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Research Article

HEALING WITH BONE GRAFTS AS A MONOTHERAPY

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ABSTRACT

Periodontitis is an inflammatory disease which is microbial in origin resulting in destruction of the periodontal ligament, alveolar bone and cementum. The major goals of periodontal therapy are to arrest the progression of the disease and reconstruction of lost attachment apparatus. The conventional mechanical therapy results in healing through the formation of long junctional epithelium. Though long junctional epithelium may be a stable attachment, absence of periodontal ligament attachment to the root surface compromises the strength of attachment between bone and the tooth. The continued function of the periodontally involved tooth requires additional support and reconstruction of the lost periodontium. This can be achieved by bone grafts and their substitutes. Bone grafts have been in use for several decades for reconstruction of bone. The bone grafts function as structural scaffolds and matrices for clot development, maturation and remodeling in osseous defects and support bone formation through osteoconduction or osteoinduction. Bone grafts are indicated in different therapies such as treatment of bone defects, reconstruction of alveolar ridge, socket preservation, sinus lift, treatment of peri-implantitis and endodontic surgeries. This review article deals with the biology of bone Healing & outcomes with the different types of bone grafts when used as a monotherapy in periodontal reconstruction.

INTRODUCTION

The periodontal disease if untreated ultimately leads to soft and hard tissue destruction around the teeth. The primary goal of periodontal therapy is to establish periodontal health with pocket reduction and attachment gain, preferably through periodontal reconstruction.

Reconstruction of the lost attachment apparatus and periodontal defects, which is the ideal and desired outcome can be achieved through bone graft & non bone graft techniques. Periodontal reconstruction is unique because it involves both soft (gingival and periodontal) and mineralized (bone and cementum) connective tissues. The healing of all periodontal components are coordinated and integrated for periodontal reconstruction. Cellular events requirement are, migration of cells by chemotaxis, their adhesion, proliferation, differentiation and production of matrix components.[1] Melcher IN 1976 SUGGESTED THAT the type of cell which repopulates the root surface after periodontal surgery determines the nature of the attachment.[2]

The periodontal reconstruction can be broadly classified into

- Non grafted associated new attachment procedures.
- Graft associated new attachment procedure.

The process of bone graft incorporation is similar to the bone healing process that occurs in fractured long bones.

Bone Healing

The healing potential of bone is influenced by a variety of biochemical, biomechanical, cellular, hormonal, and pathological mechanisms.

Mechanism of Bone Healing

Inflammation, wound healing, vasculogenesis and bone healing are all delicately intertwined. Soft tissue wound healing is required to support bone healing. A continuously occurring state of bone deposition, resorption, and remodeling facilitates the healing process.

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Three types of bone healing are: primary, secondary and gap osseous healing

Primary Bone Healing*:* Involves a direct attempt by the cortex to reestablish itself after interruption without the formation of a fracture callus.

Secondary Bone Healing: Involves the classical stages of injury, hemorrhage, inflammation, primary soft callus formation, callus mineralization, and callus remodeling

Bone healing occurs in three distinct but overlapping stages

1. Reactive Phase[3]
2. Reparative Phase
3. Remodeling Phase

Reactive Phase

Inflammatory phase

Blood clotting (haematoma formation) and inflammation, begins within 12 to 14 hours of trauma. The blood clot provides a matrix for migration of inflammatory cells, endothelial cells and fibroblasts.[3] The first cells to arrive at the fracture site are neutrophils, then macrophages, lymphocytes and plasma cells replace them. Macrophages not only phagocytose necrotic tissues and other debris, but they also release a range of growth factors and cytokines that initiate the healing process.

Granulation tissue formation

These factors stimulate the migration of the multipotent mesenchymal stem cells likely originated from the periosteum, bone marrow, circulatory system and the surrounding soft tissues and also induce differentiation of the cells into the mesenchymal cell types including fibroblasts, angioblasts, chondroblasts and osteoblasts that are necessary for tissue repair and reconstruction.

Reparative Phase

Fibrocartilage (soft callus) formation

A fibrin rich granulation tissue is produced after haematoma formation, within this natural scaffold, endochondral formation occurs between the fracture ends, and external to periosteal sites. The cartilaginous callus, which is later mineralized, is reabsorbed and replaced with bone, and this is the main feature of this stage. This semirigid soft callus is avascular, but when it is replaced by woven bone, vascular invasion occurs in its architecture.[4]

Formation of Hard callus

Proliferation of the chondrocytes within the callus, undergo hypertrophy and mineralize the cartilaginous matrix. The hard callus is formed and the calcified cartilage is replaced by the woven bone, the callus becomes mechanically rigid and more solid. The calcified cartilage acts as a stimulus for angiogenesis to the newly regenerated tissue and brings osteoclasts and osteoblasts into the fracture site.[4]

Bony remodeling

Differentiation of the woven bone

Its the remodeling of the woven bone into lamellar (cortical or trabecular) bone structure. A lamellar bone gradually replaces the hard callus so that the cortex and medulla of the bone are gradually developed.[3]

Remodeling Phase

The osteoclasts reabsorb the newly differentiated bony tissue in the injured area to shape its architecture to be comparable to the intact bone. At this stage, the osteoblasts deposit more osteoid and calcium phosphate in the newly regenerated bone and increase the density of the mineralized matrix. As this stage is continued, the cellularity gradually decreases and the bone density is gradually enhanced.[3]

Gap Osseous Healing: Gap osseous healing is noted in larger defects and they require bone grafts for bone regeneration rather than a fibrous union.[5]

Unlike long bone fractures, bone grafts are incorporated by an integrated process in which old necrotic bone is slowly resorbed by osteoclasts differentiated from monocytes recruited to the site and simultaneously replaced with new viable bone. This incorporation process is termed “creeping substitution”. [4]

Primitive mesenchymal cells differentiate into osteoblasts that deposit osteoid around cores of necrotic bone. This process of bone deposition and remodeling eventually results in the replacement of necrotic bone within the graft. [5]The incorporation and remodeling of a bone graft require that mesenchymal cells have vascular access to the graft to differentiate into osteoblasts and osteoclasts.[3]

Graft incorporation has been summarized by Bauer and Muschler into five Major steps[5]

- Hematoma formation, release of bone inducing factors and cellular recruitment
- Inflammation and development of fibrovascular tissue, connecting the graft to the adjacent bone
- Vascular invasion of the graft
- Focal resorption of the graft by recruited osteoclasts
- New bone formation, union between the graft and the surrounding bone, and graft remodeling.

Healing with Bone Grafts:

Autografts

Healing and incorporation of autogenous grafts is an orderly sequential process whose histologic sequence is similar to that seen in fracture healing. The early phase after transplantation is predominated by inflammation. Surface osteoblasts and *os*teocytes of the graft survive and are capable of producing early new bone.

In the early phase, vascular invasion from the host bed occurs. Along with these new blood vessels come pluripotential mesenchymal cells that can differentiate into osteoblasts by the mechanism known as *os*teoinduction. These newly-formed osteoblasts will secrete seams of osteoid around the central core of necrotic bone. Both the donor and the recipient contribute osteogenic cells.[4]

In the cortical autograft the main differences revolve around the amount of revascularization and the completeness of the remodeling (cancellous grafts are completely remodeled. The cortical bone may not be revascularized as quickly as the cancellous graft and contains fewer osteoblasts and

osteoclasts.[6] Osteoblasts secrete seams of osteoid on the surface of necrotic bone while osteoclasts gradually resorb the dead trabeculae. This process, known as creeping substitution, characterizes the late phase of autogenous cancellous bone grafting.[4]

Allografts

The incorporation of cortical allografts differs slightly from that of cortical autografts. In general the revascularization is much slower and the bone formation is less extensive. Resorption may play a much larger part in the graft incorporation. The temporal sequence of the cortical bone allograft shows an inflammatory response for several weeks. The major cell type at this time is the lymphocyte.

The inflammatory response lasts for another month or two, during which time a fibrous Encapsulation of the allograft takes place. Gradually the graft may be incorporated into the host tissue.

Xenografts

Grafts obtained from different species. Remodeling occurs following equalization of fibroblast proliferation, collagen production, and degradation, when fibers are aligned along different tension lines.

If the remodeling phase does not progress in a manner that contributes to overall tensile strength and host acceptance, the resultant disorganized rearrangement of tissue may lead to poor healing with chronic inflammation, scarring, or host rejection.[2] The rate of remodeling should be balanced with the rate of degradation to maximize the overall strength of the newly formed tissue.[7]

Alloplasts

Alloplasts are the synthetic bone substitutes that are readily available and eliminates the need for a donor site. The in growth of fibrovascular tissue into the pores occur. Appositional bone growth against the walls of the pores begins in a process termed "incorporation". This process proceeds from the peripheries to the centre of the graft. Bridging of the defect is important for graft incorporation. The proliferation and differentiation of undifferentiated cells from periosteum, endosteum and bone marrow enhances the thickening of the bone at bony margins of the defects.

The precursor cells differentiate into osteoblasts ⟹ grow into the defect ⟹ bridge the gap by woven bone formation ⟹ organized to lamellar Bone.[8]

Bone Grafts in Periodontal Reconstruction

Table 1 Histological outcomes of periodontal therapy with bone grafts

Sl.no	The study	Author name & year	Histological evaluation	Conclusion
	Intraoral autogenous grafts:			
1.	ANIMAL STUDY: Intra bony defects treated with autogenous bone grafts in 4 beagle dogs	KIM C-S *et al* in 2005[9]	Intra bony defects healed with new bone and cementum and well organized periodontal ligament fibers were inserted perpendicularly	Autogenous bone graft showed limited osteogenic potential.
2.	Furcation defects treated with Autogenous bone grafts at 36 sites in 6 male mongrel dogs.	Tatian *et al* in 2006[3]	Defects showed incomplete bone fill with varied thickness of cementum. Few furcation sites showed epithelial migration with connective tissue attachment.	No evidence of reconstruction in furcation defects .
3.	HUMAN STUDY: Human intrabony defects treated with osseous coagulum and Bone blend in 3 systemically healthy patients.	S.J.FROUM *et al* in 1975.[4]	Defects healed with new acellular cementum, lamellated bone and periodontal ligament showed high cellularity and vascularity.	A true reattachment consisting of new PDL, new bone and cementum was formed.
	Extraoral autogenous grafts:			
1.	ANIMAL STUDY**:** Orthopic sites treated with autogenous OC and BB in 35 female guinea pigs.	JAMES T.MELLONIG *et al* in 1981[5]	Initially the Bone grafts were surrounded by vascularized immature connective tissue. Later New Bone formation was evident on the periphery of the graft particles.	Autogenous osseous coagulum and Bone Blend showed less osteogenic potential.
2.	HUMAN STUDY: Intra osseous defects in humans treated with fresh iliac crest marrow grafts and hematopoietic marrow grafts.	MICK. *et al* in 1973[10]	Defects healed with new bone and cellular cementum. Alveolar crest showed marked osteoblastic activity at 2 months. At 3rd functional orientation of PDL fibers. At 8 months, functionally oriented PDL with sharpey's fibres embedded in new Bone and cementum was found.	Periodontal reconstruction was evident following autogenous iliac bone grafts in humans.
3.	Intrabony defects treated with iliac autonenous grafts in 3 systemically healthy patients.	S.J.FROUM *et al* in 1975[4]	Osteogenesis was evident at the alveolar crest. Smaller sized bony implants induced more bone formation. Periodontal ligament were highly cellular and functionally oriented and were embedded at the new Bone and new acellular cementum.	Periodontal reconstruction at the site of grafting was evident.
	Allogenic grafts: FDBA			
1.	FDBA placed at orthopic sites in guinea pigs. Periodontal reconstruction was confirmed with the uptake of Sr.	JAMES T. MELLONIG *et al* in 1981[5]	Graft particles were surrounded by highly vascularized immature connective tissue at day 7 and Osteogenesis was evident at day 14. Bone formation increased at day 21, 28, 35 and 42.	FDBA showed limited osteogenic potential.
2.	Surgically prepared sites in rhesus monkeys were implanted with FDBA in nylon mesh cyclinders.	RAYMOND A.YUKNA *et al* in 2005[2]	Vascular fibrous connective tissue filled the chambers at 1st month. New bone totally filled the chamber at 3rd month with no inflammation.	FDBA stimulated periodontal reconstruction in surgically prepared sites.
	DFDBA			
1.	ANIMAL STUDY: The orthopic sites were treated with DFDBA in guinea pigs	JAMES.T.MELLONIG *et al* in 1981[5]	Deposition of new bone was observed at day 7, and increased in amount of trabecular bone deposition from day 14 to day 42.	DFDBA showed high osteogenic potential.
2.	Surgically prepared sites in rhesus monkeys, implanted with DFDBA in nylon mesh cyclinders**.**	RAYMOND A. YUKNA *et al* in 2005[2]	At 1 month connective tissue attachment was observed with minimal bone formation. At 3rd month trabecular type of bone filled the cavities.	Osteogenic potential of DFDBA was limited.
	Alloplasts:			
1.	ANIMAL STUDY: β - tricalcium phosphate (β-TCP) with or without membrane protected were placed in the osseous defects of adult baboons.	GERALD I.DRURY *et al* in 1991[7]	Initially healing was by osteoid formation surrounding the graft particles. At 3rd month regenerated bone was noted at the periphery of the grafts. At 12-24 months, the grafted defects showed complete bone healing with well organised & matured bone.	Study showed significant periodontal reconstruction at the defect sites.
2.	Calcium phosphate cement (CPC) placed in the fenestration defects and three walled defects in dogs	YOSHINORI *et al* in 2002[8]	The fenestration defects showed new cementum with highly vascular periodontal ligament and bone formation was observed. The three walled defects, was filled with new trabecular bone and cellular type of cementum with functionally oriented sharpey fibers.	CPC acted as a scaffold for osteogenesis and provided healing of periodontal tissues.

Table 1 - Continue

3.	**HUMAN STUDY**: Tricalcium phosphate ceramic implants treated in the human intraosseous defects	S.S.STAHL *et al* in 1986[11]	Defects healed with long junctional epithelium. Graft particles were surrounded by connective tissue capsule at 3-8 months after graft placement with limited osteogenesis & Cementogenesis.	Insignificant periodontal reconstruction with Tricalcium phosphate.
4.	Bio-glass implanted in 5 human intrabony defects.	Nevins *et al* in 2000[12]	In patient I: Graft particles were surrounded by dense connective tissue. Defects showed limited osteogenesis and cementogenesis. No evidence of regeneration of tissues in patient II, III, IV & V healing was by long junctional epithelium.	Bio glass showed only limited osteogenic potential.
5.	Hydroxyapatite implants placed in intraosseous defects in 2 patients.	Carranza *et al* in 1987[13]	Long junctional epithelium with 3 to 5 cell layer. No evidence of cementogenesis. Width of the lamellar bone (20 to 150 μ) with numerous osteoclasts..	Insignificant periodontal reconstruction with hydroxyapatite implants.
	XENOGRAFTS:			
1.	HUMAN STUDY: 4 patients treated with bovine derived bone xenografts (BDX) in vertical osseous defects.	Mellonig *et al* in 2000[14]	In Patient 1: Grafts were encased in bone. Cellular type of cementum with functionally oriented PDL fibers. Patient 2 & 3: Evidence of bundle bone & New cementum with PDL fibers running parallel to the root surface. Patient 4: Sites healed with long junctional epithelium.	Periodontal reconstruction was possible following treatment with BDX.

Table 2 Clinical outcomes of periodontal therapy with bone grafts

Sl..no	The study	Author name & year	Clinical evaluation	Radiographic evaluation	Conclusion
1.	6 months evaluation of intrabony defects treated with Plaster of paris.	Shaffer *et al* in 1971[15]	No increase in bone level.	Bone appeared more radiopaque.	Osseous regeneration was not evident with plaster of paris in intrabony defects.
2.	Clinical evaluation of vertical intraosseous defects treated with Autogenous iliac bone with hematopoietic marrow grafts evaluated for 8 months	Dragoo and Sullivan in 1973[16]	Average Increase in alveolar bone height upon sounding is 3.8 mm vs 2.1mm respectively.	Average increase in bone height is 1.56 mm.	Osseous reconstruction was favourable with bone grafts.
3.	Intra osseous defects treated with Osseous coagulum(OC) - Bone blend (BB) and Cancellous bone.	Froum *et al* in 1975[17]	Bone fill : 60.7 % vs 73 % respectively.		BB & OC demonstrated similar osseous reconstruction.
4.	Infrabony defects treated with DFDBA and OFD.	Pearson *et al* in 1981[3]	CAG : 2.31mm vs 0.33 mm respectively.	Increase in Bone height : 1.38mm vs 0.33 mm respectively.	DFDBA is more effective in reconstructing the lost periodontal tissues than flap debridement.
5.	3 years evaluation of intra bony defects treated with Ceramic grafts, autogenous bone grafts and OFD.	Nery *et al* in 1990[18]	CAL gain : 1.0 mm vs 0.4 mm vs 0.9 mm respectively.	Avg bone fill of 1mm.	Insignificant periodontal reconstruction with autografts and ceramic grafts.
7.	6 and 12 months evaluation of intraosseous defects treated with Coralline calcium carbonate and OFD.	Yukna *et al* in 1994[19]	At 12 months: Defect fill : 2.3 mm vs 0.7 mm respectively.	Defect resolution : 76.8 % vs 44.6 % respectively.	Coralline calcium carbonate was found to be safe and clinically efficient as a bone replacement graft.
9.	6 months evaluation of intraosseous defects with Bioactive glass and DFDBA.	Lovelace *et al* in 1998[20]	PDR: 3.07 mm vs 2.6 mm respectively. CAG : 2.27 mm vs 1.9 mm respectively .	Bone fill : 2.73 vs 2.80 mm respectively. Crestal resorption: 0.53 mm vs 0.80 mm respectively.	Bioactive glass and DFDBA showed significant periodontal reconstruction. Improvements were better in 2 and 3 wall defects.
10.	Intrabony defects treated with Bioactive glass and open flap debridement.	ONG *et al* in 1998[21]	PDR: 1.24 mm vs 0.68 mm respectively. CAG : 0.87 mm vs 0.48 mm respectively	B-L defect fill 1.8 mm vs 0.6 mm respectively	Human tissues tolerated bioactive glass with better soft and hard tissue reconstruction.
11.	5 years evaluation of infrabony defects treated with Coralline calcium carbonate graft material (BIOCOR-AL)	Yukna *et al* in 1998[22]	CAL: From 5.7 mm to 4.0 mm. PPD: 6.1 mm to 3.3 mm.		Coralline calcium carbonate graft material can be used in the reconstruction of attachment apparatus.
12.	Randomized study. 6 months evaluation of intraosseous defects with BIO-OSS (BDX) and DFDBA.	Mellonig J.T *et al* in 1999[23]	PDR: 3.0 mm vs 2.0 mm respectively. CAL gain: 3.6 mm vs 2.6 mm respectively.	Bone fill : 3.0 mm (55.8 %) vs 2.4 mm (46.8) Respectively	Periodontal reconstruction is evident with both BIO-OSS and DFDBA. BDX exhibits better handling property.
13.	3 & 6 months evaluation of furcation involvement treated with Bioactive glass and OFD.	Anderegg *et al* in 1999[24]	At 6 months: PD : 3.47 mm and 3.4 mm vs 4.2 mm and 4.07 mm respectively		Bioactive glass have additive effects than the OFD alone in furcation involvement.
14.	Retrospective study. 5 and 10 years radiographic evaluation of intrabony defects treated with DFDBA and OFD.	Persson *et al* in 2000[25]		Avg Bone fill : 0.5mm vs 0.0 mm respectively.	DFDBA and OFD showed similar amount of defect resolution with bone fill.
15.	Randomized clinical trial. 12 months evaluation of intrabony defects treated with Calcium phosphate bone cement (CPC) and OFD.	Shirakata *et al* in 2008[26]	PDR : 3.4 mm vs 3.3 mm respectively. CAL gain: 2.3 mm vs 1.4 mm respectively.	Bone level gain: 1.2 mm vs 0.3 mm respectively.	Osseous regeneration was efficient with calcium phosphate bone cement than the OFD.
16.	Randomized controlled clinical trial. 6 months evaluation of intrabony defects treated with Nano crystalline hydroxyl appatite paste (Nano-HA) and OFD.	Kasaj *et al* in 2008[1]	Mean PD Reduction to 3.4 mm vs 4.9 mm respectively. CAL gain : 4.4 vs 6.4mm		The reconstruction of periodontal attachment apparatus was better in Nano-HA paste than OFD.
17.	Randomized control trial. 1 year evaluation of intrabony defects treated with (BCC) , (ABS) and OFD.	Stein *et al* in 2009[27]	Mean PDR: 3.4 vs 2.8 mm respectively. CAL Gain: 3.0 mm vs 2.9 mm vs 1.6 mm respectively.		Reconstruction of the lost periodontal attachment were similar with both the BCC and ABS.
18.	Randomized controlled clinical study. 6 months evaluation of intrabony periodontal defects treated with NHA and OFD.	Heinz *et al* in 2010[28]	PDR: 8.3 to 4.0 mm vs 7.9 mm to 5 mm respectively		Intrabony defects treated with NHA paste enhanced the periodontal reconstruction than OFD.

Table 2 - Continue

19.	6 months evaluation of intrabony defects treated with BIO-OSS and OFD.	Gokhale etal in 2012[29]	PDR: 4.33 mm vs 2.92 mm respectively. CAL Gain: 2.92 mm.vs 0.58 ± 0.51 mm 2.4 mm respectively.	Bone fill : 1.93 mm vs 0.02 mm	Bio oss is a predictable graft material for periodontal reconstruction in infrabony defects.
20.	Randomized study. Intrabony defects treated with Bovine bone mineral (BBM) and OFD.	Slotte *et al* in 2012[30]	PDR : 3.2 mm vs 4.0 mm respectively CAL Gain : 2.3 mm vs 2.8 mm respectively.		Regeneration of attachment apparatus was similar with both bovine bone mineral and OFD in intrabony defects.
22.	Randomized controlled clinical and radiographical study. infrabony defects treated with DFDBM and DFDBM treated with doxycycline.	Kaur *et al* in 2013[31]	PDR: 3.20 mm VS 3.53 mm respectively. CAG : 3.0 mm vs 3.20 mm respectively.	Bone fill : 3.0 mm vs 4.47 mm respectively.	DFDBM loaded with Doxycycline showed higher regenerative capacity than DFDBM.
23.	6 and 12 months evaluation of vertical osseous defects treated with DFDBA and Bioactive glass.	Katuri *et al* in 2013[32]	At 12 months PDR: 2.5 mm vs 1.8 mm respectively. CAL gain: 2.4 mm vs 1.7 mm respectively.	Bone fill of 64.76% vs 53.86% respectively.	Periodontal reconstruction was more effective with DFDBA and Bioactive glass.

CONCLUSION

Even though bone grafts have shown fairly good results, complete reconstruction of periodontal attachment apparatus were not achieved. They were primarily a defect filler material.[32] Further several commercially available bone grafts did not undergo complete resorption and were encapsulated by a fibrous capsule. These limitations have forced researchers to look beyond mere bone replacement grafts for periodontal reconstruction.

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