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Evolution, current concepts and future perspectives of bone grafts in periodontal regeneration

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Abstract

Objective: This comprehensive review examines the historical evolution, biological foundations, classifications, and comparative efficacy of bone replacement grafts and synthetic substitutes used in periodontal regenerative therapy.

Methodology: A detailed synthesis of anatomical, physiological, and clinical literature was conducted, incorporating historical dental milestones and contemporary systematic reviews evaluating autogenous, allogeneic, xenogeneic, and alloplastic biomaterials.

Key Results: Periodontal regeneration requires an environment conducive to restoring the hard and soft tissue attachment apparatus. Autogenous bone remains the gold standard due to its triad of osteogenic, Oste inductive, and osteoconductive properties, though limited by donor-site morbidity. Allografts (FDBA and DFDBA) exhibit strong clinical efficacy without risk of cross-sensitization. Xenografts (BDX and coralline materials) offer structural architectural scaffolds with low immunogenicity. Modern allowlists (hydroxyapatite, β-tricalcium phosphate, calcium sulfate, and bioactive glasses) show predictable clinical attachment level (CAL) gains and probing depth (PD) reductions, acting primarily through Oste conduction, which is enhanced when combined with growth factors like PDGF-BB.

Conclusion: Successful periodontal reconstruction depends on selecting appropriate biomaterials based on defect morphology, maintaining absolute graft immobilization, ensuring soft-tissue coverage, and leveraging the bone induction cascade to achieve true histological regeneration over simple tissue repair.

Keywords: Periodontal Regeneration; Bone Grafts; Biomaterials; Osteogenesis; Hydroxyapatite; Alveolar Defect

1. Introduction

Periodontal diseases denote pathological processes affecting the supporting structures of the dentition, which comprise two hard tissues (cementum and alveolar bone) and two soft tissues (gingiva and periodontal ligament). The progression of these diseases causes a progressive loss of these structures, leading to pathologically increased tooth mobility and ultimate exfoliation. Overcoming this requires targeted periodontal therapies encompassing both non-surgical and surgical modalities to regenerate the lost supporting periodontium. Within surgical interventions, regeneration is frequently achieved through the placement of bone grafts. The past few decades have witnessed a tremendous paradigm shift in the application of bone grafting within human biologic systems, transitioning from basic observation of clinical outcomes to a dynamic, scientifically driven engineering endeavor.

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The term bone graft was defined by Muschler as "any implanted material that alone or in combination with other materials promotes a bone healing response by providing osteogenic, osteoinductive and osteoconductive properties". Free bone grafting represents a dynamic phenomenon; a successful graft heals, becomes incorporated into the host bed, undergoes revascularization, and eventually remodels into the desired anatomical form. Periodontists and oral surgeons deal primarily with bone grafting inside membranous bone structures, whereas orthopedic pioneers traditionally manipulate tubular bones. For several decades, the active interest of periodontists in bone replacement grafts has emerged from the clinical desire to predictably "fill" challenging intrabony and furcation defects. The primary goal of modern periodontal regenerative therapy is the creation of a local microenvironment conducive to maintaining patient dentition in a state of optimal health, comfort, and function.

Advanced bone grafting techniques and sophisticated bone replacement graft materials make it possible to increase the volume, width, and height of bone in deficient ridges. This structural augmentation allows clinicians to regenerate supporting tissues around questionable teeth and place dental implants in ideal positions and angulations. This review discusses and elaborates upon the various bone grafts utilized in periodontal regenerative procedures alongside emerging bone graft substitutes.

2. History

Immediate reconstruction of missing osseous tissue via bone grafts was popularized during the 1980s, though the underlying logic trace back to clinical lessons from World War I. Kazanjian (1940) obtained exceptional results restoring faces with extensive soft tissue destruction and comminuted fractures from gunshot wounds by emphasizing early prosthetic stabilization and tissue preservation. Fry et al. (1992), drawing from World War II experiences, stated that soft-tissue contour depends heavily upon the underlying bony framework, which must be structurally restored to hold soft tissues in normal position. Parker (1943) observed that when extensive loss of bone occurs in maxillofacial trauma, providing skeletal support for overlying soft tissues prevents devastating collapse and contraction of facial contours.

The earliest recorded repair of craniofacial defects utilized alloplastic materials. The first documented craniofacial reconstruction using a bone graft was performed by Van Meekren in 1632, who placed a xenograft derived from a dog's calvarium. Merren reported a successful bone implant in 1809, and Macewen reported the first successful allograft in 1881 when reconstructing the humerus of a child. Seydel (1889) was the first surgeon to utilize an autogenous bone graft within the facial region, harvesting tissue from the tibia. Muller and Koenig (1890) introduced bone harvesting directly from the calvaria.

In 1901, Marchand theorized that the host tissue at the recipient site, rather than the graft itself, was responsible for new osteogenesis, describing the fundamental phenomenon of bone repair via creeping substitution. Axhausen (1908) described the first free split calvarial graft. In 1931, Pickrell utilized iliac crest grafts to repair skull defects, and Converse and Campbell (1954) described autogenous iliac bone for augmenting the facial skeleton, noting that clinical failure rates were three times higher in homografts than in autogenous bone grafts. Longacre and De Stefano (1957) utilized autogenous split rib grafts to repair cranial and facial defects.

The conceptual biological paradigm of bone induction was elaborated by Marshall Urist in 1965 following the definitive identification of bone morphogenetic proteins (BMPs). Concurrently, Ilizarov (1965) popularized distraction osteogenesis in long bones, a principle applied to the maxillofacial region by McCarthy in 1989. McKee (1969) successfully transplanted a rib to the mandible as an onlay using microvascular anastomosis. In 1973, Weaver and Smith reported using frozen autogenous mandibular stent-grafts for immediate reconstruction in oral cancer patients. Laskin (1978) described mandibular reconstruction via free iliac crest flaps, and Bradley (1978, 1982) reported a two-stage procedure for the re-implantation of autogenous freeze-treated mandibular bone blocks. Wang et al. (1980) confirmed via ultrastructural analysis that freezing procedures effectively destroy malignant tumor cells within the graft.

Tessier (1982) described wide clinical applications of cranial bone grafts, positioning the cranium as a preferred donor site over the ilium or ribs due to lower resorption rates. Gruss and Mackinnon (1986) defined the role of primary bone grafts in complex mid-facial trauma reconstructive surgeries. Finally, Gillies, Converse, and Shapiro were among the first to advocate explicit bone grafting to promote bone regeneration between buccal bone cuts during elective lateral maxillary osteotomies.

3. Review of Literature

Recent peer-reviewed clinical literature highlights several insights regarding bone grafting materials and techniques in periodontics and implant dentistry:

Cairo et al. (2023): Evaluated guided bone regeneration (GBR) performed simultaneously with implant placement via a systematic review and Bayesian network meta-analysis. The authors concluded that GBR yields predictable regenerative outcomes across varying biomaterials, provided core surgical principles are respected. However, larger initial bone defects reduced efficacy, all materials demonstrated time-dependent resorption, and cross-linked collagen membranes exhibited a higher incidence of complications.

Lee et al. (2023a): Explored a novel biomaterial solution—a sintered nonresorbable bone allograft designed to mimic the clinical utility and sintering characteristics of xenografts. Supported by a 52-week non-human primate study and in vitro data, this innovation allows clinicians to bypass regulatory restrictions combining distinct graft categories by utilizing a single product with xenograft-like structural stability.

Lee et al. (2023b): Discussed optimizing bone grafting protocols through high-temperature sintered nonresorbable bone allografts (NRBAs). These materials offer long-term architectural stability during sinus and vertical ridge augmentations while delivering superior biocompatibility over standard foreign xenografts.

Sanz et al. (2022): Conducted a systematic review comparing fresh-frozen allogeneic bone (FFB) blocks to autogenous (AT) bone blocks for ridge augmentation. The review concluded that FFB blocks are less reliable than AT blocks for significant volume deficiencies and should be restricted to limited lateral augmentations where primary implant stability can be derived from vital host bone.

Sharma et al. (2023a): Synthesized data from seven clinical studies evaluating the interdisciplinary management of periodontally compromised patients. The authors emphasized that correct treatment sequencing, appropriate bone graft selection, and precise timing of post-graft orthodontic forces are vital to optimize regeneration within deep intrabony defects.

Kim et al. (2023): Compiled a comprehensive review of autografts, allografts, xenografts, and synthetic materials utilized in oral and maxillofacial surgeries. The paper detailed the individual biological traits, limitations, and selection metrics matching specific graft profiles to defect configurations.

Stavropoulos et al. (2023): Evaluated complications across oral regenerative procedures, noting that membrane or graft exposure represents the most prevalent clinical complication. They advocated strict patient selection criteria and minimally invasive surgical entry to prevent adverse healing outcomes.

Richmond-Zhang et al. (2023): Addressed bone reconstruction strategies prior to orthodontic tooth movement through ridge defects, demonstrating that post-grafting consolidation timing heavily dictates successful tooth migration through healed sites.

Sharma et al. (2023b): Documented advancements in synthetic (alloplastic) materials and barrier membranes, outlining the evolving role of local drug delivery systems and growth factor integration to enhance standard guided tissue regeneration (GTR) therapies.

Hussain et al. (2023): Analyzed the physical properties and commercial availability of metals, ceramics, polymers, and hybrid constructs for alveolar site development, presenting tissue-engineered configurations as the future of predictable implant success.

Lee et al. (2023c): Completed a comparative global review of regulatory approval trends for alloplastic bone substitutes in the United States, Japan, and Korea. Hydroxyapatite, β-tricalcium phosphate, and biphasic calcium phosphate dominate the market as viable osteoconductive structures.

Patel et al. (2023): Reviewed particulate bone grafts in periodontal regeneration, validating through targeted case reviews how particulate autografts, allografts, xenografts, and alloplasts facilitate localized alveolar reconstruction.

Rossi et al. (2023): Investigated histomorphometric outcomes following alveolar socket preservation (ASP) using autologous demineralized tooth-derived graft materials. The material demonstrated predictable vital bone formation balanced equally between maxillary and mandibular sites.

Sutrisno et al. (2023): Polled Indonesian periodontists regarding clinical preferences; xenografts were highly favored due to superb biocompatibility and bioactivity, though cost remains a primary barrier. Practitioners frequently pair bone grafts with GTR techniques for treating vertical defects.

Salam et al. (2023): Provided an overview matching different bone graft sources to specific clinical scenarios and patient compliance limitations.

Anonymous Article (2023a): Explored therapeutic ion incorporation (e.g., strontium, copper, boron, magnesium) into dental biomaterials to induce heightened local osteogenesis, angiogenesis, and antibacterial resistance.

Anonymous Article (2023b): Synthesized indications and materials used in modern implantology, underscoring the necessity of combining structural grafts with guided bone regeneration techniques.

Anonymous Article (2023c): Explored autogenous odontogenic scaffolds for jaw restoration, emphasizing the biochemical similarity between processed human dentin matrix and vital alveolar bone.

Anonymous Article (2023d): Maintained an in-depth operational map of artificial scaffolds and natural bone matrix properties to assist clinicians in choosing optimal configuration designs for advanced bone repair.

Anonymous Article (2023e): Investigated the cost-effective extraction and synthesis of hydroxyapatite biomaterials from marine shells (Pugilina cochlidium and Babylonia spirata) via the sol-gel method, offering a affordable local alternative to expensive imported graft products.

Anonymous Article (2023f): Charted the historic timeline of regenerative periodontal materials from legacy GTR strategies to modern molecular growth factor delivery systems.

Anonymous Article (2023g): Compiled a systematic meta-analysis of 16 long-term clinical trials tracking implant survival rates. No statistically significant survival difference was found between implants placed into autogenous bone blocks (97.9%) versus those treated via guided bone regeneration (98.5%).

Anonymous Article (2023h): Outlined the distinct performance variables of ceramics, decalcified bone matrices, and bioactive glasses under high mechanical stress environments.

Anonymous Article (2023i): Reviewed the unique properties of bioactive glass to interact directly with host tissue fluids, stimulating rapid osteogenesis, cementogenesis, and functional periodontal ligament formation.

4. Bone Biology

4.1. Anatomy of Bone

Bone is a highly organized, calcified connective tissue uniquely structured to withstand tensile forces up to 12,500 psi and compressive pressures up to 7,000 psi. It alters its internal morphology and volumetric mass dynamically in response to systemic physiologic demands and localized mechanical stress. Osseous anatomy is divided into two distinct structural classifications:

- Cortical Bone: A dense, highly compacted outer layer that forms the protective exterior shell of skeletal structures.
- Cancellous Bone: A light, porous, spongy internal network composed of an interconnected latticework of mineralized trabeculae.

The differentiation between cortical and cancellous networks depends on the relative size and density of internal spaces. Active bone marrow resides within these trabecular voids. Yellow fatty marrow concentrates inside the large medullary cavities of long tubular bones, whereas red hematopoietic marrow populates flat bones and the articular junctions of long bones. Cortical bone blood supply is derived from small periosteal vessels penetrating minute exterior

orifices. Cancellous bone is vascularized by larger, sparse nutrient vessels that perforate the dense cortex to distribute throughout the trabecular cavities. Long bones display a dominant central nutrient artery entering the marrow space directly, whereas flat bones possess numerous tiny arteries and veins penetrating their cortical plates to distribute abundant local blood flow.

The dry weight of bone consists of an inorganic mineral phase (65–70%) interwoven with an organic protein matrix (30–35%). The inorganic component consists of calcium phosphate and calcium carbonate, along with trace quantities of magnesium, fluoride, and sodium. These minerals form organized hydroxyapatite crystals that precipitate around fibrous Type I collagen osteoid chains. These crystal structures are enveloped by a thin hydration shell of water, facilitating rapid ion exchange with the surrounding extracellular fluids. The organic matrix is composed of 90% Type I collagen and 10% non-collagenous proteins, glycoproteins, phosphoproteins, proteoglycans, and lipids.

4.2. Periosteum and Endosteum

The exterior surface of bone is covered by a dense connective tissue membrane known as the periosteum, which features a fibrous outer layer and a highly cellular inner layer. In developing bone, this inner layer contains numerous active osteoblasts and osteoprogenitor stem cells, termed the cambium or osteogenic layer. Bone grafts harvested with an intact periosteal sleeve show significantly decreased post-surgical resorption rates. Animal models demonstrate that periosteal blood supply originates from four distinct vascular networks: the intrinsic periosteal system, the musculoperiosteal system, the fasciopariet al system, and direct cortical capillary anastomoses.

The endosteum is a thin, highly vascular connective tissue membrane that lines the internal medullary cavities of long bones, the trabecular voids of spongy bone, and the internal Haversian and Volkmann canals of cortical plates. It consists of a single layer of epithelial cells alongside a pool of osteoprogenitor stem cells, active osteoblasts, and osteoclasts. The endosteal space receives its primary blood supply from perforating nutrient arteries and is innervated by autonomic nerve fibers that regulate local vascular tone.

4.3. Microanatomy of Bone

The basic structural unit of cortical bone is the Osteon (or Haversian system), which consists of concentric lamellar rings of mineralized matrix arranged around a central Haversian canal. Each canal accommodates one or two small blood vessels, lymphatic capillaries, and nerve filaments. Radiating throughout the lamellae are small spaces called lacunae, each occupied by a mature osteocyte. Minute micro-channels called canaliculi criss-cross the dense matrix to interconnect adjacent lacunae with each other and the central Haversian canal, housing the long cytoplasmic extensions of the resident osteocytes. In thin flat bones and spongy trabecular structures, these organized concentric Haversian systems are absent; instead, the internal canaliculi open directly into the porous marrow spaces.

- Bone remodeling and graft healing are mediated by three specialized cell types:

Osteoblasts: Mononucleated, metabolically active cells derived from mesenchymal osteoprogenitor stem cells. Induced by growth factors like TGF-β, BMPs, and PDGF, they synthesize and secrete osteoid (an unmineralized organic matrix composed of Type I collagen, osteocalcin, and osteonectin) and directly mediate matrix mineralization via alkaline phosphatase activity.

Osteocytes: Mature osteoblasts that have become entrapped within their own mineralized matrix inside a lacuna. They maintain a vast network of cytoplasmic processes within the canalicular system to sense mechanical strain and regulate local ion exchange.

Osteoclasts: Large, multinucleated bone-resorbing cells derived from hematopoietic monocyte-macrophage lineages. Controlled by the RANKL/OPG cytokine axis, they attach tightly to bare bone surfaces to form an isolated microenvironment. By pumping protons to lower the local pH and releasing lysosomal enzymes, they dissolve both the inorganic hydroxyapatite crystals and organic matrix, forming erosive depressions known as Howship's lacunae.

5. Classification of Bone Grafts

5.1. Classification by Composition (Reynolds et al. 2010)

Organizes materials primarily by their core chemical constituents (e.g., calcium phosphate) and distinct physical properties (e.g., ceramics).

5.2. The Four Basic Biological Divisions (Hoexter 2002)

- Autogenous Bone: Harvested from one site and transferred to another within the same individual.
- Allographic Bone: Transferred between genetically dissimilar members of the identical species.
- Alloplastic Bone: Inorganic, synthetic biocompatible materials.
- Xerographic Bone: Harvested from a non-human species donor.
- Comprehensive Matrix of Graft Materials and Characteristics

5.3. Type Category Characteristics Commercial Examples

Autografts Cortical/cancellous blocks or particulates containing viable osteogenic cells and growth factors. Gold standard; requires secondary surgical site. Iliac crest, maxillary tuberosity, mandibular ramus/symphysis bone chips.

- Allografts Human-derived matrix (mineralized or demineralized). Provides an osteoconductive matrix; demineralization exposes inductive BMPs.Grafton® DBM, Grafton Plus® Paste, Osseograft, Accell Connexus™.
- Synthetic Substitutes (Ceramics) Sintered or precipitated non-resorbable hydroxyapatite blocks or granules. Highly biocompatible; functions as a long-term scaffold. Hapapore, Endobon, Pro-osteon, Calcitite, OsteoGraf/D.
- Soluble Calcium Granules Resorbable tricalcium phosphate (β-TCP) or calcium sulfate formulations. Undergoes chemical dissolution as new host bone replaces it. Vitoss®, Chronos®, Ceros®, Cerasorb®, Synthograft™, Osteoset®.
- Silicon-Based Phosphates Silicon-containing calcium phosphate formulations designed to enhance early bone bonding. Medical-grade silicate-substituted calcium phosphates.
- Biologics & BMPs Recombinant growth factors (rhBMP-2, rhBMP-7, GDF-5) that stimulate rapid mesenchymal stem cell differentiation. Infuse® (BMP-2), Ossigraft® (OP-1), GEM-21 S™ (PDGF-BB + β-TCP).
- Injectable Cements Structural polymethyl methacrylate (PMMA) or calcium phosphate matrixes for immediate stabilization. Norian, HTR™ Synthetic Bone (PMMA-PHEMA core coated with Ca(OH)

6. Autografts

6.1. Intraoral Autografts

Intraoral autogenous bone particles can be reliably harvested from donor sites within the oral cavity, including the maxillary tuberosity, edentulous alveolar ridges, healing extraction sockets, the mandibular ramus, and the mental symphysis.

Cortical Bone Chips: Historically derived from shaving cortical plates with hand chisels during ostectomy procedures (popularized by Nabers and O'Leary, 1965). These present large particle sizes (1559.6×183 μm) and have a higher propensity for clinical sequestration, limiting their contemporary use.

Osseous Coagulum: Introduced by Robinson (1969), this technique collects fine intraoral bone dust using round burs mixed directly with patient blood. While easily procured within the active surgical field, its fluidity and unknown particulate consistency present clinical handling limitations.

Bone Blend: Cortical and cancellous bone collected via trephines or rongeurs is processed inside an amalgam capsule to produce a pliable osseous slush. Featuring a precise particle sizing of 210×105 μm, bone blend achieves a mean defect fill of 73% across clinical trials. Histological specimens show complete regeneration of bone, cementum, and functionally oriented periodontal ligament (PDL) fibers within 6 to 13 weeks.

6.2. Block Grafts vs. Particulate Autografts

Autogenous bone blocks provide excellent structural stability and resistance to mechanical deformation, making them suitable for vertical or horizontal ridge augmentations. Stabilization via bone fixation screws or simultaneous implant placement is crucial to prevent graft micromovement. Utilizing specialized piezoelectric surgical instruments for block harvesting reduces thermal injury and minimizes local tissue trauma compared to conventional high-speed milling rotary burs.

6.3. Extraoral Autografts

Cancellous bone and marrow harvested from the anterior or posterior iliac crest offer the highest osteogenic potential due to their dense concentration of viable hematopoietic and mesenchymal stem cells. Schallhorn (1970) demonstrated complete clinical eradication of complex furcation and interproximal defects using iliac autografts, with mean bone fills exceeding 3.33 mm. Despite high efficacy, extraoral harvesting carries distinct clinical drawbacks:

- Mandatory secondary surgical site complications and donor site morbidity.
- Increased systemic treatment costs, extended operative time, and patient post-operative pain.
- A documented risk of localized post-operative root resorption and tooth ankylosis.

7. Allograft

7.1. Demineralized Freeze-Dried Bone Allograft (DFDBA)

The processing of DFDBA involves hydrochloric acid decalcification, which removes the inorganic mineral phase to expose underlying bone morphogenetic proteins (BMPs). This processing transforms the material into an osteoinductive matrix capable of recruiting and inducing host stem cells to differentiate into active osteoblasts. Optimal osteogenic kinetics are achieved using a particle size range of 250–750 µm. Particles falling below 125 µm invoke an unfavorable foreign body giant cell reaction. Human histological verification confirms that grafting defects with cortical DFDBA yields predictable formation of a completely new attachment apparatus (bone, cementum, and functional PDL). Merging DFDBA with bioactive elements, such as Enamel Matrix Derivatives (EMD/Emdogain) or Platelet-Rich Plasma (PRP), enhances the local bone induction score and modulates the remodeling rate.

7.2. Freeze-Dried Bone Allograft (FDBA)

FDBA retains its mineralized architecture and functions primarily as an osteoconductive scaffold. It provides a three-dimensional framework for host bone ingrowth and undergoes gradual osteoclastic resorption and replacement. FDBA demonstrates predictable long-term clinical stability in adult periodontitis therapies. Combining FDBA with autogenous bone chips or mixing it with tetracycline powder in a 4:1 volume ratio improves outcomes in treating aggressive defects.

7.3. Safety and Processing Protocols

To eliminate the risk of disease transmission and reduce antigenicity, strict tissue banking guidelines mandated by the American Association of Tissue Banks (AATB) are followed. Donor exclusion criteria include a history of malignant tumors, autoimmune conditions, viral exposures (HIV, Hepatitis B/C, Syphilis), or risk factors for vCJD.

[Soft Tissue Stripping] ➔ [Rough Cortical Fragmentation (500 µm–5 mm)]

⬇

[100% Ethyl Alcohol Bath (Fat Extraction & Viral Inactivation)]

⬇

[Deep Freezing (-80°C) & Lyophilization (Removes >95% Water Content)]

⬇

[Fine Grinding & Sieving (Target: 250–750 µm Particulates)]

⬇

[0.6N Hydrochloric Acid Decalcification (Exposes Internal BMPs)]

⬇

[Sodium Phosphate Buffer Wash] ➔ [Refreeze-Drying & Vacuum Glass Sealing]

8. Xenografts

8.1. Inorganic Bovine-Derived Bone Xenograft (BDX)

BDX consists of deproteinized, sterilized cortical bovine bone featuring 75–80% structural porosity and a crystalline hydroxyapatite size of approximately 10 mm. The chemical processing removes all cellular protein components, eliminating the risk of immunological rejection or cross-sensitization. Histological evaluations show direct bone bonding at the interface, with new vital host bone bridges interconnecting individual BDX granules without intervening fibrous encapsulation tissue. BDX is widely applied in localized ridge augmentations, sinus floor elevations, peri-implantitis defect corrections, and guided bone regeneration procedures using barrier membranes.

8.2. Coralline Calcium Carbonate

Derived from the marine exoskeleton of madreporic corals (such as Porites), these substitutes mirror the architectural pore structure of cancellous bone, featuring interconnected macropores measuring 100–200 µm. The structural mineral is composed of 97–99% aragonite calcium carbonate crystals. Unlike synthetic hydroxyapatite derived via heat conversion, natural coralline calcium carbonate undergoes gradual chemical resorption in human bone beds over 6 to 12 months, avoiding fibrous encapsulation and yielding significant clinical attachment gains.

9. Alloplastic Graft Materials

9.1. Synthetic Selection Parameters

According to Ashman (1992), an ideal synthetic bone replacement material must satisfy specific clinical criteria: it must be biocompatible, osteoconductive, long-term resorbable, radiopaque, hydrophilic, and carry a negative surface charge to help inhibit bacterial colonization.

9.2. PMMA-PHEMA Polymers

This composite contains a polymethylmethacrylate and polyhydroxyethylmethacrylate core coated with calcium hydroxide. It features an internal microporosity of 150–350 µm, is highly hydrophilic, and carries a negative surface charge of −8−−10 mV. It functions as a stable scaffold for bone formation, prompting significant clinical attachment gains compared to open flap debridement alone.

9.3. Hydroxyapatite (HA)

9.3.1. Synthetic HA

serves as a highly biocompatible mineral reservoir. Sintered high-temperature ceramic HA is non-resorbable and remains encapsulated within dense connective tissue formations, often healing via a long junctional epithelium. In contrast, non-sintered nanocrystalline hydroxyapatite (NHA) pastes feature small crystallite sizes (approx. 100 nm) that resorb within 12 weeks through osteoclastic activity, supporting direct osteoid deposition.

9.3.2. β-Tricalcium Phosphate (β-TCP)

β-TCP is a porous calcium phosphate variant with calcium-to-phosphate ratios resembling cancellous bone. It exhibits clear osteoconductive properties by upregulating alpha-2 integrin subunit expression and activating downstream MAPK/ERK signaling pathways within host osteoblasts. While its mechanical compressive strength is roughly 1/20 of cortical bone, it undergoes dissolution in biological fluids. The FDA-approved GEM-21 S™ system pairs a synthetic β-TCP matrix with purified recombinant platelet-derived growth factor (rhPDGF-BB) to accelerate bone healing.

9.4. Calcium Sulfate

Commonly termed plaster of Paris or medical-grade gypsum, calcium sulfate represents the oldest ceramic bone substitute. Alpha-hemihydrate powders hydrate to form a stable dihydrate matrix that dissolves predictably over 12 weeks. It functions as a transient space maintainer and angiogenic scaffold that prevents early soft-tissue invasion. It is frequently combined with DFDBA to enhance clinical bone fill or impregnated with antibiotics (such as tobramycin) for localized infection control.

9.5. Bioactive Glasses (BG)

9.5.1. The foundational 45S5 bioactive glass matrix is composed of 46.1 mol% SiO

Upon hydration, it increases the local microenvironment pH toward 10 and generates a surface silica gel layer that binds calcium and phosphate ions from tissue fluids, precipitating a structural hydroxycarbonate apatite layer. Bioactive glass exhibits wide antibacterial efficacy against standard periodontal pathogens (A. actinomycetemcomitans, P. gingivalis, F. nucleatum). It demonstrates osteostimulatory effects, restricts apical migration of the junctional epithelium, and can occlude open dentinal tubules to relieve localized sensitivity.

9.5.2. Emerging Configurations

Porous Titanium Granules: Non-resorbable, irregularly shaped pure titanium granules (0.7–1.0 mm) that exhibit highly thrombogenic properties to stabilize blood clots, forming an osteoconductive scaffolding for managing peri-implant defects.

Composite Grafts: Combine an osteoconductive matrix (such as β-TCP or collagen) with bioactive agents (bone marrow aspirate, BMPs, or growth factors) to replicate the triad of autogenous bone functionality while eliminating donor site surgical harvest concerns.

9.6. Ideal Requirements for Bone Grafts and Substitutes

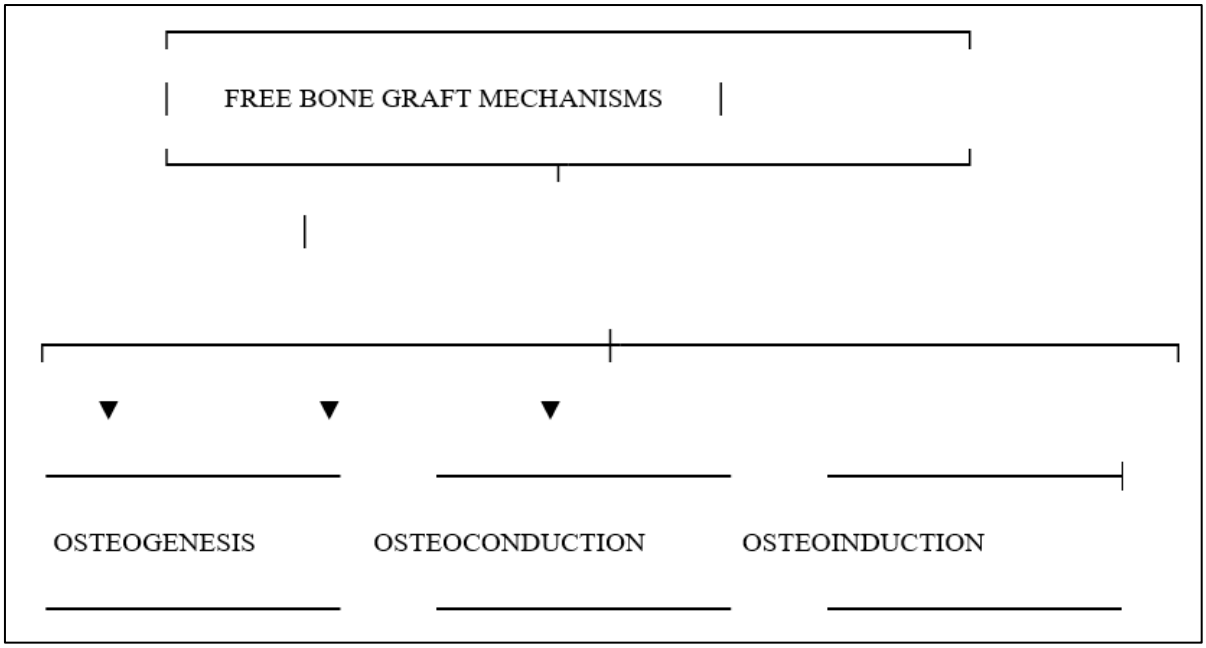
- To satisfy modern clinical expectations, a bone graft material must meet several fundamental parameters:
- Biological Acceptability: Biocompatible with host tissues, inciting minimal local inflammatory responses and no foreign-body giant-cell encapsulation.
- Predictability: Consistently achieves pocket depth reduction, clinical attachment level gains, and radiographic defect bone fill.
- Clinical Feasibility: Pliable, stable in the presence of bleeding, and easily manipulated during surgical placement.
- Minimal Operative Hazard: Eliminates secondary surgical sites, limits donor-site morbidity, and carries no risk of cross-contamination or disease transmission.
- Patient Acceptance: Cost-effective, requires minimal post-operative interventions, and aligns with ethical and cultural preferences.

9.7. Healing of Bone Grafts

9.7.1. Primary vs. Secondary Healing

Primary (Direct) Healing: Occurs without internal callus formation. It requires rigid mechanical fixation (such as compression plating) or vital vascularized transfers. Osteoclasts form specialized cutting cones that cross the interface directly along Haversian pathways, followed immediately by vascular loops and new lamellar bone deposition.

Secondary (Indirect) Healing: The primary pathway for non-vascularized free bone replacement grafts. Healing occurs via a combination of three core biological mechanisms



- Viable donor cells 3D micro-scaffold Growth factors (BMPs)
- directly synthesize guides vascular loops signal host stem cells
- new osteoid matrix. & host cell migration. to differentiate.

9.8. The Creeping Substitution Process

During free bone grafting, healing relies on creeping substitution, where the non-viable donor matrix acts as an architectural scaffold for host vascular ingrowth. Spongy cancellous autografts revascularize rapidly within hours to 2 weeks due to their open trabecular architecture, allowing rapid osteoblast differentiation and early osteoid deposition. Conversely, dense cortical grafts revascularize slowly over 1 to 2 months; entering capillaries must follow rigid Haversian and Volkmann canals, resulting in simultaneous osteoclastic resorption and osteoid production. Pockets of non-vascularized cortical bone often remain as isolated necrotic matrix islands within the newly remodeled viable bone.

9.9. The Three-Phase Bone Induction Cascade

When utilizing demineralized matrices, the biological healing sequence follows a structured, factor-driven cascade:

9.10. Phase I: Mesenchymal Cell Chemotaxis and Proliferation (Days 0–4)

Implantation forms a localized blood clot and fibrin network. Aggregating platelets release Transforming Growth Factor-beta (TGF-β) and Platelet-Derived Growth Factor (PDGF), while plasma fibronectin binds to the matrix. This triggers chemotaxis, driving the arrival of polymorphonuclear leukocytes (PMNLs) and fibroblast-like mesenchymal stem cells that attach directly to the graft matrix, initiating cellular proliferation and Type III collagen synthesis.

- Phase II: Mesenchymal Cell Differentiation Into Cartilage (Days 5–9)

Histological chondroblasts appear by Day 5, transitioning into mature chondrocytes by Day 7 that secrete a specialized cartilaginous matrix. By Day 9, hypertrophic cartilage erosion and matrix mineralization occur, accompanied by vascular invasion delivering Type IV collagen, laminin, and Factor VIII tracking loops.

- Phase III: Mesenchymal Cell Differentiation Into Bone (Days 10–21)

Active host osteoblasts appear along the calcified cartilage tracks by Day 10, synthesizing a Type I collagen bone matrix. Multinucleated osteoclasts initiate bone remodeling by Days 12 to 18. By Day 21, complete bone marrow differentiation occurs, establishing active erythrocytic, granulocytic, and megakaryocytic lineages within the newly formed bone ossicles.

9.11. Evolving Structural Roles of Growth Factors

Bone Morphogenetic Proteins (BMPs): Released from non-collagenous protein aggregates during matrix turnover, BMP-2, -4, and -7 bind directly to Type I and II transmembrane serine-threonine kinase receptors. This phorphorylates intracellular Smad 1, 5, and 8 molecules, which complex with Smad 4 and translocate into the nucleus to activate early osteochondroblastic differentiation genes.

Transforming Growth Factor (TGF-β): Released in abundance by platelets within the initial fibrin clot, it regulates periosteal expansion and serves as a primary chemoattractant for wound fibroblasts.

9.11.1. Prostaglandins (PGE 2)

Exhibit biphasic activity that regulates both localized osteoclastic resorption and osteoblastic bone mineralization rates.

10. Factors Influencing Success of Bone Graft

10.1. Physiological Metrics

Presence of Pluripotent Stem Cells: The host site must accommodate uncommitted stem cells capable of differentiating into functioning bone-producing osteoblasts.

- Oste stimulation: Local biochemical and bioelectric signals that accelerate healing. This includes the Regional Acceleratory Phenomenon (RAP)—a systemic tissue response to physical surgical injury that upgrades local bone remodeling dynamics.
- Bioactivity: Direct chemical bonding with host tissue fluids, such as the rapid calcium-phosphate precipitation layer formed by bioactive glass particulates.

10.2. Clinical Surgical Parameters

Soft-Tissue Coverage: Complete, tension-free closure of the overlying mucosal flaps prevents graft exposure and subsequent bacterial contamination.

Infection Control: Total eradication of chronic active pathogenic inflammation within the host recipient bed prior to graft introduction.

Defect Configuration: The physical volume and architectural wall setup dictate potential cell migration; narrow 3-wall defects yield higher success rates than wide, flat 1-wall defects.

Graft Immobilization: Absolute absence of micromovement across the graft-host interface during early healing phases.

Host Blood Supply: Preserving adequate local vascular perfusion through proper surgical flap design.

11. Principles of Bone Grafting

- Harvest autogenous bone from anatomical areas with which you possess high surgical familiarity.
- Contour the bone block or pack particulate material to accurately adapt to the defect configuration.
- Fix block grafts firmly to the recipient bed in a tension-free manner.
- Ensure absolute graft immobilization, differentiating between static and dynamic loading zones.
- Recognize that pediatric bone grafts exhibit rapid metabolic turnover compared to adult configurations.
- Avoid placing graft biomaterials within active or contaminated infectious sites.
- Do not leave bone graft or barrier membranes clinically exposed to the oral cavity.
- Design large flaps to ensure adequate blood supply over the grafted architecture.
- Do not compromise basic surgical steps or tissue handling protocols.
- Assess graft healing and density changes periodically via non-invasive imaging.

12. Comparative Assessment of Various Bone Grafts

Standard periodontal interventions (such as modified Widman flaps) do not predictably lead to true periodontal regeneration. If healing results in a long junctional epithelium, increased radiodensity without new attachment, or root ankylosis, the outcome is classified as periodontal repair rather than true biological regeneration.

12.1. Systematic Clinical Attachment Level (CAL) Gains vs. Open Flap Debridement (OFD)

Based on data from systematic reviews compiled by Trombelli et al., reconstructive procedures using bone grafts consistently outperform conventional debridement across critical parameters:

- [OFD Control Baseline] ⟶ Average CAL Gain: ~1.0 mm
- [Alloplast/Ceramic] ⟶ Average CAL Gain: ~1.9 mm (Significant improvement)
- [DFDBA/FDBA Allograft] ⟶ Average CAL Gain: ~2.4 mm to 2.6 mm (Superior defect fill)

Controlled clinical trials by Yukna et al. demonstrated up to 5 years of long-term post-surgical stability following defect grafting with porous hydroxyapatite. While synthetic alloplastic materials achieve significant probing depth reductions and radiographic hard tissue fill, human histological validation indicates they often heal via connective tissue encapsulation, acting as biocompatible fillers without routinely initiating new functional cementum or PDL attachment apparatus.

In comparative re-entry trials, demineralized bone allografts (DFDBA) consistently outperform simple open debridement. Oreamuno et al. and Barnett et al. demonstrated that DFDBA achieved an average of 72% bone defect fill compared to 55% achieved by synthetic hydroxyapatite. Similarly, Nery et al. confirmed that autogenous bone grafts yield significantly higher vital bone fill than pure synthetic β-tricalcium phosphate.

When comparing mineralized FDBA to decalcified DFDBA, FDBA exhibits lower osteoinductive capacity than autogenous tissue. However, FDBA has been shown to be non-immunogenic, failing to sensitize recipients or generate detectable donor-specific anti-HLA antibodies, confirming its clinical safety and biocompatibility. Ultimately, combining FDBA or DFDBA with autogenous bone chips leverages the benefits of both materials, yielding enhanced reparative potential and predictable outcomes in managing advanced periodontal osseous defects.

13. Conclusion

Predictable regeneration of the periodontium destroyed by inflammatory disease remains a key challenge in dentistry. Achieving this goal requires transitioning from basic open debridement to advanced regenerative approaches using tailored biomaterials. While autogenous bone remains the gold standard due to its complete osteogenic, inductive, and conductive properties, its clinical use is limited by secondary donor-site morbidity and volume constraints. Modern tissue banking methods have established FDBA and DFDBA allografts as safe alternatives that deliver predictable clinical attachment gains and structural defect fill without risk of cross-sensitization.

Xenogeneic matrices and synthetic alloplastic ceramics (such as hydroxyapatite, β-tricalcium phosphate, calcium sulfate, and bioactive glasses) provide highly biocompatible, osteoconductive scaffolding. Integrating these materials with recombinant growth factors (such as rhPDGF-BB) further enhances their biological performance, approaching the efficacy of autogenous bone. Ultimately, clinical success depends on matching the specific graft material to the anatomy of the defect, achieving tension-free soft tissue coverage, and ensuring absolute graft immobilization to support the bone induction cascade and achieve true histological regeneration.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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