Advancements In Bone Graft

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***Abstract*—Significant advancements in the field of bone grafting and regenerative biomaterials have resulted in the predictability of periodontal and implant therapy outcomes. After extraction resorption affects the placement and stability of dental implants and the periodontal tissues. Bone augmentation procedures are necessary in such cases to ensure the desired results. Regenerative therapy has now shifted its focus from conventional biomaterials to biologically active materials. Platelet-rich fibrin and growth factor therapy are examples of biologically active materials. Significant advancements in the field of biomaterial science have resulted in the development of bone graft substitutes such as ceramics, polymers. They are known for their excellent biocompatibility and mechanical properties. Regenerative biomaterials such as dentin-based grafts and smart biomaterials are the latest advancements in the field. They are known for their drug release properties and tissue integration. Moreover, three-dimensional printing technology has allowed the fabrication of patient-specific scaffolds based on imaging studies.**

I. INTRODUCTION

A thorough summary of current developments in bone grafting and regenerative biomaterials for periodontal and implant therapy is given in this review. This article incorporates both established ideas and cutting-edge regenerative technologies, in contrast to many earlier reviews that primarily concentrate on conventional graft materials and their biological mechanisms. It highlights contemporary biological strategies that improve the predictability of periodontal regeneration, such as platelet-rich fibrin, growth factor-mediated regeneration, enamel matrix derivatives, and stem cell-based treatments. The review also covers novel biomaterials, such as sticky bone and dentin-derived grafts, which are biologically active scaffolds with enhanced regenerative potential. The incorporation of cutting-edge technological advancements like nanotechnology, three-dimensional bioprinting, smart biomaterials, and 4D graft systems that can dynamically interact with the biological environment is a distinctive feature of this review. The article also discusses affordable and ecologically friendly graft substitutes, offering a forward-thinking outlook on bone tissue engineering and regenerative dentistry.

II. CLASSIFICATION OF BONE GRAFTS:

2.1 Based on mode of action:

- Osteo genic: Have living osteoblasts (autografts)
- Osteo inductive: Use growth factors like BMPs to get progenitor cells to grow.
- Osteo conductive: Give bones a place to grow into.
- Osteo neutral (Osteo inert): Keep space without biological induction[9]

2.2 Based on source:

- Autografts: Taken from the same person (mandibular ramus, iliac crest); they help bones grow, induce bone growth, and conduct bone growth.
- Allografts: Bone from a human donor (FDBA, DFDBA). DFDBA has growth factors but it is not as strong as FDBA.
- Xenografts are minerals from animals, usually deproteinized bovine bone mineral (DBBM).
- Alloplasts are synthetic replacements like hydroxyapatite (HA), β-tricalcium phosphate (β-TCP), and bioactive glass.[13]

2.3 Properties of Bone Grafts An ideal bone graft should be:

- Non-toxic
- Non-antigenic
- Resistant to infection
- Predictable

- Clinically feasible
- Easily adaptable
- Readily available
- Associated with minimal operative and postoperative morbidity
- Capable of adequate bone fill and new attachment formation (including cement genesis)
- Cost-effective and acceptable to patients[14]

III. BIOLOGICAL PRINCIPLES OF BONE REGENERATION

3.1 Factors Influencing Healing

A. PASS Principle

B. Melcher's Concept

C. Tissue Engineering Triad

A. PASS Principle

Successful bone regeneration relies on four key factors:

- Primary wound closure
- Angiogenesis
- Space maintenance
- Stability of clot and graft material

P – Primary wound closure

Ensuring the surgical site is primarily closed is crucial for protecting the regenerative area from contamination by saliva, bacteria, and oral fluids. Correct closure promotes undisturbed healing and helps stabilize the graft or regenerative material.

A – Angiogenesis

Angiogenesis is the process of developing new blood vessels at the healing site. An adequate supply of blood vessels delivers essential oxygen, nutrients, and progenitor cells needed for the repair and regeneration of tissue.

S – Space creation and maintenance

It is important to maintain sufficient space within the defect area to facilitate the migration and proliferation of regenerative cells. Bone grafts, barrier membranes, or scaffolds are commonly utilized to preserve this space and prevent the surrounding tissues from collapsing.

S – Stability of the wound

The stability of the blood clot is important. Movement of the wound or graft material can disrupt the healing process and interfere with the formation of new bone and periodontal ligament.[14]

B. Melcher's Concept

Melcher suggested that the specific type of cells responsible for repopulating the root surface influences the results of healing. Cells from the periodontal ligament encourage genuine regeneration, while epithelial cells result in repair characterized by a long junctional epithelium. This idea serves as the biological foundation for guided tissue regeneration (GTR).[7] Melcher noted that regenerating the periodontal ligament is essential for periodontal reconstruction. It provides a connection between the alveolar bone and the cementum. It also contains cells from four different sources: oral epithelium, gingival connective tissue, bone, and the periodontal ligament.[14]

C. Tissue Engineering Triad

Modern regenerative strategies are based on three essential elements:

1. Scaffold
2. Cells
3. Signaling molecules

1. Scaffolds

Scaffolds are three-dimensional biomaterial structures that serve as a framework for tissue growth. They support cell attachment, migration, and differentiation during regeneration.

Functions of scaffold

- Provide structural support for new tissue formation
- Maintain space in the defect area
- Deliver growth factors and cells
- Guide the formation of new extracellular matrix.

Common scaffold materials include:

- Collagen
- Hydroxyapatite
- β-tricalcium phosphate
- Synthetic polymers.

2. Cells

Cells are essential for forming new tissues during regeneration. In periodontal tissue engineering, commonly used cells include:

- Periodontal ligament stem cells
- Mesenchymal stem cells
- Osteoblasts
- Cementoblasts

These cells multiply and differentiate to produce bone, periodontal ligament, and cementum.

3. Signaling Molecules

Signaling molecules control cell behavior and encourage tissue regeneration. They include growth factors and cytokines that promote cell growth, differentiation, and matrix production.

Examples: Platelet-derived growth factor (PDGF), Bone morphogenetic proteins (BMPs), Enamel matrix proteins (EMD). These molecules coordinate the biological processes needed for periodontal regeneration.[14]

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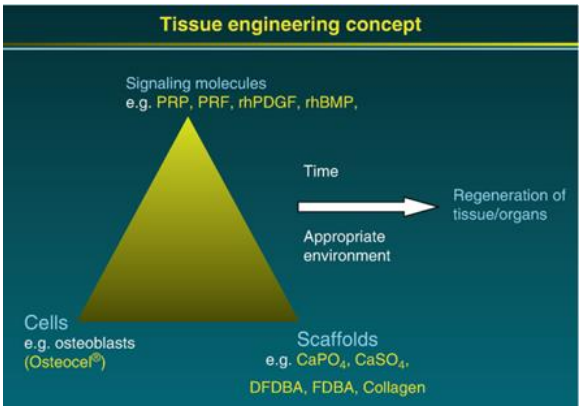

IV. DRAWBACKS OF CONVENTIONAL BONE GRAFTS

Scarce availability – Autogenous bone grafts have a limited supply of donor bone.

Donor site complications – The harvesting process may lead to pain, infection, nerve damage, and extended surgical duration.

Potential for disease transmission – Allografts and xenografts could carry pathogens despite undergoing processing.

Immune responses – Graft materials from outside sources can provoke immune or inflammatory reactions.

Variable osteoinductive properties – Some grafts do not consistently promote new bone growth.

Delayed resorption – Certain materials break down slowly, potentially disrupting natural bone remodeling.

High expenses and processing demands – The preparation, sterilization, and storage drive up treatment costs.

Limited biological function – Many substitutes serve primarily as osteoconductive scaffolds without living cells or growth factors.[47-51]

V. RECENT ADVANCES IN BONE GRAFT:

5.1 Growth factor–based regeneration

A. GEM 21S

Polypeptide growth factors represent a category of natural biological agents that oversee essential cellular processes in tissue healing. Platelet-derived growth factor (PDGF) is the best-researched growth factor in the regeneration of periodontal tissues. Periodontal treatment approaches now aim to offer one or more of the following to improve periodontal regeneration: suitable matrices, biological mediators, and/or precursor cells. Platelet-derived growth factor (PDGF) is the growth factor most extensively researched in periodontics. Since the late 1980s, when Lynch et al. (1989) first found that PDGF facilitated the regeneration of bone, cementum, and periodontal ligament (PDL) [26]

The mechanism of action of PDGF reveals that PDGF cell surface receptors are present on PDL and alveolar bone cells, explaining PDGF's stimulating influence on the proliferation and chemotaxis of osteoblasts, PDL fibroblasts, and cementoblasts [27-29.]

The existence of an optimal scaffold is crucial for periodontal regeneration [30]. Placing a biocompatible substance in the regenerative areas could enhance or speed up the periodontal regeneration process by providing additional solid surfaces for the cells to begin regeneration. Beta-tricalcium phosphate (β-TCP) is a refined, multi crystalline, and porous type of calcium phosphate that has a Ca: PO4 ratio comparable to that of natural bone tissue. It offers a matrix or framework for periodontal regeneration and

also aids in the stabilization of the blood clot [31]the platelet-derived growth factor (rh-PDGF-BB) in combination with beta-tricalcium phosphate (β-TCP) helps to achieve periodontal regeneration [28]

B. Bone morphogenetic protein (BMPs):

Initiation and promotion of osteogenesis are the problems central to periodontal regeneration. Research in molecular biology led to identification of initiators of bone differentiation called bone morphogenetic proteins (BMPs) that regulate cartilage and bone differentiation. Bone morphogenetic proteins (BMPs) are a group of proteins belonging to the transforming growth factor-β (TGF-β) superfamily. They are differentiation factors rather than simple growth factors and play a vital role in:

- Bone induction and repair
- Cartilage formation (chondrogenesis)
- Osteoblast differentiation
- Periodontal regeneration

BMPs were first identified by Urist (1965) when bone formation was observed after implantation of demineralized bone matrix. Later, purification and cloning in the 1980s identified the specific proteins responsible.

5.2 Mechanism of Action

BMPs:

- Bind to Type I and Type II serine/threonine kinase receptors
- Activate intracellular SMAD signaling pathways
- Induce mesenchymal stem cells to differentiate into osteoblasts and chondroblasts
- Act as chemotactic, mitogenic, and morphogenetic agents
- Are unique because they can transform connective tissue cells into osteoprogenitor cells

VI. IMPORTANT BMP TYPES IN PERIODONTICS

BMP-2 and BMP-4 – Strong osteo inductive potential

BMP-7 – Promotes cemento genesis and alveolar bone formation

BMP-6 – Enhances osseous healing

GDF-5 (BMP-14) – Shows clinical attachment gain in periodontal defects

VII. DELIEVERY SYSTEMS

BMPs are delivered using carriers such as:

- Absorbable collagen sponge (ACS)
- Hydroxyapatite
- β-tricalcium phosphate
- Calcium phosphate cements

Recombinant human BMPs (rhBMP-2 and rhBMP-7) are produced using recombinant DNA technology and were approved by the US FDA in 2002 for bone regeneration applications.

Role in Periodontal Regeneration

Studies in animals and limited human trials showed:

- Regeneration of cementum
- Formation of periodontal ligament (PDL)
- New alveolar bone formation

However, complications such as ankylosis and issues with controlled release and short half-life remain limitations.

BMPs show significant promise for periodontal regeneration due to their strong osteo inductive potential. However, more human clinical studies and improved delivery systems are required to optimize their use in periodontal therapy.[16]

VIII. EMDOGAIN

Enamel Matrix Protein Derivatives (EMD) in Periodontal Regeneration. In regenerative periodontal therapy, physiologically active proteins called Enamel Matrix Protein Derivatives (EMD) are utilized to replace damaged periodontal tissues such alveolar bone, cementum, and periodontal ligament

Amelogenins make up the majority of the commercially available form, Emdogain, which is produced from porcine enamel matrix proteins. Hertwig's epithelial root sheath (HERS) secretes enamel matrix proteins that are essential for cemento genesis during tooth formation. PDL and bone attachment depend on the development of acellular cementum, which is started by these proteins. When

EMD is given to a damaged root surface, it replicates this normal developmental process.
Its composition is Over 90% of EMD is made up of amelogenins, enamelins, and compounds that resemble growth factors. In order to ensure continuous activity at the root surface, it is administered in a propylene glycol alginate (PGA) vehicle that permits progressive protein precipitation at physiologic pH.

Its modes of operation are EMD encourages periodontal regeneration in several ways:

- It increases the number of periodontal ligament fibroblasts.
- It boosts the production of collagen and proteins.
- It encourages the development of mineralized nodules.
- It raises the activity of alkaline phosphatase.
- It promotes the development of cementoblast-like cells.
- It has mild antibacterial and anti-inflammatory properties.

It promotes early wound healing and regeneration and can be seen on the root surface for up to two to four weeks.

Histologic research on humans and animals have shown:
New acellular cementum formation Functional collagen fiber insertion in a new periodontal ligament development of new alveolar bone These results support periodontal regeneration as opposed to repair.

IX. CLINICAL APPLICATION

Controlled clinical studies show that EMD:

- Produces significant probing depth reduction
- Achieves clinical attachment gain
- Provides defect fill comparable to Guided Tissue Regeneration (GTR)
- Shows long-term stability (up to 10 years)

It is effective in:

- Intrabony defects
- Class II furcation defects
- Gingival recession (when combined with coronally advanced flap)
- Combination therapy with certain bone grafts may enhance outcomes, though results vary.[17]

X. STEM CELLS IN BONE REGENERATION

Stem cells play a major role in bone regeneration because they have the ability to renew themselves and differentiate into multiple skeletal cell types such as osteoblasts, chondrocytes, and stromal cells. Through these properties, stem cells contribute to the repair and regeneration of damaged bone tissue.
Several tissues can serve as sources of stem cells used in bone regeneration, including bone marrow, periosteum, adipose tissue, skeletal muscle, and umbilical cord blood. Among these, bone-marrow-derived mesenchymal stem cells are widely studied due to their ability to differentiate into various connective tissues such as bone, cartilage, muscle, and ligament when stimulated by appropriate biological signals. During bone healing, stem cells migrate to the site of injury where growth factors such as vascular endothelial growth factor and bone morphogenetic proteins stimulate their proliferation and differentiation into osteogenic cells. These cells participate in callus formation and new bone deposition, eventually leading to bone remodeling and restoration of the normal structure.
Recent studies indicate that bone formation occurs through a hierarchical system involving skeletal stem cells and progenitor cells that become activated after tissue injury. For this reason, regenerative medicine is exploring therapies that combine stem cells with biomaterial scaffolds and growth factors in order to enhance bone regeneration and treat complex skeletal defects.[18]

XI. PLATELET-RICH FIBRIN (PRF) PRODUCTS DERIVED FROM BLOOD IN HEALING

Fibrin sealants, often known as fibrin glue, were first used to treat wounds in the 1970s. They were made by polymerizing fibrinogen with calcium and thrombin.
These resources were applied to:
Topical hemostasis Sealing tissues Repairing soft tissues

As binding agents for materials used in bone grafts Nevertheless, fibrin glue had a number of drawbacks, including:

- Weak stability due to low fibrinogen concentration
- Variability in composition
- Inadequate resilience to physical strain
- High processing costs
- One second generation platelet concentrate utilized in regenerative periodontal therapy is called risk of virus transmission (PRF).

It offers a number of benefits:

- A straightforward method of preparation
- No need for biochemical additions
- Packed with growth ingredients
- Encourages quicker tissue regeneration and healing

Platelet's Function:

Biologically active proteins found in platelets attach to the extracellular matrix or fibrin mesh. Stem cells are drawn to the wound site by the chemotactic gradient these proteins produce. These stem cells undergo differentiation and aid in tissue repair and regeneration.

Platelet Derived Growth Factor (PDGF) stimulates fibroblasts, smooth muscle cells, and glial cells. Ross R. initially reported the regeneration potential of platelets in 1974.

Concentrates of Platelet:

At first, severe thrombocytopenia and bleeding were treated with platelet concentrates. In order to improve tissue regeneration and healing, researchers later paired the fibrin sealant qualities with platelet growth factors. [19]

Sticky Bone:

In the field of dental implantation and restoration, sticky bone is a novel type of composite biological material. It is typically made of Autologous Fibrin Glue (AFG) or injectable-platelet rich fibrin (i-PRF), which is prepared in combination with various bone augmentation materials, such as granular or powdered bone substitutes, to provide a solution for bone regeneration that combines growth factor release with bone scaffold functionality.

Its distinct gel texture guarantees accurate adherence at the location of bone abnormalities and prevents it from disintegrating as a result of outside influences.

By creating the perfect conditions for cell adhesion and proliferation, this characteristic not only improves the integrity of the bone graft but also speeds up bone tissue regeneration and healing.

Furthermore, compared to traditional bone grafting techniques, sticky bone exhibits greater flexibility and surgical success due to its bioactivity and plasticity.

Its potential for advancement in bone tissue engineering also creates new avenues for potential clinical uses in the future.

Overall, because of its sticky bone, scaffolding function, and capacity to contain bioactive components, sticky bone is emerging as a crucial material for encouraging bone regeneration and enhancing implant success. [20]

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XII. DENTIN-DERIVED BONE GRAFT

Dentin-derived bone graft material is an emerging biomaterial used for bone regeneration in dental and orthopedic procedures. Dentin from extracted teeth can be processed and used as a graft material because its composition and biological properties are similar to bone. Dentin contains approximately 70% inorganic hydroxyapatite, 20% organic matrix (mainly type I collagen), and 10% water, which closely resembles the composition of natural bone. This similarity allows dentin grafts to support bone healing and regeneration. Unlike many synthetic graft materials, dentin also contains bioactive growth factors, including bone morphogenetic proteins (BMPs), transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF).

These molecules stimulate osteogenic cell recruitment, differentiation, and bone formation, making dentin grafts osteo inductive as well as osteoconductive.

Clinically, dentin graft materials are prepared from extracted teeth that are cleaned, ground, and demineralized, producing particles that can be placed into extraction sockets or bone defects. The graft acts as a scaffold that supports new bone formation while gradually being replaced by natural bone during remodeling. One advantage of dentin-derived grafts is their excellent biocompatibility and low risk of immune reaction, since the material can originate from the patient's own tooth (autogenous dentin). However, the availability of autogenous dentin is limited, which has led to research into xenogeneic dentin-derived graft materials that retain the organic matrix and biological properties of natural dentin.

Overall, dentin-derived bone graft materials show promising potential as biologically active scaffolds for bone regeneration, particularly in dental implantology, socket preservation, and periodontal regenerative procedures[21]

XIII. ADVANCED BONE GRAFT TECHNOLOGIES

a) 3D Bioprinting:

3D bioprinting extends conventional 3D printing by incorporating living cells, hydrogels, and bioactive molecules into printable bioinks. This process typically involves:

- Designing the scaffold from imaging data,
- Preparing bioinks loaded with cells and hydrogels,
- Layer-by-layer printing, and
- Post-printing maturation to promote tissue integration.

Bioprinted constructs allow precise control over porosity, interconnectivity, and structural fidelity, essential for mimicking periodontal and alveolar bone microarchitecture. However, the cost of equipment, cell sourcing, and bioink optimization remain major challenges for clinical translation.[52]

b) Additive Manufacturing (3D Printing)

- Additive manufacturing (AM), also known as 3D printing, lets you make patient-specific scaffolds that are based on CBCT or intraoral imaging data. Fused deposition modeling (FDM) and robocasting are two methods that can make highly ordered porous networks that match defect geometry with better reproducibility.
- To improve mechanical properties and control degradation kinetics, these scaffolds often combine polymers like polycaprolactone (PCL) with bioceramics like hydroxyapatite (HAp) or tricalcium phosphate (TCP).
- For instance, a 3D-printed PCL/HAp scaffold has been successfully engineered to precisely match periodontal defects identified through CBCT imaging, enhancing anatomical precision and clinical results.[52]

c) Nanotechnology:

Nanotechnology has become an important area of research in dentistry, providing new possibilities for the diagnosis and treatment of periodontal diseases. Traditional treatment methods mainly involve mechanical plaque removal and antimicrobial therapy, but these approaches may be limited by incomplete biofilm elimination and inadequate drug penetration into periodontal pockets. The development of nanoscale materials has allowed the creation of advanced delivery systems capable of improving therapeutic effectiveness and promoting tissue regeneration. Nanoparticles, nanofibers, and nano-structured scaffolds can deliver drugs directly to target sites, provide antimicrobial effects, and release therapeutic agents in a controlled manner.

In addition to treatment applications, nano-biosensors and diagnostic devices may assist in early detection of periodontal pathogens and inflammatory markers, allowing improved disease monitoring and personalized treatment planning. Materials such as silver nanoparticles, chitosan nanoparticles, and nano-hydroxyapatite have demonstrated promising regenerative and antimicrobial properties in periodontal therapy.

Although nanotechnology offers considerable potential, further clinical studies are necessary to confirm long-term safety, biocompatibility, and cost effectiveness before these materials become widely used in routine dental practice.[22]

d) Smart material:

Smart biomaterials are advanced materials engineered to sense and respond to biological or environmental

stimuli, such as pH changes, temperature variations, mechanical stress, or biochemical signals.

Unlike conventional passive biomaterials, these materials possess dynamic properties that enable them to interact with surrounding tissues and deliver therapeutic effects. In dentistry and periodontal regeneration, smart biomaterials can release antimicrobial agents, growth factors, or drugs in a controlled and targeted manner depending on the local disease environment. This responsive behavior enhances tissue repair, improves biofilm control, and supports regeneration of periodontal structures such as bone, cementum, and periodontal ligament.

Furthermore, smart biomaterials including hydrogels, nanocomposites, and bioactive scaffolds are being investigated for their capacity to provide self-healing properties, antibacterial effects, and improved integration with host tissues.[23] [24]

e) 4D Grafts:

4D grafts represent an innovative advancement in regenerative biomaterials where the graft material is designed to change its structure or function over time after implantation. The fourth dimension refers to the ability of the material to undergo controlled transformation in response to physiological stimuli such as body temperature, moisture, or biochemical signals. Using technologies like 4D bioprinting and stimuli-responsive polymers, these grafts can dynamically adjust their shape, porosity, or mechanical properties during the healing process.

In periodontal and oral tissue regeneration, 4D grafts may promote better cell migration, vascularization, and bone formation by gradually adapting to the defect environment. This adaptive behavior allows the graft to more closely mimic natural tissue dynamics and may significantly improve long-term regenerative outcomes compared with traditional static graft materials[24] [25]

XIV. CLINICAL APPLICATIONS

Periodontal intrabony defects – DFDBA, xenografts, PRF/EMD[32]

Furcation defects – GTR with grafts [33]

Ridge preservation – socket grafting[34]

Sinus floor elevation – xenografts/alloplasts[35]

Ridge augmentation – autograft-xenograft mixtures[36]

Peri-implant defects – synthetic/xenogenic with collagen membranes [37]

Emerging uses – tooth-derived grafts, 3D-printed scaffolds[38] [39]

XV. COST-EFFECTIVE AND ECO-FRIENDLY ALTERNATIVES

- Tooth-derived grafts[40]
- Eggshell-derived calcium carbonate [41]
- Marine collagen and coral scaffolds [42]
- Plant-based polymers[43]
- Low-cost 3D-printed alloplasts[44]
- Agricultural waste derivatives[45]
- Green manufacturing technologies[46]

XVI. CONCLUSION

From straightforward defect reconstruction to biologically driven regenerative therapy, bone grafting techniques have advanced dramatically. Other materials like allografts, xenografts, and synthetic substitutes offer useful alternatives in clinical practice, even though autogenous bone grafts continue to be the gold standard because of their osteogenic potential. The predictability of periodontal regeneration has been enhanced by recent developments such as platelet-rich fibrin, bone morphogenetic proteins, stem cell therapy, and derivatives of enamel matrix. Additionally, new opportunities for creating sophisticated regenerative scaffolds have been made possible by developing technologies like nanotechnology, 3D printing, and smart biomaterials.

It is anticipated that future studies will concentrate on creating graft materials that are affordable, biocompatible, and environmentally sustainable. The success of bone regeneration techniques in periodontal and implant dentistry will be further improved by the integration of tissue engineering, digital technology, and biomaterial science.[40-46]

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