Allografts for Ligament Reconstruction: Where Are We Now?

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Musculoskeletal allografts are becoming increasingly accepted as a viable alternative to autografts in a variety of orthopedic procedures. A 2006 American Orthopaedic Society for Sports Medicine (AOSSM) survey indicated that 86% of the participating 365 orthopedic surgeons use allografts in their practice. Although the overwhelming majority of orthopedic surgeons use allografts, they share common concerns, including safety, tissue integrity, and biologic incorporation. It is essential for the orthopedic surgeon to understand the current standards of tissue banking, risks and benefits related to the use of allografts, and common indications for safe use in clinical practice. This article reviews the current status of musculoskeletal allografts, including tissue procurement and processing, infections, complications, and specific uses tailored to ligament reconstruction.

Donor Bank, Processing, Sterilization, and Regulation

In the United States, the American Association of Tissue Banks (AATB) is responsible for establishing the standards for more than 100 accredited tissue banks. These tissue banks recover tissue from approximately 30,000 donors annually and account for an estimated 90% of the available musculoskeletal allografts used in the United States. While not all tissue banks are accredited by the AATB, all are required to register with the Food and Drug Administration (FDA), which allows for unannounced inspections of any facility. Facilities are required to abide by the FDA-implemented Current Good Tissue Practices (CGTP), which encompasses regulations on all donor tissue collected after May 2005 to help prevent the transmission of communicable diseases. The FDA released an updated draft in January 2009 that emphasizes safe practices and regulations spanning from environmental control to specific equipment.

The safety of a transplanted allograft tissue begins within the tissue bank. Donor screening and testing is the first step in reducing the risk of transmission. Screening consists of collecting medical and social history from the family and any healthcare resources to assess the eligibility of the donor. If prior blood donations or autopsy information is available, that information is scrutinized. Donor tissue undergoes nucleic acid testing (NAT), which is required by both the AATB and FDA. All donor tissue must be screened for both types of human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), treponema pallidum, and human transmissible spongiform encephalopathies. NAT of donor tissue effectively reduces the risk of viral transmission. Additionally, routine preprocessing swabs for bacterial and fungal cultures are performed, although the sensitivity of these cultures ranges from 78% to 92%.
After donor screening and testing, allograft tissues are usually obtained under aseptic conditions, though this is not FDA-required. Once procured, the tissue undergoes sterilization. Currently, there is no standard method ubiquitous to all tissue banks, nor does the FDA require a specific method. Rather, the FDA and AATB require tissue banks to validate their sterilization process and provide supporting data. The goal of sterilization is to inactivate viruses and eradicate bacteria while maintaining the biological and mechanical properties of the tissue. The AATB requires a Sterility Assurance Level (SAL) of $10^{-6}$, meaning there is no more than one in a million chance that a nonviral viable microbe exists on or within the tissue. Sterilization techniques may include both radiation and a variety of chemical reagents. Gamma irradiation is a commonly used method of sterilizing soft tissue allografts, although some studies indicate that it is detrimental to tissue biology. Newer methods of sterilization are being tested, one of which includes carbon dioxide in combination with antioxidants and irradiation. Bui and colleagues directly compared the biomechanical and histological properties of allograft tissue after either the standard 25 kGy gamma irradiation or supercritical carbon dioxide techniques. Although there is no histological difference, the samples treated with supercritical carbon dioxide had less biomechanical damage. Finally, the terminally sterilized allograft tissue is frozen to temperatures between -40°C and -80°C.

**Infections**

One major concern of allografts is the risk of disease transmission. While numerous studies have investigated the incidence of bacterial infection following transplantation of allograft tissue, there are challenges associated with differentiating common postoperative infections from ones directly associated with the transmission of bacteria within the graft. There is a wide array of reported incidences of infection in the literature, from the Tomford and colleagues 1981 study that reported a 6.9% rate to the 2001 study by Munting and colleagues, who reported 0% in their series. Multiple confounding variables exist, such as possible contamination during handling of an otherwise noncontaminated or properly sterilized allograft with inappropriate inclusion of all postoperative infections. In contrast, recognizing viral transmission has been somewhat easier, although reporting of these incidences has been variable in the past. In either case, there is no accredited reporting system for infections related to allografts.

**Bacterial Transmission**

Clostridium species. Clostridium species are commonly found among intestinal flora. There is a general consensus that between 24 to 48 hours after death intestinal flora transmigrates into the surrounding tissue and blood. Therefore, a commonly accepted recommendation is that cadaveric tissue needs to be excised prior to 24 hours postmortem.

In 2001, a 23-year-old man underwent reconstructive knee surgery with a femoral condyle allograft. A few days after surgery, he became septic and ultimately died from the infection. *Clostridium sordellii* was cultured from the tissue. Several days later, a 17-year-old boy underwent reconstructive knee surgery with a fresh femoral condyle and frozen meniscus from the same donor. Twenty-four hours after surgery, he developed a fever and was readmitted a week later for presumed infection and treated effectively with penicillin and ampicillin/sulbactam. Tissue from the same cadaveric donor had been transplanted into 7 other patients without reports of infection. In a 2002 Centers for Disease Control and Prevention (CDC) update report, there were 26 total bacterial cases from allografts and 13 cases were attributed to *Clostridium*. Malinin and colleagues reviewed 795 consecutive cadaveric donors and found that 64 (8.1%) had positive cultures for *Clostridia*. Of all the positive cultures for *Clostridia*, 81.3% had positive blood cultures, 57.8% had positive bone marrow aspirate cultures, and 46.9% had positive tissue cultures. They concluded that multiple cultures are required for cadaveric tissue donors in order to
reach a higher sensitivity for *Clostridial* contamination, and these should be done routinely to guide the sterilization process.

Strep species. In 2003, a 17-year-old boy underwent anterior cruciate ligament (ACL) reconstruction with a patellar tendon allograft. About 1 week later, he was admitted for signs of infection and received intravenous antibiotics. He required surgical debridement, and intraoperative cultures grew Group A Streptococcus (GAS) that was also identified in the postmortem donor cultures. The tissues underwent processing in an antimicrobial solution and postprocessing cultures were negative for bacteria, but they were not sterilized. Tissues from this donor had been implanted in 5 other patients without report of infection. Following this event, recommendations have been made for prompt rejection of tissue with cultures positive for GAS, unless a sterilizing procedure is used.

Other bacteria. According to the 2002 CDC update, 11 of the 26 cases of bacterial infection reported to the agency were a combination of gram-negative bacilli, polymicrobial flora, or culture negative.11

**Viral Transmission**

The most effective way to prevent transmission of a viral disease from allografts is thorough donor screening. Since the AATB implemented NAT in 2005 for HIV and HCV, there have been no reported cases of transmission.3 Even prior to this, regular blood screening along with social questionnaires completed by donors or donor families eliminated high-risk donors and significantly decreased the rate of transmission.

Human Immunodeficiency Virus. The first reported case of HIV transmission via implantation of allograft was in 1988. Further investigation revealed that there were 8 transmissions between 1984 and 1986, when routine screening of donors had not yet been implemented. The last reported case of HIV transmission occurred in 1996 with an untested donor.13 Hepatitis C Virus. There are several reported cases of HCV transmission that occurred where the donors initially tested negative for HCV. In one case, 40 allografts from the same donor were transplanted over a period of nearly 2 years. This resulted in at least 8 patients being infected with HCV.14 Another case of HCV transmission was reported in 2005 after a patient developed acute HCV 6 weeks after transplantation of a patellar tendon allograft. Further investigation revealed that there had been 3 additional cases over a year from the same donor. Researchers determined that if the initial case had been reported, at least 3 transmissions could have been prevented.15 Human T-cell Lymphotropic Virus (HTLV). The first reported transmission of HTLV was in 1991. This was reported in an asymptomatic patient who received a femoral head allograft from a donor who had been previously infected via a blood transfusion.16 Zika virus. With recent outbreaks of the Zika virus, the FDA recently released recommendations regarding the screening and deferral of donors, mainly for blood transfusion. Orthopedists should take into consideration the potential for transmission through allografts. The FDA states that all potential donors should be screened for Zika virus using questionnaires and whole blood tests. Symptomatic donors are deferred at least 4 weeks following resolution of symptoms. While this is a recent recommendation from the FDA, orthopedists must be cognizant of the potential harms from this unfamiliar and evolving situation.17

**Graft Specifics**
Anterior Cruciate Ligament

ACL reconstruction is one of the most commonly performed surgeries by orthopedic surgeons, with an estimated 200,000 reconstructions per year. Despite the popularity of this surgery, controversies remain regarding the optimal graft for reconstruction. One would provide adequate strength, be readily available, not elicit an immunologic response from the host, rapidly incorporate, elicit low morbidity, and vascularize early. Current options include both autografts and allografts. Common autograft options include patellar bone-tendon-bone (PBTB), hamstrings tendon, quadriceps tendon, and iliotibial band. PBTB autograft remains a common choice among orthopedic surgeons, as it allows early incorporation of the graft into bone and eliminates immune rejection. However, donor site morbidity, including anterior knee pain, weakness of knee extension, joint stiffness, increased postoperative pain, and iatrogenic patella fractures, have been reported in the literature. Commonly used allograft options include donor bone-patellar tendon-bone, quadriceps tendon, Achilles tendon, anterior and posterior tibialis tendons, hamstring tendons, and iliotibial band. Allografts provide the advantage of avoiding donor site morbidity, being readily available, allowing for shorter operative times, and providing lower postoperative pain compared to autografts, although they carry the risk of disease transmission, rejection, and slower incorporation into bone.

Autograft donor site morbidities. One of the general disadvantages of autografts is the donor site morbidity associated with harvesting the grafts. In specific, PBTB grafts allow for bony blocks on both ends of the graft to incorporate into the host bone. However, this technique comes with the risk of disrupting the extensor mechanism. Milankov and colleagues published a retrospective review of over 2000 ACLs using autologous PBTB graft. They noted a 0.45% incidence of patella fracture and 0.18% patellar tendon rupture. Others have reported that intraoperative repair of the patellar tendon after tendon harvesting can increase infrapatellar fibrosis, thus increasing the risk for stiffness. Hamstring autografts include the semitendinosus and the gracilis tendons. The harvesting process is technically demanding and can be complicated by inadvertent amputation of the tendons, making the graft unsuitable for reconstructive purposes. Additionally, several reports have identified persistent numbness and hyperesthesia following hamstring harvesting due to iatrogenic injury to the prepatellar branches of the saphenous nerve. A comprehensive review by Slone and colleagues reported comparable functional outcomes with quadriceps tendon autograft compared to PBTB; however, this comes with the risk of postoperative hematoma formation and the potential for thigh compartment syndrome.

Biology and Biomechanics of Allografts

One of the major disadvantages of allografts is the reduced ability to incorporate into the host tissue. Several in vitro and animal studies have suggested that allografts incorporate in the host slower than autografts. Early studies by Jackson and colleagues on goat models demonstrated that allografts and autografts have similar structural and biological properties initially, but allografts display significantly slower incorporation into the host tissue at 6 months. Histologically, allografts demonstrated lower revascularization, a smaller cross-sectional area, and a prolonged inflammatory response at 6 months postoperatively. Muramatsu and colleagues further showed through the use of magnetic resonance imaging a slower rate of revascularization of allografts over 2 years post-reconstruction.

Given the delayed biologic incorporation of allografts, studies have identified a lower strength-to-failure rate in the early postoperative period compared to autografts. An animal model study by Nikolaou and colleagues showed that the strength of allografts was lower for up to 2 years following surgery. Additional biomechanical
studies demonstrated that allografts were nearly 75% structurally weaker compared to autografts at 1 year following surgery.\textsuperscript{42}

Acknowledging these limitations, one should use caution when choosing to use an allograft or starting aggressive early rehabilitation after an allograft reconstruction, especially in athletes and young patients.

**Clinical Outcomes**

Although in vitro studies demonstrate inferior strength and delayed incorporation of allografts in the early postoperative period, there is still controversy surrounding the clinical and functional outcomes. Numerous studies have identified allografts as a viable option for ACL reconstruction, with similar reported patient satisfaction scores compared to autografts.\textsuperscript{43,44}

The MOON Consortium recently published a prospective study of nearly 2500 subjects looking to identify risk factors for failure of ACL reconstruction. The study found that allografts had an odds ratio for failure 5.2 times that of PBTB autografts, correlating this factor to an increased re-tear rate of 6.9% in the allograft group compared to 3.2% in the PBTB group ($P < .01$).\textsuperscript{45} The elevated risk is more prevalent in younger patients, especially athletic teenagers. This issue has been reiterated in multiple studies.\textsuperscript{45-50} A meta-analysis by Hu and colleagues\textsuperscript{23} identified 9 studies, either randomized control trials or prospective cohort studies, that looked at clinical outcomes between the different graft choices. They showed there was no significant difference between graft options in terms of instrumental laxity ($P = .59$), Lachman test ($P = .41$), pivot shift test ($P = .88$), and multiple functional outcome scores, including the International Knee Documentation Committee (IKDC), Lysholm, and Tegner scores.\textsuperscript{23,51-59} Processing and sterilization techniques are thought to play a role in allograft failure. Guo and other researchers have demonstrated a significantly higher rate of failure for patients who received gamma-irradiated allografts compared to fresh frozen allografts.\textsuperscript{23,58-64} With improved sterilization techniques and a strict selection process of donors, gamma radiation has fallen out of favor to protect the biological characteristics of the tissue graft.\textsuperscript{5,65,66} Several factors need to be considered when selecting between allograft or autograft tissue for ligamentous reconstruction. The selection must be balanced between the surgeon’s experience, patient and surgeon preferences, age of the patient, level of physical activity, primary or revision surgical setting, multiligamentous failure, geographical availability of donor grafts, and economical factors.

**Medial Patellofemoral Ligament Reconstruction**

Another relatively recent application for allografts has been described for the reconstruction of the medial patellofemoral ligament (MPFL) in recurrent lateral patellar dislocations.\textsuperscript{67-74}

Typically, MPFL reconstructions make use of autografts, including quadriceps tendon, patellar tendon, and hamstring ligaments. However, allografts have the potential to limit postoperative donor site morbidity and to allow a faster rehabilitation.\textsuperscript{75,76} Allografts include semitendinosus, gracilis, anterior tibialis, posterior tibialis, and quadriceps tendons.

Calvo Rodríguez and colleagues\textsuperscript{76} performed a retrospective review in 2015 comparing allografts to autografts for MPFL reconstruction with respect to postoperative knee function and re-dislocation rates. Among the collective 28 patients, there was no difference in overall functional scores or dislocation rates between the grafts. Although this was a retrospective review and had a small number of subjects, the findings identify allografts as a reliable graft option for MPFL reconstruction.\textsuperscript{76} While there has been a surge of interest in techniques for MPFL reconstruction, there is limited research available regarding the superiority of allografts compared to autografts. For this specific
application, it seems that clinical outcomes correlate more to adequate stabilization of the patellofemoral joint than to the type of graft used. Future research should be dedicated to prospective randomized control trials to delineate any disadvantages to using allografts for MPFL reconstruction.

Discussion

Musculoskeletal allografts are gaining popularity for ligamentous reconstruction as their safety and efficacy continue to improve. With the great majority of tissue banks being accredited by the AATB and specific regulations such as NAT screening becoming common practice, infection rates and transmission of diseases have become incredibly rare. However, a thorough consideration needs to be taken into account when choosing between autograft and allograft on a case-by-case basis (Table).

Although the incidence of donor site complications is low with autografts, there are inherent risks, such as harvest site hyperesthesia, persistent numbness, cosmetic dissatisfaction, pain, weakness, functional implications, and unsuitability of the harvested graft. While it may appear that allografts may obviate donor site morbidity, one must consider the reduced potential for the donor tissue to incorporate into the host. Several studies have suggested that incorporation into the host tissue is inferior and slower for allografts. With this knowledge, factors such as clinical outcomes, future expectations, rehabilitation protocol, and individual patient characteristics all need to be considered when selecting the source of the tissue to be transplanted. Given that there is a growing need for availability of allografts, a well-rounded understanding of the biologic and physiologic aspects of the transplanted tissues is imperative. Future research will need to focus on improving the rate and quality of the biological incorporation of the transplanted graft into the host while eliminating the risk of disease transmission and infection.

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Key Info

Figures/Tables
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