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REVIEW

Unlocking the Power of Calcium Sulfate: Paving the Way for Periodontal Regeneration Across Time

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ABSTRACT

Introduction: Various bone substitutes—including autograft, allograft, and xenograft—have been used to replace missing bone. However, each has its limitations, prompting interest in alternatives such as alloplastic materials. Calcium sulfate (CS), one of the oldest alloplastic materials, has a long-standing role in regenerative medicine. **Methods:** A primary search using the keywords "alloplastic" and "periodontal regeneration" was performed in PubMed, Cochrane, and Scopus. A secondary search focused on CS, using keywords "calcium sulfate," "scaffold," and "periodontal regeneration" in PubMed and Google Scholar. Articles published from 2017 onward were included. A manual search was also conducted to identify relevant studies regardless of publication date. **Results:** A total of 42 articles were reviewed. Many studies highlight the regenerative potential of CS in periodontal therapy. Compared to xenografts, CS shows better biocompatibility, porosity, and osteoconductivity. It has been used successfully in various applications such as treating intrabony defects, gingival recession, and interproximal bone loss. CS also acts as an effective drug delivery system, especially when combined with tetracycline, and serves as a scaffold for stem cells and periodontal ligament fibroblasts, promoting osteogenic differentiation. **Conclusion:** CS is a promising alloplastic material in periodontal regeneration. Although it lacks osteoinductive capacity and presents limitations like rapid resorption and low mechanical strength, these can be mitigated by combining it with other biomaterials or using it as a stem cell scaffold. Current evidence supports its potential role in advancing future periodontal regenerative therapies.

INTRODUCTION

Periodontal disease still serves as one of the most concerning conditions when it comes to oral health. It occurs in 20-50% of the global population [1]. Periodontitis is a chronic inflammatory disease characterized by the destruction of both soft and hard tissue surrounding the tooth. If left untreated, it can lead to extensive

alveolar bone resorption and eventually tooth loss [2]. Mechanical instrumentation undoubtedly disrupts microbial biofilm formation, alleviates inflammation, and reduces further damage to the periodontium [3]. However, mechanical instrumentation alone will not be able to completely restore tissue loss experienced by the patient, resulting in the persistent loss of periodontal tissues which is needed to support the tooth. It was found that treatment using bone graft can improve periodontal status of the patient including bone height, pocket depth, and soft tissue attachment [4]. Autograft which is derived from the same individual is the current gold standard in regenerative treatment [5,6]. Despite its popular use, autograft possesses its drawbacks including limited resources [7] and site morbidity [8]. Allograft can be used as an alternative to autograft. Similar to other graft types, allografts also come with their own set of drawbacks. Firstly, there is a higher likelihood of rejection by the recipient's immune system when compared to autografts [9]. This rejection may occur if the recipient's immune system identifies the donor tissue as foreign. Another concern is the potential for disease transmission. A body of literature has documented a heightened risk of communicable diseases, such as HIV and hepatitis, associated with allografts [9,10]. This risk arises from the possibility that allografts derived from human or animal tissues may contain infectious agents. Additionally, the availability of allografts may be limited, as they are typically procured from human cadavers or animal tissues [9,10]. This limitation can pose challenges in accessing allografts for clinical use, particularly in emergencies or for smaller size patients. Moreover, there is ongoing controversies regarding the osteoinductive properties of allografts, specifically their ability to promote bone growth. While some studies have reported positive outcomes, others have presented mixed or negative results [9].

Xenografts refer to biomaterials sourced from organisms genetically distinct from the host [11]. These grafts can be obtained from various origins, such as bovine, porcine, coral, etc. Currently, a variety of xenograft products like BioOss™, Cerabone™, Algipore™, and ProOsteon™, available in granular or block forms, find applications in diverse procedures like sinus augmentation, socket preservation, addressing horizontal and vertical defects, and managing peri-implant defects [6]. One notable advantage of xenografts lies in their effective osteoconduction, given their structural and biochemical similarities to human bone. Additionally, they exhibit low immunogenicity and possess good compressive strength [6]. Despite its potential benefits, xenografts also pose a risk of zoonotic infections [12]. This risk includes exposure to viruses such as hepatitis E, Nipah Virus, and various encephalitis viruses [13]. Additionally, porcine endogenous retroviruses (PERVs), which are endogenous and typically present in multiple copies that cannot be removed, are also a concern. Moreover, xenografts from any species are likely to contain such viruses, which may become active and lead to ongoing infections when transferred to humans [14]. Additional documented drawbacks of xenografts include brittleness, poor resorption, and low tensile strength [15-18]. Consequently, these limitations should be thoroughly considered when assessing the appropriateness of xenografts for specific dental procedures, particularly in the realm of periodontal regeneration. Depending on patient's individual needs and the nature of the treatment, alternative grafting options may be preferred.

The use of alloplastic materials provides a new alternative to periodontal regeneration. Examples of alloplastic materials include polymer, hydroxyapatite (HA), bioactive glass, and tricalcium phosphate [19]. Advantages of these materials include osteoconductive, osteogenesis, the ability to combine with other materials, and most importantly no risk of infection [20]. Calcium sulfate is an example of an alloplastic material that had been used more than 100 years ago [21] and proved beneficial in the field of dentistry including for barrier membrane, ridge preservation, periodontal defects, and sinus augmentation procedures. Despite the long list of reviews available, there are lacking papers that discuss the advantages of calcium sulfate in regenerative dentistry, especially periodontal regeneration. The purpose of this review is to highlight the current evidence that concerns the promising use of calcium sulfate in dentistry. We will address the following points in this key question: 1) Which regenerative material is preferable for use; xenograft or alloplastic material? 2) What is the versatility of calcium sulfate in periodontal regeneration? 3) How can calcium sulfate and stem cell technology shape the future of periodontal regeneration?

MATERIALS AND METHODS

Even though this is a narrative review, an attempt for systematic journal selection was made to provide the reader with the most updated and relevant information. Primary search was done by entering the keywords "alloplastic" and "periodontal regeneration" using databases PubMed, Cochrane, and Scopus. A secondary search focusing on calcium sulfate was made using PubMed and Google Scholar by entering the keywords "calcium sulfate" "scaffold" and "periodontal regeneration. Articles from 2017 were included in this narrative review. A manual search was conducted online, and the studies deemed most pertinent to the discussion were incorporated into this review with no specific time frame. A total of 42 papers were selected to aid in the discussion.

RESULTS AND DISCUSSION

The discovery of the use of autograft in restoring the structure was taught to be a major boost in health and was given a gold standard title in regenerative treatment [22]. However, even the gold standard has its drawbacks and prompt alternatives. Among the alternative materials available include the use of alloplastic materials to regenerate bone. To achieve predictable alveolar bone regeneration, there are four essential principles that must be adhered to [14]. First, primary wound closure is crucial to ensure uninterrupted wound healing. Second, the presence of undifferentiated mesenchymal cells is necessary for proliferation and differentiation into periodontal tissue. Third, angiogenesis is vital to provide sufficient blood supply and support for bone regeneration. Lastly, space maintenance or creation is necessary to enable bone ingrowth and maintain wound stability during the regeneration process [14].

Xenograft or Alloplastic Material?

Selecting the appropriate materials whether it be xenograft or alloplastic materials for periodontal regeneration is always a debate. It depends on the physician's preferences as both have their advantages and drawbacks. Xenograft material can be derived from bovine, coral, equine, porcine, etc. [23,24]. Advantages of xenograft include biocompatibility, osteoconductive, readily available resources compared to autograft, and easy handling. However, despite its promising use, certain xenograft materials are prohibited by some religious beliefs [25]. Additionally, its use may lead to zoonotic infections and long-term issues such as fibrous encapsulation, chronic inflammation, foreign body reactions, soft tissue fenestration, and cyst formation, as reported in a case series published in 2019 [26].

Calcium sulfate and calcium phosphate are among the alloplastic materials which had been widely used as bone substitutes and have proven effective in repairing osseous defects [27]. However, calcium phosphate has a limitation when used alone. This includes limited osteogenic ability and slow degradation which might hinder proper bone healing, lack mechanical strength, and can cause an inflammatory reaction [28,29]. In an animal study, it was also found that calcium sulfate provides better osteointegration capacity in treating bone void compared to calcium phosphate [30].

Various studies have examined the effectiveness of xenografts and alloplastic materials in treating bone defects. One such study by Gross *et al.* (2024) evaluated the performance of two biomaterials, Blue-Bone® and Bio-Oss®, in reconstructing critical bone defects in rats. Blue-Bone®, produced by Regener Biomaterials Co in Curitiba, Brazil, is an alloplastic material composed of 80% nanometric hydroxyapatite and 20% ß-TCP. Bio-Oss®, from Geistlich Pharma AG in Wolhusen, Switzerland, is made of deproteinized bovine bone. The results showed that after 40 days, xenografts promote a high percentage of non-mineralized tissue at the defect site only when combined with autogenous grafts. In contrast, alloplastic materials were effective on their own, resulting in a more cellular and vascularized bone matrix. This ability of alloplastic materials to function autonomously without the need for mixing with other graft types underscores their versatility and potential for simplifying surgical procedures in bone regeneration [31].

The properties of materials also play a crucial role in determining the successfulness of periodontal regeneration therapy. A recent study analyzed and compared the physicochemical properties of xenograft and alloplastic materials [32]. In this study, the authors compared the 2 commercially available xenografts (Colocast and Osseograft™) with 3 alloplastic materials (B-OstIN™ - 100% hydroxyapatite (HA), Biograft HABG active® - HA + calcium-phospho-silicate, and Biograft HT® - 60% HA + 40% β-tricalcium phosphate) (Table 1). Scanning electron microscope (SEM) shows that Biograft HABG active® has the smallest particle with 18.9 µm in size while the largest particle belongs to Colocast with 131.1µm. In terms of porosity, alloplastic material was shown to be more porous compared to the xenograft. Based on these findings the author highlighted that particle size and porosity are crucial in the regeneration process. The smaller particles will degrade faster allowing a faster healing process. Meanwhile, a more porous structure will allow periodontal regeneration to occur more efficiently by providing sufficient space for osteogenesis and angiogenesis. However, to decide whether alloplastic materials are superior to xenografts, cannot be concluded based on this study alone. The advantages and disadvantages of xenografts and alloplastic materials are presented in Table 3 [33-35]. Nevertheless, the key element was made clear that the properties of the materials used are an important parameter to justify its use in periodontal regeneration.

The Versatility of Calcium Sulfate in Periodontal Regeneration

Calcium sulfate, also known as gypsum, is a low-cost material that is easy to handle and manipulate [36-37]. There was an extensive list of studies including in-vitro, animal, and human which shows the promising use of CS in dentistry (Table 2). In a study conducted by Syam et al, 2020, the author implanted CS as a graft material at the bone void area at the posterior maxilla of the samples and in the created defects on the rat legs. It was found that in all test subjects, CS was able to stimulate bone formation at the defect site [38]. When it comes to the effect of particle size on healing, Mohammed et al, 2021 found that the percentage of bone formation was significantly higher in the nano-CS group compared to the micro-CS group signifying that material size does play a role in healing. The authors concluded from this study that nano-sized CS had the upper hand in periodontal regeneration as the material can provide greater surface roughness, able to induce more cell proliferation and enhance bone marker proteins such as osteocalcin and osteopontin [39].

CS is also used in Combination with Collagen Membranes to Treat Gingival Recession

A case study was conducted to evaluate the use of CS in conjunction with collagen membranes in treating gingival recession [40]. Root coverage procedure was performed at 11 and 21 using CS graft and collagen membrane. After 6 months, it was found that at teeth 11 and 21, 100% and 97% of root coverage were achieved, respectively. In addition, there was a total reduction in recession width, a gain in clinical attachment, and an increase in the width of keratinized tissue. The authors believe that the usage of CS along with collagen membrane can provide a beneficial result in giving favorable clinical outcomes.

CS can also Be a Good Barrier to other Graft Materials to Treat the Interproximal Bone Defect

A clinical and radiological study was performed using HA (Periobone-G) together with a CS barrier to measure the treatment response of interproximal bone defect [41]. This study was conducted on eight patients (age 25-58) presented with vertical bone defects. Each patient received both HA with CS barrier and HA alone randomly in a split-mouth design clinical study. The study found that after 9 months, there was a significant reduction in probing depth in HA + CS group compared to HA alone.

The Porous Properties of CS Made Them a Good Carrier or Scaffold for Other Materials

Few studies had found the advantages of combining CS with β-tricalcium phosphate (β-TCP). A case series involving 4 patients was conducted to study the effect of applying these graft combinations in treating osseous defects following third molar extraction [42]. After 1-2 years of follow-up, no complication was noted, and all extraction sockets were fully restored. The most interesting finding from this study was no residual pocket was noticed at the distal aspect of the second molar which could provide a solution to the occurrence of persistent residual pocket at that area. In one animal study, Podaropoulus et al, 2009 found that the CS/β-TCP group produces complete bone formation compared to β-TCP alone which only showed partial filling of new bone at the defective site [43].

CS is also used as a Drug Delivery Vehicle

A study was conducted to fabricate and evaluate in vitro injectable CS bone cement loaded with tetracycline for delivering antibiotics in periodontal disease management [44]. It was found that after 14 days, compared to CS alone, the combination materials able to show sustain drug release, antibacterial activity towards *S. aureus* and *E. coli*, no alteration in cytocompatibility, and enhanced alkaline phosphatase (ALP) activity of periodontal ligament cells.

Limitation of CS

The limitations of calcium sulfate (CS) in regenerative applications include swift resorption rate, fragility, and challenges in controlling its setting time and solubility in blood and body fluids during graft procedures [45]. Moreover, using calcium sulfate solely may restrict new bone growth, and its complete absorption within a short duration can adversely affect the natural repair of the defect [46]. Nonetheless, more favourable outcomes have been observed when calcium sulfate is employed alongside other materials, such as alloplastic substance [47]. Further investigations are required to ascertain optimal proportions for blending calcium sulfate with various bone graft materials. Ongoing research continues to evaluate the efficacy of CS-based scaffolds when used with diverse materials for bone regeneration. While not typically noted for antibacterial qualities, the potential of CS in this area remains underexplored, necessitating further studies to establish definitive results regarding its antibacterial properties.

Table 1 Comparison of physicochemical properties between xenografts and allografts

Sample	Types of graft	SEM Magnification	Particle size
Colocast	Xenograft	100x	131.1µm
Osseograft™	Xenograft	100x	35.7µm
Biograft HT®	Alloplastic Material	100x	29.5µm
B-OstIN™	Alloplastic Material	100x	23.1µm
Biograft HABG active®	Alloplastic Material	100x	18.9µm

Table 2 Versatility of calcium sulfate combined with biomaterials in treating various bone defects

Author	Types of Study	Types of Bone Defects	Calcium Sulfate (CS) Usage	Results
Gupta and Vandana, 2013	Human	Interproximal defect	CS + Hydroxyapatite	Significant reduction in probing pocket depth in group with CS.
Sindhura Reddy et al 2014	In-vitro	Laboratory study	CS loaded with Tetracycline	The combination helps in sustained drug release, antibacterial effect and enhanced ALP activity of PDL cells.
Mukherji, 2016	Human	Gingival recession	CS + Collagen Membrane	More than 95% of root coverage achieved after 6 months.
Leventis, Tsetsenekou, and Kalyvas 2020	Human	Osseous defect following 3rd Molar Extraction	CS + ß-TCP	Resolution of residual pocket at distal of 2nd molar and complete bone fill at defect area.
Syam et al, 2020	Human & Animal	Bone void at human posterior maxilla & rat leg	α-CS bone graft substitute	In all test subject CS able to stimulate bone formation.
Syam et al, 2020	Animal	Artificial defect at rat's right hind leg	α-CS bone graft substitute	Site grafted with α-CS able to stimulate new trabecular bone formation at the defect site
Mohammed et al, 2021	Animal	Intrabony defect at Mandibular 2nd Premolar	Nano & Micro sized CS	Nano sized CS provides better surface roughness, induce more cell proliferation and bone marker protein expression.

CS: calcium sulfate, ß-TCP: beta-tricalcium phosphate, α-CS: alpha-calcium sulfate, ALP: alkaline phosphatase, PDL: periodontal ligament.

Table 3 Advantages and disadvantages of xenografts and alloplastic materials

Category	Graft types	Example	Advantages	Disadvantages
Xenografts	- Porcine - Bovine - Coral - Equine	- Cerabone™ - BioOss™ - OsteoGraft™	- Osteoconductive - High resource - Low patient morbidity - High dimension stability over time - Low cost	- Possible risk of disease transmission - No osteoinductive properties
Alloplastic materials	- Calcium sulfate - Calcium phosphate - Hydroxyapatite - Bioactive glass - Hydrogels	- EthOss® - PerioGlas® - Cortoss® - Eurobone®	- Osteoconductive - Low risk of disease of transmission - Low patient morbidity - High availability - Low cost	- Variable dimension stability over time - No osteoinductive properties

Table 4 Safety and effectiveness of CS used alone or with biomaterials in stem cell applications (i.e. chitosan)

Author	Types of Study	Types of Stem Cells	Calcium Sulfate (CS) Usage	Results
Sollazo et al 2011	In-vitro	Dental Pulp Stem Cells (DPSCs)	CS alone	CS is able to induce osteogenic gene expression RUNX2, osteopontin, COL1A1, ALPL.
Carinci, Girardi, and Palmieri 2012	In-vitro	Adipose Derived Stem Cells (ADSCs)	CS alone	CS is able to stimulate bone related gene expression by ADSCs including RUNX2, SP7 and SPP1.
Low et al 2015	In-vitro	Stem Cells from Human Exfoliated Deciduous Teeth (SHED)	CS (Gypsum) + Chitosan	The combination of gypsum and chitosan is able to stimulate ALP activity in a dose dependent manner.
Sundaram et al 2016	In-vitro	Human Dental Follicle Stem Cells (hDPSc)	CS + Chitosan	The combination of CS and Chitosan stimulates maximum ALP activity compared to chitosan alone.
Aquino-Martinez, Angelo, and Pujol 2017	Animal (Mice)	Mesenchymal Stem Cells (MSCs)	CS alone	CS is able to stimulate bone regeneration in the created calvarial defects by stimulating undifferentiated MSCs, promoting their migration and upregulating bone related proteins.

CS: calcium sulfate, DPSCs: dental pulp stem cells, ADSCs: adipose-derived stem cells, SHED: stem cells from human exfoliated deciduous teeth, hDPSc: human dental follicle stem cells, MSCs: mesenchymal stem cells, ALP: alkaline phosphatase.

Calcium Sulfate as a Scaffold for Stem Cells and Fibroblasts for the Future of Periodontal Regeneration

A good scaffold for periodontal regeneration must possess some criteria including bioresorbable, non-toxic, osteoconductive, osteoinductive, good in physical and chemical properties, and most importantly able to stimulate the necessary growth factor for tissue regeneration. Taking these criteria into account, previous studies proved that CS can be a suitable candidate for periodontal regeneration (Table 4).

The previous study showed that CS was able to induce differentiation and proliferation of stem cells by inducing expression of bone matrix protein including RUNX2 and SPP1 in both adipose-derived stem cells (ADSCs) and dental pulp stem cells (DPSCs) [48,49]. In addition, it was found that the presence of CS can also induce mesenchymal stem cell (MSCs) migration in vitro, increase bone regeneration in vivo, and upregulate the osteogenic gene expression such as ALP, Osterix, and Osteocalcin mice [50]. In a separate animal study, it was found that the combination of nano-calcium sulfate/platelet-rich plasma gel scaffold with BMP2 gene-modified mesenchymal stem cells promotes bone regeneration in rat critical-sized calvaria defects [51]. The use of CS as a scaffold for stem cells in bone regeneration was further highlighted in a study that explored the effects of an oyster shell/alpha-calcium sulfate hemihydrate/platelet-rich plasma/bone mesenchymal stem cells bioengineering scaffold on rat critical-sized calvarial defects [52]. Additionally, another study investigated the viability and apoptosis of mesenchymal stem cells from the stromal vascular fraction in combination with various bone substitution materials, including hydroxyapatite-calcium sulfate, demonstrating the potential of this material to support the attachment, proliferation, and differentiation of MSCs [53]. This evidence suggest that CS is a good scaffold material that can simulate different types of stem cells towards osteogenic differentiation which is required for periodontal regeneration.

CS is also being used as a scaffold for periodontal ligament fibroblasts. An *in vitro* study conducted by Das *et al.* (2019) investigated the response of primary human periodontal ligament (hPDL) cells onto a new calcium sulfate-based bioactive bone cement (BioCaS) disc in an *in vitro* cell culture model. The study found that the hPDL cells exhibited good viability, adhesion, and spreading on the BioCaS cement disc in comparison to sintered hydroxyapatite. Additionally, the cells differentiated to the osteogenic lineage in the presence of the BioCaS cement, confirming the inherent bioactivity of the cement [54]. This demonstrates the potential of calcium sulfate as a scaffold for periodontal ligament fibroblasts in the context of periodontal regeneration.

The present papers highlighted the ideal criteria of scaffold materials for periodontal regeneration. Some of the weaknesses of CS such as low mechanical properties can be enhanced by the addition of other materials (i.e., chitosan) as proven in the previous study [55]. Since there is a lack of data indicating the antibacterial potential of CS towards periodontal pathogens, it is important to incorporate other well-established materials with known properties such as chitosan to produce a much more effective material for periodontal regeneration in the future.

CONCLUSION

Calcium sulfate is undoubtedly a well-established material in medicine, particularly in periodontal regeneration. Although no "gold standard" scaffold has yet been established, the choice between alloplastic materials and xenografts should be made after considering the scientific evidence for both. The diverse applications of calcium sulfate in treating various periodontal defects demonstrate its role in periodontal regeneration. Despite some limitations, the effectiveness of calcium sulfate in periodontal regeneration could be enhanced by combining it with other biomaterials. This could improve its capabilities and help progress towards an ideal scaffold material.

CONFLICT OF INTEREST

The authors agree that this research was conducted in the absence of any self-benefits, commercial or financial conflicts and declare the absence of conflicting interests.

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I.H.M., M.F.N., and F.A. contributed to the conceptualization and development of the case report. I.H.M. drafted the manuscript. I.H.M. and F.A. reviewed and revised the manuscript critically for important intellectual content. all authors read and approved the final version of the manuscript for submission.

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