Recent Patents in Bone Graft Substitute for Bone, Tendon, and Ligament Reconstruction

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Abstract: Treatment of large bone defects poses a real challenge to the orthopaedic surgeon. The surgeon often times calls on creativity in the form of bone graft substitutes to help mend large bone defects. The bone graft substitutes used today include inorganic compounds such as calcium phosphate, osteoconductive composites which act as a scaffold to allow for new bone growth, and some may include osteoinductive proteins which provide signals to the microenvironment promoting osteogenesis. Autologous bone grafts are still the gold standard and this creates a risk of harvest site morbidity and the defect may be too large for autologous bone alone. Injuries requiring tendon or ligament reconstruction rely upon the use of bone blocks in the form of bone-tendon-bone grafts, which can also create a hurdle for the orthopaedist. We have reviewed the current literature and recent patents available on bone graft substitutes and bone blocks for bone-tendon-bone grafts and have described new biomaterials and therapeutics available to the orthopaedic surgeon.

Keywords: Biomaterial, BMP, bone, BTB, ceramic, composite, DBM, defect, glass, graft, inorganic, ligament, organic, osteoconductive, osteoinductive, scaffold, synthetic, tendon.

INTRODUCTION

In their native state, nearly all bone graft substitutes promote osteoconduction via a scaffold-like structure; provide growth factors and proteins for osteoinduction, and cells capable of inducing osteogenesis. Autologous bone grafts are still the gold standard because it has a myriad of properties including a strong scaffold for new bone formation which is promoted by osteoprogenitor cells present within the graft. Allografts are incredibly popular and are responsible for nearly one-third of bone grafts used in North America [1]. They act as a nidus for osteoconduction within the recipient, but since it’s a foreign tissue, there’s a chance for disease transmission [2]. It also has osteoinductive potential, but much of this is stripped away once the graft is treated to help minimize disease transmission [1]. Size limitations, risk of morbidity from autologous bone grafts, risk of disease transmission, and decreased osteoinductive potential have fueled research endeavors for man-made graft materials.

Many synthetic and bioengineered options are available for repairing large bone defects. Native bone is generally comprised of about 60% inorganic material with a majority being hydroxyapatite and 35-40% is organic which includes collagen, proteoglycan and non-collagen proteins. Inorganic compounds currently used closely mimic the inorganic components of bone but have limitations in load bearing applications. Some researchers have created composites made of both inorganic and organic materials which are pliable, flexible, and have great mechanical strength [3,4,5]. One of these composite materials is capable of load bearing applications such as repair of large bone defects and arthroplasty [6]. Advancements in bioactive glass have yielded grafts capable of osteostimulation in addition to their osteoconductive, flexible, and moldable properties [7,8]. Additional advancements involving mesh, putty-like materials, and small molecule therapies have been added to the list of graft materials [9,10]. Advancements have also been made in the graft options for smaller orthopaedic bone defects as well as bone loss in dentistry.

Ligament injuries are common and require attention, especially ones involving the knee, due to increased risk of further injuries and arthritis. Injuries requiring reconstruction necessitate the orthopaedic surgeon to replace the ligament with a graft strong enough to support day-to-day activities. Much like bone defect repairs, ligamentous injuries may be repaired using autologous grafts such as patellar bone-tendon-bone (BTB). Harvest site morbidity is a concern similar to autologous bone grafts, while allograft is an alternative that eliminates donor site morbidity and decreases operative times [11]. A unique design in this area of research includes cylindrical bone blocks geared towards knee cruciate reconstruction [12]. Others have developed similar bone blocks for use in tendon injuries [13,14]. Proper fixation of the graft is another popular area of research. Finally, synthetic options are available as bone blocks for ligament and tendon reconstruction.

The purpose of this review was to compile all recent patents for bone graft substitutes and bone blocks to provide a
clinical update in orthopaedics for treatment of large bone defects plus reconstruction of tendons and ligaments. We have also included novel therapies for small orthopaedic and dentistry bone defects. Since autologous grafts are still the gold standard, it is important to review all other options available to the patient with the goal to reduce morbidity and improve patient outcomes.

**BONE GRAFT SUBSTITUTES FOR BONE DEFECT REPAIR**

Many substitutes for bone graft repair of large and small defects are available. Advancements in this area of research have decreased the number of implant failures, need for revisions, and improved patient outcomes. Novel biomaterials including inorganic/organic compounds, composite materials, glass, mesh, ceramics, and small molecules have transformed the fields of reconstructive surgery and dentistry. Recent developments have produced materials which are stronger, can be impregnated with nanomolecules to support bone growth, and are highly biocompatible, making them ideal solutions for correcting bone defects.

**Orthopaedics – Inorganic and Organic Compounds Plus Composites**

Inorganic compounds such as calcium phosphates, especially type-B carbonated hydroxyapatite (HA) closely mimic mammalian bone. Different stoichiometric compositions have been extensively evaluated to match the adaptability, biocompatibility, structure and strength of native bone. The porosity and pore size that stimulate revascularization and bone remodeling have been identified. Unfortunately, calcium phosphate implants lack strength, handling and the flexibility necessary to be used in a wide variety of applications which has seen them largely promoted for non-load bearing applications as bone void fillers. Recently, they have been combined with rigid fixation systems to reinforce and help stabilize weak bony tissue sites [3-5].

Erbe et al. disclosed a composite bone substitute that includes resorbable porous inorganic calcium phosphate and collagen which is osteoconductive and has good resorption and bone formation properties [3-5]. The highly pliable and flexible composite can be shaped to the anatomy of the defect and has sufficient structural and mechanical strength to bear compressive loading. Also of importance are the highly biomimetic properties of this implant type which has been associated with reducing bacterial infections following foreign body insertion [15]. The inorganic salt is a precursor mineral which under modest heating converts to Beta-calcium phosphate (TCP). The reaction product combined with collagen yields a highly workable foaming substitute that is osteoconductive and ductile, which can be shaped into strips, cylinders or the appropriate anatomy of the defect in situ. The porous and interconnected nature of the implant promotes cell infiltration and permeation by bodily fluids. Additionally, the porous implant can be partially filled with therapeutics that may be delivered in situ at predetermined doses. The composite foam has a broad pore distribution of 1–1000 microns, which can wick and imbibe fluids, and retain them under a compressive load. Having the ability to manipulate its structure to the shape of the defect, lower rates of infection, and the addition of therapeutics to the graft make it a highly attractive option compared to the above described inorganic option.

Gower et al. disclosed a composite comprised of an organic matrix which is fluid-swellable, fibrous, and is penetrated by the inorganic mineral phase while it is in the form of an amorphous polymer-induced liquid precursor (PILP) phase [6]. Oftentimes, the organic substrate is collagen and the inorganic mineral is calcium phosphate, calcium carbonate, or a mixture thereof, wherein the inorganic mineral is deposited intrafibrillarly within the collagen substrate. By using a PILP phase, there is superior infiltration of the inorganic mineral phase into the organic matrix which closely mimics bone when it’s a composite of calcium phosphate and collagen. This synthetic bone formation process may not only produce a graft of similar composition to bone but also a structure with comparable mechanical properties plus bioresorbable potential making it a good option when working with critical-sized osseous defects or joint replacement [16].

Huipin et al. disclosed a porous calcium phosphate which is formed by microparticles with sizes ranging from 50 to 1500 microns. It is said to have excellent osteoinductive behaviors in living tissue and has good bone formation at its surface. Due to its sand-like structure, it displays flowing properties which allow it to be utilized as an injectable substance, which is an advantage compared to larger and more rigid options. Typically, porous calcium phosphates are used to treat smaller bone defects but Huipin et al. have varied its physicochemical and structural components by altering chemical composition and post-synthesis sintering temperatures for their ceramic products, which provides hope for its application in larger defects. Of note, this study was performed in sheep and needs further investigation, but it does appear to be a promising addition to the list of graft options for large bone defects [17].

The composite described by Erbe et al. is currently one of the more attractive graft options amongst inorganics, organics, and composite materials. The composite described by Gower et al. is also a good option due to its novel use of a PILP phase which allows it to closely mimic the structure of native bone. Lastly, the porous calcium phosphate described by Huipin et al. is unique and promising, but further studies are necessary to provide evidence for its use as a bone graft material.

**Orthopaedics – Glass, Mesh, and Putty-Like Materials**

Another area of orthopaedic bone graft substitutes involves the use of resorbable bioactive glass. Theodore et al. have disclosed a glass which is osteostimulative, osteoconductive, flexible, and moldable, especially when wet [7,8]. The scaffold constituents can be packaged into an injectable system and mixed homogenously just prior to use in situ. The bioactive glass is an alkali material that reacts with physiological fluids and on contact forms an apatite layer on their surface, which is stimulatory to osteoblasts and is resorbed via dissolution. The glass can be mixed homogeneously with other constituents, coated onto the collagen fibers, or coated onto a homogenous mixture of collagen and calcium phosphate. The porous calcium mineral makes the
resulting graft highly porous with a broad pore size distribution. The novel bone graft is highly flexible and readily shaped *in situ*, can deliver various therapeutic products, and retains fluids under compressive loading.

Biocompatible meshes are a new player for dealing with bone defect repairs. Bagga et al. disclosed a mesh material which has yielded novel bone restoratives [9]. One of the resulting advancements is a pliable bone graft comprised of an osteoconductive foam, resorbable polymer, and calcium phosphate that at least partially surrounds a biocompatible mesh. This material is pliable and easily shaped which provides an unprecedented utility to a reconstructive surgeon, allowing them to manipulate the restorative into shapes of their desire. They can be customized with radiopaque embodiments or coated with titanium plasma spray to significantly increase implant surface area and mechanical retention in the bone at the time of placement. The implant may also be wetted with a bone marrow aspirate, cell concentrate, liquid hemostat, fibrin sealant, blood, or saline in some embodiments. A variety of materials are available including titanium, stainless steel, nitinol, polymers, or some other composite blend depending on the embodiment selected. These materials can be modified in several ways including their mechanical interlock mechanism as well as its surface textures, which may facilitate adequate use in the body.

Recent literature suggests a synergistic role for lipids such as triglycerides, cholesterol and saturated short chain fatty acids in accelerating and inducing larger bone deposits in combination with BMP-2 delivering implants [18]. Acid (HCl)-demineralized bone matrix (DBM) contains a mixture of BMPs which is capable of inducing new bone formation at ectopic sites [19]. However, DBM of human origin is difficult to work with without a suitable carrier that will combine homogenously and improve its handling properties. Nimni disclosed a bone graft material composed of DBM that incorporates lipids such as lecithin and triglycerides which enhances osteoinductive properties of DBM and improves its handling properties for easier manipulation [20]. In addition, the improved graft is biocompatible, and the incorporation of lipids enables the graft composition to be modified as needed. In one combination, the graft is putty-like and composed of DBM, lecithin, triglycerides, and saturated fatty acid or combination thereof. This putty-like composition is however, insoluble in bodily fluids and non-extrudable. The bone graft may be further modified with an emulsion carrier which is compatible with the lipids. The bone graft paste containing an emulsifier is soluble or partially soluble with tissue fluids and extrudable through a syringe. The putty- and paste-like bone graft substitutes can also be comprised of anti-oxidants such as Vitamin E and Vitamin C, calcium salt, hydrophilic swelling polymers of methylcellulose and ethylcellulose derivatives, antibiotics, growth factors, platelets, plasma, or even autologous bone marrow. Lecithin provides phosphate ions which along with solubilized forms of calcium, nucleate around new collagen to synthesize HA. Lecithin and triglycerides have the ability to stabilize hydrophobic growth factors and delay their bio-degradation. Solubilization is delayed by the formation of insoluble calcium salts with the available organic phosphate present in lecithin molecule.

The additions of glass, mesh, and putty-like materials have several advantages compared to other, more rigid, graft options. The glass described by Theodore et al. has similar capabilities to previously described composites but it has the unique ability to be used as an injectable material. For reconstructive surgery, the mesh described by Bagga et al. has superior mechanical retention properties shortly after surgery plus several modifiable properties which make it a unique option. Lastly, the putty-like material described by Nimni et al. can be utilized as an injectable and its lipid properties enhance its osteoinductive properties making it a great graft option.

**Orthopaedics – Small Molecule Therapies**

Pyrrolidone molecules have been integrated into porous ceramic and glass materials due to the works of Pyrhonen et al. [10]. These molecules have been identified as having various stimulatory effects, and N-methyl pyrrolidone (NMP) is reportedly osteostimulatory, which accelerates the formation of new bone [18]. The inventors report a synergistic enhancement of bone formation under the stimulatory effect of bone morphogenetic proteins (BMPs) and pyrrolidone, however, this is an expensive area of research that requires further investigation. Pyrrolidone can be used in several settings due to its ability to incorporate onto porous carriers composed of calcium phosphate ceramics, bioactive glass fibers soaked in simulated body fluid to create a calcium phosphate and Si-rich layer, and bone matrix of bovine origin. Pyrrolidone can be coated onto the bone graft material surface or introduced via different mechanisms during manufacturing.

**Dentistry and Small Orthopaedic Defects – Crosslinkable Beads and Polymers**

In dentistry, bone substitute materials are necessary to overcome bone loss issues especially following tooth extraction. Implants are available for reconstruction of jaw bone damages resulting from trauma, disease or tooth loss, in the treatment of periodontal bone void defects and in replacement or augmentation of the edentulous ridge. The alveolar cavity created when a tooth is extracted undergoes resorption at a rate of 40–60% in 2–3 years, and continues yearly at a rate of 0.25% to 0.50% per year.

In an effort to treat these smaller bone defects, Ashman et al. have disclosed a crosslinkable bone graft substitute which is a combination of biologically-compatible polymeric beads (core) coated with a hydrophilic polymer (shell) that have crosslinkable reactive groups [21,22]. The polymeric beads have a diameter of 600 – 800 microns composed of biocompatible allopast such as polymethylmethacrylate (PMMA) and polymeric hydroxyethylmethacrylate (PHEMA) with a calcium surface. These core beads are non-toxic and do not elicit an immunological response in living tissues. The calcium hydroxide surface is converted to calcium carbonate apatite (bone) on exposure to bodily fluids which helps promote its interface with bone. The core can also be modified with pure calcium phosphates such as HA and TCP. Hydroxyapatite containing core polymer beads have a significantly higher modulus. Biologically compatible cadaver
bones and bovine bone materials may be mixed with the core polymer to form the polymeric beads.

The core beads are coated in a hydrophilic polymerizable shell, which contains reactive groups that aid in polymer network formation upon curing. Monomers such as polyethylene glycol (PEG), PHEMA and N-vinyl pyrrolidone (NVP) are preferred when coating the core polymeric beads. The shell polymer may be crosslinked following initiation with a photoinitiator, a redox initiator or a combination of both. An initiator and accelerator of the reaction are provided in a kit and are mixed with the shell polymer coated beads prior to curing. The resulting polymer network is a composite with homogeneous mechanical properties, and a high level of mechanical and structural integrity especially under compressive loading. The core polymer beads coated with the shell polymer may be implanted into the defect site in its granular form and crosslinked in situ. The hydrophilic shell polymer helps to facilitate infusion of body fluids into the pores of the implant and promotes tissue ingrowth. This novel creation can be modified to deliver therapeutics such as anti-inflammatory, anti-bacterial, anti-fungal, anti-viral, analgesics, growth factors, and diagnostic agents which may be mixed into the core particle, coated onto the core bead or combined with the shell polymer.

**BONE BLOCKS AS PART OF BONE-TENDON-BONE GRAFTS FOR TENDON AND LIGAMENT RECONSTRUCTION**

Ligamentous injuries, particularly knee cruciate ligament tears, are unfortunately common injuries stemming from a variety of mechanisms including recreational athletic injuries to blunt trauma. If left untreated, knee ligamentous injuries can result in further injuries and long term consequences, such as meniscal injuries and degenerative arthritis respectively. For complete knee cruciate tears, ligament reconstruction is the treatment of choice. Desirable graft characteristics for cruciate reconstruction include readily availability of the graft and ease in preparation prior to implantation. In addition, sufficient initial stable fixation to allow immediate rehabilitation is also desired. Noyes et al. studied the biomechanical properties of cruciate reconstruction [23]. The authors reported graft strengths of approximately 440-450 N are needed for most activities of daily living. Hence, the method of ligament reconstruction would ideally provide sufficient post-operative pullout strength that rehabilitation can commence without concern for graft failure.

**Bone-Tendon-Bone – Autografts**

Current preferred options for ligamentous cruciate reconstructions include autogenous grafts such as patellar bone-tendon-bone (BTB). The limitations of autografts, however, include donor site harvest morbidities such as significant anterior knee pain with BTB patellar tendon graft which could adversely affect patient outcome [11]. In addition, the availability of BTB autograft in revision and multiligamentous scenarios is also often times limiting. Considerable operative time is also needed to fashion the autograft tendon and bone blocks in order to achieve a specific geometry, length, and tension to fit a specific location and tunnel width. For those reasons, other viable sources of bone blocks to construct BTB allografts are attractive options. This section reviews some of the recent patents on the use of alternative sources of bone blocks in tendon and ligament reconstruction.

**Bone-Tendon-Bone – Allografts**

The advantages of allograft as an autograft substitute includes its readily availability, avoidance of donor site morbidities, ability to be pre-fabricated prior to onset of surgical procedure thus decreasing patient surgical and anesthetic time, and its biocompatibility and integration with host tissue over time. Steiner et al. disclosed a cylindrical bone block design that was devised to be used in femoral and tibial tunnels in knee cruciate ligament reconstructions [24]. A large central hole is machined to accommodate the tendon graft of a desired length. This allows the graft to be tailored in terms of length and tension to fit patients of different size. Parallel channels are created on the outside of the bone blocks to accommodate a tendon loop construct. Ribs are also machined on the outer surface of the bone block to provide better grip within the bone tunnel. The bone blocks are designed to be held into the respective tunnels using interference screws on both ends. The tendon grafts are secured in the blocks via sutures holes in the bone block and securing the tendon onto itself. One criticism of this patent construct, however, has been the low pullout strength of the sutured tendon loop construct used to affix the tendon onto the allograft bone block [25]. Only two of the thirteen samples tested had pullout greater than 400 N, making the initial graft fixation potentially tenuous.

Bianchi et al. disclosed a similar concept using various shaped bone blocks to attach free tendon ends for fashioning allograft BTB construct [25,26]. However, instead of suturing the tendon ends onto itself for fixation of the tendon to the bone blocks, the free tendon ends are “sandwiched” between textured surfaces of the allograft bone blocks. This design therefore similarly allows the tendon length, tension, and orientation to be customized to fit the function of the surgeon’s choosing. Furthermore, the patent disclosed the design of the bone block textured surface. The authors found enhanced grip strength with the textured bone blocks compared to smooth bone blocks, particularly the Ω-shaped channel configuration. The Ω-shaped channels actually increase the surface contact interface between the bone and tendon [27,28]. It also grips the tissues without cutting, and unlike similar designs with teeth or ridges, it only exerts its grip strength when the tissue is being pulled or squeezed [27,28]. The patent reported a pull-out strength that exceeded 500 N for the textured Ω-shaped channel bone blocks before failure with this particular design.

Zhaukauskas et al. also described various shaped textured surface bone blocks for construct of BTB grafts [29]. While the contact force of the bone block textured surface on the tendon provided one source of grip strength, the authors discovered that alteration of the bone block geometry once it was implanted with a second device, such as an interference screw, further enhanced the pull-out strength of the bone-tendon-bone construct. To that effect, grooves on the outer surface of the bone blocks were placed to accommodate and guide the interference screw along the length of the bone
allograft. The preferred embodiment of this invention is placement of the bone block attached to the tendon into a bone tunnel diameter at least 1 mm smaller than the combined diameter of the bone block and interference screw. As the interference screw advanced, the bone block would be compressed against the tunnel providing further compression of the bone block on the tendon allograft. In the results of Instron testing with this embodiment, pull-out strength well-above 450 N was regularly achieved.

New Concepts in Graft Fixation

Olsen et al. disclosed a novel approach to fixation of allograft bone block to respective bone tunnels [27,28]. Rather than the use of foreign implants to secure the ends of the BTB graft into the bone tunnels, such as interference screws, screw threads are machined into the allograft bone blocks which are attached to tendon ends. The respective graft tunnels are then tapped to accommodate the threads of the BTB bone block. Using a graft tensioner and application device, the BTB graft can then be advanced and secured into the bone tunnel similar to tightening a screw under arthroscopic visualization. By turning one graft end either clock-wise or counter-clockwise, the graft tension can be either tightened or loosened respectively. In addition, the pitch and diameter of the threads on the bone block can be varied, which can adjust the pull out strength accordingly depending on the size and demand of the patient.

Synthetic Options

In addition to allograft bone block used for ligament reconstruction, synthetic bone blocks have also been described. Synthetic bone blocks can be porous and allow ingrowth for native cells. Porous implants may also be seeded with osteogenic cells along with growth factors prior to implantation, which may enhance healing. Dinger et al. described such an invention utilizing biodegradable polymer bone blocks for fixation of tendon and ligament [30]. The implant is partially porous in order to allow ingrowth and migration of surrounding native cells with a central trough to accommodate each end of a free tendon. The tendon is affixed to the implant, and the graft is then secure to respective bone tunnels using devices such as interference screws. The outer surface of the implant may be grooved, which would increase grip within the bony tunnels once implanted. The ideal embodiment of the patent is for use in ACL reconstruction. The patent cites the pull-out strength being approximately 400 N during the healing phase with this embodiment.

CONCLUSION

Recent advancements in biomedical and tissue engineering have provided better solutions for treating challenging problems in orthopaedics, reconstructive surgery, and dentistry. Our review of the literature highlights these new developments and hopes to educate the audience on the benefits as well as any downfalls of these recent discoveries. This area of research is very promising and we are confident that novel substitutes and therapies will enable surgeons to provide even more specific treatments and ultimately better outcomes in the future.

CURRENT AND FUTURE DEVELOPMENTS

Advances in tissue engineering and biomaterial research will continue to contribute to the new development of bone graft substitutes. Stem cell and growth factors combined with an optimal osteoconductive scaffold may provide promise for difficult fractures and large bone defects. Our lab currently studies the ability of human adipose-derived stem cells (hADSCs) to generate an osteogenic response following transfection with bone morphogenetic proteins (BMPs). We have recently shown an additive response in bone formation when vascular endothelial growth factor (VEGF) is combined with BMP-6 in cloned mouse osteoprogenitor cells [31]. We believe that in the future, biosorbable scaffolds will be impregnated with growth factors like BMPs and VEGF plus MSCs. These scaffolds will have the ability to promote target specific osteogenesis and angiogenesis and hopefully provide a better approach to treating large bone defects and other musculoskeletal diseases.

Others have modified current concepts which promote bone regeneration using isotropic pore structures hydroxypatite/alumina bi-layered scaffolds [32]. These novel options promote osteointegration and osteoconduction plus the added alumina provides substantial hardness to the graft. Studies to date have been performed in the beagle tibia and further clinical studies will determine its potential role for treating bone defects. In regards to soft-tissue and bone interfaces, which is an important area of research, particularly in the knee, newly engineered bone-ligament complexes have shed light on a challenging area [33]. These complexes take advantage of fiber-guiding scaffolds and use perpendicularly oriented micro-channels, which provide guidance for cellular processes to anchor ligaments between two distinct structures. Early studies have proven that they are able to withstand biomechanical loading to restore large osseous defects. This will hopefully benefit ACL reconstruction and treatment of other ligamentous injuries in the future.

CONFLICT OF INTEREST

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