Synthetic Bone Grafts in Orthopaedic Surgery

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Bone grafting is critical for healing of large or critical-sized defects and spinal fusion. The use of autogenous sources of bone graft has been considered the ‘gold standard’ for several reasons, including the osteoconductive, osteogenic, and osteoinductive properties of autograft and the lack of immunogenicity or disease transmission when utilized. Major drawbacks of harvesting autogenous bone graft include the risk of chronic donor site pain, hematoma, limited availability and variable quality, infection, and increased operative time. Moreover, when used in spinal fusion surgery, pseudarthrosis rates with autograft have been reported to range as high as 5–44%. For these reasons, research efforts have focused on the development of synthetic graft substitutes including calcium phosphate, calcium sulfate ceramics and biodegradable polymers. The ideal synthetic material may vary accordingly with the specific osteogenic or osteoinductive factors utilized, the location and placement of bone graft, i.e. axial or appendicular skeleton, and species of animal into which the bone graft is applied.

In recent years, natural and synthetic forms of calcium phosphate have been developed as materials for bone repair and augmentation. This group of materials closely resembles the mineral composition, properties and microarchitecture of human cancellous bone and has a high affinity for binding proteins. Normal density autogenous cortical bone has pore sizes ranging from 1µm to 1,000µm whereas cancellous bone has pores from 200µm to 400µm. This microarchitecture of cancellous bone, including the size, extent and interconnectivity of the pores, affects tissue ingrowth, cell attachment, and diffusion of nutrients into the area. Studies have suggested an optimum pore size for neovascularization of at least 50–200µm for new bone appositional formation and ingrowth. Calcium phosphate materials may be classified by chemical composition and whether they are of natural or synthetic (ceramic) origin and include hydroxyapatite (HA), β-tricalcium phosphate (β-TCP), biphasic calcium phosphate (BCP, combination of TCP and HA), and calcium-deficient apatite forms.

Commercially available forms of HA of natural origin are derived from coral exoskeletons composed of calcium carbonate. Processing is performed by hydrothermal conversion of coral to HA, which maintains the interconnectivity and porosity and is available in granular or block configuration or as coating on implants, as well as differing pore sizes. This porous form of HA is brittle and carries minimal mechanical strength until bone ingrowth and replacement occurs while simultaneously being very slowly resorbed in vivo. Synthetic ceramic composites may be more suited to function as a delivery vehicle for cells and growth factors based on composition and mechanical properties. β-TCP composites are developed by compacting TCP powder with naphthalene and the latter is then removed, creating a porous structure. TCP has greater solubility than HA and is rapidly resorbed. This increase in interconnectivity and thereby surface area in TCP may offer several potential advantages, including continuous supply of nutrients, greater cellular and tissue ingrowth, and enhanced revascularization via the smaller pores.

Investigations have related bone formation with recombinant human bone morphogenetic protein (rhBMP)-2 on a biphasic ceramic carrier with the ratio of HA to TCP. Boden et al. have investigated the effect of BCP granules combined with rhBMP-2 in posterolateral spinal fusion models in human and non-human primate subjects. Previous studies have found that while a composite of 60:40 HA:TCP acted as an effective carrier, the predominance of HA made its disappearance slow and radiographic detection of bone formation more difficult. In a follow-up study, the HA:TCP ratio was changed to 15:85, which resulted in a 100% fusion rate. Additionally, the authors concluded that the new formulation of HA:TCP (15:85) was more compression resistant and resulted in better radiographic visualization of new bone formation. Others have reported that a higher HA:TCP ratio improves bone formation. In a pilot prospective randomized clinical trial, Boden et al. evaluated rhBMP-2 on a BCP carrier in single-level posterolateral lumbar fusion with or without instrumentation. Radiographic and clinical outcome data suggest that this BMP composite delivery system is an effective potential replacement for autograft.
Other forms of BCP ceramics have been developed for rapid in situ setting allowing for injection into bony defects. The newer formulations of these substances minimize heat release and shrinkage and typically set within 12 hours of insertion. Several of these formulations have been released by the US Food and Drug Administration (FDA) or are currently undergoing investigation to enhance fracture fixation or fixation of implants in osteoporotic bone and for delivery and release of antibiotics (Skeletal Repair System (SRS), Norian; alpha-BSM, ETEX, Cambridge, MA; Bone Source, Stryker-Leibinger, Kalamazoo, MI). Their role as carriers for growth factors and cells in spinal fusion applications has not been established but they may have some role that deserves investigation as devices allowing direct agent delivery into a required area. Otherwise, studies have shown that release of enzymes from these devices can be controlled by manipulation of the formulations and when a calcium phosphate paste composite with rhBMP-2 is injected into a rabbit ulna osteotomy model, accelerated healing is noted.

The combination of carriers, including collagen and BCP, as a delivery system for growth factors may have at least theoretical advantages for retention of appropriate concentrations of growth factors at a site of bone healing and has been evaluated in posterolateral rabbit spinal fusion and subcutaneous bone formation models. A ceramic–collagen composite may also have compression-resistant mechanical properties that improve handling of the graft and maintain a larger space. Collagraft (Zimmer, Warsaw, IN) is a composite of porous HA (65%) and β-TCP (35%) granules combined with bovine-derived fibrillar type I collagen. The collagen may serve as a carrier for autogenous bone marrow cells with appositional new growth occurring directly on the ceramic. Limited clinical studies have assessed the role of Collagraft with BMA in long bone fractures. Healos (DePuy Spine, Raynham, MA) is another mineralized composite of type I collagen fiber coated HA that possesses tensile strength allowing for increased graft space coverage in its moldable form. Healos may serve as a carrier for marrow cells based upon the binding affinity to HA as shown in rabbit posterolateral fusion where arthrodesis rates are equivalent with autograft alone.

Injectable forms of synthetic biodegradable polymers (PLA–PEG) are also being investigated. The biodegradable composite developed has advantageous physical properties and is temperature-sensitive—when heated it takes on a liquid, semi-solid form and following injection, cools, and forms a semi-solid providing an osteoconductive scaffold and slow release of any contained growth factors.

Calcium sulfate forms of ceramics have also been developed to harden in situ and function as space fillers preventing ingrowth of soft tissues while new bone growth occurs and may function as an osteoconductive carrier, although rapid resorption rates limit this capability. Calcium sulfate implants including Osteoset (Wright Medical, Arlington, TX) or BonePlast (Interpore Cross, Irvine, CA) provide a uniform crystalline structure with a predictable resorption rate. A calcium sulfate putty as a carrier for demineralized bone matrix has been developed as an extender for spinal fusion (Allomatrix, Wright Medical, Arlington, TX).

While organic compounds for delivery of osteoinductive agents have long been studied, a newer class of synthetic material, the biodegradable polymers, including polylactic acid (PLA) and polyglycolic acid (PGA), has recently received considerable attention. Biocompatibility has been established through their use as suture materials. These polymers are slowly degraded by hydrolysis and an inflammatory reaction may ensue. As these devices are degraded any containing factors may then be locally released making these composites an ideal substrate for a growth factor/cell delivery system.

PLA was the first such compound studied for use as a carrier for BMP Miyamoto et al synthesized PLA into several molecular weights (MW): 105KDa, 21KDa, 3Kda, 650Da, and 160Da. They concluded that the PLA at 650Da was best suited as a carrier for BMP due to its material properties, handling characteristics, and resorbability. Bone formation was less than expected and the investigators felt it was due to the high acidity and rapid degradation of the low molecular weight homopolymer. A polyethylene glycol (PEG) moiety was added to the PL homopolymer and poly-D,L-lactic acid–polyethylene glycol (PLA–PEG) block co-polymers were introduced. This adjunct reduced the acidity and increased the overall molecular weight of the compound and subsequently led to more robust bone formation and increased bone mass in a murine muscle pouch model. Other studies have also demonstrated the effects of PLA–PGA microspheres or when used as a sponge containing BMP-2 in ectopic bone formation assays, long bone defects, or osteotomy models and canine and rabbit posterior lumbar fusion models.

The options for bone grafts used in bone healing are numerous. The ideal synthetic graft material will depend upon several factors including anatomic location within the skeleton where the growth factor or cells to be delivered are needed, host factors, and biomechanical factors of the local environment. A version of this article containing references can be found in the Reference Section on the website supporting this briefing (www.touchmusculoskeletaldisease.com).