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Bone-graft substitutes in orthopaedic surgery

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As the number of products increases, patient safety must remain a top concern

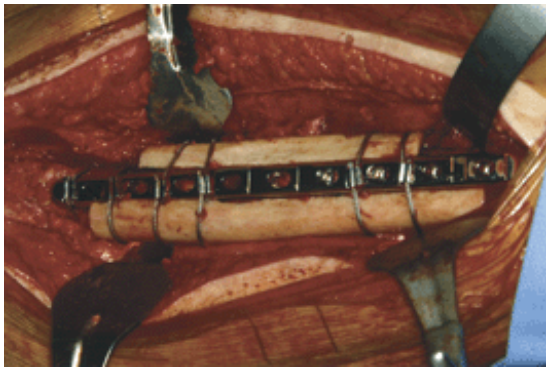
Bone grafting is a big business, generating sales of more than $2.5 billion a year.[1] Of the more than 3 million musculoskeletal procedures done annually in the United States, about half involve bone grafting with either an autograft or an allograft.[2] Worldwide, autografts or allografts are used in approximately 2.2 million orthopaedic procedures annually.[3]

Although autografts are considered the gold standard for repairs of bone defects, their usage is limited by donor-site morbidity and supply.[1,4,5] Limitations of using allografts include immunogenic response by the host to the foreign tissue of the graft and the potential for disease transmission.[5,6] Because of these limitations, the development—as well as the availability—of new orthobiologic materials to aid in the management of bony defects is increasing.

A look back

The first documented attempt at tissue engineering was made in 1668 by the Dutch surgeon Job van Meek'ren, who described the filling of a bony defect in a soldier's cranium with a piece of skull from a dog.[6,7] Interestingly, this bone graft was removed 2 years later at the patient's request so that he could be allowed back into his church, which had excommunicated him because of the xenotransplant.[7]

Fred Albee, MD, first described autologous bone grafting in 1915, using part of the tibia for spinal fusion. One of the first demonstrations of osteoinduction was in 1930 was performed by the Swedish surgeon Levander, who prepared alcohol extracts of bone and then injected them into muscle, noting bone production.[1] In 1965, **Marshall Urist, MD,** identified a compound (bone morphogenic protein, or BMP) that was noted to have osteoinductive potential. Currently, at least 20 BMPs are identified as part of the larger transforming growth factor-beta (TGF-β) family. [1,6]



Intraoperative photograph shows strut allografts with a cable plate applied to the femur.

Graft properties

An ideal bone-graft substitute must provide scaffolding for osteoconduction, growth factors for osteoinduction, and progenitor cells for osteogenesis. Furthermore, the bone graft must be able to integrate with the host. Autogenous bone graft contains osteoblasts, endosteal osteoprogenitor cells capable of synthesizing new bone, and a structural matrix that acts as a scaffold, making it the gold standard for bone grafting. However, the supply is limited and the donor-site morbidity of autograft can be as high as 25 percent.

Nearly one third of all bone grafts used in North America are allografts.[6] Allografts have osteoconductive proprieties and can serve as substitutes for autografts but carry the risk of disease transmission. The risk for transmission of human immunodeficiency virus (HIV) is 1:1,500,000; for hepatitis C, the risk is 1:60,000; and for hepatitis B, it is 1:100,000.[4]

The U.S. Food and Drug Administration (FDA) requires testing for HIV-1, HIV-2, and hepatitis C; many states require additional testing for hepatitis B core antibody.[6] The American Association of Tissue Banks additionally tests for antibodies to human T-cell lymphotrophic virus (HTLV-I and HTLV-II).[6]

Allograft tissue is treated to minimize the risk of disease transmission through several techniques, including tissue freezing, which decreases enzyme degradation and host immune response; freeze drying, which removes the water from the tissue, thus destroying all osteogenic cells and leaving no osteoinductive capability; and sterilization with gamma radiation, electron-beam radiation, and ethylene oxide[6] The sterilization process leaves most allograft tissue void of its osteoinductive potential, and thus, allograft material serves primarily as an osteoconductive scaffold during bone grafting.

DBM and BMPs in bone grafts

Demineralized bone matrix (DBM) is produced by acid extraction of allograft cortical bone.[5,6] DBM contains noncollagenous proteins: type 1 collagen, which provides the osteoconductive scaffold for osseous in-growth; and osteoinductive growth factors that include BMPs, fibroblast

growth factor, insulin-like growth factor, platelet-derived growth factor, and TGF-β.[5,6] These properties make DBM both osteoconductive and osteoinductive. DBM is available in several forms, including freeze-dried powder, granules, gel, putty, and strips. The potency of different DBM preparations, however, depends on the manufacturing process.[6,9]

Of the BMPs that have been identified, BMPs 2-7 and BMP 9 have been found to possess independent osteoinductive activity.[5] Currently, only BMP-2 and BMP-7 have been approved for clinical use. [1,6] These proteins bind to receptors on the membrane of mesenchymal stem cells. The receptors trigger an intracellular signaling pathway, resulting in the transformation of the stem cells into tissue-specific progenitor cells. These cells participate in the synthesis of extracellular matrix, musculoskeletal tissue formation, and growth.

Current research is looking at using BMPs in gene therapy. This technology will use viral proteins to deliver the gene for BMP and establish the continuous production of the protein in the local environment.[5] Contraindications for the use of BMP include pregnancy, history of cancer, skeletal immaturity, and history of bone tumors.[1] Cost is a major limitation of BMP products: one 5-ml vial could have a $5,000 price tag.[1]

Other osteoconductive bone-graft substitutes

Osteoconductive bone-graft substitutes include coralline hydroxyapatite, collagen-based matrices, calcium phosphate, calcium sulfate, and bioactive glass. These products are osteoconductive only and have no osteoinductive properties unless an osteoinductive product is added.[8] Some of these products are regulated as Class III medical devices, which require a premarket approval process. Most bone-graft substitutes currently in use in the United States, however, are cleared through a less stringent process in which the new product must be shown to be equivalent to an already approved device that was distributed before May 28, 1976.[6,8]

Coralline hydroxyapatite, approved by the FDA in 1992, is produced from marine coral exoskeleton that have pore structures resembling cancellous bone. Coralline hydroxyapatite has been proven effective for managing metaphyseal defects. Blocks of implanted coralline hydroxyapatite may remain visible on radiographs for up to 10 years.[8]

Collagen-based matrices, approved in 1991, are xenografts consisting of spongelike strips of bovine collagen combined with hydroxyapatite. The collagen-based matrices act primarily as osteoconductive bone-graft substitutes. Because their compressive strength is less than that of cancellous bone, they are better used as a surface-only graft rather than for metaphyseal defects.[8]

Calcium phosphate, an injectable calcium paste, has 4 to 10 times the compressive strength of cancellous bone.[8] Calcium phosphate cement has the highest mechanical compression strength of any of the oseteoconductive bone-graft substitutes and is useful where additional mechanical strength is desired.[8] Studies have demonstrated that 95 percent of calcium phosphate is resorbed in 26 to 86 weeks.[6]

Calcium sulfate was first introduced as plaster of paris in 1892. When it was cleared by the FDA

in 1996, it did not have to undergo the more stringent approval process.[8] Calcium sulfate resorbs in 4 to 12 weeks, making it the quickest of any of the osteoconductive products currently available.[6,8] Wound drainage occasionally is noted and is hypothesized to be the result of the osmotic effect of the calcium sulfate.[8,9] Due to its rapid rate of resorption, calcium sulfate is better used as a bone-graft extender rather than for structural support.[8,9]

Implications for orthopaedics

This article provides a cursory review of some of the orthobiologics currently available for bone grafting. Many different types of bone-graft substitutes are in various levels of premarket testing to meet FDA-approval standards. As new products continue to be developed, we, as orthopaedic surgeons, must be sure that we understand the mechanism of action of new products. We must also understand the science behind their development and the process by which these products become available to the consumer. As always, patient safety and benefit should be our first considerations.

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Did you know ...

- The business of bone grafting is an approximately $2.5 billion industry.
- The first documented bone-grafting procedure was performed in 1668 by the Dutch surgeon Job van Meek'ren using dog cranium xenograft.
- Nearly one third of all bone grafts used in North America are allografts.
- Allograft tissue use has increased from 5,000 to 10,000 cases in 1985 to almost 1.5 million cases in 2006.
- Tissue engineering and genetic therapy hold promise for new bone-graft substitutes.

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