ISSN: 2581-5989
PubMed - National Library of Medicine - ID: 101738774

International Journal of Dental Science and Innovative Research (IJDSIR)

IJDSIR : Dental Publication Service

Available Online at:www.ijdsir.com

Volume – 8, Issue – 4, August – 2025, Page No. : 95 - 101

A Comprehensive Overview of Synthetic Bone Substitutes

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Citation of this Article: Velpula Hima Varshini, Pavithra K. Ramanna, Syed Javad Saleem, Ravi Kumar N, Krishnaprasad TR, Chamarthy Kundan Chakravarthy, "A Comprehensive Overview of Synthetic Bone Substitutes", IJDSIR- August – 2025, Volume – 8, Issue – 4, P. No. 95 – 101.

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Bone replacement is a complex phenomenon and a challenging task to accomplish, as bone resorption is irreversible following the tooth loss. Bone grafting, the second most common transplanted tissue, is the only solution to reverse dental bone loss and is a well-accepted procedure. There are different graft options that are available, such as autografts, allografts and synthetic bone grafts. Because of the morbidity associated with harvesting of autogenous bone grafts, synthetic bone grafts were used as an alternative. However the lack of comprehensive literature specifically focusing on their role in prosthodontics necessitates that this review provides an in-depth discussion of synthetic bone graft substitutes, including their uses, properties, advantages, limitations, and recent advancements.

Keywords: Bone substitutes, Bone defects; Bone reconstruction; Bone graft; Dental implant; Replacing tooth loss.

Introduction

Following tooth loss, bone resorption is irreversible, leaving the area without adequate bone volume for successful implant treatment. Bone replacement is a complex phenomenon and a challenging task to

accomplish.[1] Bone grafting is the only solution to reverse dental bone loss and is a well-accepted procedure. This is the second most common transplanted tissue.[2]

A "bone graft" is defined as the augmentation or replacement of the portion of the maxillary or mandibular bone with an osteogenic material.[3] There are various graft options available which includes natural bone grafts (further divided into autograft, allograft, xenograft) and synthetic grafts (Alloplasts).[4]

It is well known that there is morbidity associated with harvesting of autogenous bone graft and limitations in the quantity of bone available. Alternatively allografts have been reported to have a significant incidence of postoperative infection and fracture as well as the potential risk of disease transmission.[5]

During the past 30 years a variety of synthetic bone graft substitutes has been developed with the aim to minimize these complications. They are fabricated in various forms with varying physicochemical properties and can be both degradable and nondegradable. The benefits of synthetic grafts include availability, sterility and reduced morbidity.[5] These biomimetic materials characterized by osteoconductive, with no osteoinductive or osteogenic potential on their own. They act as a three-dimensional scaffold to support cell growth and bone formation, increase cell adhesion and proliferation.[6]

There is no literature available on synthetic bone grafts. Hence, the purpose of this research is to elaborate and discuss about the synthetic bone graft substitutes and its uses, properties, advantages, limitations and recent advancements.

Synthetic bone grafts

Synthetic bone graft / Alloplast is defined as "an inert foreign body used for implantation within tissue / a material originating from a non-living source that surgically replaces missing tissue or augments that which remains".[3] These are synthetic, inorganic, biocompatible bone substitutes that function as defect fillers to repair skeletal defects.[7] These are generated to overcome potential immunogenicity and morbidity at donor sites, that closely mimics the biological properties of natural bone.[8]

The role of synthetic bone materials is to promote bone regeneration.[9] In the beginning, these are used as a scaffold. With evolution, synthetic graft substitute materials (GSM) acted as an osteoconductive material.

Synthetic materials have several advantages concerning the surgical method necessary for obtaining autogenous material such as biocompatibility, osteoconduction, injectability, moldability, easy manipulation, minimally invasive procedure, scar reduction (since only the affected area is surgically treated and only one surgery is required), in addition to the decreased risk of infection and other complications. Another advantage is their wide availability, since the material can be easily manufactured in scale, unlike autogenous, allogeneic, or xenogeneic materials.[9]

Bone formation in grafting procedures involves one or more of the following biologic mechanisms[10]:

Osteogenesis, The formation of new bone by osteoblasts derived from the graft material itself.

Osteoinduction, the capability of chemicals or procedures to induce bone formation through the differentiation of osteoblasts.

Osteoconduction, a passive process whereby bone grows on a surface or on a scaffolding that is conductive to bone deposition.

Types of synthetic bone grafts[11,12]:

1. Calcium phosphate cements
2. Calcium phosphate ceramics
    a. Hydroxyapatite (HA)
    b. Tricalcium phosphate (TCP) and

c. Bioactive glass

3. Metals
4. Polymers

Calcium phosphate cements (CPCs)

Calcium-phosphate-based materials (CP) have been used since the 1980s in the fields of dentistry and are currently commercially available in a wide variety of compositions.[9] Among CPCs, there are two main groups; Apatite is formed from tetracalcium phosphate (TTCP) or alpha tri-calcium phosphate (α-TCP) which have shorter hardening time, while brushite is a by-product of beta tri-calcium phosphate (β-TCP) or monocalcium phosphate monohydrate (MCPM) has longer hardening time.

CPCs are generally 2 or 3-component systems. These are available as injectable paste or moldable putty. Brand name includes Norian™, Chron^{OS}, Inject™, Hydroset™ and BoneSource™.

Calcium Phosphate Cements (CPCs) offer several advantages that make them well-suited for bone regeneration applications. They are bioactive and biocompatible, their ease of handling and injectability allow for precise placement, especially in irregularly shaped bone defects. Unlike autogenous and allogeneic bone grafts, CPCs eliminate risks such as donor site morbidity, immune rejection, and infection. Their chemical composition closely mimics that of natural bone, enhancing osteoconductivity. Additionally, CPCs possess a self-setting capability under physiological conditions, which simplifies their clinical application and reduces operative time.

CPCs face limitations such as lack of macroporosity, leading to reduced cell adhesion, poor fluid exchange, and slower healing. Incomplete setting reactions may also cause inflammation. To overcome these issues, strategies include: 3D-printed CPC scaffolds for enhanced structure. Improved injectability using binders like chitosan, gelatin, and hyaluronic acid. Material enhancement through doping with ions (e.g., silicon, strontium), adding bioactive glass, and incorporating growth factors or stem cells for better bioactivity and osteoinductivity.

However, CPCs can delay bone formation (as shown by Lyu et al.), are brittle under tensile/shear stress (limiting use to non-load-bearing sites), and risk extrusion into surrounding tissues. Clinically, CPCs are used for bone defect filling, fracture repair, and dental implantology. [8]

Calcium phosphate ceramics

Ceramic materials based on calcium phosphate (CP) can be found in the form of granules or blocks with none or different porosities and include: Hydroxyapatite (HA), Tricalcium phosphate (α-TCP and β-TCP), Biphasic calcium phosphate (BCP), and Amorphous calcium phosphate (ACP).

Hydroxyapatite (HA)

Hydroxyapatite (HA) is a widely used calcium phosphate biomaterial for bone regeneration due to its structural and chemical similarity to natural bone. It is bioactive and osteoconductive, forming direct chemical bonds with bone. However, HA is non-osteogenic and resorbs slowly, depending on factors like porosity, crystallinity, and processing temperature. High-temperature-sintered HA is dense and poorly resorbable, while low-temperature HA is more porous and slowly biodegradable.[11]

Synthetic HA comes in various forms (powder, porous blocks/beads) and can be nonresorbable or resorbable. Unlike natural HA, synthetic versions lack essential trace ions (Na^+, Mg^{2+}, Sr^{2+}) and microporosity, affecting bioactivity and mechanical performance. Its low strength limits use in load-bearing applications.[8]

Recent advances include nanocrystalline HA (nHA), such as NanoBone®, which mimics natural bone more closely,

enhances mechanical properties, and improves osteoconductivity and osteoinductivity. nHA promotes better cell adhesion and bone formation, offering promise for use in dental and maxillofacial surgery. However, limitations in bone regeneration capacity mean HA is mostly used for implant coatings and low-stress sites.

Tricalcium phosphate ceramics (TCP)

β-Tricalcium phosphate (β-TCP) is a widely used synthetic bone graft material known for its osteoconductive, osteoinductive, and biocompatible properties. It exists in two crystal forms: α-TCP (monoclinic) and β-TCP (rhombohedral), with β-TCP being more common. β-TCP exhibits good biocompatibility and osteoconductivity and is used commonly as a partially resorbable filler allowing replacement with newly formed bone.[12]

Though β-TCP has poor mechanical strength, its macroporosity promotes vascularization and bone growth, making it ideal as a filler in bone defects. It resorbs through a cell-mediated process involving macrophages and giant cells, aided by local acidification.

β-TCP is available in granules, blocks, and cylinders under brands like Cerasorb and Osferion, and is comparable in bone regenerative capacity to other graft materials like FDBA and autografts.[8]

Biphasic calcium phosphate ceramics (HA and β-TCP ceramics):

Recent advancements led to the development of biphasic calcium phosphate ceramics, combining β-TCP's resorbability with HA's osteoconductive properties. This results in faster bone regeneration and better mechanical strength than β-TCP alone. By adjusting the HA/β-TCP ratio, resorption and osteoconductivity can be controlled.

Despite the improvements in mechanical strength compared with β-TCP alone, biphasic CP ceramics still possess compressive strengths lower than that of cortical bone. The use of biphasic CP ceramics have shown effective use in periapical surgery, promoting complete alveolar bone healing via osteoconduction and osteoinduction processes which could be further explored in clinical practice.[8]

Bioactive glass

Bioactive glasses (BG) are synthetic materials with a silicate base, known for their ability to bond with bone tissue. Developed in 1969 by Larry Hench, BG's composition includes silicates and minerals like calcium, sodium, and phosphorus. BG has evolved over time from first-generation formulations to second and third generations, improving in bioactivity, resorption, and bone regeneration. BG works by forming a hydroxycarbonate apatite (HCA) layer when in contact with body fluids, which promotes bone growth.

The first commercial clinical application of BG was middle ear bone replacement for treatment of conductive hearing loss which was first marketed in 1985. It is a type of monolithic medical device employing Bioglasss®/45S5. It has been successfully used in dentistry and maxillofacial surgery, showing good osteoconductivity, antimicrobial properties, and biocompatibility. However, it is brittle, limiting its use to low-stress environments or in combination with other materials.[13]

Recent research has explored the incorporation of ions like zinc and silver into BG for enhanced properties, such as antimicrobial activity. PerioGlas® and UniGraft® are examples of commercially available BAG.8 One of the commercial products used mainly for the repair of defects in maxillofacial applications is Biogran®, which differs from PerioGlas® in its particle sizes (300–360 µm). NovaBone®, another Bioglass® 45S5-based formulation, can be mixed with blood from the defect to form a putty to fill the site.

BG has also been investigated for use in dental implants and bone regeneration, offering potential for improved osseointegration. Additionally, BG nanoparticles and scaffolds are being studied for personalized treatments, offering prospects for tailored bone regeneration therapies.

Despite challenges like low mechanical strength, BG continues to be a promising material for bone repair, with ongoing research into improving its applications and expanding its use in clinical settings.[8]

Calcium sulfates

Calcium sulfate hemihydrate ($CaSO_4 \cdot 1/2H_2O$), commonly known as plaster of Paris, has been used as a bone filler since the 1920s. When rehydrated, it forms a paste that hardens, allowing it to be molded into bony defects. Initially recognized for its osteoconductivity, recent studies have revealed its osteoinductive properties, stimulating bone healing through the release of osteoinductive molecules. Its advantages include low cost, widespread availability, excellent biocompatibility, a short setting time, and its ability to serve as a carrier for drugs and growth factors.

Calcium sulfate (CS) has become a valuable tool in various dental and surgical applications, including bone augmentation, maxillary sinus elevation, and extraction socket preservation. It supports bone regeneration and enhances angiogenesis, particularly when combined with osteogenic agents like platelet-rich plasma (PRP). CS has proven effective in the restoration of craniofacial bone defects and dental implant procedures, offering low risk of inflammation and the potential for promoting osteogenesis.

Despite its benefits, CS has limitations, including rapid resorption and insufficient biomechanical strength, restricting its use to small, non-load-bearing defects. Advances in CS formulations, such as those incorporating hydroxyapatite (HA), address these issues by improving structural integrity and extending resorption time. Current research is focused on optimizing CS's properties, particularly through the development of composite CS/HA grafts, to enhance bone regeneration while providing longer-term support.[8]

Polymers

Polymers are large molecules made up of repeating monomers, commonly used in bone tissue engineering. Polymers are classified into natural and synthetic types. Synthetic are further classified into non-biodegradable polymers like Poly methyl methacrylate (PMMA) and biodegradable polymers like Poly lacticacid (PLA), Poly glycolicacid (PGA), polycaprolactone (PCL), and their copolymers (PLGA).

The most studied are polylactic acid (PLA) and polyglycolic acid (PGA), which are biodegradable but lack mechanical strength and osteoconductivity, making them unsuitable as standalone scaffolds. To overcome these limitations, they are often combined with materials like calcium phosphate cement (CPC) or bioactive glasses (BG) to improve their handling, injectability, and osteogenic properties. Polymers like PLA and PLGA have been used in 3D printed scaffolds and as drug delivery carriers, with promising results in bone repair.[12]

While some polymers like PMMA are still used clinically for bone cement, others like PCL are being explored for their slow degradation and potential to support bone growth, and are widely used in dental and maxillofacial applications for implant placement, periodontal regeneration, and craniofacial reconstruction.

Despite their advantages, polymer-based bone substitutes face challenges like acidic degradation products and variable biological responses. Recent research is focused on combining these materials with ceramics or adding

bioactive molecules to improve their effectiveness in bone regeneration.[8]

Metals

Recent research highlights the role of metallic ions like magnesium (Mg), strontium (Sr), zinc (Zn), and silicon (Si) in bone maintenance and osteogenesis. In dental applications, nickel-titanium (NiTi) materials have been explored for bone regeneration due to their excellent mechanical strength, biocompatibility, corrosion resistance, and elastic modulus.

NiTi membranes act as structural scaffolds, supporting cell adhesion, proliferation, and differentiation to form new bone. However, their use requires a second surgery and poses risks like soft tissue exposure. Titanium membranes have been used in alveolar bone reconstruction and as a barrier for guided bone regeneration (GBR).

In addition, recent developments in magnesium-based bone substitutes, such as pure Mg and Mg-30wt% Sr alloys, show improved tensile strength, biocompatibility, and antibacterial properties compared to traditional graft materials like calcium sulfates and hydroxyapatite (HA). These Mg-based materials are promising for use in load-bearing bone regeneration areas.[8]

Composites

Composite bone substitutes are designed to enhance mechanical strength and osteoconductive properties by combining materials such as bioglass and polymers. NanoBone™, made of nanocrystalline hydroxyapatite and silicon dioxide, supports rapid bone integration and has shown success in preserving alveolar bone and aiding bone regeneration, especially when used with platelet-rich fibrin.

Another widely used composite, Fortoss Vital™ is a self-setting biphasic composite of β-TCP and calcium sulfate. Clinically, it has shown strong performance in alveolar bone augmentation, socket preservation, and implant rehabilitation.[8]

Growth factor-based substitutes (GFBSS) leverage proteins like BMPs and platelet-derived growth factors (PDGFs) to stimulate bone growth. FDA-approved products such as Infuse™ and the now-discontinued Osigraft™ (BMP-7) demonstrated the potential of GFBSS, although safety concerns have limited their widespread adoption. Recent alternatives like Augment™ incorporate recombinant PDGF and BMPs with scaffolds like collagen or β-TCP/HA.

Despite promising results, challenges persist in delivering growth factors effectively to target sites while maintaining bioactivity. Strategies like scaffold entrapment, covalent binding, or use of micro/nanoparticles for controlled release have been proposed to address these limitations. An innovative solution, "sticky bone," combines autologous fibrin glue with graft materials to improve stability, enhance osteogenic cell recruitment, and accelerate healing. When used with CGF membranes or titanium mesh, sticky bone has shown effective three-dimensional ridge augmentation within four months.

Future Directions and Innovations

- Advanced Biomaterials: Ongoing research aims to develop novel biomaterials with enhanced bioactivity, mechanical properties, and tissue regeneration capabilities.
- Bioprinting and Tissue Engineering: 3D bioprinting technologies hold promise for fabricating patient-specific scaffolds and constructs with precise architecture and cellular organization.
- Regenerative Therapies: The integration of stem cells, growth factors, and gene therapy may revolutionize bone regeneration strategies,

promoting faster healing and improved clinical outcomes.

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