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Review Article

Biology of Cancellous Bone Graft Materials and their Usage for Bone Regeneration

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Abstract

Bone grafting have been used to treat nonunion, union and acute fractures. Autologous cancellous bone grafts are still the most effective graft material for stimulating bone repair since they present osteoconduction, osteoinduction and osteogenic capacity that are mainly requirements for bone regeneration. However, there are several negative aspects of autologous cancellous grafts such as additional surgical site, post-operative complications and inadequate amount of grafts. Allogeneic cancellous bone grafts, on the other hand, have the same characteristics as cancellous autograft with the exclusion of osteogenic capacity. Understanding of various biological processes such as host mediated immune response, osteo-integration of the graft within host and new bone re-modelling leads to improve the new biological strategies for endosseous grafts. We'll discuss the biology of the cancellous bone graft which is essential to understand host-graft incorporate and also evaluate the specific factors associated with the osseous healing around the graft.

ABBREVIATIONS

MSCs: Mesenchymal Stem Cells; DBM: Demineralized Bone Matrix; PRP: Platelet Rich Plasma; HA: Hydroxyapatite; TCP: Tricalcium Phosphate; IP-CHA: Interconnected Porous Calcium Hydroxyapatite ceramics; PLA-PEG: Polymer poly D,L,-lactic acid-polyethyleneglycol block co-polymer; BMPs: Bone Morphogenetic Proteins; rhBMPs: Recombinant Bone Morphogenetic Proteins; PDGFs: Platelets include Platelet Derived Growth Factors; TGF-β: Transforming Growth Factor-beta; VEGF: Vascular Endothelial Growth Factor; EGF: Epidermal Growth Factor; IGFs: Insulin-like Growth Factors; b-FGF: Basic Fibroblast Growth Factor; AATB: American Association of Tissue Banks; FDA: The U.S. Food and Drug Administration.

INTRODUCTION

Bone tissue can regenerate and repair itself. However, in some cases such as massive bone defects or pathological fractures, bone tissue can't heal itself resulting in delayed unions or non-union, bone lesions and fractures with bone loss. Bone grafting is usually necessary when there is a great loss of healthy bone substance. After a grave injury, a tumor operation, or when an artificial joint is replaced, these grafts contribute towards the rapid anatomical and physiological restoration of tissue defects in patients. Appropriate bone graft material is generally selected taking into account several factors such as defect size, graft shape and their biological and mechanical features, preservation techniques and graft handling. Bone grafts are widely used in orthopedic field such as oral maxillofacial, reconstructive surgery, musculoskeletal injuries and sports medicine involving bone from minor defects to major bone loss [1].

BONE GRAFT PROPERTIES

Bone grafts show biological and mechanical features and provide a scaffolding so that new bone can be formed through osteogenesis, osteoinduction, and osteoconduction [2,3]. Graft materials should have at least two of these biological properties. Osteoconduction is described as one of the feature of bone graft that provides three dimensional scaffold for osteoblasts, facilitate vascularization and provide the migration of new host cells with osteogenic activity. Incorporation of bone graft materials depends on host surrounding viable tissue. Mechanical and biological properties of host-graft interface should permit the integration of the graft with the local host bone for successful osteogenic activity. As a new bone is formed, the graft could be partially or entirely resorbed through the bone formation process [4-6].

Osteoinduction is defined as the improvement of new bone formation in which MSCs are gathered from the host tissue and differentiated into bone cells by the stimulation of new bone productions such as bone proteins, growth factors and cytokines. Osteogenesis is the process of new bone formation results from the transplantation of osteoprogenitor cells along with the growth factors from the bone graft or the host bed. Only autograft materials have osteoblast cells and their precursors. In

addition, allografts could combine growth factors, MSCs, osteo-progenitor cells and osteogenic substitutes to provide direct bone development [5-8].

CANCELLOUS BONE GRAFT SUBSTITUTES

Bone grafts are classified according to their sources. Autologous graft (autograft) is described as bone graft material harvested from the host, whereas allogeneic graft (allograft) is defined as the transplant of the graft from one individual to another of the same species with a different genotype [9,10]. Autografts are still remains as the "gold standard" for bone replacement in order to display the best osteoconductive, osteoinductive and osteogenic features. Bone autografts including matrix proteins and osteogenic cells increase bone in growth. They have complete histocompatibility and don't carry any risk of disease transmission. Although, autologous grafts are the most commonly used materials, they have several disadvantages including additional surgical procedure, donor site morbidity, and significant post-operative complications such as muscle weakness, pain, infection and inadequate amounts of graft material [11].

Substitutes to bone grafting such as DBM, HA, TCP, and their synthetic variants, calcium phosphate and calcium sulfate have been used widely and they have been shown to have osteoconductive but only weakly osteoinductive potential. Growth factors can also be added to provide enhancement of graft incorporation and stimulation of bone healing [12]. DMB is capable of osteoconductive activity to enhance bone formation. Although DMB has no structural strength, it provides rapid vascularization and stable environment for the various proteins and growth factors during demineralization process [13,14]. Urist reported that DBM implants resulted in increased collagen activity. After dissolution of the matrix, new bone formation was observed [15]. Calcium phosphate based ceramics such as HA and TCP are osteo-conductive bone graft substitutes. Chemical structure of HA is similar to mineralized bone matrix and its osteoconductive matrix supports proliferation of bone cells during remodeling process [16]. It provides significant compressive strength but it has a low tensile strength. So, it has limited usage in the therapy of load bearing bone imperfection [17,18]. Even though, porous structure of HA provides osteo-conductive property, it doesn't have enough osteoinductive and osteogenic features.

Calcium based cements such as CaPO4, CaSO4 are generally used as filling materials for their compressive strength but they their tensile strength is lower than that of cancellous bone. Fast absorption rate of calcium based cements causes significant loss of their mechanical properties during their degradation. It is one of the greater limitations particularly for load-bearing applications. While they have been used as biocompatible bone graft substitutes as an expander for osteotomies, insufficient osteo-induction and osteo-integration limit their usage. Several bone derived growth factors and recombinant proteins have been shown to stimulate fracture healing to overcome these disadvantages [19,20].

TCP has been used for a long time as synthetic substitute bone filler in orthopedic and dental surgery. Bioabsorbable, biocompatible and porous structure properties of TCP present excellent timely resorption accompanying in bone remodeling process between 6 and 24 months. TCP has a higher rate of biodegradation than HA after implantation which is occurred by combined osteoclastic resorption and dissolution [21]. However, TCP undergoes reabsorption more rapidly than the host new bone formation resulting inequality between TCP and new bone replacement volumes. For that reason, TCP has been generally used as a filler or expander for autografts [18,22,23].

Growth factors as a bone graft substitutes can be used for the enhancement of the bone graft properties (Table 1). Normally, growth factors are present in bone marrow of the iliac crest and they promote bone stimulation. Autogenous bone marrow aspirate has already been used to stimulate osteogenic repair for delayed union and nonunion of bone defects. Fractured bone starts the cascade of inflammation and clotting cycle which is necessary for bone healing. Researchers have been focused on growth factors to stimulate new bone formation [5,19,24]. BMPs were first reported by Wozney et al. for the treatment of bone defects [25]. Other various subtypes such as BMP-2 and BMP-7 have been discovered in the healing of fractured bones by Tsuji et al. and Makino et al. [26,27]. Although growth factors are strong osteo-inductive agents, they have limitations regarding delivery system. Kaito et.al used combination of synthetic biodegradable porous materials (IP-CHA and PLA-PEG) as a carrier system for delivering rhBMP-2. Results showed that rhBMP-2 containing scaffold system significantly enhanced bone formation [19,28].

Another source of growth factors such as PDGFs, TGF-β, VEGF, EGF and IGFs in bone grafting is the use of autologous PRP. Beyond the pro-coagulant effects of platelets that initiate first response during wound healing process, many growth factors in PRP assist bone tissue healing [29,30].

SOURCES OF CANCELLOUS BONE GRAFT

Autograft is the most commonly used type of bone graft and particularly, cancellous autograft still remains the gold standard for bone regeneration. Autogenous cancellous bone graft is usually used in non-unions with <5-6 cm of bone loss with no strength required. It can be harvested from the ipsilateral extremity during surgery.

Large cancellous graft can be taken from the iliac crest, whereas small amount of graft can be harvested from the proximal tibial metaphysis, distal part of the radius, greater trochanter and medial malleolus of the tibia (Table 2) [31-33]. Iliac crest is the most commonly used autograft source due to the presence of viable cells, the abundance of growth factors and large surface area of the trabecular architecture [34,35]. However, for the patients who have operation risks or low amount of autograft material, allogeneic cancellous bone graft could be alternative source from a bone bank. They have osteo-conductive and osteo-inductive properties and can be found in various shapes and sizes [36,37]. This type of allograft must be screened for any bacterial, fungal and viral infection including HIV and hepatitis. Besides, donor screening, sterile processing, safety of processing technology should be screened by the AATB and FDA to ensure the high quality allografts [38-40]. Although cancellous allografts are alternative sources instead of cancellous

Table 1: Effects of growth factors on host bone-graft incorporation.

Growth Factors	Source	Function
TGF-β	Bone extracellular matrix, chondrocytes and platelets	Stimulates undifferentialed MSCs for osteoblast mitogenesis to regulate collagen and proteoglycan synthesis
b-FGF	Macrophages, MSCs osteoblasts and chondrocytes	Increases osteoblast and chondrocytes cell proliferation and promotes collagen formation
PDGF	Endothelial cells, monocytes, platelets, osteoblasts	Regulate collagen secretion; mitogenetic activity for MSCs and osteoblastic cells
IGFs	Chondrocytes, osteoblasts	Enhance bone remodeling and regulate osteoblast cell proliferation and chondrocyte formation
VEGF	Vascular endothetial cells, osteoblasts	Augments angiogenesis to stimulate mitogenesis of endothelial cells
BMPs(-2,-4,-7)	MSCs, osteo-progenitor cells, osteoblasts	Promote induction of osteoprogenitor cells to turn in to bone forming cells

Abbreviations: BMPs: Bone Morphogenetic Proteins; PDGFs: Platelets include Platelet Derived Growth Factors; TGF-β: Transforming Growth Factor-beta; VEGF: Vascular Endothelial Growth Factor; IGFs: Insulin-like Growth Factors; b-FGF: Basic Fibroblast Growth Factor; MSCs: Mesenchymal Stem Cells.

Table 2: Sources cancellous bone grafts.

Source	Indications and Advantages	Complications and Disadvantages
Distal end of the tibia	Used for foot and ankle surgery, easily accessible source of abundant cancellous bone	Small volume of cancellous graft; joint perforation
Removal of fibular graft	For the treatment of large defects such as congenital pseudo arthritis of the tibia	Mild muscular weakness
Iliac bone autograft	Abundant amount of the cancellous bone available; no significant residual disability	Concerns of donor site morbidity; superficial hematomas and infections
Distal end of the radius	Used for hand and upper extremity surgery	Limited supply; pain and immediate functional disaility in the post operative period
Greater Trochenter	Source for surgery of the ipsilateral lower extremity	Persistent hip pain, morbidity
Allogeneic cancellous blocks, cubes, chips and particulates	Bioresorbable, osteoconductive; used for replacement of auto graft to provide structural support; found any size or shape defect for Regeneration osseous defect, filing of bone defects and augmentation of alveolar crest for spinal surgery and general orthopedic reconstruction	Less potentail fro bone regeneration (compared to auto graft); risk of immunogenicity and possibility of human derived disease transmission.

autografts, they lack osteogenic properties due to the absence of viable bone cells. Another limitations of allografts are harvesting protocols and storage conditions [19,41].

STRUCTURE OF CANCELLOUS BONE GRAFT

Cancellous autograft structures provide trabecular bone with the osteogenic capacity having for superior osteogenesis under the effect of growth factors and cytokines (Table 3) [33]. They are easily re-vascularized and incorporated quickly at the stem cells of the host site since the low oxygen tension and pH of the recipient site attract host pluripotent undifferentiated stem cells to the graft site [42,43]. Although, they have more osteogenic and osteo-inductive capacity than the other graft types, they lack significant mechanical properties. Biomechanical strength during host-graft incorporation depends on biological process of graft osteo-integration. Cancellous autogenous grafts are integrated on a necrotic layer first. Then, the radio-density of the graft initially enhances; but in time, it gradually reduces as the necrotic tissue is resorbed by osteoclast cells. Consequently, mechanical strength of the graft is initially strong, but after the resorption of necrotic bone, in the course of time, structural strength of the graft gradually decreases [11,43].

Allogeneic cancellous grafts can be particulate and have a various shape and size depending on the intended use. They are commercially available and generally have been used for filling of bone defects, spinal fusion augmentation and revision joint reconstructions [11,44]. Cancellous allografts present interconnecting porous system and trabecular architecture which provide a framework for vascular ingrowth and proliferation and differentiation of the cells for bone remodeling at the surgical site [45,46].

BIOLOGY OF CANCELLOUS BONE GRAFT

Autogenous cancellous bone graft

Response of host bone tissue to cancellous bone graft involves a cascade including cellular response, extracellular cellular activity between host bone-graft interfaces until newly formed bone cover the graft surface [34]. Although biology of bone-graft incorporation isn't very well known, osteogenic process is similar to bone healing mechanism. Initial response starts with the hematoma formation, inflammation, neovascularization and then continues with the gradual focal graft resorption by bone resorption process and bone formation on the graft surfaces regulated by inflammatory cells, cytokines, growth factors and bone tissue cells [47]. Blood cells including platelets, granulocytes and monocytes are the first biological components coming

Table 3: Properties of cancellous bone grafts.

Graft Materials	Osteogeneis	Osteoinduction	Osteoconduction	Immunogenicity	Donor Morbidity
Autologus cancellous graft	+++	++	++++	-	+
Fresh allogeneic cancellous graft	-	+/-	+	++	-
Frozen allogeneic cancellous graft	-	+/-	+	-	-
Freeze dried allogeneic cancellous Graft	-	+/-	+	+/-	-
DBM	-	++	++	-	-
TCP	-	+/-	+	-	-

Marking refers to; - no activity; + poor activity; ++, +++ degree of activity; ++++ excellent activity.

into contact with the cancellous graft. They are infiltrated from the recipient site into the tissue surrounding graft and secrete cytokines and growth factors [42,48].

Hematoma formation and inflammation are preliminary interactions of blood cells. Platelets respond to the foreign surface by the formation of fibrin. Fibrin protein plays a key role as a transitory osteo-conduction matrix for osteogenic cell migration towards surface of the graft. Fibrin deposited graft surface allows formation of the osteoid tissue which then remodels into lamellar bone by migrating osteogenic cells [49,50]. MSCs and osteoblast cells attach to the graft surface and synthesize non-collagenous matrix on it leading to further cell attachment and binding of minerals [51]. In the meantime, fibrous tissue occurs at the recipient site in order to increase the osteoclastic activity. Necrotic tissue in haversian canals of the autogenous cancellous graft is removed by macrophages. It leads to the secretion of intracellular products of the recipient bone site which are chemo-attractants for host stem cells. Vascularization process is initiated after 2 days of surgery. Then, MSCs found in both host and graft start to differentiate into osteogenic lineage under the influence of osteo-inductive agents; cytokines and growth factors including TGF-β, PDGF, b-FGF, IGFs and BMPs.

Hematoma formation, inflammation, revascularization and osteo-induction continue as a process together with the bone formation-resorption throughout 4 weeks of surgery [11]. Resorption of the graft by osteoclasts and gradual new bone re-modelling on the graft surfaces are the second phase of graft-host bone osteo-integration. After differentiation of MSCs into osteoblasts, they start to lay down a seam of osteoid along the dead trabecula of the bone graft. Necrotic bone tissue is removed by osteoclasts. As a result of osteoclastic activity, graft begins to be resorbed and replaced by new host cells. Finally, MSCs form new bone marrow cells to fill within the old marrow space [33,35,52,53].

Allogeneic cancellous bone grafting

Allogeneic cancellous bone grafts provide an osteo-conductive agent for bone regeneration. They are usually used for filling of bone defects, posterior spinal fusions, tibia plateau impression fractures and impaction grafting during femoral or acetabular revisions as structural support [33]. When allogeneic cancellous bone graft is compared with autogeneic cancellous bone graft, less bone healing is obtained in allogeneic bone graft. After transplantation of fresh allogeneic cancellous graft, host mediated immune response by macrophages and lymphocytes leads to inhibition of essential growth factors causing delay of bone-graft incorporation and neo-angiogenesis. Necrosis is occurred by surrounded inflammatory cells. After 8 week of surgery, fibrous tissue starts to cover the cancellous allograft. Unfortunately, aggressive host immune response delay osteo-integration of the graft. Freeze - dried or frozen allogeneic cancellous grafts show reduced immunogenicity comparing with the fresh cancellous allograft. However, osteo-conduction and bone resorption of cancellous preserved allografts keep going faster than that of fresh allografts. The transplanted allograft can remain entrapped within the host bone [11,42,53-55].

Freeze- drying method which is the most common preservation procedure of cancellous allografts can destroy the osteo-progenitor cells and osteo-inductive factors, hereby they provide only osteo-conductive properties as a scaffold [56]. For that reason, grafts could combine with the biological elements such as rhBMPs to stimulate cell proliferation, differentiation and osteogenesis [57]. Although positive results were reported, there are also negative feedbacks. Delloye and their colleagues have been evaluated the efficacy of rhBMPs in nonunion of femoral allografts. According to the results, healing of allograft fractures and union of allograft-host junction were not observed. rhBMPs alone were not adequate to treat in allograft non-unions and fractures [58].

Bone allograft causes several histopathological results including avascular necrosis, malignant tumors and osteoarthritis since fatigue micro-fractures are formed in the necrotic bone near the fracture site and it can't remodel itself resulting in structural failure [59-62]. Osteoclastic resorption of the graft materials, loss of mineral density and unrepaired micro-cracks have been also reported after allograft reconstructions [63].

Prevalence of functional failure of allografts has been noted approximately 60 % at 10 years. The causes of these pathological conditions that influence the allograft incorporation and their effect on physiological and mechanical capacity are still unknown. Various biological process can lead to failure of allograft reconstructions [64]. Moreover, immunological response may also play a part in nonunion at the host–graft junction [65].

DISCUSSION AND CONCLUSION

Biological mechanism of cancellous graft involves bone tissue cells, growth factors, cytokines and inflammatory cells in a well-orchestrated manner during re-modelling phase of bone healing [42,66]. Autogenous cancellous bone grafts are considered as the

gold standard for bone regeneration, since they present the best osteo-conductive, osteo-inductive and osteogenic properties. Moreover, they provide complete histocompatibility and display minimum immunological rejection [67]. Even though autogenous cancellous bone grafts are effective, they are associated with several restrictions and complications regarding with donor-site morbidity, sufficient quantity of grafts, infections, increased blood loss throughout operation [67,68].

Allogeneic cancellous grafts could be used for reconstruction of the defects. Incorporation of cancellous allograft and revascularization are carried out for almost 8 months after transplantation. Osteogenesis is started by the host cells and host immune response is initiated just after the grafts are transplanted that is followed by the penetration of blood vessels. When revascularization decreases over time, allograft incorporates and necrotic bone is removed. The interface between allograft transplant and host fibro-vascular tissue is the site of osteoclastic activity and bone resorption. The balance between osteolysis and osteogenesis must be maintained for graft incorporation [59-63].

Although allogeneic cancellous graft has several disadvantages including transmission of infection and inability of osteo-conductive property, they are still being used widely in bone defect repair. Even though osteo-inductive agents such as rhBMP-2 might be the candidate to eliminate these limitations, different factors including catabolic proteins secreted by host site cells influence osteo-inductivity. A better understanding of the complex biological mechanism of the host bone-graft osteo-integration leads to develop new strategies for the limitations of the usage of cancellous allografts. Therefore, the cascade of complex biological events, including anabolic and catabolic factors should be explored to reduce pathologic results and improve local repair after allograft transplantation.

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