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 – 3, Issue – 5, October - 2020, Page No. : 334 - 345

Bone graft and its substitutes in the modern era of dentistry: A Review

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Citation of this Article: Dr. Reena Rani, Dr. Reema Malik, Dr. Josie Kurian Paul, Dr. Dhruvika Garg, Dr Amanjot Kaur Bajwa., Dr. Ritika Kataria, "Bone graft and its substitutes in the modern era of dentistry: A Review", IJDSIR- October - 2020, Vol. – 3, Issue - 5, P. No. 334 – 345.

Type of Publication: Review Article

Conflicts of Interest: Nil

Abstract

This article aims to review the literature and differentiate the properties of bone graft and various bone substitutes commonly used. The present systematic review states Autogenous bone graft is the gold standard of grafting material. Bone grafts are basically used as a filler and scaffold to facilitate new bone formation and enhance bone healing. Beta-tri-calcium phosphate ceramics being the gold standard of synthetic bone graft substitute various possess few complications like infection or nonunion. Therefore, its use should be selective. Materials and Methods: Electronic and manual literature searches were conducted on databases: PubMed/Medline, Science direct for the studies and reviews published. Systematic literature review was performed. Conclusion: Autogenous bone as a graft material is considered as the gold standard for grafting purposes. The surgeon should have a good knowledge of properties of each bone graft material and should know when to select which type of bone substitute. Most common use of bone grafts in dentistry is in placement of dental implants, for atrophic ridges of edentulous jaw, filling the cavity defect, reconstruction of bone defect due to tumor or cyst removal.

Keywords: Bone Graft, Bone Substitute, Bone Morphogenic Protein, Autograft, Allograft

Introduction

The eventual use of the bone grafts is the osseous replacement of the bone defect with a healthy bone which is well vascularized and contoured, eliminating any dead spaces. An ideal bone graft has a role to achieve the same histological features as the original bone tissue. It acts as a scaffold for the new bone formation. Indistinct, from the purpose of use it has the ability to regenerate the lost bone structure to its complete integrity. The use of which in order to regenerate relies on their ability of osteogenic, osteoinductive and osteoconductive potential.[1] the search for an ideal bone substitute has been extensively carried out for more than 20 years.[4] Demand for the use of bone graft has increased in traumatology, tumor surgery, infection, revision arthroplasty.[5]

Bone morphology

Bone as a dynamic structure forms a framework that provides supports to the human body. Consisting of cancellous and cortical bone, bone is differentiated into osteoblasts and osteoclasts. The osteoblasts get embedded into the new bone matrix formed and becomes osteocyte, which is surrounded by spaces known as lacunae.[3]

Bone healing

The bone is regenerated in stages which are the inflammatory stage, proliferative stage and bone remodeling stage, over a period of 16 weeks approximately. Originally, the process of healing starts with formation of hematoma following angiogenesis and invasion of vascular supply through the surrounding periosteum and endosteum.[3] bone healing is a multilateral process for which revascularization, stability is required. Ideally, the bone graft is a substitute which should possess few requirements i.e, thermally nonconductive, sterilizable, readily available, low cost.[5]

Phases of fracture healing [figure 1]

It involves firstly an anabolic phase which is characterized by increase in tissue volume, related to the de novo recruitment and differentiation of stem cells. Just adjacent to the fracture line a cartilaginous callus forms. The periosteum swells and the new bone formation begins at the edges of this newly callus formed.[10,11,12] Simultaneously the cells forming the nascent blood vessels are recruited and differentiated in the surrounding muscle sheath.[13,14] the cartilage extracellular matrix undergoes mineralization as the chondrocytes differentiate progressively, thereby terminating the anabolic phase by chondrocyte apoptosis.[15,16] With termination of the anabolic phase comes a long lasting phase comprising principally the catabolic activities, characterized by the decrease in the volume of callus tissue. In the course of this phase cartilage resorption and specific anabolic activities continue to occur, as the cartilage is resorbed secondary bone formation begins with primary angiogenesis. Eventually, when the bone remodeling is initiated the first mineralized matrix produced is resorbed by osteoclasts, thereafter the secondary bone formed during the period of cartilage resorption is also resorbed. This prolonged period is distinguished by coupled cycles of osteoblast and osteoclast activities remodeling the callus tissue to the bone's original cortical structure (termed as coupled remodeling). Furthermore, the marrow space is re-established. Finally, considerable vascular remodeling occurs, returning the bone to it's pre-injury level.[10,17,18]

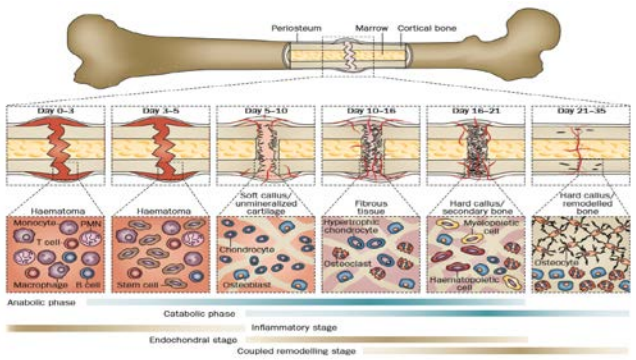

Figure 1: Illustration Of A Typical Bone Fracture Healing Process (Biological And Cellular Events)[6,10]

The biologic mechanisms of bone grafting includes osteoconduction, osteoinduction and osteogenesis [Table 1].

Osteoconduction

Occurs when bone graft material serves as a scaffold for new bone growth, which is perpetuated by the native bone. Osteoblasts from the margin of defect that is being grafted utilize the bone graft material as a frame work upon which they spread and generate new bone.[5]

Osteoinduction

Involves stimulation of osteoprogenitor cells to differentiate into osteoblasts and then begins formation of new bone. The most widely studied type of osteoinductive cell mediators are BMPs.[5]

Osteogenesis

It occurs when vital osteoblasts originating from bone graft material contributes to the growth of new bone along with bone formation.[5]

Osteopromotion

It involves the enhancement of osteoinduction property without possession of osteoinductive properties. For example, enamel matrix derivative enhances the osteoinductive effect of demineralized freeze-dried bone allograft, but it would not stimulate the bone graft alone. [2,19]

Table 1: Bone Graft Material Overview [3]

Bone Graft	Structural Strength	Osteoconduction	Osteoinduction	Osteogenesis
Autograft				
Cancellous	No	+ + +	+ + +	+ + +
Cortical	+ + +	+ +	+ +	+ +
Allograft				
Cancellous				
Frozen	No	+ +	+	No
Freeze-dried	No	+ +	+	No
Cortical				
Frozen	+ + +	+	No	No
Freeze-dried	+	+	No	No

Scaffold [Table 2]

It may be referred as a framework acting as a support which may be either temporary or permanent, natural or synthetic, a three dimensional porous, permeable, biocompatible biomaterial which allows cell adhesion to its surface inducing cell differentiation and proliferation without the risk of tissue rejection or an inflammatory response.[7,20,21] It is expected that a scaffold should

possess osteoconduction, osteoinduction and osteogenic potential.[22] Various other properties a graft material should manifest are bioinert, biocompatible, biodegradable, easy penetrability with suitable mechanical properties.[22] Various authors have reported that the graft material should be 90% porous. They are differentiated into microporous (<10 µm) or macroporous (>50-60 µm).[22]

Table 2: Scaffolds Can Be Classified Into Organic And Inorganic [23]

Scaffold Type		Examples
Organic	Natural	Collagen, Chitosan, Silk, etc
	Synthetic	Polyglycolic Acid, Polylactic Acid, etc
Inorganic		Metals, Alloys, Mineral compositions like calcium, potassium, silicate, magnesium, etc

Classification of bone graft materials

There are basically 4 types of bone graft material available for the reconstruction purposes in maxillofacial skeleton [Table 3].

Table 3: Types of Bone Grafts

Graft Type	Description
Autograft	Transplantation of viable bone tissue from one region to the other of the same individual.
Alloplast	Implantation of synthetic material(apatite, tricalcium phosphate, bioactive glass, polymers)
Xenograft	Cross- species transplantation of bone tissue
Allogenic	Graft tissue derived from other human being and transplanted to other.

Autogenous bone graft

Autologous or autogenous bone graft are secured from the same individual to whom it is received.[3] It is the most predictable and reliable bone graft material used for the reconstruction purposes in maxillofacial skeleton.[1,3] Most common harvest sites includes ramus, symphysis of mandible. Other sites, such as rib, iliac crest, fibula, calvarium, radius may also be used.[1,3] Several studies have shown the success of autografts.[1,24,25,26,27] hip, ramus, symphysis provides us both the cortical and cancellous bone.[3] The autogenous bone grafts are considered as the gold standard as a bone graft due to their immediate availability and high success rate.[3,4] The graft provides volumetric support with structural integrity.[3] Autografts have significant advantages such as there is no risk of disease transmission and immunologic reactions which is seen in alloplastic graft material.[3] Schaaf et al. in their study reported complications associated with autogenous bone graft harvest such as fracture of the anterior superior iliac spine (0.7%), persistent pain (0.4%) and sensory disturbances (2.7%).[4] The major drawbacks, include donor site morbidity, potential resorption, possible hospitalization, increased cost, size mismatch, additional surgical site is required, limited volume of graft material.[1,2,3,4,28,29] Harvesting from the symphysis region may lead to temporary or permanent sensory changes of lip and chin region.[3] while the hip grafts may cause gait disturbances. There are various other associated complications such as nerve injury, blood loss, hematoma formation, pelvic instability, cosmetic defects, even chronic pain at the harvest sites.[3]

Allogenic bone graft

Allografts are derived from the same species group and is received by a genetically dissimilar individual. Originally these grafts are prepared from the cadaveric tissues.[3] These are typically sourced from bone bank.[2] These graft

materials have a major advantage of its availability in abundance, adding to it no donor site morbidity.[3] They are used as a substitute for autografts or autograft expander, eliminating a secondary harvest site need.[1,3] The allografts are processed before being transplanted for the assurance of its safety.[3]

The processed available bone grafts are:

1. Fresh
2. Fresh frozen
3. Freeze dried
4. Demineralized bone grafts.

In comparison of mineralized bone graft the demineralized bone graft has the advantage of being osteoinductive and osteoconductive.[1,3] Over a period of time, demineralized freeze-dried bone allogaft can be used alone or in combination with other alternative factors such as platelet-rich plasma(concentration of platelets and growth factors).[4] The major disadvantage seen are disease transmission and immunologic reactions, unlike the autografts.[1,3] The risk of infection is minimized with the development of donar screening tests.[5,10] Allogenic bone grafts are processed in different particle sizes, creating an impact to a certain degree for its osteoconductive potential.[3] various particle sizes are mentioned in the literature, widely accepting the size of 100 µm to 300 µm to be processing the highest osteoconductive potential.[3] Allografts are available in various preparations such as morselized, cancellous, corticocancellous, cortical, osteochondral, bone segment and demineralized bone matrix.[5]

Alloplastic bone graft

Alloplastic bone graft materials are the bone substitute processed to enhance its properties for handling. These are made synthetically or obtained from hydroxyapitite which is made from bioactive gas.[2,3] Alloplasts uniquely has a property of bonding with bone surface, few of the examples are as follows bioactive glass (forming a chemical bond), calcium sulfate, tricalcium phosphate used in combination with hydroxapitite(both osteoconduction and resorbablity), calcium phosphate cement.[2,3,5] These materials combine with the growth factors to increase biological activity.

Bioactive glass

Bioactive glass comprises of sodium calcium salts, phosphates, silicon dioxide. It is used in irregular particle sizes measuring 90-170 µm (perioglas) or 300-355 micrometer (Biogran). The surface of the particles get coated with hydroxyl-carbonate apatite when this material comes in contact with tissue fluids, which attracts bone forming osteoblasts.[30] It's use does not induce an inflammatory response, for silica-based bio-glasses their resorption completes within 6 months.[9] In recent years, phosphate or borate-based bio-glasses have been developed.[9]

Calcium phosphate cements

Brown and Chow in 1986 invented Calcium phosphate cements [31] and in 1996 it was appoved by FDA for the treatment of non-load-bearing bone defect.[32] It is bioresorbable in nature [33] and can stay in the body in the body for up to 2 years without resorption, depending on its formulation. It comprises of calcium phosphate powder to which a liquid is mixed to form a workable paste.[32] Its major advantage is the ability of this paste to shape it according to the complex bony cavity, ignoring the gaps between the implant and the bone. CPC is brittle.[32] It should be used selectively as the clinical outcomes seems not better than the autologous bone or methymethacrylate.[34]

Beta-tri-calcium phosphate ceramics

Beta-TCP with the chemical formula ($Ca_3(PO_4)_2$) has been popularly used for dental applications.[35] It is considered as a gold standard for the synthetic bone substitute.[36] It is

bioresorbable [37,38,39],biocompatible[40,41], osteoconductive in character.[40,42,43,44] Beta-TCP resorbs and completely replaced by remodeled bone within 13-20 weeks after the implantation procedure.[44,45] Various reports have shown very few complications like infection or nonunion.[46] Though it has suitable mechanical resistance, it is considered lower when compared to the mechanical resistance of cancellous bone.[47] or of the allograft bone.[48] Thus it's use should be selective.[48,49]

Calcium sulphate

Calcium sulfate ($CaSO_4$) as a bone substitute was first reported in 1892 as the first therapeutic success.[37,50,51,52] and has been accepted by FDA in 1996. Calcium sulphate is also known as "gypsum" or "plaster of paris" [53] It offers the same structure as the bone thus possess various advantages, it is osteoconductive[54,55], cost effective[47,55] and availability in different forms (hard palets and injectables)[47,55] without producing allergic reactions.[55] Calcium sulphate resorbs within 1-3 months rapidly.[37,53,55] Furthemore, it has a crystalline structure which is osteoconductive over which the perivascular mesenchymal tissue and bone capillaries can invade.[37,56] While stimulating bone ingrowth this resorption creates porosity.[57] Although, the rate of resorption is way more fast than the rate of new bone formation.[54,58] Besides the disadvantage of fast resorption rate it is neither osteoinductive nor osteogenic with redness and swelling as a complication in many cases after the procedure.[53,55,59] Seen in 4-53% of the cases [dd,ee,ff] [59,60,61] these complications can be managed with local wound care, like other bone grafts infection may be seen post-operatively and may require surgical intervention.[60]

Hydroxyapatite

Hydroxyapatite (HA) belongs to the apatites family, of crystalline compounds with crystalline hexagonal lattice. Being a primary mineral component of teeth ($Ca_{10}(PO_4)_6(OH)_2$), it is extremely biocompatible[9,62,63,64,65] without a risk of inflammatory response..[66] However, the resorption of HA is very slow [67] retained for at least 3 years after the implantation. [64] With a slow bone ingrowth and cell colonization.[64,68] HA acquires good mechanical properties with a compression resistance of upto 160 MPa, probably to be used in small bone defects with low loading condition. [64]

Xenogenic bone graft

Xenografts are obtained and transferred between different species. Its use was first reported in 1889.[1] They are usually derived from bovine source. The considerable advantages of this graft is the availability in abundance and low cost. They can be used in conjugation with various growth factors such as BMP, PRP. In addition to it this bone graft requires placement of a membrane for its stability due to its poor handling properties.[3] They are used as a calcified matrix.[2]

Growth factors

Bone graft materials are commonly used in conjunction with the growth factors to enhance there properties. These are formed using recombinant DNA technology.[2] Growth factors are classified into 20 multiprotein growth factor families or super families. They are epidermal growth factor (EGF), insulin-like growth factor (FGF), platelet-derived growth factor (IGF), fibroblast growth factor (FGF), platelet derived growth factor (PDGF), transforming growth factor (TGF).[5,69,70]

1. Bone Morphogenic Proteins (BMP)

Bone morphogenic proteins are a group of signaling molecules that belong to the TGF-beta family.[7,71] Growth factors are either human growth factors or morphogens such as BMP with collagen (as a carrier medium).[2] specifically BMP 2 and 7 are most popularly used.[3,7,72] They are osteoinductive in nature.[3,7,73] At the cellular level, BMP is known to act on both the osteogenic and

chondrogenic linage.[7,74] These cells are stimulated and differentiated into chondrocytes within 5-7 days. Subsequently, the chondrocytes undergoes calcification and are hypertrophied ultimately replaced by new bone in 9-12 days. Thereafter the newly formed mineralized bone undergoes remodeling phase within 14-21 days.[7,75] Urist et al. named the growth factor extracted from bone organic component as BMP due to its osteogenic properties.[5,76,77]

2. Platelet Rich Proteins (PRP)

Platelets are one of the first cells to visit at the site of injury, being an important factor in wound healing. A complex cascade of events regulated by growth factors takes place for the regeneration of new bone. Besides having a procoagulant effect, platelets are a source of significant growth factors such as platelet-derived growth factors (PDGF), vascular endothelial growth factor (VEGF), transforming growth factor-b (TGF-b) which are engaged in the coagulation cascade for wound healing.[7,78,79] Marx et al. in 1998 reported that the use of PRP with an autograft results in faster regeneration and maturation of newly formed bone in an alveolar defect, when activated with thrombin and calcium chloride, by delivering a higher concentration of growth factors at the site of injury.[7,80]

Classification of bone grafts based on material groups:[2]

1. **Allograft- based bone graft** involves allograft bone used alone or in combination with other materials (e.g., Grafton, OrthoBlast).
2. **Factor- based bone graft** are the natural and recombinant growth factors, used alone or in combination with other materials like transforming growth factor-beta (TGF- beta), platelet derived growth factor (PDGF), fibroblast growth factors (FGF), bone morphogenic protein (BMP).
3. **Cell-based bone grafts** use cells to generate new tissue alone or are added onto a support matrix (e.g., mesenchymal stem cells)
4. **Ceramic-based bone graft** substitute consists of calcium phosphate, calcium sulphate, bioglasswhich can be used alone or in combination (e.g., OsteoGraf, ProOsteon, OsteoSet).
5. **Polymer-based bone graft** uses degradable and non-degradable polymers alone or in combination with other materials (e.g., open porosity polylactic acid polymer)

Conclusion

Autogenous bone as a graft material is considered as the gold standard for grafting purposes. The surgeon should have a good knowledge of properties of each bone graft material and should know when to select which type of bone substitute. Most common use of bone grafts in dentistry is in placement of dental implants, for atrophic ridges of edentulous jaw, filling the cavity defect, reconstruction of bone defect due to tumor or cyst removal. The periosteum and nutrient artery are generally removed with piece of bone in order to preserve the graft alive after the transplantation into the recipient site. Beta-tri-calcium phosphate ceramics, being the gold standard of synthetic bone graft substitute**.** various reports have shown very few complications like infection or nonunion. Therefore, its use should be selective.

Declaration of Patient Concent

The authors certify that they have obtained all the appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their/images and other clinical information to be reported in the journal. The patient(s) understand that their name and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be granted.

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