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Allografts in Soft Tissue Reconstructive Procedures: Important Considerations

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Context: Allografts offer several important advantages over autografts in musculoskeletal reconstructive procedures, such as anterior cruciate ligament reconstruction. Despite growing widespread use of allograft tissue, serious concerns regarding safety and functionality remain. We discuss the latest knowledge of the potential benefits and risks of allograft use and offer a critical review of allograft tissue regulation, management, and sterilization to enable the surgeon to better inform athletes considering reconstructive surgery options.

Evidence Acquisition: A review of sources published in the past 10 years is the primary basis of this research.

Study Design: Observational analysis (cohort study).

Level of Evidence: Level 3.

Results: Comparable outcome data for autografts and allografts do not support universal standards for anterior cruciate ligament reconstruction, and physician recommendation and bias appear to significantly influence patient preference and satisfaction. Sterilization by gamma and electron-beam irradiation diminishes the biomechanical integrity of allograft tissue, but radioprotective agents such as collagen cross-linking and free radical scavengers appear to have potential in mitigating the deleterious effects of irradiation and preserving tissue strength and stability.

Conclusion: Allografts offer greater graft availability and reduced morbidity in orthopaedic reconstructive procedures, but greater expansion of their use by surgeons is challenged by the need to maintain tissue sterility and biomechanical functionality. Advances in the radioprotection of irradiated tissue may lessen concerns regarding allograft safety and structural stability.

Keywords: allograft; anterior cruciate ligament reconstruction; sterilization; irradiation; transplantation; disease transmission; tissue biomechanics

Allograft and autograft tissues have proven to be invaluable treatment modalities for patients with a variety of injuries, from athletes with musculoskeletal sports injuries to victims of severe burns[11,73] to those requiring solid organ transplantation.[10,27,66] Skin grafting is a viable treatment in the care of large burns, and the use of allografts in organ transplantation is great in breadth—allograft cardiac, hepatic, and renal components are but a few examples of allograft utility. Allografts have seen considerable clinical success in many soft tissue reconstructive procedures, including anterior cruciate ligament (ACL) reconstruction,[2,4] one of the most common orthopaedic procedures performed today[23]; estimates indicate that 300,000 ACL reconstructions are performed annually, with approximately 240,000 (80%) performed utilizing autograft tissue and 60,000 (20%) with allograft tissue.[12] The American Academy of Orthopaedic Surgeons asserts that over 5 million musculoskeletal allografts have been allocated to surgeons in the past decade, while the American Association of Tissue Banks reports that the demand for musculoskeletal grafts has grown from approximately 700,000 grafts in 2001 to 1.5 million grafts in 2007. Reasons for increased use of allograft tissue include effective sterilization procedures, organized collection and distribution of tissue, and increased confidence in the overall stability of allografts.[3,7,30,77] The increasing utilization of allograft tissue necessitates a critical review of its regulation, management, and sterilization.

CONSIDERATIONS OF GRAFT SELECTION WITH ACL RECONSTRUCTION

Many donor site morbidity problems associated with autografts can be overcome with the use of an allograft. In ACL reconstruction, bone–patellar tendon–bone (BPTB), anterior tibialis, hamstrings, or Achilles tendon extracted from

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a cadaver may be used in place of the patient's own tissue. This allograft tissue is subsequently sterilized, as the risk of allograft-associated disease transmission and bacterial infection is of real concern.[17,50,58] When considering a surgical approach for repair of an ACL rupture, a patient will naturally pose the simple query: which graft is best? Ideally, this graft would maintain the same functionality and biomechanics of an endogenous ACL, coupled with low donor site morbidity. Unfortunately, this apparently straightforward question has no simple answer. Studies have yet to show a clear advantage of one graft over another, as there are benefits and drawbacks to each.[32,45,46] The advantages of an autograft-associated procedure include decreased risk of disease transmission, better uptake of the graft, increased biomechanical integrity, and a potentially lower cost. However, an allograft-associated procedure is associated with decreased donor site morbidity, larger graft availability, shorter time in the operating room, and less postoperative pain.[12,44]

Although there are grounds to support the expectation of an increased structural failure rate for allograft reconstructions, including increased host immunologic responses and decreased strength in animal models,[34,63] there is a relative paucity of data to support this concern. As such, a number of meta-analyses have recently been conducted with the aim of determining which graft option has the best clinical outcome associated with its use. A 2007 study by Prodromos et al[63] comparing allograft and autograft clinical stability rates in ACL reconstruction was the first of its kind. Their analysis found that allografts had substantially lower stability rates than autografts; the abnormal allograft stability rate was nearly 3 times higher than that of autografts. Given these findings, Prodromos et al[63] recommend utilizing autografts for routine ACL reconstruction, with allografts reserved for only multiple ligament–injured knees. However, as Tibor et al[76] noted, their review utilized a limited method of scoring separate studies, which may have contributed to a biased conclusion of superior autograft stability.

Most reviews to date, however, contradict the findings of Prodromos et al[63] and do not find one graft source to have significantly better outcomes than another. In one such study, Carey et al[8] investigated whether short-term clinical outcomes differed significantly for ACL reconstruction with allograft or autograft. Their review determined that short-term clinical outcomes are not significantly different; specifically, they found that Lysholm scores, instrumented laxity measurements, and clinical failure rates were no different for the 2 graft options. Carey et al[8] acknowledge, however, that the studies they reviewed do not account for confounding factors, such as age and level of activity, which could affect their conclusions.

Another meta-analysis by Krych et al[44] specifically compared patellar tendon autografts with patellar tendon allografts to determine if clinically significant differences could be found. This review found that graft rupture rates and hop test results were significantly better with patellar tendon autograft than allograft when irradiated and chemically processed grafts were considered. However, when these processed grafts were excluded from consideration, no measurable differences were found between the 2 grafts. These results suggest that there is considerable developmental potential for improved irradiation and chemical processing techniques and that with such improved techniques, the differences in outcomes for allograft and autograft procedures will become negligible.

A more recent systematic review by Foster et al[21] explored the outcomes of autograft versus allograft ACL reconstructions. Results indicated no statistically significant differences in graft failure rates, complication rates, and percentages of A or B International Knee Documentation Committee scores. The authors therefore concluded that no graft source could be identified as superior and, thus, the source of the graft has little effect on the outcome of patients undergoing ACL reconstruction.

Another extensive study published by Tibor et al[76] sought to determine whether a difference exists in functional outcomes, failure rates, and stability between allograft and autograft ACL reconstructions. Their analysis found that only 1 outcome measure (increased joint laxity in allografts observed by KT-1000 measurements) was statistically significantly different; all other negative outcome measures—such as positive Lachman test, positive pivot-shift test, International Knee Documentation Committee grade C or D, and graft failure—had larger proportions for allograft than autograft but were statistically insignificant. The authors acknowledged that their analysis had limitations, as the number of studies published for patients with allograft ACL reconstruction is relatively small; moreover, only 10% of potentially relevant ACL literature could be used in the review.

A cohort study initiated in 2002 to identify predictors of ACL reconstruction outcomes found 2 significant predictors of graft failure: patient age and graft type. The younger the patient, the higher the risk of graft rupture, as the odds of graft rupture increased 2.3 times with each 10-year age decrease. Moreover, the likelihood of graft rupture in patients with allograft reconstruction was 4 times higher than in those with autograft reconstruction.[38] Kaeding et al[38] thus argue that allograft ACL reconstruction should be approached cautiously in the young patient. This recommendation is supported by a similar comparison of cadets at the US Military Academy, which found that cadets who underwent allograft reconstruction were significantly more likely to experience clinical failure requiring revision reconstruction.[61] Because of the decreased odds of rupture in the older patient, the use of allograft reconstruction may still be well suited; indeed, the use of allografts has increased steadily and is significantly more common in older patients.[36]

A recent meta-analysis of 5182 patients evaluated the outcomes of ACL reconstruction utilizing BPTB autograft versus allograft.[43] This study found that patients who underwent reconstruction with BPTB autografts showed lower rates of graft rupture and lower levels of knee laxity and had a generally more satisfactory postoperative course compared

with patients undergoing reconstruction with allograft BPTB. Because of their focus on overall patient satisfaction and return to preinjury activity levels, the authors make a relatively strong argument for the use of BPTB autografts over allografts; nonetheless, the use of allografts still plays a major role in ACL reconstruction.[43]

Clearly, however, the extensive reviews of allograft and autograft procedure outcomes have failed to identify the ideal graft source for ACL reconstruction. Thus, several factors must be considered, including physician recommendations, comfort with surgical technique, patient preferences, expectations, and associated costs.

A 2009 study by Cohen et al[13] sought to determine the underlying factors in patients' decisions regarding graft type in ACL reconstruction. The questionnaires received from patients who had undergone ACL reconstruction yielded several noteworthy results. When asked what their primary factor was in graft selection, the majority of patients listed physician recommendation (74.2% of patients), underscoring the necessity for surgeons to understand the risks and rewards of each graft option. Curiously, when asked about their graft satisfaction, more patients were unsatisfied with allograft than with autograft (8.4% vs 4.8%, respectively), suggesting a general preference for autografts over allografts. However, when asked to provide opinion on potential future graft selection, nearly two-thirds of patients (63.3%) who preferred a different graft material (12.7% of total patients) would change from autograft to allograft, while only one-third (36.7%) would change from allograft to autograft; many who desired to change from autograft to allograft cited postoperative pain at their harvest site as their primary reason, while several who desired to change from allograft to autograft cited physician recommendation as their primary influence. This seeming discrepancy in satisfaction and graft preference may imply inadequate communication between patient and surgeon; patients may be led to believe that the likelihood of complete recovery is greater than what data would support. Another potential explanation lies in physician bias. A 2006 member survey of the American Orthopaedic Society for Sports Medicine indicated that the use of allografts was associated with physician age.[48] Approximately 93% of surgeons under the age of 35 years utilized allografts, with each subsequent age group's percentage of use declining. In fact, only 46.2% of surgeons over the age of 65 years reported utilizing allografts. Moreover, nonfellowship-trained surgeons, lower volume sites, and lower volume surgeons were more likely to perform allograft reconstructions or hamstring autografts than BPTB autografts, suggesting a biased perspective of such surgeons.[33] Such results further highlight the significance of physician input in patient's decision making and emphasize the need for complete candor and objectivity.

With the ever-increasing cognizance of the ramifications of skyrocketing health care expenditures, surgeons should bear in mind the costs associated with allograft or autograft procedures. A 2005 study by Cole et al[14] indicated that the mean total cost of an allograft ACL reconstruction was $1072 less than that of an autograft ACL reconstruction ($4622 vs $5694, respectively). The higher costs of autograft procedures were attributed to increased time spent in the operating room and a higher likelihood of overnight hospitalization. A more recent study Nagda et al[56] sought to determine the costs of allograft versus autograft ACL reconstruction if the procedure were completed entirely in an outpatient setting. This study reported that the total cost of an allograft ACL reconstruction was $593 more than that of an autograft ACL reconstruction ($5465 vs $4872, respectively). Because of the advances in ACL reconstruction procedures (from open to arthroscopic) leading to diminished donor site morbidity, the majority of these cases are now handled in the outpatient setting, indicating a financial preference for autograft ACL reconstruction.[24]

To support this financial preference, a recent study outlined an economic analysis in a hospital-based outpatient setting of allograft versus autograft reconstruction.[26] In this study, the mean direct cost and operating room time for ACL reconstruction using allografts was $4587 and 92 minutes; the mean direct cost and operating room time for ACL reconstruction utilizing autografts was $3849 and 125 minutes. The cost of allograft tissue was not offset by the shorter operating and recovery room times, which was substantiated by a study conducted by Cooper and Kaeding.[15] Of note, the additional cost of allograft use was covered by reimbursement, which may begin to play a part in physician preference as the reimbursement landscape changes in the coming years.

Setting a universal standard for ACL reconstruction is clearly impractical, as there are many elements that factor into choosing a specific graft procedure; the comparable outcomes data for allografts and autografts merely compound the complexity. More research is thus necessary to determine whether either of the graft options is superior to the other and what criteria should be met before ACL reconstruction is warranted.

ALLOGRAFT SAFETY AND STERILIZATION TECHNIQUES

The increasing utilization of allograft tissue has brought its risk-and-reward profile to the forefront of orthopaedic surgery. Allograft transplantation infection rates are very low; studies indicate that the incidence is well less than 1% (0.0004%-0.014%).[52,81] Although the reported number of infections is likely to be underreported,[12] the low incidence rate of disease transmission does not preclude physician concern. The most recent survey of members of the American Orthopaedic Society for Sports Medicine, conducted in 2006, indicated that although more than 60,000 allograft procedures were performed in the preceding year, many surgeons were concerned with the risk of allograft disease transmission.[48,52] This phenomenon has been well documented,[9,39,47,53,55] and concerns exist with regard to transmission of human immunodeficiency virus (HIV), hepatitis B and C viruses

(HBV and HCV), group A streptococcus, *Clostridium* species, and prions. Curiously, although 82% of responding surgeons were confident in the safety of sterilized grafts, nearly 46% of respondents either did not know if the tissue had been sterilized or what the sterilization technique was. Many members also listed concerns with regulatory practices and the biomechanical properties of tissue after sterilization, indicating that increased investigation into tissue quality was warranted.

A number of relatively recent works clearly elucidate the regulatory measures in place for safe transplantation of allograft tissue.[25,52,79,81] Currently, all human cells and tissue intended for transplantation into a human recipient are regulated as HCT/P, or "human cell, tissue, and cellular and tissue-based product."[79,81] The Food and Drug Administration (FDA; specifically, the Center for Biologics Evaluation and Research), which established guidelines in May 2005 for tissue banks that manufacture HCT/Ps, is responsible for this regulation; any institution that recovers, processes, stores, or handles allograft tissue consequently must register with the FDA.[52] These FDA guidelines collectively are termed *current good tissue practice*, and a more recent draft guidance was released by the FDA in January 2009.[78] Its aim is to prevent the introduction, transmission, and spread of disease by establishing guidelines that will reduce the risk of allografts containing pathogens and to prevent contamination during tissue processing. Because of past disease transmission, the FDA now mandates that all donor tissue be screened for HIV types 1 and 2, HBV, HCV, *Treponema pallidum*, and human transmissible spongiform encephalopathies using advanced nucleic acid testing techniques,[79] which allows for sharply reducing the diagnostic window and excluding donors with high viremia.[65] To ensure compliance with its guidelines, the FDA may inspect any tissue bank without notice. FDA guidelines also require that tissue banks maintain complete records with respect to tissue processing.

Although the primary governmental regulatory body, the FDA is not the only entity that shoulders the burden of regulation; the American Association of Tissue Banks provides for a measure of self-regulation. The association's voluntary accreditation program ensures that tissue banks seeking its certification follow a strict set of guidelines for tissue processing, including mandatory nucleic acid testing and negative *Clostridium* and *Streptococcus* pyogenes tissue culture results.[79,81] Although accreditation by the American Association of Tissue Banks is not required, tissue banks are urged to seek certification, as lack of accreditation can be inferred as a warning regarding the quality of the allograft processed by such a tissue bank.

To meet the growing demands for allograft tissues and their requisite safety and quality, tissue banks have responded by striving to improve donor screening, tissue processing, and sterilization techniques. Donor screening is a vital first step in ensuring the appropriate quality of tissue; indeed, it is still considered the most effective way to improve the safety of allografts.[70] Throughout this process, complete medical and social histories of the potential donor are first obtained from relevant relatives and health centers; medical records are also exhaustively reviewed. Such measures are taken to explore potential risk factors for infectious disease. Subsequent steps in donor screening include tests mandated by the FDA, including HIV, HBV, and HCV testing. Thus, a thorough workup of the potential donor's history, coupled with the results of the various mandated screens, provides an appropriate initial glimpse into the quality of the potential allograft donor tissue.

When an appropriate donor is identified, the allograft tissue in question must undergo processing to ensure that pathogens are not concomitantly transferred. Interestingly, current good tissue practice does not mandate that tissue be handled aseptically or sterilized before transplantation but rather that any processing procedure for reducing the risk of disease transmission be verified and validated.[52] Even so, tissue recovery is typically performed using an aseptic technique in a standard operating room setting.[79,81] While the aseptic technique is designed to provide the minimum risk of disease transmission, tissue procured under such conditions does not imply sterilization, as contamination may be introduced by the health care worker's handling of the tissue or through the donor's endogenous flora.[79] Studies have shown that antibiotic solutions may not sufficiently eliminate such pathogens.[28,52]

Sterilization techniques used in allograft tissue processing must accomplish balanced goals of removing any tissue-related pathogens that may lead to disease transmission while maintaining the greatest biomechanical integrity of the tissue possible. To date, there is no sterilization process that is widely agreed on, as different tissue banks use different proprietary techniques. Regardless of the method of choice, the majority of tissue banks strive for processed allografts to reach the American Association of Tissue Banks' required sterility level of 10^{-6}, meaning that the probability of a microorganism remaining on a sterilized tissue graft is, at most, 1 in 1 million.[59,79]

Irradiation

The tissue preparatory techniques of freezing alone do not eliminate all pathogens found in graft tissue. Thus, other terminal sterilization procedures are often required. Radiation sterilization is an effective technique.[41,52] In fact, allografts that have not been treated with gamma or electron-beam irradiation or ethylene oxide are typically not likely to be sterile.[37] Among the most common irradiation processes currently employed is gamma irradiation, especially Co,[60] which induces excitation of molecules and ions for radical-induced chemical reactions such as cross-linking, branching, and grafting.[29] These induced reactions subsequently lead to destruction of pathogens. A dose of 25 kGy has traditionally been used for sterilization,[59] although recent data indicate that pathogens can be destroyed with 15 kGy.[29] Terminal sterilization, however, necessitates larger doses, as 30 kGy is required to destroy HIV genes[19] and 34 kGy is recommended for destruction of parvovirus B19.[64]

Unfortunately, the generation of free radicals also distorts the integrity of the allograft tissue; several studies have correlated decreasing allograft biomechanical integrity with increasing doses of irradiation[16,29,71] and decreased enzyme resistance in irradiated tendons.[72] The underlying reasons for this poor biomechanical integrity are not well understood. Potential explanations for reductions in the biomechanical properties of BPTB grafts include free radical attack on collagen and changes in hydroxypyridinium cross-link density, collagen content, and water content.[1,70] For example, while high doses of gamma irradiation can inactivate HIV, they also lead to unacceptable levels of allograft structural alteration.[70] In general, doses above 20 to 25 kGy lead to tissue deterioration.[18] Hence, sterilization utilizing only gamma irradiation is now seldom employed.

Although gamma irradiation affects the biomechanical integrity of allograft tissue, the extent of this effect depends on the methods used in graft preservation. A 2009 study by Kaminski et al[41] found that the tensile strength of BPTB grafts that had been irradiated with 35 kGy decreased more substantially when grafts were preserved by lyophilization and glycerolization than by deep fresh freezing. Thus, Kaminski et al[41] indicate that deep-frozen irradiated grafts maintain biomechanical properties that allow for their clinical application.

A relatively new irradiation technique employs electron-beam irradiation instead of gamma irradiation. Although the chemical changes involved in electron-beam irradiation are similar to those of gamma irradiation, several advantages of the electron-beam procedure have been noted: greater control and accuracy of applied dosage, substantially reduced processing time, and potential for tissue preservation when irradiation occurs with the addition of carbon dioxide. Also, biomechanical integrity of electron beam–irradiated BPTB allograft tissue has been found to be superior to that of gamma-irradiated BPTB tissue at 34 kGy.[29]

The ultimate biomechanical response of allograft tissue after electron-beam irradiation has been mixed, however. Hoburg et al[29] found that 34 kGy of irradiation led to only small adverse effects on failure loads when carbon dioxide was used as a free radical scavenger; this reduction was comparable with failure load values found for native ACLs in a population of a similar age. Other mechanical properties were not found to be significantly affected. Seto et al,[72] however, found that the decrease in biomechanical integrity of tissue exposed to electron-beam irradiation was similar to that of tissue exposed to gamma irradiation. This study did not utilize carbon dioxide as its radical scavenger but instead mannitol, ascorbate, and riboflavin.[72] Both studies, however, indicated that viscoelastic properties were only minimally affected after electron-beam irradiation. This may be inferred as another advantage of electron-beam irradiation, as the viscoelastic properties of tissue that undergoes gamma irradiation have shown significant deterioration.[29]

Because of the biomechanical instability that accompanies the high levels of irradiation required for the destruction of allograft pathogens, especially HIV, the development of radioprotective agents that can mitigate tissue deterioration is highly desired. A 2005 study by Akkus et al[1] sought to investigate the capabilities of free radical scavengers, specifically thiourea, in protecting collagen of human femoral cortical bone. Results indicated that free radicals generated by gamma irradiation led to cleavage of the collagen backbone and, hence, biomechanical instability. When the free radical scavenger thiourea complemented irradiation, reduced collagen damage and less brittle cortical bone were observed, indicating the potential for utilizing scavengers as a means to reduce the loss of biomechanical integrity in gamma-irradiated tissue.

More recent investigations by Seto et al[71,72] have explored the radioprotective effects of 2 treatments. A preliminary study sought to determine the utility of a cross-linking treatment and addition of free radical scavengers in radioprotection of irradiated Achilles tendons.[72] Cross-linkers included 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) and glucose, which allowed for increased collagen cross-links. Scavengers included mannitol, ascorbate, and riboflavin, and the level of radioprotection was assessed via tensile and collagenase resistance testing at 25 and 50 kGy of gamma or electron-beam radiation. Seto et al[72] found that cross-linking and radical scavengers both showed positive radioprotective effects. At 25 kGy, glucose-treated specimens had strength close to that of native tendon; gamma radiation–induced radicals allow for glucose-derived cross-link formation, leading to strengthening of the tendon.[60] Free radical scavengers, especially riboflavin and ascorbate, also showed radioprotective effects. Although each treatment provides radioprotection at 25 kGy, cross-linkers provided more radioprotection over a greater dosage range; cross-linkers were superior to radical scavengers at 50 kGy. Cross-linkers also improved resistance against collagenase degradation; EDC-treated specimens even remained intact for 24 hours.

In their follow-up study, Seto et al[71] set out to establish whether radioprotection would be improved if grafts were treated with both cross-linking and radical scavenger treatments concomitantly. Achilles tendons were treated with the cross-linker EDC and 1 of 3 radical scavengers—mannitol, ascorbate, or riboflavin—and then exposed to 50 kGy of gamma or electron-beam irradiation. Results indicated that irradiated tendons treated with any of the 3 regimens had increased biomechanical integrity and higher resistance to collagenase digestion relative to EDC-only or untreated specimens. The strength of treated tendon was similar to that of native tendon, and significant increases in strength were observed when a combination of treatments was used as opposed to only EDC. These studies demonstrate the promise of radioprotective agents. If a combination of such agents that maintain optimal biomechanical integrity can be determined, a course of irradiation, complemented by these radioprotective vehicles, can be employed in the safe sterilization of allografts.

Although free radical scavengers mitigate the loss of biomechanical integrity in gamma-irradiated tissue, concerns

remain with the possible radioprotection of pathogens as well. Such an outcome leads to unsterile allograft tissue, rendering the irradiation process worthless. A recent study by Kattaya et al[42] established this phenomenon by assessing the effect of specific radioprotectors and radiosensitizers on bacterial spore count. Results indicated that 2 radioprotectors, L-cysteine and L-cysteine-ethyl-ester, did not provide radioprotection to spores of *Bacillus subtilis*, suggesting that they were unable to penetrate the bacterial spores. Specific targeting of spores by radiosensitizers was also investigated using nitroimidazole-linked phenanthridinium (NLP); they hypothesized that spore DNA/RNA could be targeted by a radiosensitizer, leading to radiation damage and, thus, nonviability. However, results suggested that NLP was unable to penetrate the spores and bind to the nucleic acids, as irradiated samples treated with NLP lost sensitization effects after rinsing with phosphate-buffered saline. At least for NLP, the nucleic acid targeting approach does not seem viable; conversely, the radioprotective results of L-cysteine and L-cysteine-ethyl-ester seem promising, although more research is required to determine the biomechanical effects of these agents. Therefore, establishing which radioprotective agent can optimally maintain the biomechanical strength of irradiated tissues and prevent the concurrent protection of pathogens should lead to substantial advances in utilizing gamma-irradiated allografts for surgical procedures.

Ethylene Oxide

The other traditional approach to terminal sterilization involves ethylene oxide gas,[40,79,81,82] an industrial fumigant that is commonly used to sterilize medical equipment.[51] This method gained favor because of its ability to effectively destroy pathogens, particularly viruses such as HIV and hepatitis.[54] However, its popularity has decreased dramatically, primarily because of synovial inflammation and reactions of the host tissue upon transplantation with ethylene oxide–sterilized grafts.[52,67] One study evaluated 109 patients over a 3-year period who had undergone ACL reconstruction with ethylene oxide–sterilized allografts. Seven patients (6.4%) developed a persistent intraarticular reaction, characterized by continuous synovial effusions. Synovial biopsies further showed a chronic inflammatory process, with a preponderance of fibrin, collagen, and phagocytic cells. Furthermore, when the allograft tissue was removed from patients, this intra-articular reaction resolved in all patients.[35]

Peracetic Acid–Ethanol

Because of the drawbacks associated with irradiation and ethylene oxide, other approaches to allograft sterilization have been investigated. One such approach involves utilizing peracetic acid–ethanol. A 2005 study by Scheffler et al[68] sought to determine what the in vitro biomechanical integrity of a human BPTB graft would be after sterilization with peracetic acid–ethanol. Upon analysis of cyclic submaximal loading and load-to-failure testing, their results indicated that viscoelastic and mechanical properties were similar before and after sterilization. In vivo biomechanical effects, however, were not addressed. In a 2008 study, Scheffler et al[67] utilized a sheep model to establish the in vivo effects of peracetic acid–ethanol sterilization by addressing recellularization, restoration of crimp length and pattern, and revascularization of ACL grafts during early healing. Peracetic acid–ethanol sterilization slowed the remodeling activity and reduced the biomechanical integrity of the graft tissue relative to nonsterilized allografts and autografts. Thus, while Scheffler et al[67,68] initially found promising results utilizing peracetic acid–ethanol as a sterilizing agent, they later concluded that this procedure should not be utilized in the sterilization of grafts typically used in ACL reconstruction.

Another potential drawback of this particular sterilization procedure is the loss of sterilization efficacy, as proteins have an adverse effect on the virus-inactivating capacity of peracetic acid–ethanol.[69] A 2007 study determined that collagenous proteins had no adverse effect on the virus-inactivating capacity of peracetic acid–ethanol and that utilizing this sterilization technique was appropriate in the processing of musculoskeletal tissue.

The variety of graft tissue sterilization processes implies that no universal standard exists. Each process presents its own unique benefits and drawbacks and necessitates further investigation into developing an ideal sterilization process. This process must sufficiently decrease the risk of disease transmission without compromising the structural integrity of the graft. Several promising advances have been developed, and the current investigation into better irradiation processes and more capable radioprotectors should lead to exciting new sterilization techniques.

FUTURE DIRECTION: SUBSTITUTES AND BIOLOGICAL AUGMENTATION

The satisfactory results of autograft and allograft ACL reconstruction procedures have not precluded further research into graft substitutes. Although prosthetic implants have historically proven to have poorer outcomes than graft reconstruction procedures, a novel artificial ligament has shown promise. The ligament-advanced reinforcement system (LARS), an implant made of polyethylene terephthalate fibers, is able to imitate the natural structure of the ACL and reduce shear stress placed on it. In a preliminary study by Nau et al[57] comparing the LARS system to a BPTB autograft procedure in patients with chronic instability, the International Knee Documentation Committee scoring system indicated that there were few significant differences between the 2 methods, suggesting that recovery time to full activity may be shortened by using the LARS ligament. However, a study by Talbot et al[75] reported increased laxity and a lower mean Lysholm score associated with the LARS artificial ligament. Therefore, although early data suggest that there is exciting potential for the LARS ligament as an alternative to standard

ACL reconstruction procedures, the risks and consequences of injury and increased laxity must first be thoroughly investigated.

Biological augmentation to aid in the healing and incorporation of allografts offers future promise. One such device is a collagen-platelet composite (CPC), which has been shown to stimulate healing of ACL injuries.[20] In a 2009 study by Fleming et al,[20] the authors placed CPC around an ACL graft at the time of reconstruction in a porcine model. Initial data (15 weeks after healing) showed a reduction in anterior-posterior knee laxity of 28% and 57% at 60° and 90°, respectively, with the CPC addition. Maximum failure loads were significantly higher with the CPC as well. Clearly, these preliminary results indicate that the addition of a CPC during ACL reconstruction significantly improves the biomechanical properties of the graft and reduces anterior-posterior knee laxity in a porcine model. This study suggests that investigation into the underlying causes of this improved biomechanical integrity could provide new insight into improving the healing process of a reconstructed ACL with autograft or allograft.

Tissue engineering advances also provide encouraging data regarding the treatment of ACL injuries, including the use of growth factors, gene delivery systems, and extracellular matrix bioscaffolds.[31] Growth factors such as TGF-β (transforming growth factor beta), PDGF (platelet-derived growth factor), IGF (insulin-like growth factor), and EGF (epidermal growth factor) have shown positive effects on improving ACL healing and are known to improve vascularization and new tissue formation. Also, the addition of platelet-rich plasma has indicated increased biomechanical integrity in animal models. Gene therapy efforts have focused on the expression of specific genes necessary for ligament healing. Because the ACL is a highly dense, organized tissue composed of collagen types I, III, and V,[22] the addition of more collagen should, in theory, improve its integrity upon injury. A study by Pascher et al[62] indicated that a gene transfer of TGF-β1 in a patient with a ruptured ACL led to increased cellularity and deposition of type III collagen, and a study by Steinert et al[74] showed that therapy with IGF-1 cDNA led to increased synthesis and deposition of collagen types I and III. These reports further verify the potential for delivering genes to improve the repair of an injured ACL. Extracellular matrix bioscaffolds have been shown to promote tissue regeneration and the repair of ligaments.[5,6,49,80] A study by Woo et al[83] showed that utilizing a porcine small intestinal submucosa bioscaffold to heal a transected ACL following repair led to new tissue formation, significant reductions in anterior-posterior joint instability relative to ACL-deficient joints, and in situ forces of the new ACL similar in scale to those of an intact ACL.

SUMMARY

Allograft tissue for soft tissue reconstructive procedures has been used for several years with favorable clinical outcomes. Allografts can reduce donor site morbidity and offer technical ease and convenience to treating surgeons. However, use of allograft tissues does not come without significant risks and concerns that must be balanced and discussed with patients. Drawbacks include the potential for disease transmission, a structurally inferior graft, and biological reaction to the sterilization process. The orthopaedic surgeon must understand and effectively communicate the benefits and risks associated with a specific procedure, as the differing risk-reward profiles may be more appealing to one patient than another. Also, surgeons should have a general understanding of the sterilization techniques utilized by tissue banks to make certain that sufficiently low risks of disease transmission are present. Recent studies have indicated the potential promise of new compounds that may lead to the preservation of native graft strength after completion of proper sterilization processes.

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