Xenografts in Periodontal Regeneration: A Viable Alternative

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Abstract

Periodontal disease is categorized by the destruction of periodontal tissues. Over the years, there have been several clinical techniques and material options that have been investigated for periodontal defect repair or regeneration. The development of improved biomaterials for periodontal tissue engineering has significantly upgraded the available treatment options and their clinical results. Bone replacement graft materials, barrier membranes, various growth factors and combination of these have been used. Autografts have been used as the bone graft material of choice since many years. But this type of grafts has many limitations to its use. In order to overcome its drawbacks, xenografts may be used as a viable alternative. Xenografts also known as heterologous graft tissues, is obtained from different species, and has been used in various different periodontal procedures. The characteristic properties of xenografts and the benefits of using it has made this type of graft to emerge as an appropriate choice for periodontal regeneration. The objective of this article is to a review xenograft as a bone replacement graft material to be used in periodontal therapy. The source, mode of bone regeneration and the respective advantages and disadvantages of xenogenic materials have been discussed in detail.

Key words: *Bovine derived grafts; Coralline derived grafts; Equine derived grafts; Periodontal Regeneration; Porcine derived grafts; Xenografts*

Introduction

Bone grafts have been used extensively in various periodontal applications. It may be used either along with barrier membranes or without, for the regeneration of periodontal tissues or reconstruction of alveolar ridge before the insertion of implants. In the early 1990s, autogenous bone or fresh frozen allografts were used for bone grafting procedures, but the emergence of efficient processing and sterilization techniques, resulted in the increased use of bone graft substitutes - Xenografts for various different periodontal procedures. The most important benefits of using bone graft substitutes is the excess availability and reduced morbidity, taking into consideration that procurement of autogenous bone leads to a second intraoral or extraoral surgical site.(1)

There are four main hard tissue replacement graft materials that are used for periodontal regenerative applications. These include autografts, allografts, xenografts and alloplasts. Autografts refer to the graft material which are obtained from the same individual. This type of graft material is considered as the "gold standard". Nevertheless, there are a few limitations related to autografts. These include, morbidity of the donor site, limited volume of bone available, and the unpredictable replacement rate(2). Xenografts on the other hand are obtained from different species. In recent times this type of graft material is being widely used in clinical periodontal regenerative applications. These grafts have the advantage of being relatively inexpensive as well as readily available.(3)

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Xenograft

Xenografts are also known as heterologous graft tissues; this is because they are obtained from different species. This type of graft material is usually osteoconductive in nature and has limited resorptive potential. The origin of the xenogeneic scaffolds which are available for periodontal regeneration, may be bovine, equine, or porcine. These materials undergo thorough processing techniques, resulting in biocompatible products. These are similar to human bone based on their structure. (4)

Xenografts have various advantages. These are readily available as they can be manufactured in excess amounts at comparatively lower processing expenses, and free of disease transmission. The overall performance for bone regeneration is related to the physicochemical characteristics of the graft. Using Xenografts eliminates the requirement for a second surgical site, as well as takes lesser time to heal, hence preferred by several patients.(5)

The comparison of the different properties of other types of grafts has been shown in Table 1.

[Table 1] Comparing properties with other types of grafts:

GRAFT MATERIAL	ORIGIN	BONE REGENERATION POTENTIAL	RESORPTION TIME
AUTOGRAFT	Patients own tissue	Osteogenic, Osteoinductive, Osteoconductive	Weeks to months
ALLOGRAFT	Tissue from individuals of the same species	Osteoconductive, Osteoinductive (DFDB)	Months (4-12 months)
XENOGRAFT	Tissue from other species	Osteoconductive	Months to a year
ALLOPLAST	Synthetically produced material	Osteoconductive	Wide range (rapidly resorbable to non resorbable)

Processing And Purification

Xenogenic bone grafts constitute of de-proteinized cancellous skeletal bone tissue. This is procured from different species, and is then placed in the recipient site. In case of unavailability of human source grafts, the preferred type of graft is considered to be the xenografts. This is used after thorough sterilization and processing techniques in order to cancel out the inadequacies of the graft.(6)

The organic contents present in the xenogenic grafts are eliminated in order to prevent any kind of immunological reaction or transmission of pathogens. The inorganic component that remains after the processing and purification techniques, serves as a structural matrix for the formation of new bone. In addition, it acts as a good source of calcium, which is crucial for the formation of bone.

At present there are two kinds of methods used for the processing of bovine bone. The first method includes a chemical extraction process which is a low temperature method. The second method uses extreme high temperatures for the removal of residual organic material. The latter method results in longer hydroxyl-apatite crystal with higher crystalline structure. (6)

These biomaterials undergo a process consisting of deproteinization and demineralization using sodium hydroxide. These processes are not completely effectively in elimination of prions.(7) In order to eliminate the probability of transmission of disease, the manufacturers utilize animals from those countries in which these kinds of diseases have not appeared.

Prions are misfolds of protein which play the role of a carrier of various disease are mainly found in the medullary tissues. Hence, tissues located distant to the medullary tissues are generally chosen to be processed. After the deproteinization process, the residual mineral component consists of calcium phosphate along with calcium carbonate. This is present in a reticular format which is made up of apatite crystals. Such architecture helps in clot stabilization as well as bone apposition. (1)

Bovine Derived:

Deproteinized bovine bone mineral is the most frequently used xenograft in periodontal applications. Bovine bones was the first bone derived from different species to be used for xenograft production. Currently there are several bovine bone xenograft products being used. Bio-Oss® (Geistlich Biomaterials, Switzerland) is a well-established xenograft. It consists of a mineral matrix of osseous origin which is acquired from bone of the spine [5]. Cerabone® (Botiss Biomaterials, Germany) is another bone grafting material which is acquired from the condyles of cattle femur, which is cancellous in nature. [8]

Previously bovine xenografts have cause graft rejection problems. This may be attributed to the fact that earlier materials would undergo chemical detergent extraction, which caused residual proteins, thus causing adverse reactions and clinically unacceptable results. Presently available bovine-derived material is thoroughly deproteinated, leaving its natural microporous structure. This residual structure supports cell mediated resorption. This is necessary for the replacement of new bone. [9]

Bovine-derived hydroxyapatite grafts act as an osteoconductive scaffold. There is expanded available surface area owing to their porosity. The mineral content of the graft is comparable to human bone, thus causing proper integration with the host bone. These have been used for the treatment of intrabony defects as well as in ridge augmentation.[10]

A study was conducted by ***Baldini et al (2011)*** in order to analyse the histological and clinical outcomes of deproteinized bovine bone in various periodontal procedures. This includes procedures such as periodontal regeneration, socket preservation, peri-implant reconstruction and alveolar bone augmentation. It was noticed that deproteinized bovine bone was effective in case of periodontal regeneration with as well as without barrier membranes. This was observed in case of favourable containing defects.[11]

A study conducted by ***Cosyn (2012)*** evaluated the clinical as well as aesthetic outcome of regenerative periodontal therapy (RPT) using minimally invasive surgery and a collagen-enriched bovine-derived xenograft. The study demonstrated that even though preservation of soft tissue aesthetics was not possible, the results revealed favourable clinical outcome.[12]

Bruyckere et al (2018) conducted a study to assess the clinical outcome of regenerative periodontal therapy in 5 years, using minimally invasive surgery along with a collagen enriched bovine-derived xenograft. This study also identified the predictors for clinical attachment level gain as well as vertical radiographic bone gain. This study concluded that patients with perfect oral hygiene along with good compliance showed significant Clinical attachment level gain when treated with xenograft.[13]

Kollati et al (2019) conducted a study to analyse the efficiency of naturally derived bovine hydroxyapatite (Cerabone) combined with platelet-rich fibrin matrix in the preservation of extraction socket. This study indicated that PRF (platelet rich fibrin) in combination with xenograft and collagen plug, reduced the resorption activity at the test site. [14]

Matteo et al (2020) conducted a retrospective 10-year follow- up study of implants placed in ridges grafted using autogenous mandibular blocks covered with bovine bone mineral and collagen membrane. It was concluded that implants placed in areas that had been reconstructed using bovine bone graft showed comparable survival rates with those placed in native bone.[15]

Porcine Derived

Porcine bone graft tissue is a porous bone graft material which is devoid of organic component. Calcium phosphate is a major part of its composition. Porcine bone is similar to human bone with regard to structure and formulation. [2] The category and structure of lipid content is similar in both types of bones. [5] These come in granular formulations, where in the size of each particle is approximately 0.25–1 mm and 1–2 mm (Gen-Os®). This bone graft material is produced by eliminating all the organic substances. [2]

This anorganic bone mineral matrix is biocompatible. It contains interconnecting macroscopic and microscopic porous architecture which enhances new bone formation at the implantation site. [2]

A study conducted by ***Giovanna Orsini et al (2006)*** related to the "histologic and ultrastructural evaluation of

porcine bone derived biomaterial in the form of granules in maxillary sinus augmentation". The bone-biomaterial interface demonstrated a close contact between the biomaterial derived from porcine and the adjacent surrounding bone. There were characteristic features of mature bone with elevated numbers of osteocytes observed. It was concluded that the biomaterial was biocompatible, and could be used in periodontal treatments such as maxillary sinus augmentation procedures.(16)

Antonio Scarano et al (2010) conducted a retrospective clinical study to evaluate the usage of porcine bone in maxillary sinus augmentation. The study consisted of one hundred twenty-one healthy patients There were no major complications reported during the healing phase of all the grafted sinuses. The study concluded that porcine bone could be in sinus augmentation procedures. It also demonstrated that rougher-surfaced implants are preferred to be used.(17)

Jung-Im Park et al (2014) conducted a study of which the aim was "to determine the efficacy of crosslinked collagenated porcine bone (CPB) for the repair of surgically prepared one-wall intrabony defects". The study concluded that by a process of crosslinking, the collagenated porcine bone could be confined in the defect during the period of wound healing. The collagenated porcine bone along with a barrier membrane combination use resulted in more effective periodontal regeneration than when applied without a barrier membrane.(18)

A clinical study conducted by ***Renzo Guarnieri (2017)*** in humans in which implant site development using porcine-derived graft was investigated, showed reduction in vertical as well as horizontal bone resorption after tooth extraction. (19)

CORAL DERIVED

The coral bone graft substitutes are derived from the exoskeleton of corals, for example Biocoral® (Inoteb, Saint Gonnery, France). The evaluation of the potential of corals being used as bone grafts was initiated in the early 1970s. Commonly used coral- Porites resembles cancellous bone in terms of structure as well as mechanical properties. (20)

Porous coralline hydroxyapatite materials have been fabricated using the microstructure of corals of the marine. (21). These grafts are manufactured by subjecting the corals to extreme temperatures in an aqueous phosphate solution kept under pressure, thus resulting in formation of calcium hydroxyapatite. This process conserves the organized, penetrable and interconnecting pore structure. The average pore diameter is approximately 200 μm, consisting of roughly 50 - 60% porosity.(2)

Coralline calcium carbonate grafts have characteristic properties of high potential of osteoconductive characteristics, thus causing rapid new bone formation in the implantation sites.(22) These grafts show refined defect filling in cases of periodontal regeneration. These grafts do not undergo fibrous encapsulation.(2)

For initial bone formation, unlike synthetic coral material, natural coralline graft material does not need surface transformation into a carbonate phase. Thus, these grafts initiates bone formation more rapidly. They have a high osteoconductive potential. The disadvantages of this graft include its brittle texture and the fact that it is difficult to handle this material. Coralline calcium carbonate provides significant clinical attachment gain, reduction of probing depth and defect fill when compared to other bone replacement grafts.(9)

Change- Sung Kim et al (2005) conducted a study to assess the healing of periodontal tissues in one-wall intra-bony defects post implantation of autogenous bone or a biomaterial derived from coral. It was observed in this study that placement of coral-derived biomaterial cause proper periodontal healing. The healing process did not involve aberrations such as root resorption and ankylosis. (23)

Puvaneswary et al (2013) conducted a study to assess the morphological as well as chemical composition of coral graft (CG) and also their osteogenic differentiation potential, by using rabbit mesenchymal stem cells (rMSCs) *in vitro.* Coral graft proved to have better surface roughness. There were higher levels of osteogenic differentiation markers in case of the coral grafts this included alkaline phosphatase, Osteocalcin and Osteonectin levels. It was concluded that coral grafts showed superior osteogenic differentiation when compared to other bone graft culture system. (24)

A study conducted by ***Yoshifum Matuda et al (2019)*** aimed to evaluate the Periodontal Regeneration Using Cultured Coral Scaffolds in Class II Furcation Defects. Coral scaffolds were found to have the potential to regenerate periodontal tissue. There was evidence of new bone as well as cementum formation in the furcation spaces. (25)

Erlina Mahanani et al (2020) conducted a study to investigate the porosity of a coral scaffold and its biocompatibility while it is attached to human gingival cells. There were various compositions of synthetic coral scaffold prepared. Measurements related to the porosity percentage as well as gingival cell attachment were carried out. It was observed that having the highest porosity percentage could provide life time favourable microenvironment to the cells.(26)

Equine Derived Bone Graft

Equine bone grafts, which are enzyme-deantigenic in nature have been used frequently for the reconstruction of bone in various fields. (27) It has been used successfully in the correction of periodontal defect, for the reconstruction of horizontal as well as vertical atrophic ridge, and sinus augmentation procedures. (28)

Equine bone mineral (EBM) is a sterile, natural bone graft substitute. It is nonantigenic in nature. It constitutes of a porous structured bone mineral matrix. The equine bone graft is manufactured by entirely getting rid of the organic components including the proteins present. It is similar to human bone in both physical as well as chemical aspects. The mineral matrix consists of a macroporous and microporous structure with a trabecular architecture. This kind of texture supports the osteoconductive formation of new bone. (27)

Type I collagen is preserved during the enzymatic process for production of equine bone graft. Type 1 collagen is proved to be the most abundant protein of its extracellular matrix. This is what differentiates it from other types of xenografts, where in, in case of the latter all forms of organic components including all proteins are removed during the processing. (29) This property could lead to faster new bone formation. (30)

Myron Nevins et al (2012) conducted a study to test the effectiveness of hydroxyapatite and collagen bone blocks of equine origin (eHAC), infused with recombinant human platelet-derived growth factor-BB (rhPDGF-BB), to augment localized posterior mandibular defects in non-human primates (*Papio hamadrya)*. There was increased regeneration in case of the test sites, but these findings were not statistically significant. This study concluded that the combination including equine bone blocks and growth factors could be used for the vertical augmentation of severely resorbed ridges.(31)

Nevins et al (2013) conducted a study "to examine the bone regenerative potential of a newly introduced equine-derived bone mineral matrix (Equimatrix) to provide human sinus augmentation for the purpose of implant placement in the posterior maxilla". The qualitative as well as the quantitative results suggests better bone regenerative results at 6 months when compared to other types of xenografts. (27)

Di Stefano et al (2016) conducted a study to assess the formation of bone over time post maxillary sinus augmentation with an enzyme-deantigenic, bone collagen-preserving equine bone graft by evaluating the histomorphometric data. This was a retrospective human study including 77 patients with bone loss of 4 to 7 mm. Formation of new bone took place earlier, when equine bone was used for sinus augmentation. Some sites showed new bone formation within 3-5 months after surgery.(32)

Ji-Young Lee et al (2017) conducted a study "to evaluate the efficacy and safety of equine-derived bone matrix as a carrier for recombinant human platelet-derived growth factor BB (rhPDGF-BB) versus beta-tricalcium phosphate (β-TCP) for the treatment of intraosseous periodontal defects in adult patients". Thirty-two adults suffering from severe periodontal disease were included in this study. Significant gain in the clinical attachment level was observed in the test group. It was confirmed in this study that equine derived bone matrix was effective as well as safe, and could be used to treat periodontal defects. (33)

COMBINATIONS WITH XENOGRAFTS

Xenografts can be used alone or in combination to enhance the osteoinductive property. They tend to integrate well in the site of placement. It is histologically confirmed that xenografts have a direct contact with the

parent bone and it tends to resorb slowly.

Nevins et al (2012) conducted a study "to evaluate the potential for periodontal regeneration of a critical-sized defect with the application of recombinant human platelet-derived growth factor (rhPDGF-BB) combined with either a particulate equine or a β-tricalcium phosphate (β-TCP) matrix". The study concluded that the combination showed potential for the regeneration of periodontal attachment apparatus.(34)

Yasuko ***Nemoto et al (2018)*** conducted a study to assess the use of enamel matrix derivative along with deproteinized bovine bone mineral in periodontal regeneration therapies. There was superior influence in the healing process of soft tissue when the combination with collagen membrane was used. This also proved to be effective in decreasing pocket depth.(35)

A randomized, controlled, split-mouth study conducted by ***Andy Temmerman et al (2019)*** compared the clinical outcome between "Bovine-derived xenograft in combination with autogenous bone chips and xenograft alone for the augmentation of bony dehiscence around oral implants". It was concluded in this study that both these treatment options were equally effective. (36)

Silvio et al (2019) conducted a prospective study aimed at investigating clinically and histologically the effectiveness of a biomimetic magnesium-enriched-hydroxyapatite (MgHA) compared to a collagen-based deproteinized bovine bone matrix for alveolar socket preservation. Both the materials proved to show similar effectiveness. It was concluded in this study that either of the two materials could be used as a viable option for bone substitute. (37)

Kollati et al (2019) conducted a study aimed to compare the efficacy of natural bovine hydroxyapatite and platelet-rich fibrin (PRF) matrix along with collagen plug to unassisted natural healing in extraction sites. The study concluded that addition of PRF along with bone graft for socket preservation provided additional growth factors which enhanced the wound healing process and maintained the dimensions. (14)

Limitations/ Disadvantages

Xenografts tend to have high osteoconductive potential, but on the other hand are brittle in texture. These grafts lack toughness. Thus making them more susceptible to failure during surgeries, such as screw fixation procedures and/or after implantation. (2) Xenografts are frequently unable to gain adequate height and width in case of large bone defects. It is not always available in formulations that allow easy adaption or modelling, hence may be difficult to use in comparison to autogenous grafts / allografts. (38)

Xenograft is bone tissue which is harvested from one species and placed into another species. Hence a vigorous immune response is the main cause of concern when using it. Deproteinated and defatted xenograft bone have shown to decrease immune response. However, these processing techniques tend to destroy valuable osteoinductive matrix proteins. The main drawback with these materials is the risk of transmission of infective agents. It can cause disease transmission, which was evident in the case of bovine spongy form encephalopathy reported in Great Britain

Conclusion

Bone grafting is the most commonly used treatment modality used in periodontal regenerative therapy. It has been established that bone replacement grafts can be utilized for adequate amount of periodontal regeneration. Autografts have the disadvantage of causing morbidity at the site of harvestation. It also has limited availability. Xenografts on the other hand has the advantage of being manufactured in excess amounts at comparatively lower processing expenses. There is no need for a second surgical site when xenografts are used. It has also been observed that the healing process takes lesser time in case of xenografts.(5) It is structurally similar to human bone and has relatively superior osteoconductive capability. These grafts have excess available surface area due to their porosity. Xenografts have proved to be effective in the treatment of intrabony defects and ridge augmentation. Xenografts has been found to be clinically effective and is being brought up as a new avenue to treat advanced periodontal defects. (9)

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