Bone Transplantation

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After blood, bone is the most frequently transplanted human tissue. Basic science and clinical research completed in recent years suggests that bone autografting may eventually become a thing of the past. Bone replacement with synthetic materials and growth factors are becoming common procedures in the orthopedic operating room. Tissue engineering technology is approaching the ability to synthesize bone for a particular patient. For now, however, traditional bone grafting remains important.

The demarcation between traditional procedures and the use of new bone graft substitutes and growth factors is blurring, as combination or composite techniques prove safe and appear effective. This blurring of boundaries represents a stage in the progression from autologous bone transplantation to a time when replacement bones can be synthesized and transplanted from one person to another.

This article reviews the history of bone transplantation and current techniques, and casts an eye toward the future.

HISTORICAL PERSPECTIVE

The first documented bone transplant was performed in 1668 by a Dutch surgeon, Job van Meekeren, when he used dog cranium (xenograft) to repair a soldier’s skull defect. Scottish surgeon William Macewan performed the first bone allograft in 1880 when he replaced the infected humerus of a 4-year-old boy with a tibia graft taken from a child with rickets. In his publication in 1914, Phemister noted the importance of “hemostasis, asepsis, and coaptation of parts” in successful bone grafting. Phemister and Albee elucidated the important factors in bone grafting in the early 20th century, paving the way for the recent work that has delineated the importance of osteoconductive scaffolding, osteoinductive growth factors, and osteogenic progenitor stem cells in bone graft healing.

AUTOGRAPH

Autografting remains the gold standard for replacing bone loss due to trauma, infection, tumor resection, revision arthroplasty, and arthrodesis. Rapid incorporation and consolidation with the lack of immunologic considerations make bone harvested from the patient ideal. Autograft bone is osteoconductive and contains osteoinductive proteins and cells able to give rise to bone-forming cells. Although the viability of osteoinductive proteins and osteogenic cells decreases following autografting, it is generally agreed that autograft bone (especially cancellous bone) and its lower risks make it preferable to allograft. Autograft bone, however, is limited in supply, particularly in children. Classically harvested from the patient’s

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iliac crest, autograft can be taken from the distal radius, olecranon, proximal and distal tibia, and ribs.

Complications associated with autologous bone graft harvesting have been well documented. Common complications include increased blood loss, increased operative time, persistent pain at the donor site, donor-site infection, herniation, and iatrogenic fracture.

Cancellous autograft is useful in situations where the bone void does not require significant structural support, as in the filling of cavities left by bone cysts and benign tumors. Similarly, it can be packed into metaphyseal defects after the depressed joint surfaces have been elevated as in fractures of the tibial plateau, plafond, and distal radius. Cancellous bone can also be added to acute fractures and delayed or non-union sites to promote union in defects <6 cm. Spinal fusions are another scenario in which cancellous (and corticocancellous) autograft is a mainstay. Cancellous bone grafts are revascularized and incorporate quickly, and although they provide no initial structural support, after 12 months their strength is equivalent to that of a cortical graft.

Cortical autografts provide immediate structural support. Sources of nonvascularized cortical autografts include the iliac crests, ribs, and fibula. Anterior cervical spinal fusion lends itself to the use of tricortical graft from the iliac crest or diaphyseal, almost entirely cortical bone from the middle one third of the fibula. Both of these methods have generally resulted in higher fusion rates than allograft options. The use of nonvascularized cortical autografts in segmental defects between 6 and 12 cm is controversial. Defects >12 cm have been shown to have higher failure rates using nonvascularized grafts compared to vascularized cortical autografts. Nonvascularized cortical grafts may provide immediate structural support but lose mechanical strength over the first few months. This is due to the revascularization process, which causes osteoporosis and subsequent graft weakening. This process requires resorption of at least some graft bone to allow ingrowth of blood vessels and takes significantly longer in cortical bone than in cancellous.

Vascularized autograft

Vascularized cortical autografts are effective structural grafts that heal quickly without the revascularization process and consequent mechanical compromise seen in avascular cortical auto- and allografts. Typically, >90% of osteocytes present in these grafts survive the transplant and bring their own blood supply, perhaps making the contribution of the recipient bed tissues less important in healing. In other words, vascularized autografts bring all components for healing with them. One of the primary indications for this type of bone transplant is a recipient bed with suboptimal vascularity of bone or soft tissues or large osseous defects. Common donor sites of vascularized autografts are the ribs, iliac wing, fibula, distal radius, and scapula.

Vascularized distal radius grafts are effective in treating osteonecrosis and nonunions of the scaphoid, Kienböck’s disease, and failed wrist arthrodesis (Figure 1). The vascularized free fibula graft has been used in numerous locations for a variety of difficult problems. Potential situations in which a patient might benefit from vascularized autograft include osteonecrosis of the femoral head, reconstruction of tumor-related defects in the proximal humerus and lower extremity, treatment of congenital

Figure 1: Vascularized distal radius autograft. Avascular proximal pole nonunion of the scaphoid (A). Vascularized radial bone graft being transplanted to the scaphoid (B). Vascularized scaphoid autograft in place with screw fixation. Radiograph shows healing 8 weeks postoperatively (C).
tibial pseudarthrosis,17 and nonunions of the femur,18 tibia,19 and femoral neck20 (Figure 2).

Donor-site morbidity has been a concern with vascularized fibula autografts.21,22 In addition to persistent pain, investigators have found motor weakness affecting primarily extensor hallucis longus and flexor hallucis longus, sensory deficits, biomechanical alterations in the ankle, deep venous thrombosis, and delayed wound healing associated with the related devascularization of overlying soft tissues with peroneal artery ligation. Vascular anatomic anomalies pose additional problems; Vail and Urbaniak21 reported having to use the contralateral leg on one occasion and interposition grafting of the peroneal artery using reverse-saphenous vein graft in another situation. Until recently, all of their patients underwent preoperative arteriography to rule out vascular anomalies. They ended this practice as a cost-cutting measure.21

ALLOGRAFT

Transplanting bone from one human to another is an idea that has been with us for hundreds of years and circumvents some of the problems with autogenous bone grafting. The risk of infection transmission from donor to host, the immunogenicity of foreign tissue, and ethical concerns are relevant with allografting—the latter increasingly so with the advent of vascularized allografting and limb transplant.

Although considered by some to be a “bone graft substitute,” demineralized
bone matrix (DBM) is bone harvested from a single donor, crushed, and demineralized with acid. The various manufacturers of DMB add or modify steps in the processing, but the essential process is the same. Treatment of allograft bone with gamma irradiation or ethylene oxide has been shown to inactivate pathogens. Ethylene oxide is a gas that destroys bacteria, spores, and viruses in a dose-dependent fashion. However, use of ethylene oxide has been complicated by host reaction to treated tissues. Gamma irradiation has been shown to destroy human immunodeficiency virus (HIV), hepatitis C, and other pathogens in allograft tissues and is more commonly used today; however, this process weakens the structural integrity of the graft.

Demineralized bone has been widely used since Urist and Dowell first reported its clinical use in 1968. Demineralized bone matrix is recognized as having a variable amount of osteoinductive capacity and some osteoconductive properties. The biologic activity varies with specific processing and storage methods, in addition to variation among donors.

Uses for DBM are numerous, although prospective, randomized, controlled studies demonstrating its efficacy are not available for all of its clinical applications. Currently, DBM is used to fill cavitary defects, facilitate spinal arthrodesis, and repair nonunions. It can also be used as a cancellous autograft extender in these situations. An interesting use of DBM combines it with autologous bone marrow, which adds the osteoconductivity and -inductivity of DBM to the osteoprogenitor cells of the recipient’s bone marrow—a true composite graft. Conveniently, this formulation can be applied percutaneously, avoiding more invasive techniques. Drawbacks of DBM include the risk of infection, although the demineralization process has been proven to destroy HIV. Infection with HIV or hepatitis from DBM has not been reported.

Cortical allograft is used in the same clinical scenarios as DBM and cancellous autograft. The differences are that cancellous allograft is not demineralized, but rather freeze-dried and vacuum-packed—conditions under which it can be stored indefinitely—and a slightly increased disease transmission risk. Freeze-drying significantly alters the biomechanical properties of bone, decreasing torsional strength by 50% and compressive strength by 10%. The risk of HIV transmission or hepatitis viruses is small but present. Allograft suppliers screen donors for these viruses as well as other markers of systemic disease.

A step higher on the disease transmission risk scale is the cortical allograft (vascular). Cortical bone is of greater density than cancellous bone, and it is believed that the density accounts for the slightly higher risk of disease transmission, as pathogens are less easily destroyed when embedded in a more dense tissue bed. Two cases of HIV transmission resulting from cortical allografts have been reported. Nonetheless, cortical allografts are used widely for bridging structural defects in long bones, spinal arthrodesis, buttress or strut grafts in limb salvage procedures, revision arthroplasty, and periprosthetic fractures (Figure 3). Advantages include vast supply and selection of bones to fit a...
specific need, and machining to better serve a given function (e.g., femoral ring allografts used in anterior spinal arthrodesis).

Cortical allografts usually are processed (debridement, cleaning) and aseptically preserved by freeze-drying or deep freezing. Freezing to approximately $-20^\circ C$ allows preservation for approximately 1 year without substantial compromise in strength; only thawing is required prior to implantation. Deep freezing bone does not alter its immunogenicity. Freeze-drying, on the other hand, decreases immunogenicity further, but reduces the mechanical strength by 50% when compared with fresh-frozen bone. Reconstitution (rehydration) is required prior to implantation. A recent study in mice suggests that treating the grafts with dimethyl sulfoxide further reduces immunogenicity in deep-frozen specimens. Although this has yet to be demonstrated in humans, it could obviate the need for freeze-drying allografts with the concomitant decrease in mechanical strength.

Cortical allografts are primarily osteoconductive scaffolds, but cortical bone offers immediate structural support as well. This support diminishes as incorporation proceeds until the revascularization process is complete and enough new bone is laid down to restore strength. Often, it is a race between incorporation of the allograft and fatigue failure of the supplemental fixation (with allograft fracture). Unfortunately, fracture occurs with significant frequency as a result of graft weakening associated with revascularization or due to the inability to obey Wolff’s law (Figure 4). If a significant portion of the graft is not revascularized, as it often is not in large allografts, a stress riser in necrotic bone can result in fracture because the bone cannot respond to stress concentrated at this site. Getty and Peabody reported a 25% fracture rate in proximal humeral osteoarticular allografts, and Gebhardt et al reported a 35% fracture rate in similar allografts.

The healing process of cortical allograft to host bone is prolonged, following the steps of hematoma formation, inflammatory process, resorption of graft bone and revascularization, and finally replacement of graft with new host bone. Often the majority of the bone graft is not replaced, but nailed to the host bone. Numerous studies have shown that after 1 year, a significant amount of necrotic graft bone remains, mixed with newly formed host bone, and after many years, some graft bone remains. This suggests that while meaningful clinical healing does occur with cortical allografts, the graft is never entirely replaced.

Osteoarticular and osteochondral allografts are used primarily in limb salvage and arthroplasty. Being able to replace large segments of bone that include the joint surface has been a significant advance in preserving function and cosmesis in limbs, which previously would have required amputation. Malignant tumors of the proximal humerus, for example, can be effectively treated with resection and reconstruction using osteoarticular allograft attached to the shoulder through repair of the soft tissues including joint capsule and rotator cuff tendons (graft to host), and attached distally with plate and screw fixation or an intramedullary prosthesis (Figure 5). In most cases, this allows limb preservation, excellent hand function, and reasonable shoulder function.

Osteoarticular grafts are usually deep-frozen for preservation and thawed prior to implantation. Fresh osteoarticular allo-
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Vascularized Allografts

Transplanting (or implanting) allograft bone requires dampening of the recipient’s immune response, and this can be accomplished in two ways: treat the graft to make it less immunogenic or treat the recipient to make the immune system less “sensitive.” The advent of vascularized allograft has required a shift from manipulating the grafts to manipulating the recipient’s immune system.

Hoffman et al39 and Kirschner40 reported their experience with transplantation of vascularized diaphyseal femora and vascularized knees. Using an immunosuppressive regimen consisting of antithymocyte globulin, cyclosporine, azathioprine, and methylprednisolone, which was tapered over 6 months to cyclosporine monotherapy, three patients underwent transplantation of vascularized femoral diaphyses and five patients underwent transplantation of the entire knee, including the extensor mechanism and joint capsule. According to their most recent report, four of these eight patients (two from each group) are currently weight bearing on their transplants. The authors state that these vascularized bone transplants were “fraught with complications,” largely related to the immunosuppressive medications. Whereas transplanting allograft bone into a previously infected soft-tissue bed and then adding long-term immunosuppression to the equation seems inherently risky, it may be reasonable to attempt this procedure in these (previously infected) patients, as they stand to gain the most from successful new therapies for segmental bone or joint loss.

Hoffman and Kirschner40 acknowledge that their immunosuppressive regimen was inadequate, citing the more effective protocols used by investigators involved with composite tissue transplantation, but also that life-long immunosuppression is mandatory. In addition to the complications associated with immunosuppression, possible complications of anticoagulation must be considered because bone is a low-flow organ, and thrombosing of the graft vessels would defeat the purpose of using vascularized graft rather than avascular allograft bone. Two of these transplant patients were managed initially with postoperative heparin and later switched to aspirin and phenprocoumon. How long anticoagulation is required is undetermined.

Although it appears this technique is potentially feasible, the indications remain elusive. Is it logical to attempt transplanting allograft bone into a previously infected soft-tissue bed and then immunosuppressing the patient? The investigators suggest that vascularized femoral or knee transplant is a “last line of defense” for patients facing arthrodesis or above-knee amputation. Do the drawbacks of knee fusion or amputation? For now, both knee arthrodesis and above-knee amputation are widely performed and accepted procedures, whereas vascularized bone allotransplants remain experimental and controversial. With advances in transplant immunology and the ongoing development of new drugs this may change.

Composite Tissue Allograft

In the past 3 years, nine unilateral and four bilateral human hand transplants have been performed. As of January 2003, only the first hand transplant performed with immunosuppressive therapy had failed, and this has been attributed to the patient’s lack of cooperation and noncompliance with immunosuppressive medications. The other three were evaluated using the Carroll test, which assesses global upper extremity function, and were rated good (one patient) or fair (two patients).41

The most detailed reporting of experience with hand transplantation has been provided by Margreiter et al,42 who recently reported on the first 18 months following a bilateral hand transplant performed in Innsbruck, Austria. The patient was a healthy 47-year-old policeman who lost his hands attempting to defuse a bomb 6 years prior to his transplant. The immunosuppressive regimen used in his case included antithymocyte globulin induction therapy, methylprednisolone (later tapered to prednisone), tacrolimus, and mycophenolate mofetil. Additionally, ganciclovir and cotrimoxazole prophylaxis was required against cytomegalovirus and Pneumocystis carinii, respectively. Postoperative rehabilitation was intensive, lasting 6 hours per day, 5 days per week for the first 12 months. Bone healing was complete by clinical and radio-
The only wound complication was necrosis of a split thickness skin graft performed at the initial operation, which required debridement and regrafting of a 3- to 4-cm area on the left forearm. Acute rejection occurring on postoperative days 55 and 188 as characterized by diffuse erythema. The earlier episode was more severe and required treatment with intravenous methylprednisolone and topical steroids and tacrolimus. The second, milder episode was treated with topical tacrolimus alone.

Functional results at this time are described as 60% of normal hand function, meaning active range of motion of the fingers, wrist, and forearm average 60% of normal. Full reinnervation occurred with sensation present throughout (although decreased in the ulnar distribution of one hand), normal skin texture, sweat pattern, and hair growth. The patient has some weakness but is able to demonstrate grip and pinch strengths in both hands and is able to perform activities such as turning the pages of a newspaper, writing with a pen, using a telephone and computer, eating, and caring for personal hygiene. He continues to have difficulty buttoning a shirt, but has returned to work and reports that the results have exceeded his expectations. He is able to perform activities that he was unable to do using the myoelectric prostheses.

Composite tissue allografting is a complex subject. Although this policeman has avoided complications of immunosuppressive therapy to date, he remains at high risk for infections, drug toxicities, and malignancy. Steroids are known to cause healing and transplantation technologies? Who is a worthy recipient and who will handle the costs will be an ongoing debate among ethicists as it has been in the field of solid organ transplantation. Will it be more difficult to solicit donation of nonvital but cosmetically and psychologically important body parts from donor family members?

**The Future**

These are exciting times in orthopedic surgery. We are closing in on the ability to replace bone with synthetic materials, which will spare our patients pain and additional surgery while providing optimal healing. We are also investigating transplanting bones, joints, and limbs using immunosuppressive drugs borrowed from our transplant surgery colleagues as a means of repairing or replacing the most devastating bone loss. Who will win the race between tissue engineering and transplantation technologies? Across the broad spectrum of bone loss problems, both approaches are making valuable contributions.

**References**


