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Review Article

Applications of xenografts in periodontal regeneration

G Meenu[1], Thomas George V[1], Rakhi Manohar[1], Nebu George Thomas[1,*]

[1] *Dept. of Periodontics, KUHS, Pushpagiri College of Dental Sciences,, Thiruvalla, Kerala, India*

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ABSTRACT

Periodontitis is a disease with a high prevalence among adults. If not treated, it can lead to loss of teeth. New attachment with periodontal regeneration is the ideal outcome of periodontal therapy since it results in reconstruction of the periodontium. The biological regenerative potential of the periodontium is high, and hence the bone grafts can be utilized to improve the outcome of periodontal therapy. The different bone replacement used in periodontology analyzed in this review are: autograft, allograft, alloplasts and xenografts. There has been a recent increase in interest in using xenografts in periodontal regeneration. Xenograft materials generally are biocompatible and widely accepted. When compared to open flap debridement, treatment of intrabony, furcation defects, sinus lift and socket preservation using xenografts are gaining increasing attention. The purpose of this review is to provide an overview of the different bone replacement grafts used in periodontal regeneration, methods of bone formation and fabrication of scaffolds. Emphasis is placed on the xenografts; its different sources and also the applications of xenografts used in periodontal regeneration.

1. Introduction

Over the years, several clinical techniques and material options have been investigated for periodontal defect repair/regeneration. The use of improved biomaterials for periodontal regeneration has significantly improved the available treatment options and their clinical results. Bone replacement grafts, various growth factors and combination of these have been commonly used for this purpose. Bone grafts and bone substitute materials are commonly used materials in periodontal regeneration.[1]

A bone graft is defined as a living tissue capable of promoting bone healing, transplanted into a bony defect, either alone or in combination with other materials.[2] These materials can be used in conjunction with endosseous dental implants as well as in the more demanding environment of intrabony defects associated with periodontal disease. Bone grafts have been claimed as useful adjunctive to gain blood clot stability into the periodontal defect and hence significantly greater loss of alveolar crest height was demonstrated in non-grafted than grafted defects; regeneration of new attachment apparatus, showing new bone, and new cementum occurred more frequently in grafted when compared to nongrafted defects.[3] Although not all bone grafting materials support the formation of a new periodontal attachment apparatus, there is conclusive evidence that periodontal regeneration is achievable with bone replacement grafts in humans.

The available bone replacement graft materials include: autografts which consist of bone harvested from the same individual's body and transferred to the site of restoration (e.g. iliac crest bone transferred to the oral cavity); allografts comprise material that is procured and processed from another member of the same species

* *Corresponding author.*
E-mail address: nebugt@gmail.com (N. G. Thomas).

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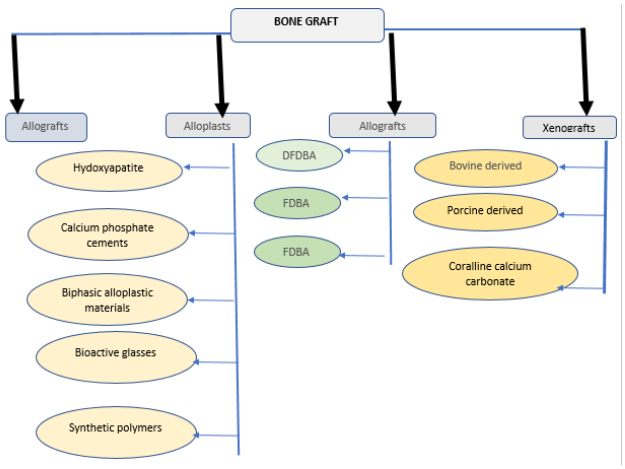
(e.g. demineralized freeze-dried human bone); xenografts which constitute material harvested from a different species than the recipient (e.g. bovine-derived used in humans); and, alloplastic materials which are derived totally from synthesized components (e.g. synthetic hydroxyapatite or polymer).[1]

The purpose of this review is to provide an overview of the different bone replacement grafts used in periodontal regeneration, methods of bone formation and fabrication of scaffolds. Emphasis is placed on the xenografts; its different sources and also the applications of xenografts used in periodontal regeneration.

Classification of bone grafts and substitute materials used for periodontal regeneration.



2. Methods of bone formation by bone grafts

Bone graft can aid in bone regeneration by three different methods, which include:

2.1. Osteogenic

It is the synthesis of new bone by donor cells derived from either the host or graft donor. Cells involved in this process include mesenchymal stem cells, osteoblasts and osteocytes.The techniques currently used in the medical field are based on auto-grafts and allografts.[4]

2.2. Osteoinductive

Involves stimulation of osteoprogenitor cells to differentiate into osteoblasts and then begins formation of new bone. The most widely studied type of osteoinductive cell mediators are bone morphogenetic proteins.[1,5]

2.3. Osteoconductive

The property by which bone graft material serves as a scaffold for new bone growth, which is perpetuated by the native bone. Osteoblasts from the margin of defect that is being grafted, utilize the bone graft material as a framework upon which to spread and generate new bone.[1,6]

2.4. Osteogenic

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3. Types of Bone Graft-based on Source

3.1. Autograft

Autogenous grafts are considered the current gold standard bone replacement graft material.[7] Autograft is a tissue transplanted from one part of the body to another in the same patient. Typically, if the material needed to fill the defect is small, the site from which autograft materials obtained are intraoral, in particular from the extraction sockets, edentulous ridges, ramus, symphysis, tuberosity, or from the surrounding buccal plate. In large bone defects, the material needed is larger and is typically obtained from extra orally areas, such as the iliac crest or the tibia.[7,8] Drawbacks associated with autogenous bone however include the need for a second surgical site and associated morbidity.[9]

The great advantages in using this approach are represented by the fact that these grafts are osteogenic, prevent disease transmission and are low cost. Clinical tests show excellent periodontal regeneration with new cementum formation. Schallhorn et al. used iliac crest grafts to treat infrabony defects and reported up to 4 mm gain in bone healing.[10]However, the main complication is that they require a second surgery and it is important to consider the possible donor site complications, such as infection and pain. Furthermore, the limited supply of autograft materials is an additional issue that makes this approach always less attractive.[9–11]

3.2. Allograft

An allograft is a graft derived from a donor of the same species, but genetically dissimilar. Allograft materials allow overcoming the issue of a second surgical procedure and the limited supply source.[12] The graft is typically obtained from tissue banks that process the donor tissues and, on the base on which the tissues are processed, allografts could be divided into freeze-dried bone allografts (FDBA) and decalcified freeze dried bone allografts (DFDBA).[1] These types of graft have the great disadvantage to potentially include a foreign body immune response and the possibility of diseases to be transmitted; furthermore, a high risk of graft contamination during processing is present.[13,14] Despite these drawbacks, allografts have relatively high success rates and, depending on the remaining proteins

into the matrix, they could act as osteoconductive or osteoinductive materials.[15]

3.3. Alloplasts

Alloplastic grafts may be made from hydroxyapatite, a naturally occurring mineral (main mineral component of bone) or made from bioactive glass. Hydroxyapatite is a synthetic bone graft, which is the most used one now due to its osteoconduction, hardness, and acceptability by bone. Bioglass is the most widely employed biomaterial because of its bioactive property.[16]

An alloplast is a biocompatible, inorganic synthetic bone grafting material. At present, alloplasts marketed for periodontal regeneration fall into 2 broad classes: ceramics and polymers. The composition, morphology, and surface topography of alloplasts provide the osteoconductive platform for promoting bone formation along the surface of the grafting material.[17] The fate of an alloplastic bone grafting material is dependent primarily on its chemical composition, structure, and physical properties. Synthetic and coral-derived porous hydroxyapatite has been shown to support significant clinical improvements in periodontal measures following implantation in intrabony defects. Human histologic evidence of ossification of the graft pores and the graft periphery of porous hydroxyapatite has been found in periodontal intrabony sites, with residual graft particles present 12 months following implantation. Porous hydroxyapatite appears to exhibit osteoconductive properties, as reflected clinically in bone formation; however, no evidence of periodontal regeneration has been shown.

3.4. Xenograft

Xenografts are bone grafts from other species (typically bovine and porcine) and transplanted in humans. It is osteoconductive, biocompatible and structurally similar to human bone. Plenty of donor sources can found for bone grafting. Bovine, Equine Porcine bones and natural coral are used for xenografting.[18] Among them bovine bones are commonly used for grafting procedures due to structural similarity with human cancellous bone.[18,19] Anorganic bovine bone graft (ABM) is a naturally derived porous and deproteinized bovine bone mineral with comparable mineral composition and microporous structure similar to native human bone. Anorganic bovine bone has been shown significant improvement in clinical attachment level and hard tissue fill in human intrabony defects. The bovine derived xenografts BIO-OSS and OSTEOGRAF/N-300 currently are in widespread clinical use. Bio-Oss exhibits osteoconductive properties with a crystalline structure similar to human bone and is said to resorb within 12 to 24 months based on human histological sections of sinus core samples.

However, despite the positive results obtained from studies conducted in xenograft materials, the tissue /bone regeneration with this graft material might be unpredictable.[19] In one study, where defects were treated with bovine derived bone grafts, at one year follow up,78% of defect healed successfully.[20] Furthermore, in another study, eight intrabony defects were filled with xenografts and the results showed that seven defects went through successful healing, but one defect healed by repair. Great advantage of these types of graft is that only one surgical procedure is necessary.[21]

Table 1: Commercially available xenograft materials

Brand	Manufacturer	Available as
Bio-Oss cortical and cancellous	Osteohealth Co.	Granular 25- 1 -0 or 1 .O-2.0mm block
Osteograft / N-300 /N-700	CeraMed	Granular 250-420mm Granular 420-1000mm
Bovine derived graft material not used in dentistry: Endobon@, Laddecm		

4. Xenografts in Periodontal Rregeneration

4.1. Sources

4.1.1. Bovine substitutes

Bovine bone (BB) derived xenografts were widely used for alveolar bone regeneration, with a high success rate, especially in intraoral procedures.[22]

The most common source of xenograft materials in the dental field is deproteinized bovine bone which is commercially available as BioOssTM.[23] This material is said to be derived from highly selected and exclusively bred, young herds usually young calves, free of any known diseases. A chemical low heat processing procedure removes all organic components and preserves mineral structure with a calcium phosphate ratio of 2.1: 1 and porosity of 75 to 80%, i.e. similar to natural hydroxyapatite. The porous structure exhibits a vast surface area, and promotes the growth of new blood vessels via angiogenesis which enhances bone growth.[24]

Bovine bone substitutes have been used extensively in maxillary sinus lifting and implant procedures due to their superior stability and low immunogenicity.[24] Studies have found that maxillary sinus defect sites grafted with BioOssTM resulted in 39% new bone formation after 6 months, which was comparable to 40% new bone formation following grafting with autograft bone after the same time period. Furthermore, they found that 31% of grafted BioOssTM remained at the graft site, compared with just 18% of the autograft bone Bio-Oss exhibits osteoconductive properties with a crystalline structure similar to human bone

and is said to resorb within 12 to 24 months.[17,25]

Periodontal application of Bio-Oss was investigated by Clergeau et al (1996) in a study in which Bio-Oss was incorporated with porcine collagen fibers and grafted into periodontal defects created in the dog. The animals were sacrificed at 6, 18, and 36 weeks after the regenerative surgery. The results indicated that sites implanted with the collagen-Bio-Oss material had greater bone regeneration than the control sites.[26]

Other commercially available products based on bovine bone are also available, such as OsteoGrafTM and CeraboneTM. Like BioOssTM, these products exhibit very similar structural and biochemical properties to human bone and can act as effective osteoconductive grafting materials.[17,25,26]

Despite having many advantages, bovine bone xenografts possess several limitations. A material used for therapeutical purposes in periodontology or alveolar bone regeneration must be safe for the patient's long-term health and infection-free.[27]The complications reported were severe and they are different forms of sinusitis, maxillary fungus ball, material displacement, chronic inflammation and other inflammatory reactions, and foreign body reaction. Hence, the validity and effectiveness of bovine bone-derived grafts should be questioned and new methods must be tried using different materials.[27,28]

4.1.2. Porcine substitutes

Porcine derived substitutes, recently developed are considered to exhibit similarities regarding structure and formation compared to human bone. Porcine bone graft tissue is a porous anorganic bone graft material consisting predominantly of calcium phosphate.[29]These are supplied in granular form with a particle size of 0.25–1 mm and 1–2 mm (Gen-Os®) and are produced by removal of the organic components from porcine bone.[30]

They exhibit osteoconductive characteristics and a low risk of disease transmission.[29,30]Porcine collagen offer excellent osteoconductivity, cell viability and osteoblast like cell differentiation in vitro. The anorganic bone mineral matrix is biocompatible, having interconnecting macro- and microscopic porous structure that supports the formation and ingrowth of new bone at the implantation site Hence it indicates that porcine collagen graft is a potential bone substitute for clinical application.[29–31]

4.1.3. Equine substitutes

Equine derived bone substitutes have the ability to induce osteoblastic differentiation and angiogenesis In addition, the presence of neoplastic bone associated with remodeling effects was observed around the graft material 6 months postoperatively in case of successful sinus lift.[32]

4.1.4. Marine substitutes

Marine skeletons with its unique structural networks can function as templates for growth of human tissues. Corals, sponges, mollusus shells, cuttle fish and fish bones are commonly used for this purpose. Coral skeletons and converted coralline calcium phosphates are excellent to be used as scaffolds.[33]

Calcium carbonates and phosphates such as hydroxyapatite have similarities with the mineral constituents of bones. The coral skeletal carbonate also possess unique architectural properties like porosity, pore size and pore interconnectivity which are important in periodontal regeneration. Significant gain in clinical attachment level, reduction of probing depth and defect fill have been reported.[34]

A promising xenograft material currently being researched is chitosan, a naturally occurring polymer derived from the exoskeletons of crustaceans composed of glucosamine and N-acetylglucosamine.[35]Chitosan is able to stimulate bone regeneration by providing a structural scaffold that supports osteoblastic activity, the formation of mineralized bone matrix and inducing differentiation of MSCs into osteoblasts in various in vitro environments.[36]

Chitosan is available in a variety of forms, including beads, films, hydrogels, and more complex structures, such as porous scaffolds. Due to the poor mechanical properties exhibited by chitosan, it is often combined with other materials such as gelatin, calcium phosphates and bioglass to provide more desirable properties.[35,36]

Fishbone-derived and fish scale-derived scaffolds (FSS) are another de-mineralized bone matrix (DBM) alternative against the bovine bone grafts. Demineralized bone matrix has successfully been practiced in various studies to fill defects, reconstruct cranio-maxillofacial fractures, bridge large bone and high risk defects, and induce bone formation.[37]It contains type I collagen, noncollagenous proteins, and osteoinductive growth factors but provides little structural support. DBM is harvested from the cadaveric bone and then processed in acid to remove the mineral components and leave a trabecular structure which is osteoconductive.[37,38]

The skeleton of fish is either made of bones or cartilage. Demineralized bone matrix (DBM) is one of the commonly used bone-graft replacement materials .The bone is rich in HA and the bone protein is mainly composed of collagen.[39]Collagen acts as a structural framework in which plate-like small crystals of hydroxy apatite (HA) are embedded to strengthen the bone. Hence these marine based biomaterials offer excellent osteoconductivity and supports cell adhesion, proliferation and differentiation making them an attractive option in regenerative scenario.[39,40]

5. Methods of Fabrication of Scaffolds

Porogen leaching, solvent casting, thermal-induced phase separation (TIPS), freeze-drying, gas foaming, electrospinning, rapid prototyping (RP), stereolithography, fused deposition modeling, selective laser sintering (SLN), and 3-D printing were all used to make scaffolds.[41]

5.1. Solvent casting and particle leaching

This technique is mainly used for the fabrication of marine collagen and chitosan based scaffolds. Scaffolds developed by this methods possess advantages which include simplicity, versatility and ability to control pore size and geometry.[42]

5.2. Three -Dimensional Printing

3-D printing is a versatile technique that allows for the development of a wide variety of scaffolds and the incorporation of multiple materials into a single object. This technique allows printing of multi layered scaffolds seeded with different types of cells in each layer thus forming tissues that mimic the orginal structure.[43] A range of 3D printing methods has been developed in the recent years. According to their technique characteristic, printing methods are classified into inkjet bioprinting, extrusion bioprinting or filament printing, laser-assisted bioprinting.[44]

6. Clinical Applications

6.1. Dental tissue engineering

Marine biomaterials like collagen, alginates and collagen have been employed for a wide variety of applications.[38] Collagen isolated from tilapia aids in dentin and pulp regeneration. They also enhance the viability of human periodontal ligament stem cells and up regulated the expression of osteogenic markers thus aiding in alveolar bone regeneration.[40] Fish derived collagen can be used as membranes, local delivery agents and haemostatic agents in dentistry.[38,40] Another principle agent for is chitosan, due to its excellent biocompatibility, bioactivity and antimicrobial properties can be used for a wide variety of applications in dentistry.[35,36] Chitosan hydrogels used as bone defect fillers in treating chronic periodontitis. Chitosan based scaffolds aids in pulp and dentin regeneration.

6.2. Furcation defects

Application of anorganic bovine bone with or without GTR in the treatment of class III furcation defects has resulted in improved clinical outcomes as measured in terms of clinical attachment gain, pocket depth reduction and change in gingival margin position.[41] The combination of GTR using bio absorbable collagen membrane and anorganic bovine bone /collagen resulted in improved resolution of furcation defects.[45] Several studies suggest that the application of combined regenerative approaches, such as barrier membrane and graft material may provide better clinical outcomes. More advanced osseous defects such as one and two wall intrabony and class II furcation defects, appear to respond most favourably to combination therapy. Morever, longitudinal evidence suggests that combination therapy using GTR and xenograft graft material provides stable long term clinical outcomes, particularly in furcation defects.[45–47]

6.3. Intrabony defects

Intrabony defects are commonly described by the number of bony walls (1, 2, or 3 walls) and depth of the defect (measured from the crestal height of bone to the base of the defect. Bone grafts provide better clinical outcome in the treatment of periodontal bone defects than surgical debridement alone. With respect to the treatment of intrabony defects, bone grafts increase bone level, reduce crestal bone loss, increase clinical attachment level, and reduce probing pocket depths when compared to open flap debridement procedures.[48]

Deproteinized bovine bone has the ability to augment the effects of enamel matrix protein in reducing probing pocket depth, improving clinical attachment levels, and promoting defect fill when compared to presurgical levels.[49] Deproteinized bovine bone has been tested in several human clinical studies in periodontal defect alone or in association to autogenous bone, collagen membranes, enamel matrix derivate, or collagen matrix. Recent studies demonstrated that periodontal reconstruction obtained with a GTR therapy, with or without the adjunction of deproteinized bovine bone, seems to remain stable over time.[50,51]

6.4. Sinus lifting procedures

Xenografts produced from inorganic bovine bone are the most popular bone substitutes used in Maxillary sinus floor elevation surgery. Other sources such as porcine and equine bone are also available. Changes in the physicochemical properties could influence the biocompatibility, osteoconductivity, integration, and resorption of bone substitutes. Numerous reports have shown successful regenerative procedures in patients treated with maxillary sinus augmentation using bovine bone.[52]

Osteoplant Osteoxenon® derived from equine bone is composed of flexible cortical and cancellous bone tissue, and is resorbable by osteoclast activation, promoting new bone formation as a scaffold. Previous in vitro studies have shown that it is able to induce osteogenesis on human stem cells and is actively resorbed, making it an ideal bone substitute for oral surgical procedures. P-score value has suggested that it is the most effective xenograft material for

bony healing, showing greater newly-formed bone after six months than the other xenografts.[53]

6.5. Socket preservation

To preserve alveolar bone and avoid the need for ridge augmentation, different materials were used immediately following tooth extraction to ensure the formation of alveolar bone within the sites. The ridge preservation procedure has been tested with membrane alone or membrane plus graft, showing reduced ridge alteration compared to extraction alone.[54]

Recently, some investigators studied a xenogenic bone substitute that consists of corticocancellous porcine bone in the form of particles with a high porosity and a diameter ranging from 600 to 1,000 microm. The ridge-preservation procedures using corticocancellous porcine bone and collagen membrane limited the reabsorption of hard tissue ridge after tooth extraction compared to extraction alone and allowed a more favorable implant position. The histologic analysis after 7 months of tooth removal showed higher percentages of trabecular bone and total mineralized tissue in ridge-preservation sites compared to extraction-alone.[54,55]

6.6. Wound healing

Collagen from marine sources had stimulating effects on fibroblasts proliferation, collagen synthesis and re-epithelialization there by assisting in wound contraction and dermal reconstitution. Hence they are valuable agents for scaffold fabrication.[56]The dual properties of wound healing and antimicrobial activity makes them an optimal dressings suitable for wound management.[56]Chitosan is also gaining attention due their desirable qualities of non-toxicity, biocompatibility, biodegradability and thus helps in wound healing.[56,57]

7. Conclusion and Future Perceptive

Xenografts serve as a biocompatible grafting material due to its excellent regenerative potential. Use of these materials in periodontal regeneration is widely accepted. When compared to open flap debridement, treatment of intrabony or furcation defects using bovine bone alone or in combination with GTR generally results in significantly better short and long term clinical outcomes, with results similar to other bone substitutes that are used in periodontal therapy. Although bovine derived xenografts have been shown to support periodontal regeneration, the extent of periodontal regeneration using xenogenic bone is not always predictable. Currently fishbone-derived and fish scale-derived scaffolds (FSS) are emerging as an effective alternative against bovine grafts. These scaffolds exhibited good bio-compatibility in vitro, thus it can be used as a scaffold in regenerative medicine to induce tissue regeneration without eliciting any strong inflammatory response.

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9. Conflict of Interest

The authors declare no potential conflicts of interest concerning the authorship and publication of this article.

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Author biography

G Meenu, Post Graduate Student

Thomas George V, Professor & Head

Rakhi Manohar, Post Graduate Student

Nebu George Thomas, Professor

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