Revision Risk After Allograft Anterior Cruciate Ligament Reconstruction

Association With Graft Processing Techniques, Patient Characteristics, and Graft Type

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Background: Allograft tissue is a common graft choice for anterior cruciate ligament reconstruction (ACLR). Allograft sterilization methods vary widely across numerous commercial tissue vendors. Multiple studies, despite being limited in sample size, have suggested a higher rate of clinical failure associated with the use of allograft tissue in ACLR when compared with autograft.

Purpose: To examine the association of graft processing techniques, patient characteristics, and graft type with risk of revision surgery after allograft ACLR.

Study Design: Cohort study; Level of evidence, 3.

Methods: A retrospective cohort study was conducted that used an integrated United States health care system’s ACLR registry to identify primary unilateral cases in which allografts were used. Aseptic revision was the endpoint of the study. Allograft type, processing methods (irradiation dose, AlloWash, AlloTrue, BioCleanse), and graft donor age were assessed as potential risk factors for revision, with adjustment for patient age, sex, and body mass index (BMI) by use of logistic regression analysis models. Hazard ratios (HRs) and 95% CIs were calculated.

Results: A total of 5968 primary ACLR cases with allograft were included in the study, of which 3688 (61.8%) were male patients. The median age of the cohort at the time of surgery was 34.1 years (interquartile range, 24.1-42.9 years). The mean time to follow-up (±SD) was 2.1 ± 1.5 years. There were 3751 (62.9%) allograft ACLRs using soft tissue, 1188 (19.9%) with Achilles tendon, and 1029 (17.2%) with bone–patellar tendon–bone (BPTB). Graft processing groups included BioCleanse (n = 367), AlloTrue or AlloWash (n = 2278), irradiation greater than 1.8 Mrad (n = 1146), irradiation up to 1.8 Mrad (n = 3637), and no irradiation (n = 1185). There were 156 (2.6%) aseptic revisions. After adjustment for patient age, sex, and BMI, the use of BioCleanse (HR = 2.45; 95% CI, 1.36-4.40) and irradiation greater than 1.8 Mrad (HR = 1.64; 95% CI, 1.08-2.49) were associated with a higher risk of revision when compared with all other methods of processing. BPTB allografts were at higher risk of revision (HR = 1.79; 95% CI, 1.20-2.66) when compared with soft tissue allografts. Conversely, with every 5-year increase in age, the odds of revision were 0.67 (95% CI, 0.61-0.73) times lower. Male patients were found to be at higher risk of revision when compared with females (HR = 1.47; 95% CI, 1.04-2.07). The use of AlloWash or AlloTrue processing, patient BMI, and graft donor age did not affect revision rate significantly.

Conclusion: In the largest known study of its kind examining outcome after primary allograft ACLR, graft irradiation greater than 1.8 Mrad, BioCleanse graft processing, younger patient age, male patients, and BPTB allograft were all associated with a higher risk of clinical failure and subsequent revision surgery.

Keywords: ACL reconstruction; ACL registry; allograft; revision

The goal of anterior cruciate ligament reconstruction (ACLR) is to restore the native anatomy and stability of the knee using supplemental tissue. In 1999, the majority of members of the American Orthopaedic Society of Sports Medicine (AOSSM) reported bone–patellar tendon–bone (BPTB) autograft as their preferred choice for ACLR. While long considered a gold standard, BPTB autograft is associated with notable harvest-site morbidity. These drawbacks, among other factors, have driven the use of alternative graft choices for ACLR, including hamstring

References 1, 2, 12, 15, 27, 33, 35, 44, 48, 49, 51, 52.
tendon (HT) or quadriceps tendon autograft, allograft composed entirely of soft tissue, or soft tissue allograft with attached bone. A 2013 AOSSM survey of 833 surgeons, who on average performed 43 primary ACLRs in the year prior, found that allograft was selected in 27% of those cases, with use trending higher in patients 40 years and older. These surgeons were more likely to use allograft for primary ACLR because of decreased donor site morbidity, decreased postoperative pain, improved cosmesis, and decreased surgical time.

Previous studies from the Kaiser Permanente ACL Reconstruction Registry (KPACLRR) have provided descriptive and outcome data on ACLR from a large community-based sample. Of the 21,926 ACLRs between 2005 and 2013 registered in the KPACLRR, 41.4% were performed with allograft, followed by HT autograft (31.9%) and BPTB autograft (24.7%). In a 2013 study of 9817 ACLRs, after adjustment for age, sex, ethnicity, and body mass index (BMI), allografts had a 3.02 times higher risk of aseptic revision than BPTB autografts. Another KPACLRR study of 16,192 ACLRs found an overall revision rate of 1.7%, with allograft also associated with lower rates of graft survival. Most recently, a 2014 study of 14,522 ACLRs identified allograft use as a risk factor for nonrevision reoperations after ACLR, raising novel concerns regarding the implications of allograft choice on global knee health after ACLR. Numerous additional studies, despite being limited in sample size, have suggested slower revascularization, inferior biological properties, increased postoperative laxity, and decreased clinical outcome scores associated with the use of allograft tissue in ACLR when compared with autograft. The explanations for these findings have been multifactorial, and they remain incompletely understood.

Allograft sterilization methods vary widely across numerous commercially available tissue vendors. Concerns about bacterial, viral, and fungal disease transmission have resulted in the use of gamma irradiation and other methods to sterilize allografts, with proven efficacy. While oversight exists from the American Association of Tissue Banks, there is no established standard for tissue processing, which can include a combination of hydrogen peroxide, high temperature, chemical washes, irradiation, supercritical CO₂, antibiotics, fresh-frozen preservation, freeze-drying preservation, cryopreservation, and other proprietary techniques. It is unclear whether higher allograft failure rates in ACLR are related to graft properties, patient attributes, or a combination of both. The purpose of this study was to examine the association of graft processing techniques, patient characteristics, and graft type with risk of revision surgery after allograft ACLR.

METHODS

A retrospective analysis of prospectively collected data from a cohort of ACLRs registered in the KPACLRR was performed. The KPACLRR data collection procedures, participation, and data integrity have been published previously. In brief, all demographic and surgical data were collected by the surgeon and sent to the registry data repository. The registry prospectively monitors patients for postoperative complications, including reoperation and revision. All postoperative events are reviewed by trained research assistants, using the institution’s electronic medical record (EMR) system. Between February 1, 2005, and September 30, 2012, a total of 264 surgeons from 49 medical centers in 6 regions throughout the United States (Hawaii, Southern California, Northern California, Northwest, Mid-Atlantic, and Colorado) registered patients in the KPACLRR. Patients were included in the study if they underwent a primary single-bundle ACLR with allograft tissue. Patients with concomitant ligament injuries noted at the time of surgery were excluded.

The outcome endpoint of this study was defined as the aseptic failure of a primary allograft ACLR that required revision surgery. Revision operations were prospectively captured by the registry using direct surgeon reporting supplemented by independent review of patient EMRs. Medical records were examined to confirm graft failure. Revisions due to infection were excluded (n = 2). The main exposure of interest was allograft type, which was subclassified as BPTB allograft, Achilles tendon (AT) allograft, or soft tissue allograft from any site, as determined from the intraoperative KPACLRR forms. The registry provided covariates such as patient sex, patient age, and preoperative BMI for this study. Six individual commercial tissue vendors provided covariates on graft processing, including donor age; whether BioCleanse, AlloTrue, AlloWash, or irradiation was used; and the irradiation dosage, if any. Preliminary analysis revealed no significant increased revision rate with AlloTrue or AlloWash; those groups were accordingly combined for final analysis to reduce the overall number of study groups. Irradiation dosage was provided by each vendor in ranges varying from 0.3 to 0.6 Mrad. These data could thus not be studied as a single continuous variable. Instead, the raw ranges were grouped into continuous ordinal categories for analysis (Table 1).

Study population characteristics and allograft characteristics were described by use of frequencies, proportions, means, SDs, medians, and interquartile ranges (IQRs). Categorical characteristics were compared by use of chi-square tests. A Poisson regression model with a likelihood ratio test was used to compare revision per 100 years of

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observation. Method of allograft processing survival analysis was performed by use of Kaplan-Meier curves (log-rank test compared survival distributions) and Cox proportional hazard models (Wald test). Follow-up time was defined as the difference between the original ACLR operation date and the date of revision, the date of membership termination from the integrated health care system, the date of death, or the end date of the study period. Both statistical techniques used lost to follow-up dates (membership termination or death) to censor patients. Cox proportional hazard models were used to assess hazard ratios (HRs) and 95% CIs for method of processing with adjustment for other studied risk factors. Proportionality assumptions for age and BMI were verified by use of the Supremum test for functional form. Collinearity was assessed with variance inflation factors and tolerance values. No outliers were observed in age or BMI. To account for missing values in BMI (n = 173; 2.9%), sensitivity analysis was conducted to evaluate the robustness of the estimates. Data were analyzed by use of SAS v9.2 software (SAS Institute) with \( P < .05 \) as the statistical threshold.

**RESULTS**

A total of 7614 isolated primary ACLR cases with allograft were captured in the KPACLRR from 2005 to the third quarter of 2012, of which 98 double-bundle ACLRs were excluded. Of the remaining cases, 1548 (20.6%) did not have complete vendor information to enter this analysis, leaving 5968 cases with complete vendor processing data for the final study sample. Of these, 156 cases had an

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<th>TABLE 1</th>
<th>Study Sample Characteristics(^a)</th>
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<td>Cases, n (%)</td>
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| **Total** | 5968 (100) | 156 | 2.61 | \n
| **Sex** | | | | |
| Female | 2280 (38.2) | 54 | 2.37 | \n
| Male | 3688 (61.8) | 102 | 2.77 | \n
| **Patient age, y** | | | | |
| <14 | 31 (0.5) | 2 | 6.45 | \n
| 14-17 | 646 (10.8) | 49 | 7.59 | \n
| 18-21 | 564 (9.6) | 34 | 6.03 | \n
| 22-25 | 506 (8.5) | 11 | 2.17 | \n
| 26-29 | 569 (9.5) | 19 | 3.34 | \n
| 30-34 | 806 (13.5) | 14 | 1.74 | \n
| 35-39 | 860 (14.4) | 11 | 1.28 | \n
| 40-49 | 1415 (23.7) | 13 | 0.92 | \n
| >50 | 571 (9.6) | 3 | 0.53 | \n
| **BMI, kg/m\(^2\)** | | | | |
| <25 | 2042 (34.2) | 75 | 3.67 | \n
| 25-29 | 2242 (37.6) | 45 | 2.01 | \n
| ≥30 | 1511 (25.3) | 31 | 2.05 | \n
| **Allograft type** | | | | |
| BPTB | 1029 (17.2) | 37 | 3.60 | \n
| Achilles tendon | 1188 (19.9) | 37 | 3.11 | \n
| Soft tissue | 3751 (62.9) | 82 | 2.19 | \n
| **BioCleanse** | | | | |
| Not used | 5601 (93.9) | 142 | 2.54 | \n
| Used | 367 (6.1) | 14 | 3.81 | \n
| **AlloTrue or AlloWash** | | | | |
| Not used | 3690 (61.8) | 95 | 2.57 | \n
| Used | 2278 (38.2) | 61 | 2.68 | \n
| **Irradiation dosage, Mrad** | | | | |
| None | 1185 (19.8) | 27 | 2.28 | \n
| <1.2 | 726 (12.2) | 21 | 2.89 | \n
| 1.2-1.8 | 2911 (48.8) | 65 | 2.23 | \n
| >1.8 | 1146 (19.2) | 43 | 3.75 | \n
| **Donor age, y** | | | | |
| <20 | 276 (4.6) | 6 | 2.17 | \n
| 20-40 | 1301 (21.8) | 37 | 2.84 | \n
| 41-59 | 3497 (58.6) | 87 | 2.49 | \n
| ≥60 | 892 (15.0) | 26 | 2.91 | \n
\(^a\)BMI, body mass index; BPTB, bone–patellar tendon–bone. 
\(^b\)BMI data missing on 173 (2.9%) of the observations.
aseptic revision, for a rate of 2.61%, which was not statistically different from the cases with incomplete vendor information (2.58%), based on a chi-square test (P = .948) (Figure 1).

Of the study sample (n = 5968), 3688 (61.8%) were male, the median age of the cohort at the time of surgery was 34.1 years (IQR, 24.1-42.9 years), and the median BMI was 26.6 kg/m² (IQR, 23.8-30.1 kg/m²) (Table 1). The mean time to follow-up after ACLR (±SD) was 2.1 ± 1.5 years, with 1201 cases (20.7%) lost to follow-up due to membership termination. There were 3751 (62.9%) allograft ACLRs using soft tissue, 1188 (19.9%) with AT, and 1029 (17.2%) with BPTB. The median age of allograft donor was 50 years (IQR, 39.0-58.0 years). There were 367 (6.1%) cases with allograft processed by use of BioCleanse, 2278 (38.2%) processed by use of either AlloTrue or AlloWash, 1146 (19.2%) processed by use of greater than 1.8 Mrad irradiation, and 3637 (60.9%) processed with any irradiation up to 1.8 Mrad.

The revision rate per 100 patient observation years of follow-up was 1.26 (95% CI, 1.08-1.48). Statistically significant differences were found in the distribution of patient age (P < .001), allograft type (P = .021), and irradiation dosage (P = .041) between the cases with and without revision. After adjustment for patient age, sex, and BMI, the use of BioCleanse (HR = 2.45; 95% CI, 1.36-4.40) and irradiation greater than 1.8 Mrad (HR = 1.64; 95% CI, 1.08-2.49) after 1 year were associated with a higher risk of revision when compared with all other methods of processing. Within the first year of primary ACLR, allografts processed with irradiation greater than 1.8 Mrad were not statistically different from other allografts. A Kaplan-Meier curve was created for univariate aseptic survival for BioCleanse processing, more than 1.8 Mrad of graft irradiation, and all others by use of the log-rank test (P = .004) (Figure 2).

Adjusted HRs for allograft ACLR revision risk were calculated for the study risk factors. When compared with soft tissue allografts, BPTB allografts were at higher risk of revision (HR = 1.79; 95% CI, 1.20-2.66). Conversely, with every 5-year increase in age, the risk of revision was 0.67 (95% CI, 0.61-0.73) times lower. Male patients were found to be at higher risk of revision when compared with females (HR = 1.47; 95% CI, 1.04-2.07). The use of AlloWash or AlloTrue processing, patient BMI, and graft donor age did not affect revision rate significantly (Figure 3). The effect of the 173 (2.9%) cases with missing BMI data was evaluated; patients with missing BMI were not statistically different from those with complete data. The crude revision rate was 2.89% (5 revisions in 173 patients with missing BMI data), which was not statistically different from those with complete data (2.60%). The risk of revision without BMI data were modeled, and the estimates for all covariates did not change by more than 5%.

DISCUSSION

A 2013 AOSSM surgeon survey revealed that concerns most commonly voiced regarding allograft use for primary ACLR included a younger patient, graft failure rates reported in the literature, patient intent to return to activity with high ACL demand, graft incorporation rate, disease transmission, personal experience with graft failure, and cost.3 With the escalating use of allograft tissue for ACLR in the United States, safe but effective processing techniques and correct patient selection are of high interest. The goal of graft processing remains to sterilize tissue to a minimum sterility assurance level of 10⁻³ as mandated by the Food and Drug Administration for implanted biological medical devices, without compromising the mechanical properties or biological potential of the tissue. This study
presents the largest known cohort of primary allograft ACLRs, finding among all graft processing methods evaluated a correlation between BioCleanse and irradiation greater than 1.8 Mrad with higher risk of aseptic failure and subsequent revision. Younger patients, BPTB allograft, and male patients were also associated with a higher revision risk.

In direct comparison, allograft has been found to yield inferior results to autograft for ACLR. Prodromos et al performed a meta-analysis of 20 allograft ACLR series compared with a published set of autograft studies, concluding that abnormal stability was more common in allografts (14%) than autografts (5%), for both BPTB (16% vs 6%) and soft tissue (12% vs 4%). Yao et al performed a meta-analysis of 13 studies on 1046 patients comparing BPTB autograft to BPTB allograft in primary ACLR. Significant difference in clinical failure in favor of autograft was observed, although there were no differences in terms of single-legged hop test, range of motion, International Knee Documentation Committee (IKDC) score, Lysholm score, Lachman test, pivot-shift test, anterior knee pain, or crepitus. In 2015, Mascarenhas et al published a systematic review of 2 meta-analyses with level 2 evidence and 6 with level 3 evidence, totaling 15,819 ACLR patients. The authors found no differences in rupture rates or outcomes in the higher quality studies, while lower quality meta-analyses indicated that autografts may provide a lower rerupture rate, better hop test performance, and better objective knee stability than allografts. Of specific interest is the role of graft processing techniques and patient characteristics in these findings.

To eliminate graft processing and particularly irradiation as an outcome variable, Lamblin et al performed a meta-analysis of 11 ACLR studies (evidence levels 1 to 3) to compare autograft to nonirradiated, non-chemically treated allograft. No differences were found as measured by Lysholm score, IKDC score, Lachman test, pivot-shift test, KT-1000, or failure rates. Mariscalco et al performed a similar systematic review of 9 studies (evidence levels 1 to 3) comparing ACLR with BPTB autograft vs BPTB allograft (6 studies), HT autograft vs HT allograft (2 studies), or HT autograft vs tibialis anterior allograft (1 study). No significant differences were found in graft failure rate, postoperative laxity, or patient-reported outcome scores when the investigators compared ACLR with autografts to the nonirradiated allografts. These studies suggest that nonirradiated allografts, while lacking in the benefit of the sterilization achieved by irradiation, appear suitable for ACLR.

Given the variance observed in tissue processing, numerous studies have been performed to examine the effects of sterilization techniques on the mechanical integrity of allografts. These studies provide insight into time-zero mechanical properties before implantation. BioCleanse is a proprietary technique that sterilizes tissue through vacuum and pressure, followed by chemical sterilants and finally germicide removal. In 2007, Jones et al compared 40 BPTB allografts treated with and without BioCleanse processing. Mechanical testing showed no difference between the 2 groups in relation to stiffness, creep, maximum force, or ultimate stress at failure. In a similar study, Schimizzi et al tested 36 tibialis anterior allografts treated with BioCleanse, irradiated or left untreated, finding no difference between the groups for creep, failure load, stiffness, or failure stress. Mikhael et al also found no difference in ultimate stress, strain, or fracture energy between cylindrical cortical bone specimens treated with BioCleanse in comparison to those irradiated or left untreated; this is a particularly relevant study given that ACLR allografts such as BPTB and AT have associated bone block(s) that may exhibit unique biomechanical behavior postoperatively compared with soft tissue. In 2013, Conrad et al published results after testing 20 AT allografts, finding those sterilized by BioCleanse to have higher stiffness compared with irradiated grafts. Collectively, these studies suggest that at time zero, allografts sterilized by the BioCleanse technique do not demonstrate any notable compromise in mechanical integrity.

Indelicato et al performed a prospective randomized clinical trial on 67 patients undergoing isolated ACLR
with BPTB allograft, processed with either BioCleanse (n = 43) or aseptically (n = 24). At 2-year follow-up there were no differences in IKDC score, KT-1000 arthrometer results, or range of motion. The present study included 367 primary ACLRs with BioCleanse processed allografts, the largest such cohort published. After adjustment for patient age, sex, and BMI, this subset of patients was found to have a higher risk of revision when compared with other methods of graft processing. Considering the validation of BioCleanse processing at time zero, these novel findings may be explained by the postoperative behavior of the graft during the process of ligamentation. In a laboratory study of 21 specimens, Dunn et al found lower osteoinduction scores for tissue treated with BioCleanse (0%) in comparison with AlloWash (43%) or a third processing method involving nonionic detergents, hydrogen peroxide, and denatured ethanol (100%). It is unclear whether there is a specific step within the BioCleanse process that could result in altered graft incorporation and remodeling postoperatively, resulting in clinical failure and aseptic revision in select instances, or whether another explanation for the increased revision risk exists. Further study is warranted.

Irradiation is effective in sterilizing allograft tissue before implantation; however, concerns persist regarding deleterious effects that the process may have on graft integrity in a dose-dependent fashion and whether this decrease in strength correlates to higher clinical failure rates. Hoburg et al tested BPTB allograft specimens sterilized with 2.5 or 3.4 Mrad of irradiation. Compared with nonirradiated controls, both irradiiation dose groups had lower stiffness, lower failure load, and higher creep. Yanke et al examined the effect of lower dose irradiation on BPTB allografts, finding that 1.0- to 1.2-Mrad irradiation decreased stiffness by 20% but had no significant effect on load to failure, suggesting that these “low-dose” levels may not create clinically significant changes.

Multiple outcome studies have been performed comparing irradiated versus nonirradiated allografts for ACLR. While each provides valuable information, general limitations regarding sample size have prompted multiple related meta-analyses, particularly in light of conflicting results. Rihn et al compared ACLR with BioCleanse (34%) or BPTB allograft irradiated with 2.5 Mrad (39 patients). Patients undergoing allograft ACLR were older (44.0 vs 25.3 years) and at mean follow-up of 4.2 years had lower KT-1000 arthrometer side-to-side difference (1.3 vs 2.2 mm) when compared with the autograft group. However, after adjustment for age, both groups had similar functional outcome as measured by IKDC score and laxity testing, leading the authors to conclude that irradiation at 2.5 Mrad can be safely used to sterilize BPTB allograft without adversely affecting clinical outcome. Ghodadra et al retrospectively examined 238 patients who underwent ACLR by a single surgeon with either BPTB autograft, nonirradiated BPTB allograft, or low-dose irradiated BPTB allograft (1.3 Mrad). No significant differences were detected among the groups with regard to postoperative laxity up to 1 year, as measured by Lachman test, pivot-shift test, and KT-1000 arthrometer examination. Regarding the potential effect of irradiation on delayed biological healing, no changes were observed in graft laxity from 6 weeks to 1 year postoperatively in any of the groups. Of note, in the present study, the effects of irradiation greater than 1.8 Mrad on graft failure were seen only after 1 year postoperatively, suggesting that follow-up beyond 1 year may be necessary in this patient population to fully elucidate outcomes as patients return to ACL-dependent activities.

Extensive research has been performed by Sun et al, who conducted 3 noteworthy prospective randomized ACLR studies specifically examining the clinical effects of allograft irradiation on clinical outcome. The first compared ACLR in 99 patients with either BPTB autograft, nonirradiated BPTB allograft, or BPTB allograft irradiated at 2.5 Mrad. At mean follow-up of 31 months, failure rate was 34.4% in the irradiated allograft group, 8.8% in the nonirradiated allograft group, and 6.1% in the autograft group. Side-to-side differences of less than 3 mm by KT-2000 arthrometer assessment were present in 87.8% of the autograft group, 85.3% of the nonirradiated allograft group, and only 31.3% of the irradiated allograft group. The authors concluded that nonirradiated BPTB allograft is a reasonable alternative to autograft for ACLR, while gamma irradiation at 2.5 Mrad should not be used as a secondary sterilizing method due to the high failure rate observed in that group.

In the second study, a prospective comparison was made between ACLR in 98 patients with either HT autograft or 2.5-Mrad irradiated HT allografts. At minimum 2.5-year follow-up (mean, 42.2 months), 86.1% of patients in the autograft group and only 32.3% in the irradiated allograft group had a side-to-side difference of less than 3 mm as measured by KT-2000 arthrometer. Of note, outcomes between both groups as measured by IKDC score, functional and subjective evaluations, and activity level testing were not significantly different, suggesting that the increased laxity in the irradiated allografts was not generally perceptible to the patients. The third study prospectively compared 2.5-Mrad irradiated and nonirradiated HT allograft for ACLR. Of the 69 patients evaluated postoperatively, 84% of the patients in the nonirradiated allograft group compared with only 32% in the irradiated allograft group had side-to-side differences of less than 3 mm according to KT-2000 arthrometer assessment, further suggesting that irradiation may have a deleterious effect on the implanted allograft tissue. No significant differences were found in IKDC results, functional and subjective evaluations, or activity level testing between the 2 groups, although the development of osteoarthritis was more likely to occur postoperatively in the irradiated allograft group, raising concerns about the long-term implications of using these grafts.

Rappe et al retrospectively examined 90 patients who underwent primary ACLR with AT allograft, half of which were nonirradiated and the other half irradiated at a dose of 2.0 to 2.5 Mrad. At minimum 6-month follow-up, 1 of 42 (2.4%) of the nonirradiated group had catastrophic failure, in contrast to 11 of 33 (33%) of the irradiated group, leading the authors to discontinue the use of irradiated allografts for ACLR altogether. Park et al performed a meta-analysis of 21 publications reporting on a total of 1453 patients undergoing ACLR, with 415 irradiated
(<2.5 Mrad) and 1038 nonirradiated allografts. The mean patient age was 32.2 years, and mean follow-up was 49.8 months. Knees with nonirradiated allografts had a higher mean Lysholm score and a higher proportion of <5-mm difference of KT-1000/2000 arthrometer measurements, grade 0 and 1 pivot shift, and grade 0 and 1 Lachman test than did those with irradiated grafts. Knees with irradiated allografts had a higher proportion of revision surgery compared with nonirradiated grafts. The authors concluded that primary ACLRs using nonirradiated allografts may provide superior outcome than those using low-dose (<2.5 Mrad) irradiated grafts. In totality, multiple ACLR outcome studies suggest a notable effect on graft integrity when irradiation above 2.0 Mrad is used and a less clear effect when low-dose irradiation is used, with possible confounding variables such as graft type, patient age, surgical technique, fixation, and postoperative rehabilitation clouding the issue.

Similar to previous reports, our study found that ACLR performed with allograft sterilized with greater than 1.8 Mrad of irradiation carries an increased risk of aseptic failure and subsequent revision surgery as opposed to allograft sterilized with 1.8 Mrad or less. In comparison to nonirradiated allografts, low-dose irradiation provides the benefit of enhanced tissue sterilization and potentially lower disease transmission without known compromise in mechanical integrity, making it a common technique used by multiple tissue vendors. Given the implications for clinical failure and reoperation, surgeons should be aware of the precise gamma irradiation dosage used for their allografts, as lack of industry standardization exists.

In this study, BPTB allograft was found to have a higher risk of failure when compared with soft tissue allograft. The explanation for this is unclear but may result from the structural difference between the graft types. The 2 bone blocks attached to the patellar tendon of the BPTB graft may undergo changes in mechanical properties or biological behavior, secondary to processing techniques, that could contribute to the higher observed failure rate. It is known that with increased exposure time to hydrogen peroxide during allograft bone processing, for example, a linear decrease in osteoinductivity occurs. Likewise, in both static and fatigue testing, terminal high-dose gamma irradiation has been found to lessen the mechanical strength of allograft bone and has been shown to reduce its osteoinductive potential as well. This potential decreased mechanical strength and osteoinductive behavior of the BPTB bone blocks may result in suboptimal postoperative graft incorporation. In a study on BPTB ACLR performed on patients 18 years and younger, Ellis et al found that the allograft group was 15 times more likely to require revision reconstruction than was the autograft group. Similarly, a meta-analysis of 5182 patients found a 3-fold increase in revision rate with allograft BPTB ACLR in comparison to autograft BPTB. Further study on BPTB allograft and its associated risk factors for failure is warranted.

The current study found that revision risk after primary allograft ACLR is notably higher in younger patients, particularly those younger than 21 years. With every 5-year increase in age, the risk of revision was 0.67 times lower. These findings are similar to previous studies examining the relationship between patient age and clinical outcome after ACLR. In a prospective multicenter cohort study performed by the Multicenter Orthopaedic Outcomes Network (MOON) group, for each 10-year decrease in age, the odds of graft rupture after primary allograft ACLR increased 2.3 times, suggesting that allograft ACLR should be performed with caution in younger patients. In a 2014 retrospective review of 73 adolescents who underwent ACLR at a mean age of 15 years, Engelmann et al found a 29% failure rate in the allograft group compared with 11% in the autograft group; hazard of graft failure was 4.4 times greater for the allografts. Of note, when comparing ACLR with BPTB in 81 patients younger than 25 years, Barber et al reported no difference in failure rates between autografts (9%) and nonirradiated non–chemically processed allografts (7%), suggesting that graft irradiation and chemical processing likely play a critical role in clinical failure. When combining the findings on irradiation dosage and patient age, the present study suggests that primary ACLR in a young patient using an allograft sterilized with more than 1.8 Mrad of irradiation may carry an unacceptable risk of aseptic failure and revision surgery.

It has been hypothesized that higher donor age for allograft may increase the risk of subsequent revision surgery, due to lower inherent tissue quality from patients in their later years. In 1991, Woo et al performed a biomechanical laboratory study on 27 pairs of human cadaver knees, separated into different groups based on donor age. Graft stiffness, ultimate load, and energy absorbed were found to decrease significantly with specimen age, most notably in the 60- to 97-year-old group, suggesting that allografts from this donor population should be implanted with caution. Flahiff et al later evaluated the biomechanical properties of BPTB allografts from donors aged 18 to 55 years. Regression analysis showed slightly decreasing tensile stress with increasing age, but the correlation was not significant. No difference was noted among the age groups for load at failure, stiffness, or elongation, suggesting that donor age below 55 years is not a factor at time zero. Similarly, Greaves et al concluded that donor age up to 65 years did not significantly affect initial failure load, stiffness, or displacement at failure of tibialis anterior allografts treated with 1.46 to 1.80 Mrad of gamma irradiation terminal sterilization. In 2015, Swank et al published a controlled laboratory study examining 550 allograft posterior tibialis tendons, observing decreased ultimate tensile strength in patients over age 50 years, although the magnitude of these changes was small in relation to the strength of the native ACL and thus believed to be clinically insignificant for ACLR. In a retrospective clinical study, Hampton et al examined 75 patients at mean 2-year follow-up after BPTB allograft ACLR. Donor age ranged from 14 to 65 years and as a continuous variable was not found to have an effect on postoperative Lysholm or Tegner scores. The present study is consistent with these published reports, finding that donor age did not significantly affect revision risk after primary allograft ACLR. These results pertain to grafts over 60 years of age as well, suggesting that surgeons can...
potentially be comfortable when implanting tissue from this donor age group if necessary due to limited availability of younger specimens.

There are numerous limitations to this study. Patients were not randomized to treatment groups. Surgical technique, graft choice, and postoperative rehabilitation guidelines were not standardized and were left to the discretion of the surgeon and patient. Activity level and return to sport were not captured by the registry and could not be evaluated, both of which might affect the likelihood of revision. Since revision was used as the endpoint, patients who suffered a graft failure but did not have a revision were not included. Allograft processing information was missing from 20.6% of patients, although revision rates were not different between those with and without complete data so it is unlikely that this factor skewed the results. In addition, health plan membership termination resulted in 20.7% of study patients being lost to follow-up. A notable strength of this study is the large sample size, enabling the evaluation of multiple variables of interest (allograft type, various processing methods, donor age, sex, and BMI). The population is representative of a community-based practice in the United States, making the results generalizable. Finally, the prospective data collection and validated methods of outcome ascertainment give the study high internal validity.

In conclusion, in the largest known study of its kind examining outcome after primary allograft ACLR, graft irradiation greater than 1.8 Mrad, BioCleanse graft processing, younger patients, BPTB allograft, and male patients were all associated with a higher risk of clinical failure and subsequent revision surgery. Patient BMI, graft donor age, and the use of AlloWash or AlloTrue processing did not affect revision rate significantly. High-dose irradiation has been found to directly compromise the mechanical integrity of allograft tissue, which can contribute to clinical failure. BioCleanse processing may alter the ability of an allograft to successfully incorporate postoperatively, resulting in clinical failure in certain instances; further study is warranted. Surgeons selecting allograft for primary ACLR should be aware that vendor-specific graft processing methods, graft type, patient age, and patient sex have implications for higher postoperative revision risk. Future interest lies in evidence-based industry standardization of graft processing methods, further exploration of safe and effective alternative sterilization methods such as electron beam irradiation, and creation of bioengineered platforms for ligament reconstruction that could eliminate the need for autograft or allograft use altogether.22,43

REFERENCES


8 Tejwani et al

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