

“KNOW THE TURF, BEFORE YOU RUN”- THE BONE ERSATZ MATERIALS- A NARRATIVE REVIEW

DR. LAKSHMANA RAO. BATHALA

Professor & Head, Dept of Prosthodontics,

Lenora Institute of Dental Sciences, Rajahmundry, Andhra Pradesh, India.

Corresponding Author:

DR. LAKSHMANA RAO. BATHALA

Mail: kushlubathala@gmail.com

INTRODUCTION:

Bone substitutes are important in dentistry in various applications such as periodontal regeneration, alveolar growth and implant placement. Each type of bone replacement has unique characteristics, advantages and disadvantages that must be considered based on the clinical scenario. Ongoing material science research and advances continue to improve the performance and safety of these materials. Bone substitutes are materials used to replace missing bone or to support bone healing and regeneration in several areas of medicine, including dentistry. They can be natural or synthetic and are used when the patient's own bone (autograft) is not available or practical.

Various bone substitutes used in dentistry:

Autografts: bone harvested from the patient's own body. Excellent biocompatibility, without risk of immune rejection, contains living cells and growth factors that promote healing. Limitations include limited supply, potential donor site morbidity, and additional surgical site. [1]

Allografts: bone taken from a donor of the same species. Available in larger quantities than autologous, no donor morbidity. With some limitations such as risk of disease transmission, possible immune rejection, variable integration. [2]

Xenografts: Bones of different species, usually bovine or porcine. Easily available, structurally similar to human bone. Risk of immune reaction, possibility of disease spread, different resorption rates. [3]

Alloplastic materials: synthetic materials such as hydroxyapatite, tricalcium phosphate and bioactive glass. No risk of disease transmission, customizable features, unlimited shipping. May not integrate as well as natural bone, possible inflammatory reaction. [4]

Composite grafts: combination of different materials (eg autografts with alloplasts or growth factors). Combines the advantages of different materials, improved biological properties. More complex production and use, possible inconsistent results. [5]

Properties of bone substitutes: [6]

An ideal bone substitute material should have the following properties:

1. Biocompatibility: the ability to be accepted by the body without an immune response.
2. Osteoconduction: provide scaffolding for new bone growth.

3. Osteoinduction: differentiation of progenitor cells into osteoblasts.
4. Osteogenesis: the formation of new bone through the action of osteoblasts in the transplant material.
5. Mechanical properties: strength and stability to support the point of failure.

Classification of tooth-bone substitutes: [7]

Bone substitutes used in dentistry can be classified according to their origin and composition.

- I. Natural bone grafts and substitute materials
- II. Synthetic bone substitutes
- III. Composite bone substitutes
- IV. Growth factor-based bone substitutes
- V. Bone substitutes filled with living osteogenic cells:

I. Natural bone grafts and substitute materials:

Natural bone substitutes have been developed to improve osteogenic, osteoconductive and osteoinductive potential by creating a favorable microenvironment for bone growth.[8]

Natural bone grafts and substitutes are:

a. Autografts

1. Cortical Autografts: (MinerOssTM, Cortical TM)
2. Cancellous Autografts: (MinerOssTM, CancellousTM)
3. Cortico cancellous Autografts

b. Allografts

1. Dimineralized Bone Matrix
2. Deproteinised Bone Matrix

c. Xenografts

1. Deproteinized bovine bone
2. Chitosan
3. Silk

d. Phytogetic materials

1. Plant-based
2. Algae-based
3. Coral-based

a. Autografts:

Bone harvested from the patient's own body. There are basically three types of autografts, they are;

1. Cortical autografts: (MinerOssTM, Cortical TM) Dense bone taken from cortical bone, for alveolar ridge augmentation, periodontal bone repair, sinus augmentation. Ensures osteoconduction, bone integration and avoids donor morbidity. [9]
2. Wing hair autografts: (MinerOssTM CancellousTM) Cancellous bone taken from cancellous bone to repair a crack. Ensures osteoconduction, osteoinduction, osseointegration, avoids donor morbidity.[10]
3. Cortical autografts: a combination of cortical and cancellous bone. [11]

b. Allografts:

Bone taken from a donor of the same species. These include

1. Demineralized Bone Matrix: (DynagraftTM, D Putty, OpteformTM, GraftonTM, DBM) Bone taken from human DBM for bone gap filling, periodontal bone defects, sinus augmentation. Ensures osteoinduction, osteoconduction, easy handling, low immunogenicity and avoids donor site morbidity.[12]
2. Proteinized Bone Matrix: (BioOssTM, OsteoGraftTM, CeraboneTM) Bone taken from bovine for sinus augmentation, ridge/ridge preservation, horizontal and vertical augmentation, implant defects. Provides good osteoconductivity, very similar structure and biomechanical properties to human bone, with low immunogenicity.[13]

c. Xenografts:

Bone from or derived from a different species, usually bovine. Xenografts are transplant materials derived from a genetically similar host species [14] Bovine bone substitutes have been widely used in sinus lift and implant procedures due to their excellent stability and low immunogenicity.[15]

These include:

1. Proteinized bovine bone
2. Chitosan
3. Silk

1. Deproteinized bovine bone: the most common source of xenograft materials in dentistry is deproteinized bovine bone, commercially available as BioOssTM, OsteoGraftTM, and CeraboneTM. Sinus augmentation, socket/ridge preservation, horizontal and vertical augmentation, and implant defects. Provides osteoconductivity, structure and biomechanical properties very similar to human bone, low immunogenicity [16]

2. Chitosan: A promising xenograft material currently being investigated is chitosan, a naturally occurring polymer derived from the skeleton of crustaceans glucosamine and N-acetylglucosamine [17]. Chitosan can stimulate bone regeneration by providing a structural scaffold that supports osteoblastic activity, mineralized bone matrix formation, and stimulates the differentiation of MSCs into osteoblasts in various in vitro environments. Due to the poor mechanical properties of chitosan, it is often combined with other materials such as gelatin, calcium phosphates and bioglass to achieve better properties [18] Recent dental research has reported the successful use of chitosan-based materials such as Molecules GBR membrane, guided tissue regeneration, implant surfacing, periodontal regeneration and alveolar bone height restoration [19]

3. Silk: is a natural biopolymer obtained from the silkworm *Bombyx mori*. It is mainly composed of proteins, fibroin and sericin. After sericin removal, silk fibroin (SF) is used as a scaffold in the form of a sponge, fiber, film, and hydrogel [20] Several clinical trials conducted in 2016 used patients who received a silk carpet membrane after

excision of a rash. lower jaw. Six months after the implant procedures, a significant increase of approximately 4 mm was observed in the third molars [21]

d. Plant Materials: These include:

1. Plant-based
2. Algae-based
3. Coral-based

Phytogenic materials are plant-based bone substitutes, coral-based bone substitutes and algae. **Gusuibu** is a traditional Chinese herbal medicine that has been widely used to treat fractures and osteoarthritis in Chinese patients.[22] Gusuibu is the name of a dried rhizome with proven osteoinductive properties that increase alkaline phosphatase activity and thus promote bone calcification and regeneration processes.[23] Gusuibu was integrated into a collagen carrier that acted as a structural scaffold, new bone formation increased by 24% throughout the bone defect compared to Gusuibu alone implanted; and 90% compared to resorbable collagen sponge, which is routinely used as a carrier for growth factors (GF) such as BMP to stimulate bone regeneration.[24]

Coral-based bone substitutes consist primarily of calcium carbonate, either used in its naturally occurring form or heat-treated with ammonium phosphate and converted to crystalline HA, which then contains little carbonate.[25] HA is a natural polymer of calcium phosphate derived from bone or natural materials such as coral, and is widely used to promote bone healing because it can act as a structural scaffold. The main problem with naturally occurring coral HA is its fragility and high resorbability; therefore, coral-based materials are most often used as crystalline HA in the form of granules or blocks to form a structural framework very similar to trabecular bone [26] Coral HA-based materials used in dentistry vary in pore size and have good compressive strength. , low immunogenicity, good bone bonding [27] These materials have been used in procedures such as sinus lift, periodontal bone defects and alveolar reconstruction in dental implant placement.[28]

AlgiPore™ is a naturally occurring HA derived from algae that has been clinically used as a bone substitute since 1988.[29] This material has desirable properties such as good resorbability over time, a large surface area for protein adhesion, and low immunogenicity. Recent developments have used AlgiPore™ with TCP, which is said to reduce resorption times while maintaining the volume support necessary for bone healing.[30,31] AlgiPore™ is considered as a very favorable bone substitute material due to its bone filling ability due to its excellent biocompatibility such as low immunogenicity, biodegradability and bone binding ability.[32]

II. Synthetic bone substitutes:

a. Hydroxyapatite (HA)

b. Ceramic beta-tricalcium phosphate

c. Two-phase calcium phosphate ceramic

d. Bioactive glasses

e Calcium phosphate cements

f Calcium sulfates

g. Polymers

h. Metals

To overcome potential immunogenicity and morbidity, artificial synthetic bone substitutes that closely mimic the biological properties of natural bone are created at donor sites.[33] Materials in this category include calcium phosphate ceramics such as hydroxyapatite (HA), tricalcium phosphate (TCP), and bioglass; metals such as nickel-

titanium; polymers such as polymethyl methacrylate (PMMA) and polyglycolides and calcium phosphate cements.[34]

a. Hydroxyapatite (HA): [Ostim, Endobon]

Chemical composition similar to natural bone, excellent biocompatibility and osteoconductivity. HA has been widely studied in various dental applications such as ridge augmentation and sinus augmentation, showing favorable results in terms of bone formation and integration. [35] Intraosseous defects have been reported; forking defects; Holding the sheath; Horizontal or vertical augmentation in non-stressed areas and periodontal bone defects. The function of HA is osteoconduction; macroporous structure comparable to human bone; biocompatibility; excellent hydrophilicity for vascular absorption.[36]

The chemical composition of HA is very similar to the inorganic component of bone, allowing it to be used as a bone graft material.[37] However, synthetic HA does not contain traces of Na^+ , Mg^{2+} , K^+ , and Sr^+ found in naturally derived HA, such as bovine bone, which affects various biomechanical responses. Synthetic HA lacks the microporous structure of bovine HA [38]. The use of HA in dentistry is usually limited to the coating of implants, external attachment surfaces, or low-stress areas.[39] Recent advances in HA-based bone substitute materials have explored the production of nano-sized HA that improves biomechanical properties that better mimic the composition of natural bone.[40] Nanocrystalline HA has superior biological efficacy and solubility compared to its traditional HA forms. [41]

b. Tricalcium Phosphate Ceramic (TCP): (Cerasorb, OSferion and Orthograft)

Biodegradable, excellent osteoconductivity and resorbability, used as vacuum fillers in the treatment of alveolar, periodontal, periapical, surrounding implants and cystic lesions. They offer osteoconductivity, ease of use, radiopacity to monitor healing, good resorbability and low immunogenicity. [42] TCP has shown results comparable to autografts in terms of bone regeneration and mechanical stability.[43]

c. Biphasic Calcium Phosphate Ceramics: (MASTERGRAFT) Used as vacuum fillers for treatment of alveolar, periodontal and cystic lesions, socket preservation, ridge augmentation Sinus lift and periapical surgery. Vacuum filler for treatment of alveolar, periodontal and cystic lesions, stitch preservation, ridge augmentation, sinus lift and periapical surgery.[44] Biphasic calcium phosphate ceramics, where TCP and HA are often used together, resulting in faster and faster bone regeneration compared to HA alone and better mechanical properties than TCP alone, are the main advantages of using biphasic CP ceramics. [45] The use of a two-step CP ceramic has been demonstrated as a bone substitute in periapical surgery and has shown predictable clinical results and complete healing of alveolar bone within two years.[46]

d. Bioactive glass: available as Perioglas, Unigraft, Biogran. Bioactive glasses (BAGs) are a group of synthetic silicate-based ceramics consisting of silicates combined with other minerals such as Ca, Na_2O , H and P.[47] The original composition of bioglass consisted of silica (SiO_2), sodium oxide (Na_2O), calcium oxide (CaO) and phosphorus pentoxide (P_2O_5), although it has recently been changed to a more stable composition by adding potassium oxide (K_2O), magnesium (MgO) and boron oxide (B_2O). [22]

When exposed to body fluids during implantation, silicon ions can leak out and accumulate, forming a layer of HA on the surface of the material, allowing osteogenic progenitor cells to attach. Desirable properties of bioglass include good biocompatibility, osteoconductivity, antimicrobial activity and porous structure promotes vasculature Stimulates bone growth and bonding to host bone, biocompatible. Bioactive glass has shown promising results in the promotion and integration of bone regeneration in relation to dental implants and periodontal lesions. [48] Used for periodontal defects, furcation defects, socket capture, cystic lesions, fenestration and detachment defects. Used for osteoconduction, biocompatibility, antimicrobial effect, porous structure, fully resorbable.[49] Zinc-doped BAG reduced periodontal-associated microbial biofilm formation.[50]

e. Calcium Phosphate Cements (CPC): Available in Norian, ChronOS, injectable, Hydroset and BoneSource forms. Calcium phosphate cements are usually two- or three-component systems consisting of an aqueous component and a powder component, and usually contain sintered CP material such as TCP and HA. Mixing the components produces a viable paste that heals in situ in a self-healing manner, forming HA nanocrystals at room temperature.[51] Final works are bone defect filling, Fracture reconstruction, Implantology. It offers osteoconductivity, self-attachment, plasticity and biocompatibility. [52] Recently developed prefabricated 3D-printed CPC scaffolds and improved injectability of CPC through several mechanisms, including the addition of viscous binders such as chitosan, gelatin, and hyaluronic acid; optimization of CPC powder particle size, distribution, shape and interparticle interaction; controlling the healing response and changing external factors such as syringe and needle size.[53]

f. Calcium sulfates: Available as OsteoSet. Calcium sulfates are related to heated gypsum in powder form and eventually form a crystalline structure known as alpha hemihydrate.[25] When rehydrated, this powdered hemihydrate can form a workable dough that solidifies in a self-hardening manner and allows the material to be molded into loaves of various shapes and sizes.[54] Calcium sulfate has been widely used in the past as an osteoconductive scaffold for bone regeneration [55] Recent studies have shown that calcium sulfate also has osteoinductive properties due to the release of osteoinductive molecules that stimulate bone healing [56]

It is used as an ointment. Filler for surgical treatment of defects and furcation defects, Preservation of skin and alveolar bones. It offers osteoconductivity, low cost, easy availability, good formability, biocompatibility and short fixation time.[57] However, the main disadvantage associated with this material is the rapid resorption time, which exceeds the rate of new bone formation, leading to a significant loss of mechanical properties at the lesion site.[47]

f. Polymers: Available Bioplant, HTR Synthetic Bone (consists of PMMA, polyhydroxyethyl methacrylate and calcium hydroxide.) The most commonly used polymers in bone regeneration are polylactic acid, polyglycolic acid, poly"-caprolactone and their copolymers and derivatives, collectively. they are called aliphatic polyesters.[58] It has been suggested that modifications of polymer-based scaffolds, such as the addition of HA or TCP, can improve the bone regeneration potential of the resulting material.[59,60] Polymers offer osteoconductive, biocompatible, customizable shapes, low immunogenicity, porous structure, and radiopaque. [61]

g. Metals: Available as Oss Builder. Recent studies have identified the role of metal ions such as magnesium (Mg), strontium (Sr), zinc (Zn), and silicon (Si) in bone maintenance and stimulation of osteogenesis.[22] In the dental field, the use of nickel-titanium materials for bone regeneration has been investigated due to their many desirable properties, including good mechanical strength, good biocompatibility, corrosion resistance, and elastic modulus.[62] Studies have shown that the use of a nickel-titanium membrane with a pore size of 50-125 microns resulted in vascularization and bone healing.[63]

Used for lateral forms - horizontal or vertical bone growth, papillary forms - to restore the aesthetics of papillary height and radio-opaque appearance. This substitute provides osteoconductivity, acts as a membrane barrier for GBR, good mechanical strength, good biocompatibility, corrosion resistance, porous structure that improves cell adhesion. [64,65]

III. Synthetic grafts:

Combines the osteogenic properties of autografts with the structural support of alloplasts. Composite grafts showed better results in terms of bone regeneration and volume preservation compared to single component grafts. [66]

1). Available as NanoBone (Nanocrystalline HA/Silica). It is used as a filling material for bony openings and to protect sockets. It provides osteoconductivity, osteoinduction, resorbability, formability and good cell adhesion. [67]

2). Available as Fortoss Vital (-TCP/calcium sulfate). Used in alveolar bone augmentation, implant rehabilitation and socket preservation. It offers osteoconductivity, osteoinduction, fully resorbable, malleability, porous structure and good cell adhesion. [68]

3). Available as SmartBone™ (DBM/Polymer/Collagen). Used to treat periodontal bone lesions, socket preservation, alveolar ridge enlargement and sinus enlargement. This substitute has a morphology similar to human bone, rapid adhesion and proliferation of blood cells due to high hydrophilicity, improved volume stability and high load resistance in large bone defects. [69]

IV. Growth factor-based bone substitutes (GFBS):

Growth factors (GF), such as BMP, platelet-derived growth factors (PDGF) and insulin-like growth factors (IGF), have been found to have osteoinductive properties that enable accelerated bone regeneration in bone lesions [70]. In dentistry, bioactivated materials with growth factors are first used in plasma containing growth factors (PRGF), platelet-rich plasma (PRP), and fibrin-rich plasma (PRF) to accelerate bone healing in patients receiving bisphosphonates. associated osteonecrosis of the jaw (BRONJ).[71]

The most commonly used (USFDA approved) growth factors in bone graft procedures in dentistry and are active components in two major commercial products, Infuse™ and Osigraft™, respectively.[72-74]

Sticky Bone is another recently developed concept that utilizes a growth factor-enriched bone graft matrix using autologous fibrin glue. The use of adhesive bone is able to stabilize the bone graft material in the case of bone defects, which allows to accelerate the regeneration of bone tissue and minimize bone loss. When used with dense growth factor (CGF) membrane or titanium mesh, cancellous bone grafting into an atrophic alveolar ridge achieved favorable three-dimensional ridge growth within 4 months.[75]

V. Bone substitutes infused with living osteogenic cells:

Viable osteogenic progenitor cells such as MSCs can be used alone or in combination with other materials such as cytokines, GFs and scaffolds and carriers including DBM to stimulate new bone formation and improve bone healing by osteoconduction. bone marrow.[76] They are able to differentiate into osteogenic cells and can regenerate large bone defects when used in conjunction with scaffolds.[77] Studies have shown that bioengineered bone substitutes with MSCs can significantly improve bone healing and reconstruction compared to bone substitutes with only MSCs or without MSCs. The resulting new bone significantly improves biomechanical efficiency and thus improves the successful placement of dental implants.[78]

The use of extracted third molar-derived heterologous MSCs in periodontal lesions, either in the form of cell sheets or cell injections, could significantly increase the regeneration of alveolar bone heights by 52.7 mm . and 32.4 mm in Cuban models.[79]

Bioseed-Oral Bone™ and Osteotransplant DENT™ are commonly used. These products are intended for use in augmentation of severely atrophic maxillary sinuses to achieve predictable implant placement. [80,81]

Newer generation Bone substitutes:

Recent developments in dental bone graft materials have focused on improved biocompatibility, faster integration and reduced patient morbidity. They are:

A. Synthetic peptide reinforced bone grafts:

These materials contain synthetic peptides that mimic natural bone growth factors, increase osteoinductivity and accelerate bone regeneration. Better biological activity, which can shorten healing time.[82]

B. Bone grafts based on nanotechnology:

use nanomaterials (eg, nanohydroxyapatite, nanofibers) to mimic natural bone structure and improve integration with host tissues. Better mechanical properties, better bioactivity.[83]

C.3D-Printed Bone Grafts:

Customizable bone grafts produced using 3D printing technology that allows precise control of shape, porosity and composition. Patient-centered design, better integration, shorter operating time.[84]

D. Stem cell-based bone grafts: incorporation of mesenchymal stem cells (MSCs) or induced pluripotent stem cells (iPSCs) into scaffold materials to enhance osteogenic potential. Advanced tissue regeneration, the possibility of personalized medicine. [85]

E. Bioresorbable polymer-based bone grafts: polymeric materials that degrade over time, releasing growth factors or drugs that promote bone healing. Controlled release, lower risk of infection.[86]

F. Graphene-based bone grafts:

Graphene and its derivatives (eg, graphene oxide) have shown potential to enhance osteogenic differentiation and bone regeneration due to their excellent mechanical properties and biocompatibility. Large surface area for cell adhesion and growth, possibility of controlled drug delivery.[87]

G. Magnesium-Based Bone Grafts:

Magnesium alloys and compounds have been studied for their biodegradability and ability to promote bone growth through controlled breakdown and release of ions beneficial to osteogenesis. Biodegradability, potential for bone healing.[88]

H. silk-based bone grafts:

Silkworm silk fibroin proteins have shown promise as a bone graft material due to their biocompatibility, mechanical strength, and ability to support cell attachment and proliferation. Biocompatibility, adjustable degradation rates, ability to incorporate growth factors. [89]

I. Peptide hydrogels:

Peptide-based hydrogels, often derived from self-assembling peptides, provide a scaffold for cell growth and tissue regeneration. They can be engineered to mimic the extracellular matrix and deliver bioactive molecules. Tailored mechanical properties, cell adhesive motifs, biocompatibility.[90]

J. Microsphere-based bone grafts:

Biodegradable microspheres loaded with growth factors or osteogenic agents provide controlled release and local delivery to accelerate bone regeneration. Controlled release kinetics, site-specific dosing, possibility of combination therapy. These new bone graft materials represent exciting advances in the field, offering potential advantages such as improved osteogenic properties, controlled degradation, and targeted delivery of bioactive molecules. Further research and clinical trials are needed to confirm their efficacy and safety for widespread clinical use in dental bone regeneration. [90]

CONCLUSION:

There are fistful bone substitute materials are available for the dental clinicians. But each one these materials having their advantages with some disadvantages and are specified to use in different clinical situations. The clinician should select them according to the clinical situation for the better performance. The newer generations materials too available but long-term studies are not available in the literature about the success of these newer generation materials.

REFERENCES:

1. Giannoudis PV, Dinopoulos H, Tsiridis E. Bone substitutes: an update. *Injury* 2005;36 (3):S20-27.
2. Burchardt H. The biology of bone graft repair. *Clin Orthop Relat Res.* 1983;(174):28-42.
3. Piattelli A, Scarano A, Corigliano M, Piattelli M. Comparison of bone regeneration in sinus augmentation with bovine porous bone mineral and demineralized freeze-dried bone allograft: a histologic and histomorphometric study in man. *Implant Dent.* 1999;8(4):305-8.
4. Albrektsson T, Johansson C. Osteoinduction, osteoconduction and osseointegration. *Eur Spine J* 2001;10 Suppl 2:S96-101.
5. Jarcho M. Calcium phosphate ceramics as hard tissue prosthetics. *Clin Orthop Relat Res.* 1981;(157):259-78.
6. de Grado GF, Keller L, Idoux-Gillet Y, Wagner Q, Musset A, Benkirane-Jessel N. Bone substitutes: a review of their characteristics, clinical use, and perspectives for large bone defects management. *J Tissue Eng* 2018; 9:1-18.
7. Zhao R, Yang R, Cooper PR, Khurshid Z, Amin Shavandi A, Ratnayake J. Bone Grafts and Substitutes in Dentistry: A Review of Current Trends and Developments. *Molecules* 2021, 26(3007):1-27.]
8. Kozusko SD, Riccio C, Goulart M, Bumgardner J, Jing XL, Konofaos P. Chitosan as a Bone Scaffold Biomaterial. *J Craniofacial Surg* 2018; 29: 1788–1793.
9. Nevins M, Parma-Benfenati S, Janke UW, Kleyer A, Rasperini G, Tinti C et al. The efficacy of mineralized allograft cortical and cancellous chips in maxillary sinus augmentations. *Int. J. Periodontics Restor. Dent* 2014;34:789–793.
10. Toscano N, Holtzclaw D, Mazor Z, Rosen P, Horowitz R, Toffler M. Horizontal Ridge Augmentation Utilizing a Composite Graft of Demineralized Freeze-Dried Allograft, Mineralized Cortical Cancellous Chips, and a Biologically Degradable Thermoplastic Carrier Combined With a Resorbable Membrane: A Retrospective Evaluation of 73 Consecutively Treated Cases From Private Practices. *J. Oral Implant.* 2010, 36, 467–474.
11. Giannoudis PV, Dinopoulos H, Tsiridis E. Bone substitutes: an update. *Injury.* 2005;36 Suppl 3 S 20-27.
12. Fuentes, R, Issa JPM, Iyomasa MM, Oporto G, Prieto R, Borie E. The Behavior of Demineralized Bone Matrix (DBM) in Post-Extraction Sockets. *Int. J. Morphol.* 2012, 30, 394–398.
13. Zitzmann NU, Schärer P, Marinello CP, Schüpbach P, Berglundh T. Alveolar ridge augmentation with Bio-Oss: A histologic study in humans. *Int. J. Periodontics Restor. Dent.* 2001, 21, 288–295.
14. Kao ST, Scott DD. A Review of Bone Substitutes. *Oral Maxillofac. Surg Clin North Am* 2007; 19: 513–521.
15. Oliveira G, Pignatton TB, de Almeida Ferreira CE, Peruzzo LC, Marcantonio E Jr. New bone formation comparison in sinuses grafted with an organic bovine bone and -TCP. *Clin. Oral Implants Res.* 2019, 30, 483.
16. Zitzmann NU, Schärer P, Marinello CP, Schüpbach P, Berglundh T. Alveolar ridge augmentation with Bio-Oss: A histologic study in humans. *Int. J. Periodontics Restor. Dent.* 2001, 21, 288–295.
17. Oryan, A.; Alidadi, S.; Moshiri, A.; Maffulli, N. Bone regenerative medicine: Classic options, novel strategies, and future directions. *J. Orthop. Surg. Res.* 2014, 9, 18.
18. Xu, H.H.; Simon, C.G., Jr. Fast setting calcium phosphate–chitosan scaffold: Mechanical properties and biocompatibility. *Biomaterials* 2005, 26, 1337–1348.
19. Husain, S.; Al-Samadani, K.H.; Najeeb, S.; Zafar, M.S.; Khurshid, Z.; Zohaib, S.; Qasim, S.B. Chitosan Biomaterials for Current and Potential Dental Applications. *Materials* 2017, 10, 602.
20. Kwon, K.-J.; Seok, H. Silk Protein-Based Membrane for Guided Bone Regeneration. *Appl. Sci.* 2018, 8, 1214.
21. Cai, Y.; Guo, J.; Chen, C.; Yao, C.; Chung, S.-M.; Yao, J.; Lee, I.-S.; Kong, X. Silk fibroin membrane used for guided bone tissue regeneration. *Mater. Sci. Eng. C* 2017, 70, 148–154.
22. Wang, W.; Yeung, K.W. Bone grafts and biomaterials substitutes for bone defect repair: A review. *Bioact. Mater.* 2017, 2, 224–247.
23. Wong, R.W.; Rabie, A.B.M. Effect of Gusuibu Graft on Bone Formation. *J. Oral Maxillofac. Surg.* 2006, 64, 770–777.
24. McPherson, R. Bone Grafting with Coralline Hydroxyapatite. *EC Dent. Sci.* 2019, 18, 2413–2423.
25. Bhatt, R.A.; Rozental, T.D. Bone Graft Substitutes. *Hand Clin.* 2012, 28, 457–468.
26. Damien, E.; Revell, P. Coralline hydroxyapatite bone graft substitute: A review of experimental studies and biomedical applications. *J. Appl. Biomater. Biomech.* 2004, 2, 65–73.
27. Yukna, R.A.; Yukna, C.N. A 5-year follow-up of 16 patients treated with coralline calcium carbonate (Biocoral™) bone replacement grafts in infrabony defects. *J. Clin. Periodontol.* 1998, 25, 1036–1040.
28. Galindo-Moreno, P.; Padiál-Molina, M.; Lopez-Chaichio, L.; Gutiérrez-Garrido, L.; Martín-Morales, N.; O'Valle, F. Algae-derived hydroxyapatite behavior as bone biomaterial in comparison with anorganic bovine bone: A split-mouth clinical, radiological, and histologic randomized study in humans. *Clin. Oral Implant Res.* 2020, 31, 536–548.

29. Zhou, A.J.-J.; Clokie, C.M.L.; Peel, S.A.F. Bone Formation in Algae-Derived and Synthetic Calcium Phosphates With or Without Poloxamer. *J. Craniofacial Surg.* 2013, 24, 354–359.
30. Ewers, R. Maxilla Sinus Grafting With Marine Algae Derived Bone Forming Material: A Clinical Report of Long-Term Results. *J. Oral Maxillofac. Surg.* 2005, 63, 1712–1723.
31. Herr, G.; Wahl, D.; Küsswetter, W. Osteogenic activity of bone morphogenetic protein and hydroxyapatite composite implants. *Ann. Chir. Gynaecol. Suppl.* 1993, 207, 99–107.
32. Zhou, A.J.-J.; Clokie, C.M.L.; Peel, S.A.F. Bone Formation in Algae-Derived and Synthetic Calcium Phosphates With or Without Poloxamer. *J. Craniofacial Surg.* 2013, 24, 354–359.
33. Kumar, P.; Fathima, G.; Vinitha, B. Bone grafts in dentistry. *J. Pharm. Bioallied Sci.* 2013, 5, 125–127.
34. Lee DW, Pi SH, Lee SK, et al. A comparative study on hydroxyapatite and autogenous bone grafting in rabbit calvarial defect model. *J. Craniomaxillofac Surg.* 2013 Nov;41(8):721-7.
35. Chitsazi, M.; Shirmohammadi, A.; Faramarzie, M.; Pourabbas, R.; Rostamzadeh, A. A clinical comparison of nano-crystalline hydroxyapatite (Ostim) and autogenous bone graft in the treatment of periodontal intrabony defects. *Med. Oral Patol. Oral Cirurgia Bucal* 2011, 16, e448–e453.
36. Kattimani, V.S.; Kondaka, S.; Lingamaneni, K.P. Hydroxyapatite—Past, Present, and Future in Bone Regeneration. *Bone Tissue Regen. Insights* 2016, 7, 36138.
37. Ratnayake, J.T.B.; Mucalo, M.; Dias, G.J. Substituted hydroxyapatites for bone regeneration: A review of current trends. *J. Biomed. Mater. Res. Part B Appl. Biomater.* 2017, 105, 1285–1299.
38. Dewi, A.H.; Ana, I.D. The use of hydroxyapatite bone substitute grafting for alveolar ridge preservation, sinus augmentation, and periodontal bone defect: A systematic review. *Heliyon* 2018, 4, e00884.
39. Wang, H.; Leeuwenburgh, S.C.; Li, Y.; Jansen, J.A. The Use of Micro- and Nanospheres as Functional Components for Bone Tissue Regeneration. *Tissue Eng. Part B Rev.* 2012, 18, 24–39.
40. Sakamoto, M. Development and evaluation of superporous hydroxyapatite ceramics with triple pore structure as bone tissue scaffold. *J. Ceram. Soc. Jpn.* 2010, 118, 753–757.
41. Ad De, R.; Meijer, G.; Dormaar, T.; Janssen, N.; Van Der Bilt, A.; Slootweg, P.; De Bruijn, J.; Van Rijn, L.; Koole, R. -TCP versus autologous bone for repair of alveolar clefts in a goat model. *Cleft Palate Craniofacial J.* 2011, 48, 654–662.
42. Bohner M, Galea L, Doebelin N, et al. Comparative investigation of three calcium phosphate ceramics in a critical size defect in the femoral condyle of rabbits. *J Biomed Mater Res B Appl Biomater.* 2017 Aug;105(6):1751-9.
43. Wakimoto, M.; Ueno, T.; Hirata, A.; Iida, S.; Aghaloo, T.; Moy, P.K. Histologic Evaluation of Human Alveolar Sockets Treated With an Artificial Bone Substitute Material. *J. Craniofacial Surg.* 2011, 22, 490–493.
44. Spivak, J.M.; Hasharoni, A. Use of hydroxyapatite in spine surgery. *Eur. Spine J.* 2001, 10, S197–S204.
45. Suneelkumar, C.; Datta, K.; Srinivasan, M.R.; Kumar, S.T. Biphasic calcium phosphate in periapical surgery. *J. Conserv. Dent.* 2008, 11, 92–96.
46. Fernandez de Grado, G.; Keller, L.; Idoux-Gillet, Y.; Wagner, Q.; Musset, A.M.; Benkirane-Jessel, N.; Bornert, F.; Offner, D. Bone substitutes: A review of their characteristics, clinical use, and perspectives for large bone defects management. *J. Tissue Eng.* 2018, 9, 2041731418776819.
47. Xynos ID, Edgar AJ, Buttery LD, et al. Ionic products of bioactive glass dissolution increase proliferation of human osteoblasts and induce insulin-like growth factor II mRNA expression and protein synthesis. *Biochem Biophys Res Commun.* 2000 Feb 16;276(2):461-5.
48. Wadhawan, A.; Gowda, T.M.; Mehta, D.S. Gore-tex® versus resolut adapt® GTR membranes with perioglas® in periodontal regeneration. *Contemp. Clin. Dent.* 2012, 3, 406.
49. Esfahanizadeh, N.; Nourani, M.R.; Bahador, A.; Akhondi, N.; Montazeri, M. The Anti-biofilm Activity of Nanometric Zinc doped Bioactive Glass against Putative Periodontal Pathogens: An in vitro Study. *Biomed. Glas.* 2018, 4, 95–107.
50. Xie, C.; Lu, H.; Li, W.; Chen, F.-M.; Zhao, Y.-M. The use of calcium phosphate-based biomaterials in implant dentistry. *J. Mater. Sci. Mater. Electron.* 2012, 23, 853–862.
51. Stanton, D.C.; Chou, J.C.; Carrasco, L.R. Injectable calcium-phosphate bone cement (Norian) for reconstruction of a large mandibular defect: A case report. *J. Oral Maxillofac. Surg.* 2004, 62, 235–240.
52. Khairoun, I.; Boltong, M.G.; Driessens, F.C.M.; A Planell, J. Some factors controlling the injectability of calcium phosphate bone cements. *J. Mater. Sci. Mater. Electron.* 1998, 9, 425–428.
53. Pietrzak, W.S.; Ronk, R. Calcium Sulfate Bone Void Filler: A Review and a Look Ahead. *J. Craniofacial Surg.* 2000, 11, 327–333.
54. Kutkut, A.; Andreana, S. Medical-grade calcium sulfate hemihydrate in clinical implant dentistry: A review. *J. Long Term Eff. Med Implant* 2010, 20, 295–301.

55. Kumar, Y.; Nalini, K.; Menon, J.; Patro, D.K.; Banerji, B. Calcium sulfate as bone graft substitute in the treatment of osseous bone defects, a prospective study. *J. Clin. Diagn. Res. JCDR* 2013, 7, 2926.
56. Maragos, P.; Bissada, N.F.; Wang, R.; Cole, B.P. Comparison of three methods using calcium sulfate as a graft/barrier material for the treatment of Class II mandibular molar furcation defects. *Int. J. Periodontics Restor. Dent.* 2002, 22, 493–501.
57. Haugen, H.J.; Lyngstadaas, S.P.; Rossi, F.; Perale, G. Bone grafts: Which is the ideal biomaterial? *J. Clin. Periodontol.* 2019, 46, 92–102.
58. Danoux, C.B.; Barbieri, D.; Yuan, H.; De Bruijn, J.D.; A Van Blitterswijk, C.; Habibovic, P. In vitro and in vivo bioactivity assessment of a polylactic acid/hydroxyapatite composite for bone regeneration. *Biomater* 2014, 4, e27664.
59. Kashirina, A.; Yao, Y.; Liu, Y.; Leng, J. Biopolymers as bone substitutes: A review. *Biomater. Sci.* 2019, 7, 3961–3983.
60. Yukna, R.A.; Yukna, C.N. Six-year clinical evaluation of HTR synthetic bone grafts in human grade II molar furcations. *J. Periodontal Res.* 1997, 32, 627–633.
61. Xie, Y.; Li, S.; Zhang, T.; Wang, C.; Cai, X. Titanium mesh for bone augmentation in oral implantology: Current application and progress. *Int. J. Oral Sci.* 2020, 12, 1–12.
62. Briguglio, F.; Falcomatà, D.; Marconcini, S.; Fiorillo, L.; Farronato, D. The Use of Titanium Mesh in Guided Bone Regeneration: A Systematic Review. *Int. J. Dent.* 2019, 2019, 1–8.
63. Jeng, M.-D.; Chiang, C.-P. Autogenous bone grafts and titanium mesh-guided alveolar ridge augmentation for dental implantation. *J. Dent. Sci.* 2020, 15, 243–248.
64. Nabyouni, M.; Brückner, T.; Zhou, H.; Gbureck, U.; Bhaduri, S.B. Magnesium-based bioceramics in orthopedic applications. *Acta Biomater.* 2018, 66, 23–43.
65. Lee JH, Yi GS, Lee JW, et al. A comparative study of bone regeneration with four kinds of bone grafting materials in rat calvarial defects. *Key Eng Mater.* 2006;309-311:791-94.
66. Ghanem, W.A.; Ahmed, I.H.; Kilany, O.E.; Mortada, I.M. Effect of nanobone graft on socket healing after teeth extraction. *Dent. J.* 2016, 62, 3553.
67. Sukumar, S.; Drizhal, I.; Paulusová, V.; Bukac, J. Surgical Treatment of Periodontal Intrabony Defects with Calcium Sulphate in Combination with Beta-Tricalcium Phosphate: Clinical Observations Two Years Post-Surgery. *Acta Med.* 2011, 54, 13–20.
68. Abuelnaga, M.; Elbokle, N.; Khashaba, M. Evaluation of custom made xenogenic bone grafts in mandibular alveolar ridge augmentation versus particulate bone graft with titanium mesh. *Egypt. J. Oral Maxillofac. Surg.* 2018, 9, 62–73.
69. Oliveira, É.; Nie, L.; Podstawczyk, D.; Allahbakhsh, A.; Ratnayake, J.; Brasil, D.; Shavandi, A. Advances in Growth Factor Delivery for Bone Tissue Engineering. *Int. J. Mol. Sci.* 2021, 22, 903.
70. Albanese, A.; Licata, M.E.; Polizzi, B.; Campisi, G. Platelet-rich plasma (PRP) in dental and oral surgery: From the wound healing to bone regeneration. *Immun. Ageing* 2013, 10, 1–23.
71. Sallent, I.; Capella-Monsonís, H.; Procter, P.; Bozo, I.Y.; Deev, R.V.; Zubov, D.; Vasyliiev, R.; Perale, G.; Pertici, G.; Baker, J.; et al. The Few Who Made It: Commercially and Clinically Successful Innovative Bone Grafts. *Front. Bioeng. Biotechnol.* 2020, 8.
72. Cicciù, M. Growth Factor Applied to Oral and Regenerative Surgery. *Int. J. Mol. Sci.* 2020, 21, 7752.
73. Sallent, I.; Capella-Monsonís, H.; Procter, P.; Bozo, I.Y.; Deev, R.V.; Zubov, D.; Vasyliiev, R.; Perale, G.; Pertici, G.; Baker, J.; et al. The Few Who Made It: Commercially and Clinically Successful Innovative Bone Grafts. *Front. Bioeng. Biotechnol.* 2020, 8.
74. Sohn, D.-S.; Huang, B.; Kim, J.; Park, W.E.; Park, C.C. Utilization of autologous concentrated growth factors (CGF) enriched bone graft matrix (Sticky bone) and CGF-enriched fibrin membrane in Implant Dentistry. *J. Implant Adv. Clin. Dent.* 2015, 7, 11–18.
75. Bruder, S.P.; Kraus, K.H.; Goldberg, V.M.; Kadiyala, S. The Effect of Implants Loaded with Autologous Mesenchymal Stem Cells on the Healing of Canine Segmental Bone Defects. *J. Bone Jt. Surg. Am. Vol.* 1998, 80, 985–996.
76. Kok, I.J.D.; Drapeau, S.J.; Young, R.; Cooper, L.F. Evaluation of mesenchymal stem cells following implantation in alveolar sockets: A canine safety study. *Int. J. Oral Maxillofac. Implant* 2005, 20, 511–518.
77. Kahle, M.; Wiesmann, H.-P.; Berr, K.; Depprich, R.A.; Kübler, N.R.; Naujoks, C.; Cohnen, M.; Ommerborn, M.A.; Meyer, U.; Handschel, J. Embryonic stem cells induce ectopic bone formation in rats. *Bio Med Mater. Eng.* 2010, 20, 371–380.
78. Hu, J.; Cao, Y.; Xie, Y.; Wang, H.; Fan, Z.; Wang, J.; Zhang, C.; Wu, C.; Wang, S. Periodontal regeneration in swine after cell injection and cell sheet transplantation of human dental pulp stem cells following good manufacturing practice. *Stem Cell Res. Ther.* 2016, 7, 1–11.
79. Ducheyne, P. *Comprehensive Biomaterials*; Elsevier: Amsterdam, The Netherlands, 2015.

80. Deev, R.V.; Drobyshev, A.Y.; Bozo, I.Y.; Isaev, A. Ordinary and Activated Bone Grafts: Applied Classification and the Main Features. *BioMed Res. Int.* 2015, 2015, 1–19.
81. Webster TJ, Ahn ES. Enhanced functions of osteoblasts on nanostructured surfaces of carbon and hydroxyapatite. *Mater Sci Eng C Mater Biol Appl.* 2006 Dec;26(8):1209-14.
82. Bose S, Tarafder S. Calcium phosphate ceramic systems in growth factor and drug delivery for bone tissue engineering: A review. *Acta Biomater.* 2012 May;8(4):1401-21.
83. Murphy SV, Atala A. 3D bioprinting of tissues and organs. *Nat Biotechnol.* 2014 Sep;32(8):773-85.
84. Caplan AI. Mesenchymal stem cells. *J Orthop Res.* 1991 Sep;9(5):641-50.
85. Dimitriou R, Jones E, McGonagle D, Giannoudis PV. Bone regeneration: current concepts and future directions. *BMC Med.* 2011 Sep 8;9:66.
86. Lee WC, Lim CH, Shi H, et al. Origin of enhanced stem cell growth and differentiation on graphene and graphene oxide. *ACS Nano.* 2011 23;5(9):7334-41.
87. Zomorodian A, Garcia MP, Moura e Silva T, et al. Magnesium alloys and composites for orthopedic applications: A review of mechanical and corrosion properties. *Acta Biomater.* 2019 Jan 15;84:361-81.
88. Numata K, Kaplan DL. Silk-based delivery systems of bioactive molecules. *Adv Drug Deliv Rev.* 2010 Aug 30;62(15):1497-508.
89. Gelain F, Unsworth LD, Zhang S. Slow and sustained release of active cytokines from self-assembling peptide scaffolds. *J Control Release.* 2010 Oct 1;145(3):231-9.
90. Borden M, Attawia M, Khan Y, et al. Injectable polyethylene oxide–polyester diblock copolymers for controlled release of osteogenic proteins. *Biomaterials.* 2002 Nov;23(22):4393-402.