Chapter 5 | Clinical Perspectives on the Use of Allogenic Tissue Substitutes

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INTRODUCTION

Bone and soft tissue human allografts are used extensively to replace or repair damaged tissue. Their use extends beyond bone reconstruction. Cartilage restoration and ligament substitution are common indications. Bone allograft is also processed into bioactive proteins to aid bone repair. Allograft mesenchymal stem cells (MSCs) are now available and used as a bone graft substitute. The following is a review of the clinical perspectives on the use of allogeneic tissue substitutes. Published clinical outcomes studies will be discussed.

Allograft in Tumor Reconstruction

Bone allograft is an attractive alternative for the reconstruction of the skeleton after tumor surgery. There is no donor site morbidity or pain, and they are readily available and cost-effective. There still are some unanswered questions, including graft incorporation, disease transmission, strength, and the most effective means of processing of the allograft. The first use of bone allograft in tumor reconstruction dates back to the late 1800s. Lexer reported on the substitution of a whole or half joint from freshly amputated extremities by free plastic operation in 1908 [**1,2**]. In 1912, Carrel described the preservation of tissues and bone allograft application in surgery [**3**]. During the 1940s and 1950s, the U.S. Navy Bank was established, and it popularized tissue banking. Three surgeons around the world championed the use of bone allografts for tumor reconstruction. They published their experience and include Ottolenghi [**4**] from Argentina in 1972, Parrish [**5**] from M.D. Anderson in Houston, TX, in 1973, and Volkov [**6**] from the Soviet Union in 1976. In general, they reported that one third of their patients had excellent results, one third had good results, and one third failed. This high failure rate was unacceptable and was largely related to technical complications. It was not until the late 1970s that Henry Mankin at Massachusetts General Hospital reported on his extensive use of bone allografts in tumor reconstruction [**7**].

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He noted that frozen allografts had diminished immunogenicity, they needed to be rigidly fixed, that sizing is critical, and that there is a need to be prepared for complications. Despite the diminished immunity associated with freezing of bone allografts, an immune response is easily detectable. It is a cell-mediated response to surface antigens on the allograft tissue. The most active immune response is CD4 and CD8 cytotoxic T cells. It is known that the more robust the immune response, the poorer the outcome with large bone allografts. It is also known that residual bone marrow is highly immunogenic and for that reason it should be removed. If cartilage is transplanted along with bone, then it is minimally immunogenic because of the antigen isolation. The active antigen is embedded in a proteoglycan matrix, which protects it from the immune response. Most bone allografts for tumor reconstruction are fresh-frozen. Although freezing is advantageous to the bone, it has a negative effect on the articular cartilage. Articular cartilage is largely water, and freezing creates crystals that tend to damage the chondrocytes. Several techniques have been tried to minimize cell death, including immersion in glycerol or dimethylsulfoxide (DMSO) for a period of time before freezing. The cryoprotection achieved with these techniques is quite minimal; thus, one of the major complications of a frozen osteoarticular allograft is cartilage degradation. William Tomford published his research on approaches to articular cartilage preservation, and his work represents a major source of our knowledge [**8–11**].

Bone allografts are currently used clinically in three reconstructive techniques for tumors [**7–31**], including osteoarticular allograft arthroplasty, intercalary reconstruction of long bones, and in allograft prosthetic composite arthroplasty. Although there are still some enthusiasts around the world promoting the use of osteoarticular allografts, many have abandoned this technique for allograft prosthetic composite arthroplasty. The reason is that the articular cartilage degrades over time. One other problem with this technique is joint instability. Even if meticulous ligament reconstruction is performed, the joint remains unstable; thus, there is significant risk of cartilage and joint degradation along with fracture of the graft. Muscolo et al. [**23**] published their outcomes with osteoarticular allografts of the distal femur in 2005. They reported on 75 distal femoral osteoarticular allografts with a minimum follow-up of 7 years. The graft survival at 5 and 10 years was approximately 78 %. The Musculoskeletal Tumor Society score was good at 26 of 30 points. In the series of patients, joint deterioration secondary to anatomical mismatch and joint instability were cited as the primary cause for failure of the osteoarticular allografts of the distal femur. The same group published their outcomes with proximal tibial osteoarticular allografts, which did not perform as well [**25**]. The allograft survival was approximately 65 % at 5 and 10 years, but still with good functional outcomes. Unlike distal femoral osteoarticular allografts, proximal tibial osteoarticular allografts most commonly failed from infection secondary to prolonged wound exposure, dead space created by tumor resection, and insufficient soft tissue coverage. They also reported on hemi-joint osteoarticular allografts for tumor reconstruction in 2007. They reported

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on 40 unicondylar osteoarticular allografts with a survival of 85 % at 5 and 10 years, thus making this application for tumor reconstruction the most successful [**22**]. Similar to osteoarticular allografts of the distal femur, unicondylar osteoarticular allografts would fail because of anatomical mismatch and joint instability.

Intercalary allografts represent another application in tumor reconstruction [**10,11,17,21,24,28,31**]. Here, the center of a long bone is transplanted without involvement of the proximal or distal joint. These grafts need to be rigidly fixed, either with a rod, or better yet a plate, to achieve osteosynthesis at both allograft host bone junctions. Locking plates are now frequently used to fix an intercalary allograft. An intercalary allograft can be combined with an onlay vascularized autograft to improve healing and minimize complications. Frisoni from the Rizzoli Institute reviewed 101 patients treated with an intercalary allograft of the femur [**32**]. The mean age was 20 years with a mean follow-up of 9.3 years. The rate of allograft failure was 24 %. They observed several adverse variables, including the use of a rod instead of a plate, chemotherapy, and grafts greater than 17 cm. The Italian group recommended combining a vascularized fibular autograft to optimize outcome. Muscolo et al. [**21**] published their experience with 124 femoral and tibial intercalary allografts. Their patients had a mean follow-up of 6 years. The allograft survival was 82 % at 5 years and 78 % at 10 years. The functional score using the Musculoskeletal Tumor Society system was 27 of 30 points. Farfalli et al. [**33**] from Buenos Aires reported on 26 intercalary allografts after tumor reconstruction of the tibia. Their mean follow-up was 6 years. Their survivorship was 84 % at 5 years and 79 % at 10 years. The most common complications included infection (three patients), fracture (three patients), and nonunion (two patients). Intercalary reconstruction can also be used in children after a transphyseal resection. This is when the sarcoma involves the metaphysis of the long bone near the growth plate. The sarcoma can be resected through the physis, preserving the joint, and an intercalary allograft transplanted. Fixation is somewhat difficult with this type of reconstruction. Only a small wafer of epiphysis remains for the upper fixation. Locking plates are a good choice in fixing an intercalary allograft after a transphyseal resection.

Allograft prosthetic composite arthroplasty is a technique that combines a long bone allograft with metallic implant arthroplasty. The metallic implant is either in the form of a total hip or total knee replacement. It is attached to the allograft to not only restore the bone stock but also to replace the joint. Allograft prosthetic composite arthroplasty does not require maintenance of cartilage viability. The joint is replaced with a metallic and plastic implant. Joint stability is also improved because of the mechanics of the metallic arthroplasty. Donati from the Rizzoli Institute reported on 62 patients treated with allograft prosthetic composite arthroplasty of the upper tibia [**34**]. Their reconstructive survivorship was 74 %. They did have a significant infection rate of 24 % and recommended the common use of a gastrocnemius flap to cover the allograft prosthetic composite arthroplasty.

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When allografts are used in tumor reconstruction, complications should be anticipated [12]. This is particularly true when an allograft is used to reconstruct the pelvis. Campanacci from Florence, Italy, reported on 33 pelvic allografts with 33 months of follow-up [35]. There was a 24 % incidence of sciatic nerve palsy, an 18 % incidence of hip dislocation, and a 15 % incidence of infection. Mankin and Hornicek [36] reported on a 30-year experience with allografts for giant cell tumor. They had 144 patients in their series, and their complication rates included allograft fracture, 21 %; nonunion, 8 %; and infection, 8 %. Gebhardt also saw a significant complication rate in his review of 53 patients for high-grade extremity osteosarcoma [17]. His mean follow-up was 25 months. There were 16 infections, 12 nonunions, 6 fractures, and 6 cases of instability. Eighteen of 53 grafts failed. However, most of his complications were salvageable with preservation of the limb.

Overall, allografts are a reasonable alternative for limb reconstruction after tumor surgery. The most common applications currently include osteoarticular allograft, intercalary allograft, and allograft prosthetic composite arthroplasty. Survivorship of the bone transplant remains reasonably good out to 10 years. Complications should be anticipated, such as infection, fracture, and nonunion. Osteoarticular allografts are associated with a significant incidence of joint degradation. To minimize that risk, the allograft can be combined with an implant in which the cartilage is not necessary to restore the joint.

Fresh Osteochondral Allograft for Joint Restoration

Observation of focal chondral pathology in the knee is common during knee arthroscopy [37]. A wide spectrum of chondral disease exists and ranges from superficial articular cartilage injury to large, full-thickness osteochondral lesions. Defects may progress to osteoarthritis on the basis of several patient-, limb-, knee-, and defect-specific factors [38]. The ideal candidate for cartilage restoration surgery is the symptomatic, young or middle-aged, motivated individual with either normal or correctable comorbidities (alignment, meniscal, or ligament deficiency). However, patients that meet these criteria only make up 5 % of those with articular cartilage injury in the knee [39]. The challenge in the identification of symptomatic chondral pathology warrants caution in proceeding with the surgical techniques used to treat them; thus, "treat the patient and not the MRI." The exact mechanism of symptom initiation and progression with isolated chondral lesions is not completely known. Nonetheless, it is recognized that chondral lesions may cause significant pain and limitation of function [40]. In symptomatic patients who have failed conservative treatment, there are several viable surgical treatment options. Although many procedures are simple and inexpensive arthroscopic procedures (e.g., debridement, drilling, microfracture), others require considerable financial and time investments (e.g., cell-based therapies or allograft transplants [osteochondral, meniscal]). Furthermore, comorbidities are addressed simultaneously or sequentially: (1) meniscal repair or transplantation, (2) high tibial valgus-producing osteotomy (for varus) or distal femoral varus-producing

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osteotomy (for valgus), (3) tibial tubercle osteotomy (for patellofemoral compartment), and (4) ligament reconstruction as indicated. Therefore, it is the responsibility of the surgeon to understand the advantages and disadvantages of all potential options and educate the patient for the best treatment option for "the here and now." Prophylactic surgery for the incidental lesion is not recommended.

In the setting of symptomatic, large lesions with subchondral bone involvement, treatments such as microfracture, osteochondral autograft, autologous chondrocyte implantation (ACI), and other cell-based therapies are insufficient to address underlying osseous deficiency. Thus, fresh osteochondral graft is advantageous with viable hyaline cartilage and structural subchondral bone transplanted as a single-stage procedure. Grafts traditionally were frozen or cryopreserved (inferior chondrocyte viability, matrix preservation, and clinical outcomes vs. fresh grafts) whereas now they are aseptically processed and stored at 4°C [**41**]. Although chondrocyte viability is decreased beyond 14 days after allograft harvest, this is a necessary step to allow for disease testing [**41**]. Modern tissue banks have created guidelines to ensure the safety of implanted grafts. Most banks recommend transplantation by 28, to a maximum of 35, days postharvest.

The indications for osteochondral allograft transplantation include symptomatic chondral or osteochondral defects of the knee that have failed prior cartilage repair techniques and previously untreated primary chondral or osteochondral lesions greater than 1–2 cm^2 on the femoral condyles, trochlea, or patella. The surgical technique varies based on lesion location. Exposure typically involves medial or lateral parapatellar mini-arthrotomy. Defect preparation involves recipient site sizing, ensuring sufficient surrounding osteochondral walls to support the donor plug. Preoperative sizing images match the recipient and donor sites. Once the recipient site is reamed to a healthy subchondral bone bed (typically between 6 and 9 mm), a surface area- and depth-matched donor plug is press-fit with gentle manual pressure. It is imperative to ensure flush placement of the donor plug because proud or recessed graft placement significantly increases the contact pressure and subsequent degeneration [**42**]. If graft fixation security is in doubt, then a recessed bioabsorbable compression screw (Arthrex, Inc., Naples, FL) may be placed in the center of the graft. High-quality evidence using reliable and validated patient-reported outcomes is currently lacking for cartilage repair in the knee [**43**]. However, new meta-analyses have indicated significant recent improvements in quality [**43**]. For focal and diffuse single compartment chondral or osteochondral lesions, osteochondral allograft predictably and significantly improves patient-reported outcomes and results in high patient satisfaction (**Table 5.1**) [**44**]. At short-, mid-, and long-term follow-up, nearly half (46 %) of patients undergo concomitant or staged osteotomy or meniscal surgery [**44**]. At 5 years follow-up, overall satisfaction approaches 90 %, and 65 % of patients have little or no radiographic osteoarthritis [**44**]. Short-term complications are infrequent (<3 %). Although failures are variably defined (repeat surgery, revision cartilage surgery, osteotomy, or conversion to arthroplasty), they are uncommon (<18 %). Survival rates

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TABLE 5.1 Selected Clinical Outcomes after Fresh Osteochondral Allograft Transplantation.

Authors	Year	(*N*)	Age (years)	Defect Size (cm^2)	Defect Location	Follow-Up (years)	Method Preservation (days to implant)	Primary Outcomes
Lyon et al. [**137**]	2013	13	15	5.1	11 FC, 2 PF	2.0	Fresh (14–21)	• Merle d'Aubigne-Postel 12.7 to 16.3 at final follow-up • All patients returned to unrestricted sports at 9-12 months
Giorgini et al. [**138**]	2013	11	34	10.3	7 FC, 4 TP	2.2	Fresh (14–21)	• Subjective IKDC 27 to 59 ($P < 0.001$) • Defect size < 8 cm^2 IKDC improved 38 vs. >8 cm^2 IKDC improved 23 ($P = 0.01$) • One failure (conversion to unicompartmental arthroplasty)
Haudenschild et al. [**139**]	2012	1	48	10.2	Trochlea, FC	3.0	Fresh (12)	• Gene expression, proliferation rate, chondrogenic potential graft/host • No chondrocyte chimerism, shorter doubling times in host • Retained XX host and XY donor (FISH)
Krych et al. [**140**]	2012	43	33	7.3	80 % FC	2.5	Fresh (7–30)	• Preinjury level return to sport in 34 of 43 (79 %)—9.6 months • Age > 25 years ($P = 0.04$) and preoperative duration symptoms ($P = 0.003$) decreased RTS • Improved ($P \leq 0.01$) in IKDC subjective, KOOS ADL, and Marx activity score
Scully et al. [**141**]	2011	18	27	2.2	100 % FC	3.4	Fresh	• One soldier returned to previous military position • Ten soldiers to Medical Evaluation Board for discharge (23 months) • Seven soldiers still active duty but with permanent running/athletic restrictions

(Continued)

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TABLE 5.1 (Continued)

Authors	Year	(N)	Age (years)	Defect Size (cm^2)	Defect Location	Follow-Up (years)	Method Preservation (days to implant)	Primary Outcomes
Gortz et al. [**142**]	2010	22	24	10.8	100 % FC	5.5	Fresh (5–21)	• 89 % graft survival rate (avoided reoperation) • Knee Society Score improved ($P = 0.0005$) 60–86 • Merle d'Aubigne-Postel ($P < 0.001$) 11.3–15.8 • IKDC pain 7.1 to 2.0 ($P < 0.001$) and IKDC function 3.5 to 8.3 ($P = 0.002$)
LaPrade et al. [**143**]	2009	23	31	4.8	100 % FC	3	Fresh (15–28)	• IKDC subjective 52 to 68.5 ($P < 0.03$) • Modified Cincinnati score increased 27.3 to 36.5 ($P < 0.01$) • Zero failures
Pascual-Garrido et al. [**144**]	2009	16	34	4.5	100 % FC	4	Fresh	• Tegner 0 to 6 ($P < 0.001$); Lysholm 25 to 37 ($P = 0.015$); IKDC subjective 31 to 45 ($P = 0.004$) • KOOS: Pain 52–74 ($P = 0.002$); Sport 32–46 ($P = 0.037$) • Lower ($P < 0.03$) increase in KOOS Sport and Quality of Life scores vs. ARIF and LBR
Gross et al. [**145**]	2008	35	53	n/a	n/a	21	Fresh	• At retrieval study, long-term graft survival shows viable chondrocytes, functional matrix, complete replacement of graft bone with host bone at 1–25 years after operation

ADL: activities of daily living; ARIF: arthroscopic reduction and internal fixation; FC: femoral condyle; FISH: fluorescent in-situ hybridization; IKDC: International Knee Documentation Committee; KOOS: knee injury and ostoearthritis outcome score; LBR: loose body removal; n/a: not applicable; PF: patellofemoral; RTS: return to sport; TP: tibial plateau.

decline with time: 91–95 % at 5 years [**45,46**], 76–85 % at 10 years [**45,46**], and 74–76 % at 15 years [**45,46**]. Prognostic factors that may negatively influence clinical outcomes include diagnosis of spontaneous osteonecrosis of the knee (SONK), bipolar lesions, age greater than 50 years, patellofemoral lesions, Workers' Compensation status, preoperative duration of symptoms greater than 12 months, and failure to address malalignment or meniscal deficiency [**46–51**].

Patients with osteochondral lesions can frequently present with meniscal pathology. In the past, full-thickness chondral defects were considered to be a contraindication for a meniscal allograft transplant [**52**]. As a result of advancement in the treatment of osteochondral lesions, it is no longer a considerable risk factor for failure of a meniscal allograft transplant [**52**]. In fact, clinical outcomes have demonstrated excellent results in concurrent procedures with osteochondral allograft and mensical allograft transplant [**53**]. The options for mensical allografts include free soft tissue allografts, separate anterior and posterior bone plugs, and bone bridges. In the presence of concomitant procedures, the bone bridge-in-slot has been cited as offering secure bony fixation along with the flexibility for concomitant procedures [**54**]. The most important factor of successful meniscal allograft transplantation when using bone plugs or bridge-type allograft is accurate size matching of the allograft to the native meniscus [**53,55,56**]. Overall, mensical allograft transplantation has offered encouraging results, with good to excellent results in almost 85 % of patients [**54**].

Allograft for Cruciate Ligament Reconstruction

Despite autograft being considered the gold standard in anterior cruciate ligament (ACL) reconstruction, the use of allograft tissue has recently become more widely used in cruciate ligament reconstruction [**57–59**]. Allograft tissue had become unpopular in the 1990s because of concern over the increased risk of viral disease transmission [**57**]. However, one institution between 1986 and 2006 demonstrated a significant increase from 2 % to almost 50 % of the patients using allograft tissue for ACL reconstruction [**59,60**]. Other recent estimates of allograft utilization in ACL reconstruction have been reported between 20 % and 30 % [**61–64**]. When allograft is used for ACL reconstruction, several options exist that include grafts with or without a bone block(s). Allograft options with bone block(s) are the patellar tendon, Achilles tendon, and quadriceps tendon. The available options for soft-tissue-only allograft include the quadriceps tendon and the semitendinosus, tibialis anterior, tibialis posterior, peroneus longus, and iliotibial band. The choice of graft is often tailored to the patient because no study has been able to identify a single allograft option as superior to another in ACL reconstruction [**65**].

The use of allograft tissue for ACL reconstruction offers advantages over autograft tissue that have caused a greater demand for allografts. Commonly cited advantages include decreased donor site morbidity, shorter operative time, decreased rehabilitation period, improved cosmesis, decreased postoperative pain, the ability to easily customize the bone blocks, lower overall cost for primary ACL reconstruction, use in

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patients with insufficient or poor quality donor tissue for autograft, and readily available grafts for complex ligamentous injuries [**57–59,61,62,65–71**]. Advantages to the patient for allograft versus autograft were noted in a survey in which 63 % of the patients would have chosen allograft instead of their bone-patella tendon-bone (BTB) autograft despite being satisfied with the overall results [**72,73**].

Most orthopedic surgeons consider allograft tissues safe for use; a survey of American Orthopedic Society for Sports Medicine members cited that 86 % of the respondents stated that they use allograft tissue [**58**]. Despite a strong belief in the safety and efficacy of allograft tissue, the commonly cited disadvantages include disease transmission, immunogenic response of the host toward the graft, slower incorporation, and the possibility for higher failure rates [**57,65,74**]. Allograft incorporation after ACL reconstruction was previously believed to have been completed after 18 months; however, a histological study of allografts retrieved during autopsies at 2 years demonstrated poor central vascularization of the allografts [**57,75,76**]. On the basis of the more recent findings, allograft tissue incorporation is likely further delayed from prior estimates. Regardless of the limited number of documented cases of disease transmission from allograft tissue, the risk of human immunodeficiency virus (HIV), hepatitis C virus (HCV), bacteremia, and septic arthritis must still be considered when using allograft tissue. The transmission of viral disease from properly screened allograft tissue has been cited as approximately 1 in 1.5 million [**57**]. Documented cases of viral transmission have primarily been isolated to case reports [**77,78**]. Bacterial transmission from allograft tissue has been documented in a series of 14 patients with an allograft-associated Clostridium infection during the period of 1998–2002, which resulted in one patient death [**79**]. An investigation of the series of Clostridium infections showed that the same tissue bank processed all 14 allografts [**79**]. Overall, the risk of septic arthritis after ACL reconstruction has been reported to range between 0.2 % and 4.0 % [**80**]. Despite the theoretically higher risk of bacterial transmission with allograft tissue, Greenberg et al. demonstrated no statistical significance in the rate of septic arthritis in ACL reconstruction with allograft and autograft tissue [**81**].

The advent of improved sterilization techniques, which retain the biomechanical properties of the graft, are credited with the repopularization of allograft tissue in ACL reconstruction [**57,82**]. The most commonly used method of allograft harvesting involves an aseptic technique. Processing of allograft tissue for orthopedic procedures has not been standardized, which results in varying processes between tissue banks. The protocol of allograft tissue processing typically involves terminal sterilization with gamma-irradiation, freeze-drying, or chemical disinfection, or combinations thereof. Most tissue banks use a low-dose irradiation with 1–3.5 Mrd, which is only effective in killing bacteria [**83,84**]. The high-dose irradiation required to kill viral contamination is no longer used because of its deleterious effects on the allograft tissue's biomechanical properties [**85,86**]. Chemical disinfection is used as an adjuvant to the process with the attempt to limit the effects on graft integrity and minimizing the risk of disease transmission. Significant differences exist regarding the chemical disinfectant used by

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tissue banks because of the proprietary techniques such as Allowash (Lifenet, Virginia Beach, VA), Biocleanse (Regeneration Technologies, Alachua, FL), and Clearant Process (Clearant, Inc., Los Angeles, CA) [**58**].

Because gamma-irradiation has proven to exhibit dose-dependent deleterious effects on allograft tissue, it is important to understand the key variables of gamma-irradiation, including target dose, dose range, and temperature of irradiation. Gamma-irradiation doses are typically reported as a single target dose or dose range. When a single target dose has been reported, it represents the intended minimal irradiation exposure of the tissue. Because the method of irradiation does not allow for all tissue in a given batch to receive the same dose, some tissue will have received a much higher dose of irradiation. On the other hand, the dose range provides a more accurate representation of the irradiation exposure of the allograft tissue in the batch. The temperature during exposure to irradiation affects free radical generation, with lower temperatures working to minimize free radical generation and successive tissue damage [**87–89**]. As a result, low-dose irradiated allograft tissue with a narrow dose range and performed at low temperatures will provide an ideal condition for minimizing the deleterious effects of irradiation on allograft tissue. The dose-dependent effects on allograft tissue integrity have been extensively researched in controlled laboratory studies with the conclusion that irradiation doses below 2.0–2.5 Mrd at low temperatures minimizes the biomechanical effects compared with matched nonirradiated grafts [**89**]. Performing clinical outcome research to compare irradiated and nonirradiated grafts is difficult because of the variable processing between tissue banks and multiple forms of allograft available. The current literature has not provided a consensus on whether or not a clinically measurable difference exists between irradiated and nonirradiated allograft tissue [**89**].

Regardless of any potential measurable difference between allograft and autograft tissue in a controlled laboratory setting, the primary concern is how allograft tissue performs clinically compared with autograft tissue. Providing an accurate evaluation of allograft and autograft tissue in ACL reconstruction is difficult because of the multiple types of graft, the variable processing of allograft tissue, and differences in graft fixation and surgical procedures (e.g., single vs. double bundle). The orthopedic literature has multiple level II–IV evidence studies investigating the clinical outcomes between autograft and allograft tissue in ACL reconstruction, with results ranging from no statistical difference to more favorable outcomes for autograft tissue. However, many of the studies lack randomization because the patients are provided the option to choose the graft. In contrast to most studies, Sun et al. published a prospective randomized study comparing 86 BTB autograft knees and 86 BTB allograft knees with an average follow-up of 5.6 years for both groups [**71**]. The results demonstrated no statistical difference between the allograft and autograft groups with the Lachman test, pivot-shift test, mean laxity with KT-2000 arthrometer testing, and percentage of knees with laxity greater than 3 mm [**71**]. In addition, three meta-analysis studies have been performed to investigate the clinical outcomes

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between allograft and autograft tissue [**70,90,91**]. Two earlier meta-analysis studies showed no statistical difference between the groups in regards to the Lachman test, pivot-shift test, and laxity on arthrometer testing [**70,90**]. The most recent meta-analysis demonstrated with statistical significance a mean laxity with arthrometer testing of 1.4 ± 0.2 mm for allograft and 1.8 ± 0.1 mm for autograft ($P < 0.02$) [**91**]. Despite the small difference in measured knee laxity, no statistical difference existed in the percentage of knees with less than 3 mm of laxity between the two groups [**91**]. The literature has not provided a consensus regarding the clinical outcomes between allograft and autograft tissue, but the belief is currently that allografts and autografts are clinically equivalent in ACL reconstruction.

DEMINERALIZED BONE MATRIX

Demineralized bone matrix (DBM) is a material derived from donor bone that is essentially the pure protein of bone. The cellular, fatty, and calcium components of the bone are removed during processing. DBM is used as a conductive and inductive biomaterial to produce bone healing in humans. Within this material are multiple bone growth factors (bone morphogenic proteins [BMPs]). These proteins have been shown to be active and important in bone formation. Therefore, DBM is a biological biodegradable substance that promotes bone formation in the proper environment. DBM can be provided by itself, but it is most often combined with a carrier for improved handling properties. DBM has a long clinical and scientific history, and it is the most commonly used bone-promoting agent in the allograft market, being involved in approximately 20 % of all procedures done per year [**92**].

It was in the 1930s that it was discovered that acid digestion of bone resulted in a material that would induce ectopic osteogenesis when injected into skeletal muscle [**93,94**]. Marshall Urist subsequently published his landmark paper in *Science* [**95**] that demonstrated that demineralized bone would induce osteogenesis when implanted into a nonbony site. It was Dr. Urist who coined the terms BMP and osteoinduction. Subsequent to Dr. Urist's work, Hari Reddi [**96**] characterized the various BMPs that were present in DBM. This work eventually led to the production and commercialization of individual BMPs—BMP-2 and BMP-7. It has been shown through extensive laboratory and clinical research that DBM is osteoconductive and osteoinductive and is effective in bone healing situations in humans [**97–98**].

DBM is acquired through the procurement of human bone tissue through the tissue donation system. This process and the subsequent manufacturing of this Class I medical device is regulated by the U.S. Food and Drug Administration (FDA) and is further overseen by the American Association of Tissue Banks [**99**]. Once the bone is initially cleaned, it is further processed into very small particles of various diameters and then demineralized, freeze-dried, and prepared for application. The various tissue processing facilities have developed detailed and proprietary techniques for preparing these materials. Although DBM can be used by itself, it comes in a dry powder form and is somewhat difficult to handle and introduce into a surgical site. Therefore, most

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DBM is combined with a carrier material to produce a product that can be injected or packed into and around a surgical site where bone healing is necessary. There are a myriad of types of carriers, which may or may not affect the activity of the DBM. Examples of these carriers are calcium sulfate, hyaluronic acid, glycerol, and various polymers.

Because DBM is acquired from tissue donors, each individual donor lot may have varying characteristics in regards to its initial biologic activity, processing methods, sterilization technique, and its eventual combination with a carrier substance. Multiple studies have been performed that show varying quantities of BMPs within various lots of DBM, although processing within each facility may be equivalent [**100–102**]. As expected, these biologic differences are difficult to predict and measure [**103–105**]. There have been many efforts to standardize a bioassay for the activity of DBM, but because of these variables, specific protein assays and in vitro tests have been unreliable. The in vivo tests using an athymic rat implant model seem to be the most reliable method of assessing the overall osteoinductive potential of DBM products [**106**]. The commercial providers of DBM products have the option of testing the biologic activities of their materials before release. Some manufacturers test the DBM before sterilization and the addition of carrier materials; other manufacturers test the end product. It seems logical that the second method would give the surgeon the best indication of biologic activity.

DBM has been used in almost all bone healing instances, including dental, craniofacial, neurosurgical, and orthopedic applications [**92,100,101**]. There have been many papers using preclinical animal models that illustrate the bone healing capabilities of DBM [**92**]. There have also been numerous studies exhibiting its effectiveness in general orthopedic and spine grafting situations [**97,100,101,107,108**].

Over 50 % of allograft procedures in the United States involve spine grafts [**109**]. Of these, a high percentage involves the use of DBM product. Although most of the studies reported are case series, there have been several comparative studies. A study by Kang et al. [**107**] compared fusion rates in patients who underwent single-level instrumented posterolateral lumbar fusion with either local autogenous bone and DBM or iliac crest autograft. At 2 years follow-up, the groups demonstrated statistically equivalent computed-tomography-verified fusion rates. In the general orthopedic area, there have been multiple papers published on the effectiveness of DBM for the treatment of unicameral bone cysts [**108**], fractures, and nonunions. Tiedman et al. demonstrated that demineralized bone, with or without autogenous bone marrow aspirate, was effective in bone healing application [**97,107**] comparing BMP-7 to demineralized bone protein in fibular defects. At 1 year, there was no difference in bone mineral density scores between those two products.

Controlled studies and anecdotal reports suggest that DBM is a product that may induce local bone healing and improve outcomes. DBM is osteoconductive; osteoinductive; and, with a carrier compound, is easily used clinically. It can be used to expand

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the volume of autograft procedures, such as spine surgery, and it can be used effectively in any area where bone growth is necessary.

HUMAN ADULT STEM CELLS

Over recent years there has been a tremendous amount of interest in using stem cells for the regeneration and repair of injured and missing tissues. Embryonic and adult stem cells have been investigated for their regenerative properties. These studies have exhibited a dramatic potential for tissue repair [**110,111**]. Because of many factors, embryonic stem cell technology has been difficult to access and commercialize because of limited availability and cellular mechanism complexity [**112**].

Adult stem cells are multipotential, undifferentiated cells with proliferative and self-renewal capacity. With the appropriate environment and local growth factor signals, adult stem cells can be directed toward specific cell lineages, including musculoskeletal tissues [**113**]. These adult MSCs have been shown in laboratory and clinical situations to assist in the regeneration of connective tissues [**114–119**].

There are two basic sources for adult MSCs: autologous and allogeneic. Autologous MSCs are generally derived from bone marrow and have been shown to have an effect in particular on bone healing. Multiple studies have demonstrated that MSCs will differentiate into an osteoblast line in vitro with the appropriate growth factors and nutrients [**120,121**]. As these cells mature in the appropriate environment, bone formation occurs.

Various clinical studies have supported these properties. Connolly et al. [**122**] show the effects of autologous marrow-derived MSCs as well as Hernigou et al. [**123**] in healing nonunions. There appeared in the Hernigou study to be a dose response related to the number of MSCs present in the marrow aspirate. Clinical and preclinical studies alike have demonstrated that a higher number of bone marrow cells may enhance fracture repair [**123,124**]. The optimal number or biologic activity of MSCs necessary for bone regeneration has not been elucidated. One of the difficulties in dealing with autologous bone marrow stem cells is their relative paucity within the aspirate or the bone graft material [**125**].

The other source of adult MSCs is from allograft donor tissue. Allograft MSCs have been shown to be nonimmunogenic when applied to local areas [**112,126**]. These cells are isolated from tissue from donors that have been designated for tissue and organ donation. Strict adherence to FDA and American Association of Tissue Bank criteria is mandatory for these donors [**99**]. These are naturally occurring MSCs and have not been cultured and expanded. There are two common sources of allograft MSCs. One source involves the actual in situ cells found in cancellous bone where the non-stem-cell components of the bone marrow have been removed [**127,128**]. The actual number of stem cells present in these materials is not well understood. At least one study suggested that bone marrow contains less than 1000 MSCs per cubic centimetre [**129**].

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The other source of adult MSCs is from allograft adipose tissue. It has been shown in vitro and in vivo that adipose-derived MSCs have at least as much potential or perhaps more potential to form along an osteoblastic line than marrow-derived cells [**112,130–133**]. The presumed advantage of using adipose-derived MSCs is that they preferentially bind to demineralized bone and in numbers much higher than that found in naturally occurring cancellous bone [**112,130–132,134,135**].

The ideal materials necessary for bone generation involve an appropriate substrate or scaffold, MSCs that are able to respond and proliferate, and the appropriate growth factor signals to stimulate the differentiation and proliferation of those cells. Currently available adult MSC products are available in two varieties. The first and most prevalent is a cancellous bone material that has been procured from a donor and processed in an attempt to save the MSCs but remove the myeloproliferative cells and bone inhibitor cells. These products generally come in a particulate form and are commonly used in spine fusions, arthrodesis, and problem bone healing situations [**119,128,136**]. The second material comprises DBM upon which adipose-derived MSCs have been added, which biologically bind to the scaffold. Although both of these materials are in common use, there has been no consensus on a method to measure their overall osteogenic activity. It seems important that methods be developed that can accurately measure the numbers of active stem cells and quantitate the growth factors necessary to provide adequate bone formation.

Human-derived stem cells are already being used in clinical medicine to promote bone healing in various situations. Further work is necessary to define and quantitate their actual biologic potential and regenerative properties.

SUMMARY

A wide range of soft tissue and osseous allografts are currently available for clinical use in orthopedic surgery. Allograft tissue has more recently gained popularity because of the abundant supply and lack of donor site morbidity. However, the primary concern regarding allograft tissue has been related to disease transmission and a perception that allograft tissue is not an equivalent substitute for autograft tissue. When using allograft tissue, the goal is to provide a comparable or superior outcome to the use of a synthetic implant or autograft tissue. In the process of deciding on an allograft tissue, the surgeon must take into account many considerations, including the type of operation, patient demographics, patient expectations, and the patient's willingness to use allograft tissue.

Human allograft remains a viable alternative for bone and joint reconstruction. We have been able to demonstrate the successful use of allograft tissue in a broad range of orthopedic applications; however, continued research and development is needed to improve allograft tissue. The focus of future research must include studies with high levels of evidence to confirm the equivalence of allograft and autograft tissue. The primary barrier toward achieving equivalent biomechanical properties of allograft tissue with autograft tissue is centered on the processing of the allograft.

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We must work to develop improved methods of tissue processing that limit disease transmission without altering the biomechanical properties of the tissue. In addition, new tissues are being developed that have a significant potential for skeletal repair. Although much is known about human allograft, questions still remain. What are the clinical outcomes and how do they compare to autogenous tissue or manufactured product? How do they work? What is the risk of disease transmission? Does processing affect performance? What are the long-term effects of implantation of these bioactive materials? These are other questions that need to be answered before we have a thorough understanding of human allografts and their use in clinical practice.

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