BONE GRAFTING MATERIALS AND SUBSTITUTES – A LITERATURE REVIEW

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Abstract

The field of bone grafting has made great strides. Newer materials and techniques to enhance and improve the mechanical resistance, durability and compatibility are currently being developed and studied. As described in the literature over the last few years, the qualitative characteristics of bone graft scaffolds are critical for cell and nutrient infiltration; and that it greatly enhances the post operative compatibility. Currently, most researchers are studying the introduction of various biologically safe and acceptable materials and their use to improve the mechanical integrity of grafts. This article presents review of advanced bone graft materials and their contribution in managing bone defects.

Keywords: Bone graft materials, Bone defects, Biocompatibilty

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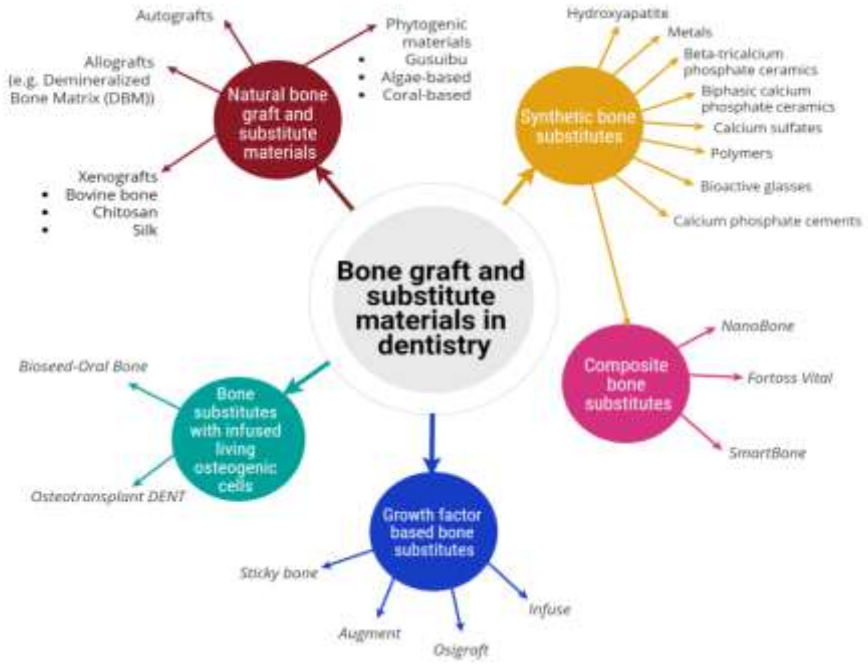

Figure: 1 Classification of bone grafts and replacement materials for dental use, grouped into five categories and showing their associated subcategories[30]

1. Introduction

Bone grafting is a surgical procedure in which bone is reconstructed by grafting bone tissue. A dental bone graft is often necessary if a patient has lost one or more adult teeth or has gum disease, as both of these conditions can lead to bone loss. After tooth loss, bone resorption is irreversible, leaving the area with insufficient bone mass for successful dental surgery. Bone grafting is the only solution to reverse dental bone loss and is a widely accepted procedure. Bone grafts are used as pillars and scaffolding on which to regenerate and heal. Dental implants increase the volume and density of the jawbone in areas where bone loss has occurred. Experts have been using bone grafting techniques for over 100 years. Successful incorporation of graft materials involves many factors, including type of graft, preparation site, vascularity, mechanical strength, and pore size of the material. These parameters make the use of bone substitutes difficult in terms of reliability and predictability.[1]
Bone grafts are generally evaluated based on their:

- osteogenic,
- osteoinductive
- osteoconductive potential.

The material to be grafted can come from the same individual (autograft), from another individual of the same species (allograft) or from another species (xenograft) 1923 [2] and was revived in 1965 by Nabers and O'Leary . [3] Buebe and Silvers (1936) successfully repaired intrabony defects in humans using boiled bovine bone meal. Forceberg (1956) used Ox purum in 11 human intrabony defects.Melcher and Dent [4] used organic bone from bovine bone in bony defects, showing that sequestration and slow resorption compete with the use of organic bone. Scopp et al,[5] used Boplant bovine bone and reported a decrease in pocket depth at 6 months. Now, with the introduction of advanced bone grafting techniques, it is possible to increase the volume, width and height of bone in the area of the defect.
The biological mechanisms that justify bone grafting are osteoconduction, osteoinduction and osteogenesis.
1.Osteogenesis : Osteogenesis is the ability of a graft to generate new bone, a process that depends on the presence of viable bone cells in the graft, i.e. when vital osteoblasts derived from bone material ,bone graft contributes to the growth of new bone as well as bone formation. Osteogenic grafts contain living cells that have the ability to form bone (osteogenic progenitors) or have the potential to differentiate into bone-forming cells (including osteogenic progenitors). Osteogenesis is a property that occurs only in fresh autologous bone and bone marrow cells.
2. Osteoconductivity: This is the physical property of a bone graft material that acts as a scaffold for the healing of living bone and the growth of new bone, with the continuation by natural bone. This allows for the growth of new vasculature and the infiltration of osteogenic precursor cells into the graft site. Osteoconductive properties have been found in cancellous bone autografts and allografts in demineralized bone matrix, hydroxyapatite,

collagen and calcium phosphate. Osteoblasts form the margin of the grafted defect and spread to form new bone as part of the bone graft material. Bone graft materials should be osteoconductive for their long term survival.

3. Osteoinduction: Osteoinduction is the ability of a graft material to differentiate stem cells into mature bone cells. This process is usually related to the presence of bone growth factors in the graft material or bone grafting aids. This involves stimulating the differentiation of osteoprogenitor cells into osteoblasts, which then begin to form new bone. The most studied type of osteoinductive cellular mediator is BMP.

4 Osteoconductive and osteoinductive bone graft materials can not only serve as a scaffold for existing osteoblasts, but also stimulate the formation of new osteoblasts, thereby promoting faster graft integration. For example, enamel matrix derivatives enhanced the osteoinduction of demineralized freeze-dried bone allografts (DFDBAs), but did not stimulate bone grafting alone.[6]

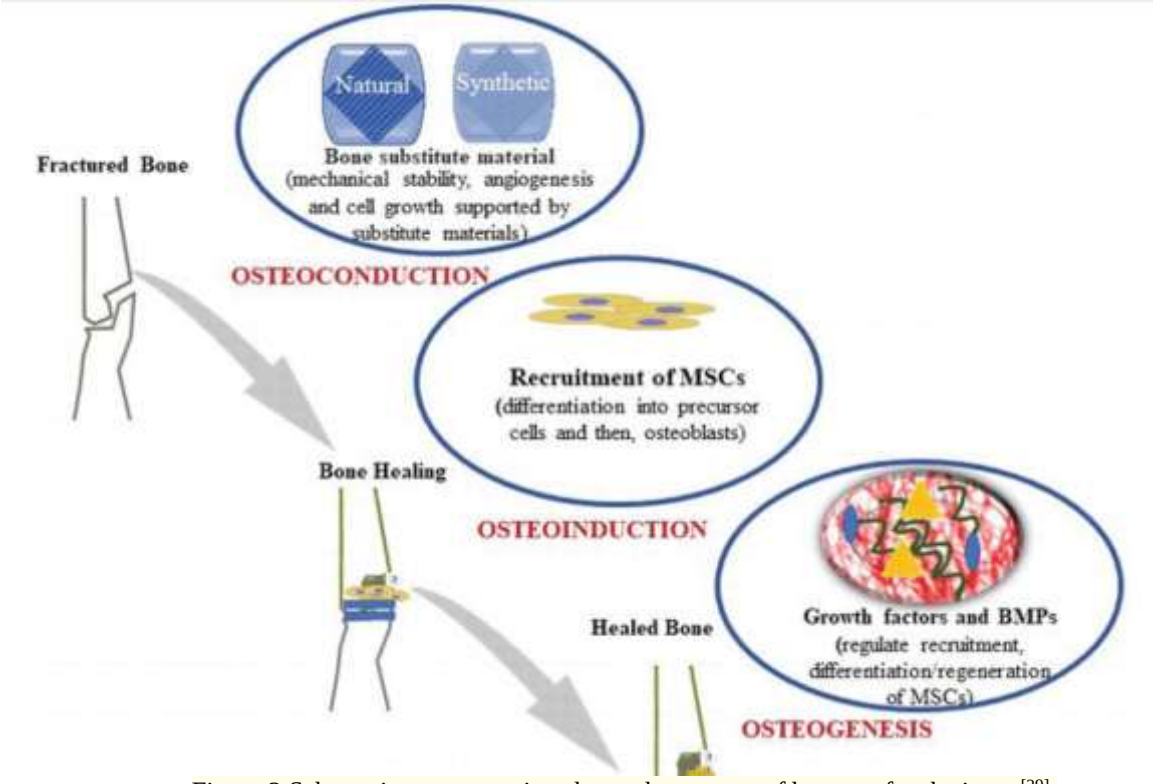

Figure:2 Schematic representation shows the process of bone graft substitutes[29].

Classification of Bone Graft[7]

Based on the type of graft used:

These are available as large or small particles, a combination of porosities, and from specific locations of origin (e.g. cortical, cancellous).

Based on the Source : Autograft, Allograft, Xenograft ,Alloplast

Advantages	Limitations
Osteogenic	Donor site pain
Osteoconductive	Increased blood loss
Osteoinductive	Inappropriate amount of tissue availability
No graft rejection	Increased risk of nerve injury

Table:1 The common advantages and disadvantages with the use of autograft[29]

Advantages	Disadvantages
Less chance of donor morbidity	Chances of disease transmission
No size limitation	Possibility of host immune response
Less surgical intervention	High cost
Cosmetically better results	Delay in incorporation
Reduce period for rehabilitation	Local bone resorption

Table:2 The advantages and disadvantages associated with the use of an allograft[29]

Based on Bone Graft Substitutes (Laurencin): Allograft based**,** Factor based**,** Cell based**,** Ceramic based**,** Polymer based.

Allograft Based: Allograft bone used alone or in combination **.**For example: allegro, orthoblast, graft on. Action: osteoconductive, osteoinductive

Factor Based: Natural and recombinant growth factor used alone or in combination For example: Transforming growth factor-beta, platelet-derived growth factor, fibroblast growth factor, BMP. Action: Osteoinductive, osteoinductive, and osteoconductive with carrier materials.

Cell Based: Cells used to generate new tissue alone or seeded onto a support matrix. For example: Mesenchymal stem cells**.** Action: osteogenic, both osteogenic and osteoconductive with carrier materials.

Ceramic Based: Includes calcium phosphates, calcium sulfate, and bioactive glass used alone or in combination.For example: Osteograft, osteoset, Novabone • Action: Osteoconductive, limited osteoinductive when mixed bone marrow.

Polymer Based: Includes degradable and nondegradable polymers used**.** For example: Cortoss, OPLA, Immix**.** Action: Osteoconductive, bioresorbable in the degradable polymer

Class	Grafting material	Properties of action
Autograft based	Cortical and cancellous autologous graft	Osteoconductive Osteoinductive Osteogenic
Allograft based	Fresh allograft Frozen allograft Frozen-dried allograft Graft	Osteoconductive Osteoinductive
Growth factor based	BMP and other growth factors TGF-β, PDGF, FGF, BMP	Both osteoconductive and osteoinductive with carrier materials Platelet-rich plasma (PRP) or autologous platelet concentrate
Cell based	Stem cells Collagen Gene	Osteogenic Both osteoconductive and osteoinductive with carrier materials
Ceramic based	Calciumhydroxyapetite(HA) Tricalcium phosphate Bioactive glass Calcium sulfate	Osteoconductive Limited osteoconductive when mixed with bone marrow
Polymer based	Natural or synthetic polymers Degradable or non-degradable polymers	Osteoconductive Limited osteoconductive when mixed with bone marrow

Table: 3 Diagram showing the bone graft materials with the properties of action[29].

Indications of Bone Grafts

Deep Intraosseous Defects - Double and Triple Walled Defects, Tooth Retention. Support of Critical Teeth – Abutments, Bone Defects Associated with Juvenile Periodontitis, Aesthetics (Shallow Intraosseous Defects), Bifurcation defect Grade II, III bifurcation, Augmentation of the alveolar ridge, Elevation of the maxillary sinus Peri-implant regeneration and filling of the bone defect in the donor site[8].

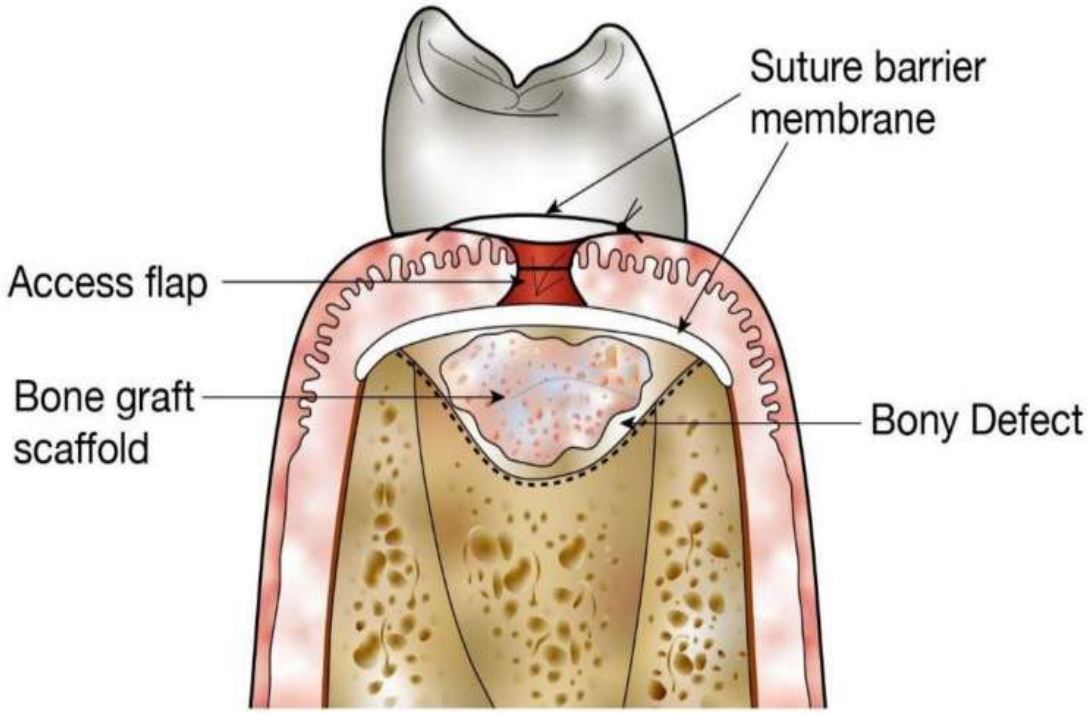

Figure: 3 Bone defect repair using structural scaffolding. This image shows placement of a bone graft scaffold into an alveolar bone defect after surgical creation of an access valve.

Ideal requirements for bone grafting

- Osteoinductive properties
- Non-toxic
- Non-infectious
- No root resorption or ankylosis
- Non-antigenic and biocompatible
- Predictable adaptability and availability
- Rapid angiogenesis
- Should stimulate new attachments and may induce osteogenesis[9].

Bone Morphogenetic Protein (bmp)

BMP belongs to the family of transforming growth factors. Fifteen different bmps have been identified, all with varying degrees of cellular activity, including cartilaginous or osteoinductive properties. There are currently two recombinant proteins - recombinant human bone morphogenetic protein (rhBMP-2) and (rhBMP-7). Two rhBMP-related vector systems have been approved by the United States Food and Drug Administration. 1) Osteogenic Protein 1 (OP-1) is composed of rhBMP-7 and bovine collagen (Stryker Biotech Hopkinton, MA) 2) InFuse System (Medtronic Sofamor Danek Warskou, IN) is composed of rhBMP-2 in bovine resorbable I. The support sponge is made of collagen type. BMP products are packaged in sterile vials as a lyophilized powder that can be reconstituted with sterile water and applied to the wearer.[10]

Osteoinductive	• Allograft bone I • Demineralized bone matrix • Purified human BMP (not commercially available) • OP-1 device • INFUSE
Osteoconductive	• $CaPO_4$ • $CaSO_4$ • Allograft • Hydroxyapatite
Osteogenic and osteopromotive	• Selective cellular retention (Cellect) • Bone marrow aspirate injection/ implantation

Table: 4 Bone graft Substitutes[31]

Platelet-rich plasma (prp)

PRP is a source of platelet-derived growth factor (PGDF) and transforming growth factor-beta (TGF-b), obtained by isolating and concentrating platelets by a centrifugation process at density gradient[11].

Platelet-Derived Growth Factor (PDGF)

PDGF, a glycoprotein with a molecular weight of approximately 30kd. It was first described in the alpha granules of platelets, but can also be synthesized and secreted by cells such as macrophages and endothelial cells. There are approximately 0.06 ng of PDGF per million platelets underlines the powerful function of this molecule[13].

Its mechanism is to activate cell membrane receptors on target cells, leading to the formation of high-energy phosphate bonds on internal cytoplasmic signaling proteins, which then activate signaling proteins, thereby initiating specific activities within cells, (Target cells). The most specific activities of PDGF are mitosis, angiogenesis and macrophage activation[13].

TGF-b

The term transforming growth factor beta applies to the superfamily of growth and differentiation factors. Bone morphogenetic proteins (BMPs) are part of this family which includes at least 13 BMPs. TGF-b1 and TGF-b2 are proteins with a molecular weight of approximately 25kd[14].

Like PDGF, they are synthesized and found in macrophages and other cell types. When released by platelet degranulation or actively secreted by macrophages, they act as paracrine growth factors and affect cells such as fibroblasts, bone marrow stem cells and preosteoblasts. Each of these target cells has the ability to synthesize and secrete its own TGF-b protein. Thus, TGF-b represents a mechanism to support the long-term healing process and even develops into a bone remodeling factor. The most important functions are chemotaxis and mitogenesis of osteoblast progenitors.

They also have the ability to stimulate wound healing and the deposition of osteoblasts from the collagen matrix of bone. Additionally, TGF-b inhibits osteoclastogenesis, thereby promoting bone formation rather than resorptionThe present invention combines the advantages of inorganic molded bodies with macropores, mesopores and micropores and polymers such as collagen [16]. Different stoichiometric compositions of calcium phosphate, such as hydroxyapatite (HaAP), tricalcium phosphate (TCP), tricalcium phosphate (TTCP) and other calcium phosphate salts and minerals, were used to match the biofacies of natural bone capacity, structure and strength. The role of pore size and porosity in promoting bone revascularization, healing and remodeling has been recognized as a key property of bone graft materials.

To increase porosity, the present invention includes redox products of at least one metal cation, at least one oxidizing agent, and at least one oxidizing precursor anion. The reaction products can be inorganic compounds containing calcium phosphate, biphasic calcium phosphate or β-tricalcium phosphate (o-TCP) [17]. The redox products provide the grafted material of the present invention with macropores, mesopores and micropores, which provide the grafted

material with excellent absorption properties. The incorporation of polymers such as structural protein collagen improves handling and flexibility. The porosity and macropore distribution (1 μm-1000 μm) of these bone grafts increases their ability to absorb fluids such as bone marrow aspirate, blood or saline, and cell-laden solutions (eg. g. fibroblasts, mesenchymal cells, stromal cells, myeloid cells and stem cells) for in vivo use. Applications of this property include the ability to incorporate growth factors such as BMPs into grafts to promote wound healing [18]. The flexibility of the bone graft allows the graft to be molded into any basic shape, including cylinders, blocks, strips, sheets, and wedges. This graft can also be used as a covering for any orthopedic appliance.

Further, unlike traditional bone graft substitutes, the present invention is highly compressible and therefore can be packaged to provide maximum contact with adjacent bone, thereby promoting healing of bony defects.

Porous Ceramic Composite Bone Graft

This porous ceramic composite material developed by Smith contains a biodegradable polymer (polycaprolactone) and is used as a bone substitute in orthopedics and dentistry or as a tissue engineering application. The biodegradable polymers allow passage and/or delivery of various drugs through the porous ceramic matrix and improve the mechanical properties of the implant in vivo. A disadvantage of currently commercially available bone grafts is their poor mechanical properties, which limits the use of these implants in non-load bearing applications [19]. Therefore, the main objective of this particular bone graft was to improve the mechanical properties through the use of porous ceramic composites without the risk of joint fragmentation.

A bone graft is a porous bone substitute that limits fragmentation and migration of fragments during conventional orthopedic fixation practices[20]. The Graft consists of a porous osteoinductive ceramic matrix and biodegradable polymer with optimal pore size, pore size distribution, porosity, and pore connectivity to promote rapid ingrowth of bone tissue during implantation. Compared to previous ceramic bone grafts, this graft has superior mechanical properties due to the repeated coating of the organic matrix with a mixture of thickeners (suspensions) with different solid loadings[21]. The coated structure is heated to burn off the flexible organic foam, which is then sintered to provide a molten ceramic foam with many interconnected voids. When used as a biodegradable polymer coating, it helps improve the functional (mechanical) properties of implants in the body.

Taken together, the porous ceramic graft proposed by Smith has many advantages both in vitro and in vivo, and can be used in orthopedics and dentistry. As implants, grafts are available in non-load-bearing and weight-bearing applications[22].

Bioactive Bone Graft Substitute –

Collagen Enriched

Clineff presents a biocompatible bone graft composed of resorbable calcium phosphate, resorbable collagen and bioactive glass. The present invention is a biocompatible, absorbable and substantially homogeneous calcium phosphate blend composition with macropores, mesopores and micropores. The graft replicates the natural bone activity of natural bone through the addition of bioactive glass.

The bioactive glasses studied in the present invention include combinations of glass-ceramics, crystal-phase materials and acrylic polymers [23]. The purpose of bioactive glass is to react on contact with physiological fluids, including but not limited to blood and serum. The reaction of the bioactive glass with the surrounding fluid will lead to bone formation by forming a layer of apatite on the surface of the graft. Bioactive glasses can have a glassceramic composition composed of heterogeneous particles of irregular morphology and crystalline regions. Similar to other biocompatible synthetic bone grafts, collagen is included to enhance the graft's ability to be shaped or cut with various instruments such as scalpels and scissors.

Some basic shapes can be discs, hemispheres, half-pipes or tori. Collagen and bioactive glass were mixed with calcium phosphate by mixing to form a homogeneous mixture and composite matrices of different shapes and sizes[24].

The proposed graft material acts both as a barrier against the migration of other implants or graft material, and as an osteoconductive resorbable bone graft capable of promoting bone formation. The bone graft resorbs into the surgical site after delivery. The inclusion of bioactive glass as an osteoinductive component is considered a new application of bone technology[25].

Growth Factor Encapsulation System for Enhanced Bone Formation

Lu has developed bone technology that enhances bone formation by releasing various growth factors and/or platelet-rich plasma (PRP) from solid materials. PRP is known to contain many autologous platelet growth factors that help accelerate bone regeneration. These growth factors include platelet-derived growth factor (PDGF) and transforming growth factor-1 (TGF-1), both of which are produced by platelets and released during granulation. PDGF stimulates mitogenesis of osteoblast progenitor cells, while TGF-1 stimulates proliferation and collagen synthesis of osteoblasts and osteoblast progenitor cells. PRP gel has recently been used as a binder for cancellous bone particles in bone grafting procedures in oral an

d maxillofacial surgery.
The present invention consists of capsules of protei n-
permeable material containing growth factors, poro us releasable calcium alginate beads encapsulated with growth factors, PRP gel and bone regeneration promoting material[26].
Bone regeneration promoting material is a solid ma terial or scaffold that acts as an accelerator for bone forming cells to form new bone. These materials in clude collagen, BioOss (a bone graft substitute base d on calcium phosphate), Pepgen P-15 (synthetic P-15 peptide bound to natural forms of hydroxyapatit e) and AlloGraft (a demineralized bone matrix base d on same bone graft substitutes for allografts). The bone graft is designed in such a way that the contai ned growth factors are released and delivered to the desired location upon implantation. Porous alginat e beads containing autologous PRP allow growth fa ctors to be released from the PRP and then released from the beads to be transported to the defect site. The controlled release of the present invention is es sential for improved bone regeneration because gro wth factors can be released at different stages throu ghout the natural healing process. Chitosan beads a re also studied and mentioned in the patent as possi ble containers for growth factors/PRP. This novel h ydrogel delivery system allows sustained and contr olled release of growth factors associated with bone regeneration[27].

Polymer Bone Defect Filler

Deslauriers presented a bone defect filler to be impl anted into a patient's bone defect. Bone fillers inclu de particulate polymers dispersed in a polymeric bi nder.
The granular polymer includes a plurality of particl es, which may be of the same material as the polym er binder. The particles within the particulate poly mer can take a variety of shapes and/or sizes to pro vide bone defect fillers with enhanced pore interco nnectivity, material expansion, and contamination p roperties. The proposed bone defect filler also retai ns sufficient mechanical strength and handling prop erties for bone repair applications. The proposed po lymeric bone defect fillers benefit from currently sy nthesized nondegradable bone defect fillers that ret ain their chemical and mechanical properties, such as titanium. Synthetic bone fillers can have poor te nsile and shear properties.They also have poor adhe sion properties, so they can be washed away from t he defective area before new bone grows. Tradition al bone grafting techniques, such as the use of PM MA, are problematic because, as permanent bone fi llers, they are not resorbable and/or cannot be mold ed and shaped for healing in situ. A bone technolog y similar to the proposed innovation is the use of po lymer particles mixed with biological fluids, but the mixture of polymer particles and fluid tends to be difficult to adhere to surrounding bone and also exh ibits low initial structural properties[28].
DBM has most of the biological properties of nativ e bone that are important for successful bone grafti ng. Bone morphogenetic proteins present in DBM s ignal stem cells to differentiate into osteoblasts to g enerate new bone, which makes DBM osteoinducti ve. DBM is also osteoconductive, as it promotes ne ovascularization and osteoblast invasion. DBM can be made from the same species as the recipient, or from a different species with similar genetic change s to ATM.[29] The inventors of this skeletal technolo gy were able to create ATMs and DBMs in various forms, including fibers, pellets, or wires.
The final product or bone graft can be made from a combination of any form of ATM and any form of DBM (e.g., ATM fibers and DBM particles) and fr eeze-dried to long term storage.

Market name	Allograft type	Form of/additive with	Carrier used
Grafton	DBM	Gel, putty, and flexible sheets	Glycerol carrier
Opteform	DBM	Cortical bone chips	Gelatin carrier
Osteofil	DBM	Injectable bone paste	Collagen-based hydrogel matrix
Dynagraft	DBM	Syringe	Pleuronic reverse phase copolymer
Orthoblast	DBM	Cancellous bone	Bioresorbable reverse phase copolymer

Table: 5 Types of Commercially Available DBM Bone Graft Substitutes[29]

This particular bone graft is secured with sutures an d can be placed around superficially damaged or de fective bone from damaged or defective bone, or pl aced in non-bony sites to induce bone formation[30].

2. Conclusion

Bone graft and their substitute materials which can either be in the form of particulate or blocks are most commonly used in the field of dentistry to regenerate the unavailable hard tissue structures. There is a great increase in the demand for newer

and more enhanced grafting materials. Currently the bone grafts and their substitutes primarily are required to serve as the structural and functional framework for osteo-regenerative processes that only satisfy the osteoconductivity criteria. The exact and indepth understanding of these materials and (the growth factors associated) at the molecular level is growing, which allows for better control and modification in their structure, to better understand the surface properties, and their interaction ability with the other materials or a different environment. This progress would eventually help to determine the design and development required in dental bone substitutes more effectively. Despite the progress highlighted in this review article more work will be required to develop dental biomaterials that have a porous structure, mechanically stability, controlled degradation, and remodeling ability which is comparable with the rate of new bone formation.

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