Systematic Review

Anterior Cruciate Ligament Reconstruction With Autografts Compared With Non-irradiated, Non-chemically Treated Allografts

Cory J. Lamblin, M.D., Brian R. Waterman, M.D., and James H. Lubowitz, M.D.

Purpose: Allograft anterior cruciate ligament (ACL) reconstruction obviates donor site morbidity and may accelerate postoperative recovery. However, allograft use can lead to increased rates of surgical failure, particularly when chemical processing or irradiation is used. Few studies have rigorously evaluated the comparative outcomes of autografts and fresh-frozen allograft tissue for ACL reconstruction. Methods: We performed a PubMed search to identify and systematically evaluate outcomes of autograft and non—chemically treated non-irradiated allograft tissue in ACL reconstruction between 1980 and 2012. We included studies with Level of evidence of I to III, determinate graft treatment, a minimum of 25 patients per treatment arm, a minimum 2-year follow-up, and selected subjective and objective outcome measures. Results: After the exclusion of 585 citations, we isolated 11 studies for further review. All patients showed improvement in clinical outcome measures and knee stability end points from injury to definitive surgical management. No statistically significant differences were detected between autografts and non-chemically processed non-irradiated allografts in Lysholm scores, International Knee Documentation Committee (IKDC) scores, Lachman examinations, pivot-shift testing, KT-1000 measurements, or failure rates. Conclusions: Further large-scale, well-designed studies are required to better evaluate the comparative outcomes after fresh-frozen allograft ACL reconstruction. The current study suggests that the results after autograft ACL reconstruction are comparable to those using non-chemically processed nonirradiated allograft tissue. Level of Evidence: Systematic review of Level I to III studies.

Anterior cruciate ligament (ACL) reconstruction is among the most common orthopaedic procedures, particularly among athletes. In addition to inherent decreases in the stability of the knee, ACL rupture can also lead to an increased risk for subsequent chondral or meniscal injury and diminished athletic performance. As a result, the optimal treatment of ACL injury has generated significant laboratory and clinical research.

Given the indisputable importance of a functional ACL, surgeons have attempted a multitude of treatment options. Early surgical intervention included repair techniques with suboptimal long-term results. Xenograft tissue and nonbiologic grafts (e.g., Gore-Tex, polyester, carbon fiber) have also been used for ACL reconstruction. However, with the improvement of autologous and allograft-based techniques, these alternative graft sources have been largely supplanted by human tissue reconstruction in the orthopaedic community.

Patellar bone-tendon-bone autografts have been considered the gold standard, although combined semitendinosus and gracilis grafts (hamstring) have also gained significant popularity. Conversely, the use of allograft tissue (e.g., patellar bone-tendon-bone, hamstring, Achilles, and posterior tibialis) obviates donor-site morbidity, is readily available, and may expedite postoperative rehabilitation. However, tissue processing and sterilization are not currently standardized, and some tissue banks irradiate or chemically treat the grafts as a means of sterilization or preservation.

Decision making in graft selection is complex and serves as a source of controversy among orthopaedic surgeons. Some studies have shown comparable success with both autograft and allograft tissue in ACL reconstruction, whereas other studies have found an...
increased failure rate with irradiated allograft tissue.\textsuperscript{8,13} Currently to date, no known study has systematically compared surgical outcomes of autograft ACL reconstruction with those of non-irradiated non-chemically treated allografts. To this end, the purpose of this systematic review was to summarize the existent orthopaedic literature evaluating the outcomes of ACL reconstruction with autograft and non-irradiated non-chemically treated allograft tissue, with a particular focus on both objective and subjective outcome measures. We hypothesized that after the exclusion of certain processing techniques, there would be no difference in ACL reconstruction outcomes using non-irradiated non-chemically treated allografts compared with autografts.

**Methods**

We conducted a computerized literature search of the electronic databases PubMed/Medline, the Cochrane Central Register of Controlled Trials, Cumulative Index for Nursing and Allied Health Literature, and Embase in October 2011 and updated it in July 2012 to identify all randomized controlled trials and cohort studies evaluating ACL reconstruction with autograft and non-irradiated non-chemically treated allograft tissue. We isolated for review investigations that included the keywords “anterior cruciate ligament” and “allograft” published in the English language between January 1, 1980 and August 1, 2012. We included for analysis studies with Level of evidence I to III that evaluated unilateral ACL reconstruction (with or without concomitant meniscal surgery) using either autografts or non-irradiated non-chemically treated allografts, with a minimum of 2-year follow-up, 25 patients in each treatment arm, and selected outcome measures (Lachman examination, Pivot-shift testing, KT-1000, International Knee Documentation Committee [IKDC]}
Four hundred fifteen articles were appropriate for initial review. Exclusion criteria consisted of nonhuman studies, Level of evidence IV or noncomparative study design, irradiated or chemically treated graft tissue, indeterminate graft sterilization, insufficient outcome measures, and inadequate follow-up (less than 2 years) or study size (fewer than 25 patients per treatment arm). All 3 reviewers (C.J.L., B.R.W., and J.H.L.) independently assessed the methodologic quality of each study included. We elucidated the design features of these studies, including the following: intervention type, graft source, patient outcome measures, follow-up duration, and presence of perioperative complications. Secondary, other relevant data and study characteristics were reviewed, including number of enrolled patients, patient demographics, specific graft treatment and preparation, and postoperative rehabilitation. Additionally, patient outcomes, such as laxity on physical examination, IKDC score, Lysholm score, and rates of postoperative failure were extracted for analysis. For the purpose of this study, failure was defined as revision ACL reconstruction, 2 to 3+ pivot-shift, more than 10 mm laxity asymmetry seen with KT-1000 evaluation, or functional instability. Discrepancies between reviewers prompted a review of the article, and a consensus decision was reached.

### Results

#### Study Selection

With studies published between 1996 and 2012, most included a prospective design (5 randomized trials and 5 comparative studies), with 2 retrospective cohort studies. One study incorporated both patients who refused randomization and other prospectively enrolled patients who refused randomization in 4 studies. Frozen allograft tissue was preferred by 2 studies, and other studies preferred allograft tissue. A total of 533 patients were included in 11 studies. One study included 11 studies, 7 Level II analyses, and 1 Level III study. The exclusion criterion was noncomparative study design (one study), and small study size (one study).

### Table 1. Characteristics of Selected Studies Evaluating Autograft and Non-irradiated Non-chemically Treated Allograft Tissue In ACL Reconstruction

<table>
<thead>
<tr>
<th>Author</th>
<th>Date</th>
<th>Methods</th>
<th>Level of Evidence</th>
<th>Enrolled Patients</th>
<th>Follow-up Duration (Average mo)</th>
<th>Age</th>
<th>Autograft Type</th>
<th>Allograft Type</th>
<th>Standardized Rehabilitation</th>
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<td>Harner et al.</td>
<td>1996</td>
<td>Retrospective comparative</td>
<td>III</td>
<td>90</td>
<td>45 (30-75)</td>
<td>23.9</td>
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<td>64</td>
<td>PT-FF/NI</td>
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<td>Prospective nonrandomized</td>
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<td>24 (NR)</td>
<td>20.65</td>
<td>PT</td>
<td>30</td>
<td>PT-FF/NI</td>
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<td>Kleipool et al.</td>
<td>1998</td>
<td>Prospective nonrandomized</td>
<td>II</td>
<td>62</td>
<td>49 (32-74)</td>
<td>15-55</td>
<td>PT</td>
<td>26</td>
<td>PT-FF/NI</td>
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<tr>
<td>Peterson et al.</td>
<td>2001</td>
<td>Prospective nonrandomized</td>
<td>II</td>
<td>60</td>
<td>NR (55-78)</td>
<td>15-55</td>
<td>PT</td>
<td>30</td>
<td>PT-FF/NI</td>
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<tr>
<td>Barrett et al.</td>
<td>2005</td>
<td>Prospective nonrandomized</td>
<td>II</td>
<td>63</td>
<td>44 (24-99)</td>
<td>40-58</td>
<td>PT</td>
<td>25</td>
<td>PT-FF/NI</td>
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<tr>
<td>Edgar et al.</td>
<td>2008</td>
<td>Prospective randomized/nonrandomized</td>
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<td>84</td>
<td>NR (36-70)</td>
<td>15-55</td>
<td>HS</td>
<td>37</td>
<td>HS-CP and FF/NI</td>
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<tr>
<td>Sun et al.</td>
<td>2009</td>
<td>Prospective randomized</td>
<td>I</td>
<td>156</td>
<td>71 (48-96)</td>
<td>20-65</td>
<td>HS</td>
<td>76</td>
<td>HS-FF/NI</td>
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<tr>
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<td>2011</td>
<td>Prospective randomized</td>
<td>II</td>
<td>102</td>
<td>24 (NR)</td>
<td>16-53</td>
<td>HS</td>
<td>54</td>
<td>HS-FF/NI</td>
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<tr>
<td>Sun et al.</td>
<td>2012</td>
<td>Prospective randomized</td>
<td>II</td>
<td>102</td>
<td>24 (NR)</td>
<td>16-53</td>
<td>Achilles-FF/NI</td>
<td>48</td>
<td>TA-FF/NI</td>
</tr>
<tr>
<td>Guo et al.</td>
<td>2012</td>
<td>Retrospective comparative</td>
<td>III</td>
<td>74</td>
<td>80.4 (50-98)</td>
<td>16-40</td>
<td>PT</td>
<td>41</td>
<td>PT-FF/NI</td>
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</table>

ACL, anterior cruciate ligament; CP, cryopreserved; FF/NI, fresh-frozen nonirradiated; HS, hamstring (gracilis/semitendinosus); NR, not reported/nonrandomized; PT, patellar tendon; TA, tibialis anterior.
although one study included 20 patients with non-chemically sterilized non-irradiated hamstring grafts that had undergone cryopreservation.18 Seven of the studies used autologous patellar bone-tendon-bone (n = 254 [54%]) and allograft patellar bone-tendon-bone (n = 311 [58%]).14-18,20,24 Four studies used hamstring (n = 215 [46%]) autografts compared with hamstring allografts (2 studies; n = 142 [27%]),19,22 tibialis anterior (one study; n = 48 [9%]),23 and Achilles tendon (one study; n = 32 [6%]).21

In nearly all studies, one or 2 experienced surgeons at single centers performed all the ACL reconstructions. However, one study involved 5 investigators at 5 separate centers.23 Surgical technique was standardized between treatment groups in all studies. Concomitant procedures, including those for meniscal and low-grade chondral pathologic conditions, were permitted and controlled for among treatment arms. Similarly, demographic variables, time interval from injury to surgery, presence of previous surgical interventions, and preinjury activity levels were among factors controlled for in all studies.

All 11 studies used a similar rehabilitation protocol for both ACL groups, although return to running and sporting activities varied between studies. Return to running varied from 3 to 6 months postoperatively, and return to sporting activities varied from 6 to 12 months. All rehabilitation protocols allowed early motion, early weight bearing, and mobility with the assistance of a postoperative brace.

**Patient Outcome Measures**

Patient-reported outcome measures were documented in all 11 studies (Table 2). No statistically significant differences were found between patients treated with autografts and those treated with non-treated allografts in the individual studies. Lysholm scores were collected in 8 of 11 studies,14-18,20,22,24 with no differences discerned between autograft (mean, 90.6; range, 86.6 to 98) and allograft (mean 91.4; range, 85.6 to 99) ACL reconstruction at short-term follow-up. IKDC scores were evaluated in 7 of the 11 studies (Fig 2),14,16,18,20,22,23 and no differences were detected in the rates of normal or near-normal knee function knee ratings (autograft, 293 of 335 [87.5%] v allograft, 339 of 408 [83.1%]).

**Physical Examination and Instrumented Laxity Measures**

We reviewed selected musculoskeletal testing and instrumented measures to assess knee laxity for the current study. Eight of the 11 investigations reported graded Lachman examination after ACL reconstruction, with none demonstrating a statistically significant difference between the treatment groups (Fig 3).15-18,20,22,24 Pivot-shift testing was performed in 10 of 11 studies and failed to show any differences by graft tissue (Fig 4).14-18,20,24 Independent assessment of knee laxity with the KT-1000 was also reported in 10 studies; no differences were detected with graded or maximal force displacement by graft type (Fig 5).14-20,22-24

**Failure Rates**

For the current study, we defined failure as persistent functional instability, 2 or 3+ on pivot-shift testing, greater than 10-mm laxity asymmetry with KT-1000 evaluation, or revision ACL reconstruction. Failure rates were comparable between autograft (mean 2.8%; range 0 to 8.1%) and allograft ACL reconstruction.
(mean, 3.6%; range, 0% to 9.1%) and showed no statistically significant differences (Fig 6).15-24

Discussion

Graft selection in ACL reconstruction remains controversial. Although bone–patellar tendon–bone autografts remain the gold standard for young active athletes in many centers, several studies have determined equivalence with semitendinosus-gracilis autografts in ACL reconstruction.25-27 Conversely, tendon-bone and soft tissue allografts also represent viable alternatives and have increased in popularity. In addition to shorter operative times, allograft use may obviate concerns for donor-site morbidity associated with autograft harvest, including persistent anterior knee pain, knee flexion weakness, patellar tendinitis, altered quadriceps function, patellar fracture, and saphenous nerve injury.28-33 However, current tissue processing and sterilization protocols may significantly diminish the mechanical properties of allograft tissue and increase rates of postsurgical failure.34 Multiple small contemporary studies have attempted to comparatively evaluate fresh-frozen allografts without chemical or radiation treatment and autograft tissue for ACL reconstruction.14-24 In an attempt to summarily assess these clinical outcomes, we revealed in the current study that ACL reconstruction with autograft tissue or non-chemically treated non-irradiated allografts produced no statistically significant differences in terms of patient-reported outcome measures, laxity measures, and clinical failure.

Potential concerns associated with the use of allograft tissue include disease transmission, autoimmune response, delayed or incomplete biologic incorporation, and increased cost. McGuire and Hendricks34 evaluated

<table>
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<th>P Value</th>
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</table>

![Fig 2. Forest plot of International Knee Documentation Committee (IKDC) knee evaluation score according to graft source. (CI, confidence interval.)](image-url)
detrimental immune responses to nonhost tissue in ACL reconstruction; they reported on a number of studies comparing autogenous and allogeneic fresh-frozen, cryopreserved, and fresh grafts. They found no difference in local or systemic immune responses affecting ultimate graft healing or clinical outcome. Similarly, Rihn and Harner\(^3\) reviewed the use of allograft tissue in knee surgery, including primary and revision ACL reconstruction. They observed no adverse clinical consequences with allograft tissue use, particularly with regard to immunogenicity. Conversely, other authors have implicated a cytokine-mediated immune response in patients receiving fresh-frozen grafts, although these instances of acute synovitis were self-limited and did not ostensibly affect surgical outcomes.\(^2\)

Although judicious donor selection and screening produce limited disease transmission, secondary infections may still represent a significant risk with allografts despite current sterilization measures. Low-grade radiation (1 to 2.5 mrad) may diminish bacterial load, but viral contaminants may persist because higher radiation exposure further compromises the structural and mechanical graft properties.\(^8,13\) Some authors\(^16,37\) have ascertained that radiation imposes dose-dependent deleterious effects on patellar tendon allografts in the laboratory setting, even with low-dose radiation. Further studies have shown significantly higher rates of graft laxity and clinical failure with low-dose radiation when compared with nonirradiated allograft and autograft ACL reconstruction.\(^13,38\) Increasingly, authors are abandoning irradiation as a secondary sterilization technique in favor of alternative methods.

Processing with antibiotic soaks, various chemical rinses (e.g., hydrogen peroxide, peracetic acid), and proprietary treatments (e.g., AlloWash [LifeNet Health, Virginia Beach, VA] and BioCleanse [RTI Biologics,
Alachua, FL]) also limit bioburden and associated immune response. Similar to radiation, use of these solvents is not without potential harmful side effects. Ethylene oxide has been largely eliminated from current chemical processing practices because of strong associations with intense foreign body reaction, chronic synovitis, and graft dissolution.\textsuperscript{39,40} Other authors have also encouraged caution with the continued widespread use of peracetic acid, which may further inhibit graft incorporation in animal models.\textsuperscript{41} Continued clinical surveillance and US Food and Drug Administration scrutiny of current sterilization practices used by the American Association of Tissue Banks are warranted, particularly with increased use of musculoskeletal allograft tissue in current orthopaedic practice.

Although debate exists, the current literature shows a trend toward a longer remodeling period and delayed biologic healing in allograft tissue when compared with autografts,\textsuperscript{42-44} possibly up to 2 years or more after surgery.\textsuperscript{45} Animal model research has also shown a significantly longer time to biologic incorporation after ACL reconstruction, even with fresh-frozen allografts.\textsuperscript{46} However, despite an underlying premise that allografts are prone to stretch or have a clinically higher failure rate,\textsuperscript{38} this did not result in any fundamental differences in clinical outcomes in this systematic review.

Allograft use in young active patients and high-demand athletes has been increasingly scrutinized.\textsuperscript{38,47-50} In surveying cadets at the United States Military Academy, Pallis et al.\textsuperscript{47} showed that allograft tissue was associated with a 6-fold higher rate of failure after ACL reconstruction when compared with autografts. When evaluating the Multicenter Orthopedic Outcome Network cohort, allograft tissue was associated with worse clinical results based on IKDC scores and Knee Injury and Osteoarthritis Outcome Score results.\textsuperscript{48} Similarly in their athletic cohorts, other authors\textsuperscript{39,50} found that younger

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**Meta-analysis for Pivot-Shift**

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<td>Noh</td>
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**Meta-analysis for Failure**

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**Fig 5.** Forest plot of side-to-side instrumented knee laxity measurements greater than 5 mm by KT-1000 evaluation according to graft source. (CI, confidence interval.)

**Fig 6.** Forest plot of clinical failures according to graft source.
age was associated with a significantly higher rate of clinical failure after anatomic single- or double-bundle ACL reconstruction. With higher levels of activity and increased demand for an accelerated return to competition, younger patients may experience excessive mechanical stress before complete remodeling of allograft ACL reconstruction has occurred. Further research should better evaluate the utility of non-chemically processed and non-irradiated allograft tissue in young athletes undergoing ACL reconstruction, particularly vis-à-vis current autograft options.

Limitations
Our findings in the current systematic review indicate that short-term to midterm clinical outcomes of autograft ACL reconstruction are not significantly different from those with non-chemically treated non-irradiated allografts. Of 11 included studies, none showed statistically significant differences between Lysholm scores, IKDC scores, KT-1000 evaluation, Lachman test results, pivot-shift test results, or rates of clinical failure between the groups. However, certain limitations must be acknowledged. Five of the 11 studies did not involve randomization or blinding, thereby predisposing to selection and investigator bias. Furthermore, only one Level I study was available for inclusion in this study. External validity may be limited by the certain components of study design, particularly because most studies involved single experienced surgeons at high-volume sports medicine centers. Additionally, individual and cumulative enrollment is relatively small; larger study size may more effectively differentiate outcomes between autograft and allograft with limited processing.

Conclusions
This systematic review failed to show any significant differences in various functional and objective outcome measures after ACL reconstruction with autografts or non-chemically treated non-irradiated allografts. Although the included studies do support the use of allografts without irradiation or chemical processing, further comparative studies are necessary to fully evaluate their role in certain active cohorts and associated risk profiles.

References


