASP guide, by subjecting each of them to 11 questions and answering with an affirmative, negative, or uncertainty supposition. Being the first 3 questions a way to assess the validity of the articles in the present study, and the following questions a further assessment of the quality of methodology, results, and application (10).

RESULTS

From an initial search, a total of 243 articles were found from 3 different databases (Medline, Scopus, and Cochrane). The title and DOI of each article were then scanned for duplicates through an excel spread sheet, which lead to the finding of 20 duplicate values which were removed yielding 223 articles for scanning. From the reading of the abstract and title already 176 articles were removed since they were not relevant to our research or because not

pertinent to the discipline of dentistry. Of The remaining 47 articles, only 39 were able to be retrieved since some trials from the Cochrane database were still not completed and results not yet published. Following to assess the remaining 39 articles by applying our inclusion and exclusion criteria. Which lead to the removal of 24 articles being the main cause that they were studies on animals, or the material was only part of a composite and no control with the pure substance was performed, finagling a total yield of 14 articles. 5 assessing CS and 9 DBBM. The Flow diagram is visually represented in fig 1(annex).

ANALYSIS OF THE CHARACTERISTIC OF THE STUDIES

Studies included spanned from 2008 to 2012 lead to the finding of 5 studies providing data about the implantation of CS graft being used in 2 different forms of application, 3 of them as bone filler and 2 of them as a barrier to avoid soft tissue migration but using a different material as filler. A total of 142 patients which the main age for the CS group spanned from 20 years old up to 62 years old was taken into consideration, for a totality of 202 periodontal defects, half of which were subjected to CS and the remaining half to a different filling material or debridement alone. All these studies about CS recurred all to an initial OFS in order to clean the defects from any granulomatous tissue and had an overall sample size of 101 defects that have been treated this way. A multitude of variables was analyzed but not all of them were the same in each study, throughout its shown that CAL and PPD are the ones that are common to all the studies included not only CS but also, as we'll see further, DBBM studies, the majority had a follow-up between 9 months and 1 year, and one article at 6 months from baseline

Regarding DBBM final selection led to the inclusion of 9 studies studying and compering DBBM spanning from 2009 to 2021. The patient pool amounted to a total of 287 patients whose ages spanned from 18 to 65 years old being the main age of 41.5 years old. The total amount of defect periodontal bony defects treated reached an overall 671 sites of intervention, to which different procedures and materials were used, an extraction of procedures in which DBBM was used as graft material was performed yielding an overall of 222 defects

The selected articles together with their general characteristic are shown in table.1 (ANNEX)

EVALUATION OF THE METHODOLOGY AND RISK BIAS ASSESSMENT

Risk of bias assessment was carried out using the CASP guide each article was subjected to scrutiny and passed through a set of 11 questions to evaluate its biases. The first 3 questions were eliminatory followed by a quality assessment. All questions could be answered by an assertive, negative, or not assessable register. The precision of each study was not included since only groups where the material of interest was extracted, as well as the economical assessment of benefits of the treatment. All the proceedings of each study are shown into fig2(annex)

VARIABLE ANALYSIS

Values of CAL and PPD pre and post treatment have been extracted and shown together with their standard deviation in table2. From them a weighted average was performed in order to obtain average values for each type of surgery and material as shown in table3. And fig.3 (Annex)

Total regeneration power was obtained by joining the values for each surgery type for the corresponding material as shown in table.4 and graphically in fig.4. (annex)

It's appreciated that CS and DBBM obtain very similar results in terms of increase of CAL and PPD reduction with the slightly better result obtained by OFS+CS graft when compared to the same procedure performed with DBBM. Using a collagen membrane combined with DBBM produced the highest increase in CAL between all the surgeries and a similar PPD reduction compared to DBBM+OFS and OFS+CS barrier, being second to OFS+CS. CS barrier produced the 3rd lowest results regarding CAL increasing. The worst performance is evidenced to be the one produces by the MIST technique + DBBM filling with the lowest increase in CAL and PPD reduction.

It is Determined that if the type of surgery performed is not considered, CS seems to perform better in improving the PPD, compared to DBBM, and has very similar results regarding the increase in CAL, although slightly worse when compared to DBBM.

DISCUSSION

From an overall analysis of the performances of the two materials it can be valued that both materials have very similar prognosis in terms of regeneration, with a slight advantage in the improvement of PPD for CS compared to DBBM, if not considering each singular surgery type, therefore both materials show similar levels of regeneration power

When analyzing the surgical techniques applied, the worst outcome between the different techniques was given by the MIST using DBBM, this may be due to the fact that MIST is a difficult technique to be performed and needs special training and equipment also when comparing the values obtained with other studies it is observed that Dannan (2011) et al. (25) obtained better results with the technique compared to those found in our systematic review although theirs would implement the used of enamel Matrix derivates which could aid in the regeneration process (25). Moreover, some authors used an acrylic or silicone occlusal stent with vertical grooves to record the site of probing for reproducibility(16,17,19), step not considered in most of the other studies(11–15,18,20–24), the sum of this differences could have produced inconsistencies and some degree of imprecisions in the comparisons of the final measurements.

Articles included in this systematic review also didn't specify the morphology of the defects that were treated (11–14,16–19,22,23), only some of them registered the data about its 3-dimensional characteristics by classification (15,21,24), and only one recorded the exact measurements to implement a volumetric analysis (20).

When comparing this work with other studies it is found that our results are in accordance with the amount of regeneration obtained by Sculean (2015) et al (26) which analyzed in his systematic review different types of materials, including DBBM, obtaining similar results when analyzing xenografts reaching a percentage of 70% of obtained regeneration comprehensive of bone and junctional epithelium together. This is in concordance with our study since if the linear measurements of total regeneration are converted in percentage it would correspond to 65%, and the difference in between the two could be explain by the inclusion of the MIST technique (11), which if applied to our reduced sample size could have lowered our general percentage of regeneration for the material. When looking for other

systematic reviews abording regeneration of periodontal defect with CS, no other studies have been found, if not only the trials included in this review.

The Limitation regarding the methodologies implemented in this systematic review are tied of course to the language barrier since only articles in English, Spanish and Italian have been used. Furthermore, the limited number of databases used, is considered another limiting factor, since only 3 databases have been implemented for the search. With a broader spectrum of databases used and languages for the search, the possibility of a greater variety of articles increases.

Regarding the clinical implication of our findings, it is an important reminder to consider the accessibility of the 2 materials. DBBM is generally very expensive therefore limiting its accessibility to patients which could refuse treatment in case of not being able to sustain the cost of the treatment, meanwhile medical-grade CS is relatively cheaper and produces satisfactory results. The use of DBBM alone can bears acceptable results still it would be recommended the use in conjunction with a collagen membrane to obtain the best possible result. While the MIST technique with a filling of DBBM may not be suggested to due to its complexity of execution and the probable level of regeneration obtained. Still, more research is needed to further evaluate the effectiveness of the technique. Due to the lack of sufficient scientific literature more research is needed to be carried on, especially in the use of CS, to which only a few clinical randomized control trials could be retrieved. Also to better focus on the differences between CS and DBBM more clinical research is needed that would compare the 2 directly between them, following a standardized surgical protocol of application and control.

9.CONCLUSION

1) According to the general objective, it is reasonable to assume that the use CS offers a similar grade of regenerative potential when compared to DBBM, which proportioned only a slightly less yielding of total regeneration of bone and junctional epithelium. Therefore, justifying the use of CS into the clinical practice of treating periodontal bony defects.

2) According to our first subobjective, the type of surgery that bore the best results: Staring DBBM, an OFS together with a collagen membrane proportioned highest amount of

regeneration, followed by the performance of only OFS and DBBM graft and finally the MIST technique which presented the worst outcome.

3) According to our second subobjective the best way to implement CS for the regeneration of periodontal bony defects seemed to be the performance of an OFS with a CS graft, secondly its use as a barrier.

4) Nevertheless, more studies have to be performed in order to obtain a better grade of validation and precision.

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ANNEX

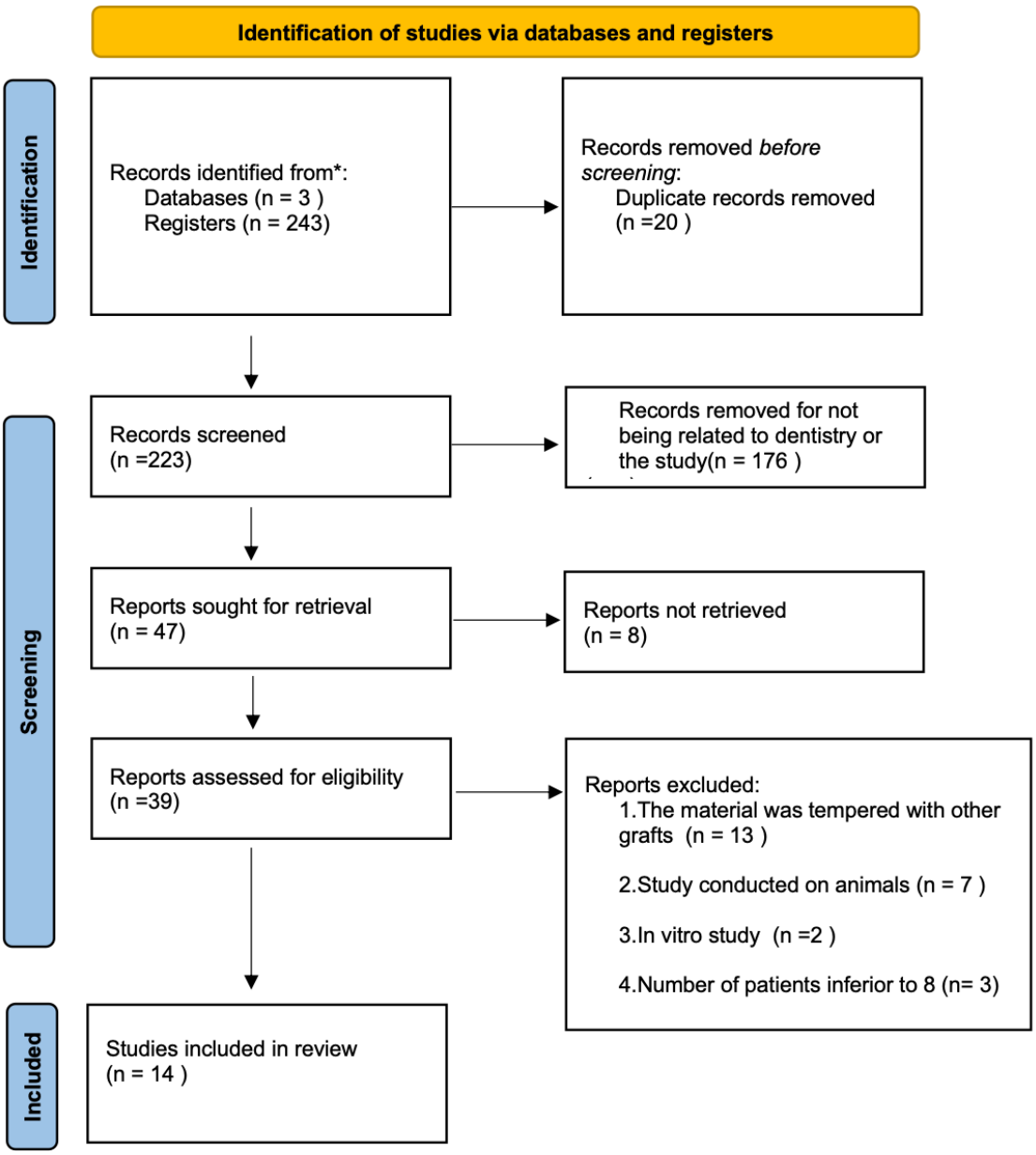

Fig 1. Prisma flowchart

FIG2. CASP risk of bias assesment

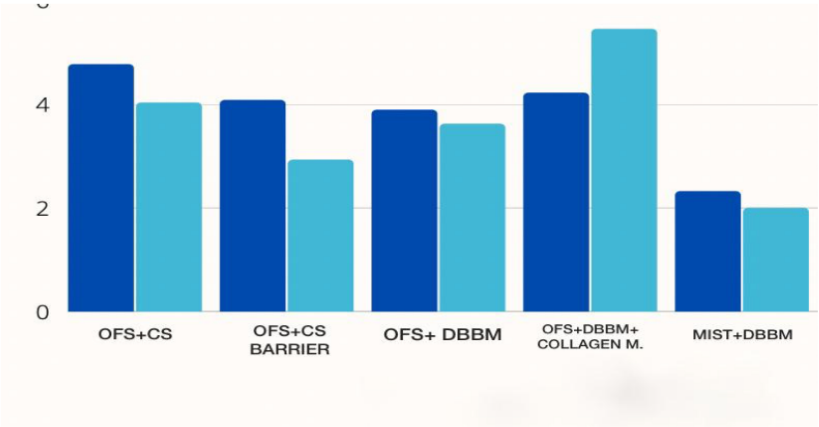

Fig.3 **Visual representation of CAL increase (light blue) and PPD Reduction (dark blue) increase depending on the type of surgery**

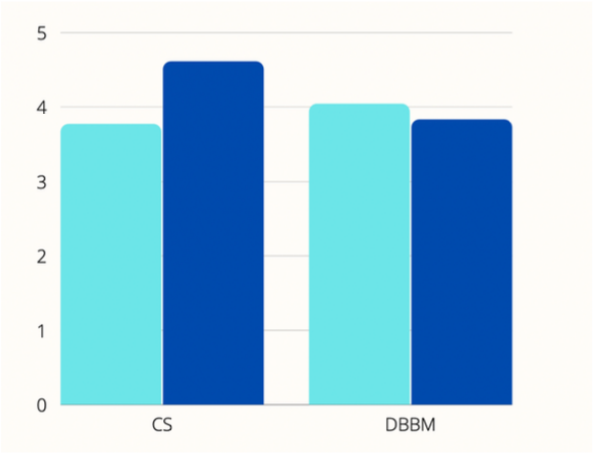

Fig4. **Visual representation of the increment in CAL Increase(dark blue) and PPD reduction(light blue)**

TABLE 1. Studies included

AUTHORS	YEAR	SAMPLE SIZE	AGE SPAN	EXPERIMENTAL GROUP/S	CONTROL GROUP	CLINICAL PARAMETERS	FOLLOW UP
Bei Liu et al(11)	2021	36 patients	18-65	MISTms + DMMB	MISTms alon	Probing depth, CAL, gingival recession, Cej- defect base, Radiografical defect dept	1,2,3,6 weeks and one year
Yan Xu et al(12)	2019	54 patients 120 one Wall intrabony defects	55.2±8.3	OFS+bio-oss: 30 OFS+ concentrated growth factors(CGF) OFS+bio-oss+ CGF	Open Flap surgery alone: 30 defects	Probing Depth, CAL, PD, Gingival margin level	6 and 12 months
Daniela guimaraes de melo et al(13)	2015	20 patients x 40 defects	21-27	Bovine bone matrix 20 defects	Blood cloth 20 defects	Probing depth, CAL, bone density	30 and 60 days and 1 year
Vikram Blaggana et al(14)	2014	15 patients x 30 defects	25-50	OFS+DFDBA 15 defects	OFS+DBBM 15 defects	Probing depth, CAL, linear bone fill	At 12 and 24 weeks
Vincenzo Lorio siciliano et al(15)	2014	40 patients one defect per patient was treated	33-57	Enamel matrix derivate+ DBBM	OFS+DBBM+ collagen membrane	Probing depth, gingival recession, cej-defect base. Width of defects at base level	1 year
Deepthi Palachur et al(16)	2013	14 patients with 28 bone defects	20-60	BIO-OSS+ fibrin fibronectin sistema(tissel)	BIO-OSS(DBBM)+ collagen type 1 membrane	Probing depth, CAL, gingival recession, Cej-alveolar crest,	6 and 9 months
Sanjay Gupta et all(17)	2012	8 patient 16 defects	26-58	CS membrane+periobone G as filling	Periobone g	Plaque index, CAL, gingival margin positioning, percentage of bone filling.	9 month
Col VB Mandlik et all(18)	2012	50 patients x 100 defects	30-50	Bioactive glass (periobone g) graft	CS graft	Osseous gain, probing depth, CAL, gingival recession, plaque index, gingival index.	9 months
Silpha budhiraja et all(19)	2012	12 patient	20-50	CS membrane+DFDBA	Collagen membrane +DFDBA	Pocket depth, relative attachment level, gingival margin level, percentage of change of defect filled	6 month
Christer Slotte et al(20)	2012	32 patients each one presenting 1 defect	55-61	OFS+ DBBM	OFS alone	Probing depth, Cal, plaque index, gingival index, bleeding on probing, radiographic defect depth, and width	6 and 12 month
R. Farina et al(21)	2009	21 patients with one defect each	42-61	OFS+CS	OFS alone	Pocket probing depth, CAL, gingival recession, local bleeding score, plaque index,	1 year
Andreas Stavropoulos et al(22)	2009	45 patients x 45 defects	26-62	OFS+ Deproteinized bovine matrix + gentamicina sulphato 15 defects, OFS+DBBM + saline :15 defects	OFS alone 15 defects	Probing depth, CAL, plaque index, bleeding on probing, radiographic bone level, intrabony component.	At 1 and 6 years
Ferenc Döri et al(23)	2009	30 patients each one presenting 1 defect	28-65	OFS+Prp+ DBBM 15 defects	OFS+DBBM+OFS 15 defects	Probing depth, CAL, gingival recession, plaque index, bleeding on probing, defect location	1 year
Michele Paloantonio et al(24)	2008	51 patients 51 defects divided into 3 groups	41-62	OFS+ CS(17 defects), OFS +collagen membrane	OFS alone	Probing depth, CAL, DBL	1 year

Table 6. includes the studies selected by the screening process and their chracteristicsñ

Table 2. Measurements extracted from articles that included CS and DBBM categorized by type of surgery

AUTHOR	Intervention	Nº defects	baseline CAL+SD	Baseline PD+SD	CAL +SD at control	PD +SD-At control
Col Vb Mandlik et al(18)	CS graft+OFS	50	7.20 -1.06	7.2-1.06	2.32-0.47	2.14-0.35
Michaele pantolino et al.(24)	CS graft+OFS	17	8.5 – 1.1	7.8 – 1.3	5.8 – 1.0	3.4 – 0.7
R. Farina et al(21)	CS graft+OFS	10	8.6-1.7	7.4-1.03	5.8- 1,8	3.5-0.9
Sanjay Gupta et al.(17)	OFS+CS as barrier	8	7.13±1.46	7.63±1.69	4.38±1.30	4.13±1.36
Shilpa Budhiraja Et al(19)	OFS+ CS Barrier	6	9.42 ± 1.08	6.92 ± 0.90	6.25 ± 1.35	3.25 ± 0.75

Authors	intervention	Nº of defects	Baseline CAL +SD	Baseline PD+SD	CAL+SD at control	Pd+SD at control
Yan Xu et al.(12)	DBBM +OFS	30	8.82-2.18	7.91-1.14	4.64±1.57 1y	4.18±0.75
Vikram Blaggana et al(14)	DBBM +OFS	15	6.93-0.46	6.86-0.45	4.67±0.44	4.60±0.36
Andreas Stavropoulos et al(22)	DBBM +OFS	15	9.6 -1.6	8.5 – 1.1	5.0 – 2.0	4.6 -1.0
Ferenc Do¨ri et al(23)	DBBM+OFS	15	9.6 – 1.9	8.5 – 2.0	4.9 – 1.5	3.2 – 1.3
Christer Slotte et al.(20)	DBBM +OFS	18	10.4 – 0.8	7.9 – 0.7	8.3-0.8	4.7-0.7
Daniela Guimaraes de Melo et al.(13)	DBBM + collagen membrane	20	9.6 – 1.6	8.5 – 1.1	2.5 -2.5	4.6 -1.0
Vincenzo Iorio-Siciliano et al.(15)	DBBM+ collagen membrane	20	9.3 – 2.5	8.1 – 2.1	5.6 – 2.3	3.7 – 1.3
Deepthi Palachur et al.(16)	DBBM+ collagen membrane	14	11.74-1.97	7.14-1.35	7.52±1.19	2.71-0.47

Table 3. A report of the linear measurements of CAL and PPD and their corresponding increase subdivided by type of surge and material

MATERIAL	INTERVENTION	Nº of Defect	STARTING PPD+SD	POST PPD + SD	STARTING CAL +SD	POST-CAL+ SD	PPD reduction	CAL increase
CS	GRAFT +OFS	77	7.36-1.15	2.59-0.52	7.67-1.15	3.64-0.76	4.77	4.03
CS	AS BARRIER+ OFS	24	7.33-1.42	3.25-1.03	8.11-1.30	5.18-1.32	4.08	2,93
DBBM	GRAFT	93	8.15-1.08	4.26-0.81	9.07-1.50	5.45-1.30	3.89	3.62
DBBM	GRAFT+ COLLAGEN MEMBRANE	54	8.00-1.54	3.78-1.55	10.4-2.03	4.95-2.29	4.22	5.45
DBBM	MIST+GRAFT	18	6.63 ± 1.06	4.31 ± 1.50	7.50 ± 1.61	5.50 ± 2.08	2.32	2

Table4. Added Measurement of all the articles included Categorized by DBBM and CS

MATERIAL	Nº DEFECTS	BASELINE PPD+SD	POST PPD +SD	STARTIN CAL+SD	POST CAL+SD	CAL INCREASE	PPD reduction
CS	101	7.35-1.12	2.25-0.64	7.76-1.19	4.01-0.89	3.77	4.61
DBBM	222	7.94-1.23	4.11-1.13	9.33-1.77	5.29-1.71	4.04	3.83