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Periodontology

# PERIODONTAL REGENERATION WITH OSSEOUS GRAFTS: A REVIEW

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**ABSTRACT** Modern periodontics strives on the maintenance of teeth and their supporting structures in the prime of their health. Most periodontal practices focus on prevention of disease, initial therapy and corrective surgical treatment to eliminate deep periodontal pockets. However, restoring supporting tissues to their healthy level is a critical area that offers a much more appealing and in fact a more desired outcome for the patients. Over the last decades different modalities of regenerative treatments have been developed and applied clinically. One such treatment is use of osseous grafts, this article discusses the various types of osseous grafts, their mechanism and advances in regenerative periodontal therapy.

**KEYWORDS :** Autogenous graft, Allograft, Xenograft, Alloplast

## INTRODUCTION

Periodontitis is a chronic multifactorial inflammatory disease associated with dysbiotic plaque biofilm and characterized by progressive destruction of the tooth supporting structures.[1] It is characterized by clinical attachment loss, increased pocket depth, gingival bleeding and radiographically by decreased alveolar bone height. Contemporary periodontal therapy aims to control the disease and regenerate periodontal structures that are lost. Regenerative periodontal therapy aims to restore the supporting periodontium such as periodontal ligament, cementum and bone to their original level. A lot of new treatment modalities have emerged over time that aims to regenerate the lost periodontium, one such treatment modality is use of osseous grafts. It is believed that these osseous grafts can alter biological response of the periodontium from reparative to a regenerative response of periodontal healing. The objectives of periodontal regeneration are to reduce probing depth, to gain clinical attachment, to achieve bone fill and to regenerate periodontal ligament, cementum and new bone.[2]

## METHODS OF EVALUATION OF PERIODONTAL REGENERATION

Methods used to evaluate periodontal regeneration are periodontal probing method, re-entry method, comparison of pre-treatment and post-treatment radiographs and histological evaluation method.

Clinical attachment level (CAL) measurements although is the most commonly used method, but is not adequate, as CAL gain can occur after periodontal therapy because of reduced inflammation, re-establishment of the gingival collagen fibres, genesis of long junctional epithelium and bone fill without true regeneration.[3] Re-entry procedures involves direct comparison of bone levels by re-flapping the site after surgical therapy. It measures bone, but cannot differentiate if the bone and root are attached via a periodontal ligament or not, therefore, it is an inadequate method. Pre- and post-treatment radiographs can compute variations in bone density, height, and volume but cannot distinguish whether the regeneration is true regeneration or not.[4] Histological evaluation is the most reliable method that can be accurately determine the efficacy of regenerative therapies but due to ethical considerations, it is not used.[5,6]

## MECHANISM OF PERIODONTAL REGENERATION WITH OSSEOUS GRAFTS

Hegedus in 1923 was the first person to use osseous grafts for the reconstruction of intra-osseous defects [7], later on Nabers and O'Leary used osseous grafts in the year 1965.[8]

Osseous graft aids in bone regeneration by following three mechanism namely osteogenesis, osteoinduction and osteoconduction.

Osteogenesis is the process of formation of new bone by the cells present within the graft material. Osteoinduction is a chemical process in which molecules present within the graft material (bone morphogenetic proteins) convert the patient's cells into cells that are capable of bone formation. Osteoconduction is a physical effect by which a scaffold is formed by the matrix of the graft on which cells of the recipient site form a new bone.[9]

**BOX-1 CLASSIFICATION [9]**

Osseous grafts can be broadly classified as follows:

- Human bone grafts
  - Autografts or autogenous graft
    - Extraoral
      - Intraoral
  - Allografts or allogenic grafts
    - Fresh frozen bone
    - Freeze-dried bone allografts (FDBA)
      - Demineralized freeze-dried bone allografts (DFDBA)
- Bone substitutes
  - Xenografts or xenogenic grafts
    - Bovine-derived hydroxyapatite
    - Coralline calcium carbonate
    - Porcine-derived hydroxyapatite
  - Alloplast or alloplastic grafts
    - Absorbable
    - Non-absorbable

Ideal osseous grafts should be biologically acceptable, clinically feasible and have minimal operative hazards, minimal postoperative sequelae and maximum patient compliance.

## TYPES OF OSSEOUS GRAFTS

### 1) AUTOGENOUS GRAFTS

Autogenous grafts are gold standard as they are non-antigenic and have viable osteoblasts and osteoprogenitor stem cells.

### Mechanism

Osteoprogenitor cells (or preosteoblasts) on adequate vascularization proliferate and lay down initial bone deposits, the osteocytes that were transplanted die due to surgical injury and anoxia, transplanted osteoclasts that survived transplantation initiate the resorption of the graft, restoration of circulation takes place by micro anastomoses. The survived cells start laying new bone and later bone is formed by osteoinduction.

**BOX-2 SOURCES OF AUTOGENOUS GRAFTS**

Intra-oral
- Ramus area
- Maxillary tuberosity region
- Mandibular symphysis region
- Edentulous areas
- Tori

Extra-oral
- Iliac crest
- Calvarium
- Tibial region[12]

Most preferred site is the iliac crest but is usually not recommended for intra oral defects because the procedure is technique sensitive and needs hospitalization.[13, 14] As compared to extra oral sites, intraoral donor site has the advantage of proximity of donor and recipient sites, which decreases the anaesthesia duration, operative time and patient's discomfort. It is also lesser morbid than extra oral, therefore it ideal for periodontal surgeries.

## TYPES OF AUTOGENOUS BONE GRAFT

### Cortical bone graft

It has osteoconduction, minimal osteoinduction and minimal osteogenic properties. Advantages are that it is an ideal graft material for use in structural defects and provides immediate stability which is required for healing. Disadvantages are relatively slow incorporation, revascularization and limited perfusion due to dense cortical matrix. It is also poorly osteogenic due to donor osteocytes.[15,16]

In 1965, Nabers and O' Leary used cortical bone chips obtained by the hand chisels during osteoplasty and osteotomy and reported that there was an increase in coronal bone height. Cortical bone chips has a potential for sequestration because of their larger particle size 1,559.6 × 183 µm and suggested to replace it by autogenous osseous coagulum and bone blend.[17] For effective osteogenesis the particles size should be more than 75-125 µm as particle size less than this get rapidly resorbed.

### Cancellous bone graft

Cancellous bone is the commonly used source of autograft. It has osteogenic, osteoinductive and osteoconductive properties. Functional osteoblasts lines the porous trabeculae resulting in high osteogenicity.[18]

### Cortico-cancellous bone graft

Cortico-cancellous bone grafts have benefits of both cortical bone as well as cancellous bone: Cortical bone provides an osteoconductive medium and immediate structural stability, whereas cancellous bone provides the osteoinductive and osteogenic property.

### Intraoral cancellous bone and marrow

Donor area are usually mandibular retromolar areas, healing extraction sockets, and maxillary tuberosity. A 3.65mm and >50% mean bone fill can be achieved with this graft[18]

### Extraoral cancellous bone and marrow

Anterior or the posterior iliac crest are the main extraoral donor sites. Complete healing of furcation, interdental craters and bone growth ranging from 3.53-4.36 mm have been observed.[19,20,13,21]

### Osseous coagulum

Osseous coagulum can be obtained by using high or low speed round burs and mixing of bone particles with blood. [16,22,23] Advantage of small particle size is predictable resorption and replacement by host bone. The disadvantage of osseous coagulum is that the collection process is technique sensitive and quality, quantity and fluidity of the material is highly unpredictable.

### Bone blend

Trephine or rongeur are used to obtained cancellous or cortical bone that is placed in an amalgam capsule and triturated to the consistency of a slushy osseous mass to obtain bone blend with particle size of 210 × 105 µm.[24]

### Block grafts

Cortico-cancellous or cortical bone blocks can be used for the alveolar bone horizontal augmentation, reconstruction around implants and jaw reconstruction in pre-prosthetic surgery. The healing of autogenous block grafts involves replacement of the necrotic bone within the graft by viable cells known as “creeping substitution”. Healing is highly dependent on revascularization and angiogenesis of graft.[25, 26] Harvesting sites are mandibular symphysis[25], ramus, or external oblique ridge, and areas beyond the root apices. Conventional osteotomy or milling procedures can cause structural bone changes and is toxic to viable cells due to overheating. Advances like piezoelectric device have advantages over conventional osteotomy such as lesser surgical trauma and faster healing.

## 2) ALLOGRAFTS

Allografts are grafts obtained from genetically dissimilar members of the same species. Examples are frozen, freeze-dried and freeze dried demineralized bone grafts. The high antigenicity, the need for extensive cross-matching and risk of disease transfer has led to the disuse of fresh frozen bone. To overcome this disadvantage freeze-drying was introduced which reduced the antigenicity and other health risks associated with fresh frozen bone.[27, 28] FDBA is more osteoconductive and have a slower resorption rate. Demineralized freeze-dried bone induces the mesenchymal cells of host to differentiate into osteoblasts. [29] DFDBA is osteoinductive as well as osteoconductive and has a rapid rate of resorption. Demineralization and freeze-drying of cortical bone graft material increases its osteogenic potential as observed by Urist et al. [30-32]

Demineralization with Hydrochloric acid exposes the bone inductive proteins present in matrix collectively called bone morphogenic proteins which are acidic polypeptides[33]. BMPs stimulate the host stem cells to differentiate into osteoblasts, demineralized freeze-dried bone allografts (DFDBA) are considered more inductive than non-demineralized bone that acts through osteoconduction [34]. Both types of grafts undergo multiple immersions in absolute Ethanol but for decalcification added immersion in 0.6 N HCI is needed.[35] Human Immunodeficiency Virus (HIV) is inactivated by both of these processes.[36-38] Advantages are that there is no need of donor site and enough quantities of graft can be procured. Disadvantages are that freeze-drying and irradiation of bone affects integrity of material and decreases its osteogenicity. It can be antigenic, there is risk of disease transfer, viral infections like HIV [39]. Examples are Puros® and Grafton DBM®.

### Bone banks

The bone allografts are procured within 12 hours of death of the donor, cortical bone is harvested which is preferred over cancellous bone as it contains more bone-inductive proteins and is less antigenic.[35] 0.5- to 5 mm size particles sectioned from bone are immersed for 1 hr in 100% Ethanol. Viruses are inactivated, within 1 min of this treatment[38] the Ethanol penetrates completely into cortical bone[40]. Freezing of bone, decreases antigenicity, risk of disease transfer and allows long term storage.[41,43,44] 250 to 8OO mm sized particles are grounded, this particle size promote osteogenesis, whereas particles smaller than 125 mm is known to induce a macrophage response.[42] The bone is immersed again in Ethanol. Demineralization if needed can be done.

## 3) XENOGRAFTS

A xenografts are grafts taken from a donor of different species. Examples are the bovine-derived hydroxyapatite, porcine-derived and coralline calcium carbonate.

**Table -1**

| Bovine-derived hydroxyapatite | Coralline calcium carbonate | Porcine-derived hydroxyapatite |
|---|---|---|
| Preparation involves chemical or low-heat extraction of the organic component from the bovine bone | Obtained from exoskeleton of a natural coral of genus *Porites* [45,46] | Anorganic porcine derived graft is produced by thermal treatment at high temperature. |
| Act as an osteoconductive scaffold and integrate easily with human bone as its mineral content is comparable to that of human bone. | It has porous structure like spongy bone and provides a large surface area for resorption and bone replacement[48, 49]. | Stiffness and calcium/phosphate ratio of porcine are closer to human trabecular bone than bovine bone[47] |
| Example -Bio-Oss® and Osteograf® | Example – Biocoral® | Example-Bone-XP® |

Advantages are that xenografts are osteoconductive and easily available. Disadvantage is that the risk of disease transmission like bovine spongiform encephalopathy is seen with use of bovine-derived grafts a case of which was reported in Great Britain[9]

## 4) ALLOPLASTS

Alloplastic grafts are synthetic, inorganic, biocompatible, or bioactive bone graft materials. They act by osteoconduction and are dependent on viable periosteum/bone for their action. Their primary function is to act like defect fillers.

**BOX-3 CLASSIFICATION (BASED ON BIOABSORBABILITY)**

Absorbable
- Alpha tricalcium phosphate
- Beta tricalcium phosphate
- Calcium sulphate
- Non-sintered hydroxyapatite

Non-absorbable
- Sintered hydroxyapatite
- HTR polymer
- Bioglass

**Alpha tricalcium phosphate** has a monoclinic crystalline structure which is produced by heating the beta tricalcium phosphate above a temperature of 1180 degree Celsius followed by quenching it to allow it to retain its structure.[50] It has lesser stability but greater stiffness.

**Beta tricalcium phosphate** is the most commonly used alloplastic graft that has a rhombohedral crystalline structure with compressive and tensile strength equivalent to cancellous bone. Resorption period of this graft is 6 to 18 months. Used with other less resorbable bone substitutes or as an expander for autogenous bone graft. Examples are SynthograftTM® and Cerasorb®

**Calcium phosphate/ Plaster of paris** primarily function as a defect filler and has osteoconductive properties. Has a greater compressive strength but slightly lesser tensile strength than cancellous bone. Resorption period of this bone graft is 5 to 7 weeks. As this graft requires a moisture free environment to set, it is used more commonly in contained defects. Example osteoset® (calcium sulfate with tobramycin).

**Non sintered hydroxyapatite** produced at low temperature is a resorbable graft. It act as a physical scaffold for bone replacement. As its resorption rate is slower it functions as a reservoir of minerals.[53, 54] Example Osteogen®.

**Sintered hydroxyapatite** produced at high-temperature (sintering), is a non-resorbable, non-porous, dense material.[52] it is an osteoconductive, osteophilic, inert biocompatible defect filler. Examples are OsteoGraf/D300® and OsteoGraf/D700®.

**HTR Polymer** HTR stands for hard tissue replacement synthetic bone graft that is a composite of calcium hydroxide with methylmeth acrylate and hydroxymethylmethacrylate polymers. It has osteoconductive properties and its hydrophilic nature amplify clotting and its negative surface charge allows it to stick to bone. Examples are Healos®, Collagraft® and Tricos®.

**Bioactive Glass** is a silicone based osteoconductive and osteogenic material that attaches to bone by forming carbonated hydroxyapatite. It is bilayered consisting of a silica gel and a calcium-phosphorous rich (apatite) layer. The later enhances adsorption and concentration of proteins which is used by osteoblasts to form a mineralized extracellular matrix. Examples are Perioglas® and Biogran®.

## BIOLOGICS

Various biological agents, such as BMP (bone morphogenetic proteins), PDGF (platelet-derived growth factor), EMD (enamel matrix derivatives) and FGF (fibroblast growth factor) can be used to amplify the periodontal regeneration clinical outcomes. They have the ability to regulate immune function, enhance proliferation and differentiation of epithelial and connective tissue cells.

### Platelet-Derived Growth Factor (PDGF)

PDGF is a functionally versatile polypeptide with five isomeric forms, namely PDGF-AA, PDGF-AB, PDGF-BB, PDGF-CC, and PDGF-DD. It acts by binding to cell membrane tyrosine kinase receptors and subsequently exerts its biological effects by increasing the stem cells and osteoblasts, stimulate endothelial cell proliferation causing capillary ingrowth and promotes fibroblast proliferation enhancing the collagen synthesis.[58-62]

### Bone Morphogenetic Proteins (BMP)

Bone morphogenetic proteins (BMP) is also a functionally versatile polypeptide which belongs to the family of transforming growth factor-β. It induces ectopic bone formation, regulates bone and cartilage formation and promotes development and repair of other organs, like nerves, brain, and kidney. BMP-7 has shown to enhance bone regeneration around teeth, dental implants and in sinus lift procedures.[63-65] As per recent evidence a BMP-family member, growth and differentiation factor-5 (GDF-5) has also shown early stage results for periodontal regeneration.[66]

### Enamel Matrix Derivative (EMD)

EMDs are the most commonly used agent and are composed of Amelogenins. They act by mimicking the events that occur at time of periodontal tissue development.[67] During tooth development, cells of the Hertwig's epithelial root sheath (HERS) deposit enamel matrix proteins on the root surface prior to cementum formation, these proteins are the initiating factor for cementogenesis. When periodontal ligament cells are exposed, EMD alter their phenotype by increasing expression of growth and differentiation factor related genes[68, 69], including transforming growth factor beta.[70] All these factors together promotes periodontal regeneration.

### Fibroblast Growth Factor (FGF)

Two type of proteins with different acidic and basic isoelectric points were recognized as acidic FGF (aFGF, FGF-1) and basic FGF (bFGF, FGF-2).[71] FGFs acts by transmitting signals via receptor-type tyrosine kinase. When FGF binds to a receptor, tyrosine kinase is activated by receptor dimerization and autophosphorylation. This generates signals that plays a crucial role in regeneration and repair of tissues. FGF-2 acts enhancing fibroblastic and osteoblastic proliferation, increases periodontal ligament cells, promotes angiogenesis and release of osteopontin, heparin sulfate, and macromolecular hyaluronan from PDL cells.

## RECENT ADVANCES

Biologics once delivered can undergo receptor mediated endocytosis, proteolytic breakdown resulting in instability and quicker dilution reducing their half-lives. The exposure period may not be optimal for cementoblasts, osteoblasts and periodontal ligament cells to act. Therefore, newer methods of growth-factor delivery have been discovered to optimize regenerative signals. Two such methods are cell and gene-based therapy.[72]

## CELL THERAPY

Cell therapy is the most common technique for periodontal regeneration. It involves direct introduction of new cells and secreted growth factors for treatment of periodontal defects.[73] Cells used are periodontal ligament cells, bone marrow stem cells and dental pulp stem cells. Advantage is that this technique allows local delivery of patient own cells and is known to increase bone formation.[74-75] Disadvantages include difficulty in harvesting stem cells and unpredictable outcome.[76]

## GENE THERAPY

Triggering of the right cellular signals by growth factors to direct host cells to recapitulate endogenous regenerative differentiation potential is essential to regenerative procedures[77]. Vectors used are adenovirus, plasmids, lentivirus, retrovirus, adeno-associated viruses and baculoviruses. It promotes cell mediated production of proteins with authentic post translational modifications and enhanced biologic activity[78]. Disadvantages include risk of host immunogenicity and high viral load can cause cytotoxicity[79].

## CONCLUSION

Over the past decades major advancements have been made in the field of regenerative periodontics. Regeneration of periodontal wounds that have resulted from disease or injury have been made possible with the use of various kinds of graft materials available, showing significant impact on periodontal regeneration**.** Although autograft is gold

standard and shows greater periodontal regeneration, other grafts can also be used based on clinical requirements .Significant clinical and histological evidence supports that autogenous bone grafts and demineralized freeze-dried bone allografts are effective for treatment of intrabony defects. Although synthetic grafts does not have osteogenic or osteoinductive properties but its osteoconductive properties results in improved clinical parameters. The clinical outcomes of periodontal regeneration can be enhanced with the multidisciplinary research in the field of dentistry, medicine, and engineering that will help in the clinical success of periodontal regenerative therapy.

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