Sex Influences the Biomechanical Outcomes of Anterior Cruciate Ligament Reconstruction in a Preclinical Large Animal Model
Ata M. Kiapour, Braden C. Fleming, Benedikt L. Proffen and Martha M. Murray
Am J Sports Med published online May 4, 2015
DOI: 10.1177/0363546515582024

The online version of this article can be found at:
http://ajs.sagepub.com/content/early/2015/05/02/0363546515582024

Published by:
SAGE
http://www.sagepublications.com

On behalf of:
American Orthopaedic Society for Sports Medicine
AOSSM

Additional services and information for The American Journal of Sports Medicine can be found at:
Published online May 4, 2015 in advance of the print journal.

Email Alerts: http://ajs.sagepub.com/cgi/alerts
Subscriptions: http://ajs.sagepub.com/subscriptions
Reprints: http://www.sagepub.com/journalsReprints.nav
Permissions: http://www.sagepub.com/journalsPermissions.nav

>> OnlineFirst Version of Record - May 4, 2015

What is This?
Sex Influences the Biomechanical Outcomes of Anterior Cruciate Ligament Reconstruction in a Preclinical Large Animal Model

Ata M. Kiapour,* PhD, Braden C. Fleming,† PhD, Benedikt L. Proffen,* MD, and Martha M. Murray,*‡ MD

Investigation performed at Boston Children’s Hospital, Harvard Medical School, Boston, Massachusetts, USA, and Rhode Island Hospital, Brown University, Providence, Rhode Island, USA

Background: The risk of anterior cruciate ligament (ACL) injury is 2 to 10 times greater in women than men. While the effect of sex on injury risk is well established, its effects on surgical outcomes remain controversial.

Purpose/Hypothesis: To investigate whether the biomechanical outcomes of ACL reconstruction are affected by sex using an established porcine model that displays similar sex-specific differences in knee anatomy and ligament structural properties to humans. The hypothesis was that there will be sex differences in ACL reconstruction outcomes with regard to the graft structural properties, knee laxity, and cartilage damage.

Study Design: Controlled laboratory study.

Methods: A total of 41 adolescent Yucatan minipigs (23 male, 18 female) underwent unilateral ACL transection and ACL reconstruction using sex-matched bone–patellar tendon–bone allografts (with or without additional bioenhancement). Graft biomechanical and histological properties, knee laxity, and cartilage damage were assessed after 15 weeks. A 2-factor analysis of variance was used to investigate the effect of sex on all the measured outcomes after adjusting for the treatment effect.

Results: After 15 weeks of healing, female pigs had a significantly lower mean normalized graft yield load (by 18.5% ± 7.7%; P = .023) and linear stiffness (by 11.9% ± 5.6%; P = .043) compared with male pigs. Female pigs had significantly greater side-to-side differences in anteroposterior knee laxity at 30° (by 1.4 ± 0.6 mm; P = .028) and 90° (by 1.8 ± 0.8 mm; P = .032). Female pigs had a lower graft vascular density (by 0.8 ± 0.3 [analog scoring]; P = .021) with similar cellular and collagen-based histologic scores in both sexes (P > .6). Female pigs also had a significantly larger area of cartilage damage (by 43.3 ± 14.8 mm²; P = .014) after conventional ACL reconstruction compared with their male counterparts.

Conclusion: Female pigs had significantly worse outcomes (ie, graft structural properties, knee laxity, and cartilage damage) compared with male pigs in this translational model after 15 weeks of healing.

Clinical Relevance: These data suggest that further optimization of ACL injury treatments may be needed to accommodate each sex instead of using a “one fits all” approach to improve surgical outcomes, decrease incidence of reinjury, and decrease posttraumatic osteoarthritis risk after ACL reconstruction.

Keywords: anterior cruciate ligament; reconstruction; sex; biomechanical outcomes; posttraumatic osteoarthritis
injury risk,24 the role of sex on the outcomes of ACL surgery has been a topic of considerable debate. A limited but growing number of studies have investigated the sex-specific differences in various aspects of ACL reconstruction outcomes including graft failure risk, reinjury rates, knee laxity, and patient-oriented outcomes.5 However, the findings are inconclusive, as some authors reported poorer outcomes in female patients1,4,8,13,18,35,39,42,43 while others noted no difference.3,10,19,47,48

Women have been reported to have significantly higher rates of graft failure compared with men by as much as 20%.35 Prior studies have reported significantly greater side-to-side differences in anteroposterior (AP) knee laxity in women than men after ACL reconstruction by as much as 1.6 mm with either bone–patellar tendon–bone (BPTB) or hamstring tendon grafts.4,8,13,18,35,43 Moreover, women have been found to have significantly higher pain frequency and intensity35 with worse patient-reported outcomes compared with men after ACL reconstruction.1,13,18,39 Female sex has also been associated with a lower rate of return to sport and preinjury activity levels after an ACL surgery.35,49 However, a recent systematic review of the 13 studies in the literature reported no systematic differences in graft failure (7 studies), contralateral ACL injury (3 studies), knee laxity (Lachman test [5 studies], pivot-shift test [5 studies], and instrumented knee laxity [7 studies]), and patient-reported outcomes (9 studies) between men and women who had undergone ACL reconstruction.47

These discrepancies in determining statistically significant sex-related differences in outcomes of ACL surgery in clinical studies may be the result of various factors, including a lack of outcome measures with the sufficient sensitivity to detect differences between the sexes. While instrumented knee laxity assessment can be performed in patients, the results can be affected by the errors in measurements caused by various factors such as soft tissue motion artifact and intraobserver variability. Direct measurements of graft healing (ie, biomechanics and histology) are also challenging, if not impossible, in clinical trials. Most importantly, the critical outcome of postransplant OA risk and severity may not be detectable in a clinical cohort for a decade or more as there are currently no reliable early predictors of this disease.

Some of these limitations can be mitigated when animal models are used to study the outcomes of ACL surgery. Posttraumatic OA in animals often occurs within 1 to 12 months after injury, with smaller animals developing macroscopic changes in cartilage structure sooner than larger animals. Animal joints can be opened and evaluated to examine the integrity of the graft and cartilage. For these reasons, animal models have long been used to study ACL injuries, treatments, and associated complications.5 Among those, the porcine model has been shown to be the closest to the human based on its size, anatomy, and functional dependency on ACL.6,31,45,55 Furthermore, it has been shown that pigs develop postransplant OA after ACL transection and reconstruction in a pattern similar to that reported in humans.29 Finally, the porcine knee develops postransplant OA at a faster rate than is seen in humans, with the findings at 12 months in the porcine model reflective of those seen at 10 to 15 years after ACL reconstruction in humans.29 This faster onset of postransplant OA allows for more rapid assessment of factors that may influence the development of postransplant OA after ACL injury and treatment.

More recently, the porcine model has been validated as a sex-specific large animal surrogate model for the human knee, with similar sex differences seen for knee laxity, ACL structural properties and size, tibial slope, femoral notch size, and cartilage thickness.25 Using this model, we are now poised to investigate the role of sex on the biomechanical outcomes of ACL reconstruction. We hypothesized that there are sex-specific differences in the outcomes of ACL reconstruction with regard to graft structural properties, knee laxity, and cartilage damage.

METHODS

After approval from the Institutional Animal Care and Use Committee (IACUC), 41 normal adolescent Yucatan minipigs (23 male, 18 female; age, 15 ± 1 months; weight, 48.0 ± 9.6 kg) underwent unilateral ACL transection and were randomly assigned to 1 of 4 treatment groups: conventional ACL reconstruction (n = 13; 8 male, 5 female) or bioenhanced ACL reconstruction with 1× (n = 10; 7 male, 3 female), 3× (n = 9; 3 male, 6 female), and 5× (n = 9; 5 male, 4 female) platelet-rich plasma (PRP).16 The surgical knee was randomly selected, and the contralateral ACL-intact knee served as a control. The data were obtained from a previously published study evaluating the effect of PRP concentration on the functional outcomes of the ACL surgery.16 In the current study, we analyzed this data set to determine whether sex had any influence on the biomechanical, histological, and OA outcomes of ACL surgery.

PRP Preparation

Before surgery, 60 mL of autologous whole blood was drawn into a syringe containing 10% acid-citrate-dextrose

---

9References 1, 3, 4, 8, 10, 13, 18, 19, 35, 39, 40, 42, 43, 47, 48.
10Address correspondence to Martha M. Murray, MD, Department of Orthopedic Surgery, Boston Children’s Hospital, Harvard Medical School, 300 Longwood Avenue, Boston, MA 02115, USA (email: Martha.Murray@childrens.harvard.edu).
11Sports Medicine Research Laboratory, Department of Orthopaedic Surgery, Boston Children’s Hospital, Harvard Medical School, Boston, Massachusetts, USA.
12Department of Orthopaedics, Warren Alpert Medical School of Brown University & Rhode Island Hospital, Providence, Rhode Island, USA.
13The article content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. One or more of the authors has declared the following potential conflict of interest or source of funding: Funding for this study was received from the National Institutes of Health [RO1-AR054099 to M.M.M.], AR056834 [to B.C.F. and M.M.M.], and P20 GM104937 [to B.C.F.] (Bioengineering Core), Translational Research Program at Boston Children’s Hospital (to M.M.M.), and the Lucy Lippitt Endowment (to B.C.F.).
frozen BPTB allografts from age-, weight-, and sex-matched
ventional ACL reconstruction was performed using fresh-
transection was confirmed by a positive Lachman test. Con-
30 minutes of preparation.
were maintained at room temperature and used within
ually presented by Fleming et al. PRP concentrates
details of platelet and blood cell concentrations for whole
and PRP concentrates for each group have been pre-

Surgical Procedures

After a medial arthrotomy, the ACL was isolated and trans-
ected at midsubstance as previously described. Complete
traction was confirmed by a positive Lachman test. Con-
ventional ACL reconstruction was performed using fresh-

Knee Laxity. The AP knee laxity values were measured
using a custom fixture at 30°, 60°, and 90° of knee flexion
(Figure 1A). The knees were locked at each flexion
angle with axial tibial rotation constrained in the neutral
position while tibial translation/rotation was uncon-
strained in the coronal plane. The knees were subjected
to 12 cycles of ±40 N AP shear loads at each specific flexion
angle while the AP displacements were measured. AP knee
laxity was defined as the overall translational motion of
the femur with respect to the tibia within the AP shear
load limits of ±30 N.

ACL Structural Properties. After the laxity assessment,
all remaining soft tissues were dissected from the joint,
leaving the ACL intact. The femur-ACL-tibia constructs
were then secured in a custom designed tensile testing fix-
ure so that the mechanical axis of the ACL was collinear
with the load axis of the test frame (Figure 1B). The fem-
oral axial rotation was unconstrained, and the tibia was
connected to the test frame through a sliding X-Y table,
helping the specimen to seek its own physiologic position
under tensile loading. Specimens were then loaded in ten-
sion to failure at 20 mm/min. The recorded load
displacement data were used to quantify ACL linear stiff-
ness, yield, and maximum loads.

Graft Histological Characteristics

Subsequently, the grafts were dissected, fixed in formalin
embedded in paraffin, sectioned, and then stained with
hematoxylin & eosin or α-smooth muscle actin antibodies.
The Ligament Maturity Index was used to assess a central
sagittal slice through each graft following previously estab-
lished techniques. The Ligament Maturity Index con-
ists of 3 subscores evaluating the cellular, collagen, and
vascular organization. The cellular subscore evaluated
the presence of inflammatory cells, number of fibroblasts,
fibroblast nuclear aspect ratio, and the orientation of the
fibroblast nuclei relative to the collagen fascicles; the cola-
gen subscore considered bundle orientation and crimp
appearance; the vascularity subscore assessed blood vessel
density, orientation, and maturity. Ligament scoring was
conducted by 3 independent investigators (intraclass corre-
lation coefficient [ICC] = 0.92), blinded to the treatment and
sex, and the values were averaged for final analysis.

Physical Examination

A physical examination, to establish weight and passive
knee range of motion of both knees, was performed on
anesthetized animals in a supine position preoperatively
and before limb harvest.
Macroscopic Cartilage Assessment

After biomechanical testing, the articular cartilage across the medial and lateral femoral condyles and the medial and lateral tibial plateaus, for both the treated and contralateral intact knees, were stained using India ink to highlight surface irregularities. The length and width of all visible lesions in all 4 regions of interest, medial and lateral femoral condyles and medial and lateral tibial plateau, were measured using calipers. Lesion areas were estimated assuming elliptical fits. The lesion areas for each region were summed to give the total lesion area for each knee joint. Moreover, cartilage samples were scored using a common macroscopic scoring method with a 5-point scale ranging from 0 (no damage) to 4 (lesions with exposed bone >10% of the lesion area). The total score was the sum of the scores from each region. A larger score correlated with more cartilage damage. Two independent examiners (ICC = 0.96) blinded to the knee, treatment, and sex, performed all measurements, and the values were averaged.

Statistical Analysis

A 2-factor analysis of variance (ANOVA) using a multivariate general linear model was used to investigate the effect of sex on all the measured outcomes. All the sex-related comparisons were adjusted for the treatment effect by adding the treatment type as a fixed factor to the model. Analyses were conducted on normalized graft structural properties (% contralateral intact), side-to-side differences in AP knee laxity (between the treated and contralateral intact knees), and graft histological properties and cartilage damage data obtained from the treated knees. In the event that any of the measured outcomes were significantly affected by the combined sex and treatment interaction, the analysis for the corresponding outcome measure was repeated on each group separately to isolate the effect of sex and avoid errors due to the treatment effect. Comparisons were considered to be statistically significant for $P \leq .05$. All results are reported as mean ± standard error of the mean (SEM).

RESULTS

Animal Welfare and Physical Examination

All animals recovered well from surgery and survived the full 15-week follow-up term with no signs of infections or other complications. There were no statistically significant differences between male and female pigs with regard to the changes in the weight or range of motion from preinjury to postinjury levels ($P > .1$ for all comparisons) (Table 1).

Biomechanical Outcomes

After 15 weeks of healing, the grafts in the female knees had a significantly lower normalized yield load (by 18.5% ± 7.7%; $P = .023$) and linear stiffness (by 11.9% ± 5.6%; $P = .043$) than their male counterparts (Figure 2). Female
pigs also had a lower mean normalized graft maximum load (by 11.8% ± 6.0%) compared with the males, a difference that approached statistical significance \((P = .058)\).

The ACL reconstructed knees in the female pigs had a greater side-to-side difference in AP knee laxity (by 1.4 ± 0.6 mm, 1.6 ± 0.9 mm, and 1.8 ± 0.8 mm at 30°, 60°, and 90°, respectively) compared with their male counterparts (Figure 3). These differences were statistically significant at 30° \((P = .028)\) and 90° \((P = .032)\) and approached statistical significance \((P = .072)\) at 60° of knee flexion.

**Graft Histology**

Female pigs had a lower vascular density within the graft than the males (by 0.8 ± 0.3 [analog scoring]; \(P = .021\)). However, all other histologic qualitative measures were the same in both sexes with similar cell \((P = .742)\) and collagen \((P = .619)\) subscores at 15 weeks of healing (Figure 4). There was no evidence of inflammatory cells within any grafts.

**Cartilage Assessment**

Sex differences in cartilage damage were significantly affected by the treatment type \((sex \times treatment interaction, P < .05)\), with significantly greater damage observed after ACL reconstruction (Table 2). \(^{16}\) Therefore, separate analyses were conducted on the animals that received conventional ACL reconstruction and those that underwent bioenhanced ACL reconstruction. Female pigs had a greater degree of cartilage damage after conventional ACL reconstruction than did their male counterparts (Figure 5). These differences were statistically significant for the area of cartilage damage on the medial femoral condyle (by 43.3 ± 14.8 mm\(^2\); \(P = .014\)) and total cartilage score for the entire knee (by 3.3 ± 1.5 [analog scoring]; \(P = .043\)), with differences in damaged area for the entire knee (by 42.8 ± 20.4 mm\(^2\)) and the medial femoral cartilage score

---

**TABLE 1**

**Differences in Physical Examination Outcomes**

<table>
<thead>
<tr>
<th>Measured Outcome</th>
<th>Males</th>
<th>Females</th>
<th>(P) Value, Sex Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, kg</td>
<td>Preoperative</td>
<td>Postoperative(^b)</td>
<td>Change</td>
</tr>
<tr>
<td>Preoperative</td>
<td>46.0 ± 1.9</td>
<td>56.6 ± 1.6</td>
<td>10.6 ± 1.6</td>
</tr>
<tr>
<td>Change</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum knee flexion, deg</td>
<td>Preoperative(^b)</td>
<td>Postoperative(^b)</td>
<td>Change</td>
</tr>
<tr>
<td>Preoperative</td>
<td>36.0 ± 1.7</td>
<td>40.8 ± 1.9</td>
<td>4.7 ± 2.9</td>
</tr>
<tr>
<td>Change</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum knee extension, deg</td>
<td>Preoperative(^b)</td>
<td>Postoperative(^b)</td>
<td>Change</td>
</tr>
<tr>
<td>Preoperative</td>
<td>137.9 ± 2.4</td>
<td>142.1 ± 2.4</td>
<td>135.1 ± 2.5</td>
</tr>
<tr>
<td>Change</td>
<td>−2.8 ± 3.4</td>
<td>−6.9 ± 3.6</td>
<td>.406</td>
</tr>
</tbody>
</table>

\(^a\)Adjusted for treatment effect.

\(^b\)Fifteen weeks after the surgery.
Female pigs had significantly lower graft structural properties and greater AP knee laxity compared with their male counterparts 15 weeks after ACL reconstruction (with and without bioenhancement) using BPTB allograft. In addition, ACL grafts in male knees showed significantly greater vascularization when compared with female knees, while other histological parameters showed no sex-related differences. Lastly, female knees had greater cartilage damage than male knees after an isolated ACL transection and conventional reconstruction. Interestingly, this difference was not statistically significant. Other studies have reported greater vascularization in male pigs than female pigs. However, the meta-analysis indicated that this difference was not statistically significant. Other studies have reported significantly greater side-to-side differences in AP knee laxity in female than male patients (by ~19%). As demonstrated by our results, a poorly healed graft can be manifested with inferior structural properties with no signs of gross failure, which can lead to lowered functional outcomes such as increased knee laxity and cartilage damage.

In terms of knee laxity, the meta-analysis by Ryan et al found no significant effect of sex on knee laxity when measured by Lachman testing or instrumented knee laxity. In the same study, the percentage of patients with a pivot-shift test grade other than 0 was 12% in males and 20% in females. However, the meta-analysis indicated that this difference was not statistically significant. Other studies have reported significantly greater side-to-side differences in AP knee laxity in female than male patients for both the patellar tendon (up to 1 mm) and hamstring tendon (up to 1.6 mm) grafts after ACL reconstruction. These findings compare with our findings of significantly greater side-to-side differences in AP knee laxity in female pigs than male pigs by 1.4 mm (at 30° of knee flexion).

In addition to the measured biomechanical outcomes, graft vascularization was also shown to be sex dependent, with greater vascularization in male pigs than female pigs. Prior studies have reported greater vascularization in the graft healing process to be associated with significantly higher graft strength with respect to the graft yield and maximum loads as well as graft linear stiffness. Our data are consistent with those findings, as the grafts in male knees were significantly more vascular.
and stronger when compared with the grafts from the female knees. This increased vascularity of the grafts may be a key determinant in outcomes of ACL reconstruction, and its link to both the graft structural properties and the sex of the animal is intriguing and will be the subject of future studies.

Patient-reported outcomes are also important outcome measures for clinical studies. With regard to the patient-reported outcomes, Ryan et al.14 suggested that the heterogeneity of the measurement tools precluded examining these outcomes as a function of sex. However, multiple cohorts of patients with reconstructed ACL have shown worse patient-reported outcomes in female compared with male patients, including Knee Injury and Osteoarthritis Outcome Score (KOOS),18 Single Assessment Numeric Evaluation score (SANE),18 International Knee Documentation Committee score (IKDC),18 HSS radiographic score,13 and Cincinnati knee score.39 In the current study, a significant effect of sex on the development of cartilage damage after ACL reconstruction was also observed in the porcine model. The greater cartilage damage area and worse cartilage scores in the female pigs is in agreement and may be related to the findings of prior clinical trials showing an increased pain frequency and intensity,35 along with worse knee function and patient-oriented outcomes, in women.1,13,18,35,39 While “primary” knee OA has shown to be sex dependent, with substantially higher risk and progression rate in female compared with male patients,36,52 the role of sex on risk of posttraumatic OA after an ACL injury has been less studied. The data here would suggest that females might be more likely to develop posttraumatic OA at a faster rate than their male counterparts. The higher rates of ACL injuries in female patients,24 along with the current observation of greater degree of cartilage damage when compared with males, are indicative of higher risk of posttraumatic OA development for women. Given that over 75% of young individuals develop posttraumatic OA within 14 years of an ACL injury53 and that the peak age of ACL injury in female patients is 15 to 19 years,46 these data suggest that there may be a large cohort of young women who are currently at high risk for developing posttraumatic OA before the age of 35 years.

There are potential shortcomings with this study. The pig is a quadruped, and postoperative rehabilitation is difficult to control. However, similar anatomic and biomechanical features between the pig and human have been noted.6,45,55 The surgeries were conducted using a fresh-frozen allograft instead of autografts. Harvesting the patellar tendon autograft would compromise the extensor mechanism in a porcine model, while the hamstring autograft is not of sufficient length. It is possible that autografts would have provided different results. This is unlikely a major concern in that all treatment groups utilized the same type of allograft and the structural properties of the allografts in this study were similar to those reported for autografts in other quadruped models.11,21 Moreover, the investigations were only conducted on adolescent pigs (15 months old). Previous studies have shown that Yucatan minipigs reach sexual and skeletal maturity at 7 to 10 months5 and 26 to 30 months,26 respectively. More studies are needed to determine whether the current findings are affected by skeletal maturity and if they will translate to younger (premature) and older skeletally mature animals, since ACL healing is affected by age.30 Finally, male and female pigs were not evenly distributed within each treatment group, which might have affected the reported sex differences. However, the fact that all the tested groups had a combination of both male and female pigs and the relatively small effect of PRP concentration on the outcomes of bioenhanced ACL reconstruction16 has given us a reasonable statistical power to investigate the sex-specific difference in measured outcomes after adjusting for the treatment effect of PRP. A post hoc power analysis has indicated a power of 0.8 for most of the measured outcomes. Future studies with higher sample sizes and a more specific study design to investigate the sexual dimorphism in reported outcomes are required to better understand the effect of sex on the outcomes of interest.

To our knowledge, this is the first time that sex has been demonstrated to significantly alter the outcome of ACL surgery in a large animal preclinical model. The porcine large animal model has previously been validated as a sex-specific model with similar sex differences in knee anatomy, laxity, and ACL biomechanics as to the human knee.25 Moreover, the pig knee has been shown to be the closest surrogate model for the human knee based on the anatomy and functional dependency on ACL.6,31,45,55 These

### Table 2: Average Quantified Macroscopic Cartilage Damage Across the Treatment Groups

<table>
<thead>
<tr>
<th>Cartilage Damage</th>
<th>Mean ± SEM</th>
<th>P Value</th>
<th>Treatment-Related Differences</th>
<th>Sex × Treatment–Related Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ACLR</td>
<td>B-ACLR</td>
<td>B-ACLR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1× PRP)</td>
<td>(3× PRP)</td>
<td>(5× PRP)</td>
<td></td>
</tr>
<tr>
<td>Lesion area</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MFC</td>
<td>25.4 ± 9.2</td>
<td>3.6 ± 2.6</td>
<td>7.6 ± 6.0</td>
<td>6.9 ± 4.6</td>
</tr>
<tr>
<td>Total</td>
<td>30.9 ± 11.2</td>
<td>11.4 ± 6.3</td>
<td>7.9 ± 6.1</td>
<td>11.1 ± 7.8</td>
</tr>
<tr>
<td>Cartilage score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MFC</td>
<td>3.3 ± 0.5</td>
<td>1.6 ± 0.2</td>
<td>2.1 ± 0.3</td>
<td>2.3 ± 0.2</td>
</tr>
<tr>
<td>Total</td>
<td>6.8 ± 0.8</td>
<td>4.3 ± 0.4</td>
<td>4.4 ± 0.6</td>
<td>4.3 ± 0.6</td>
</tr>
</tbody>
</table>

*ACLR, anterior cruciate ligament reconstruction; B-ACLR, bioenhanced anterior cruciate ligament reconstruction; MFC, medial femoral condyle; PRP, platelet-rich plasma.

*Combined sex × treatment interaction term in the model.
support the current model as a valid approach to study the sex-specific differences in human knee injuries and surgical interventions with a special focus on ACL. Current findings further support the use of the validated preclinical animal models as reliable means to overcome the technical and ethical challenges associated with human trials and enhance our abilities to measure the relevant structural outcomes of interest with sufficient resolution to further define the role of sex on the outcomes of ACL surgery.

CONCLUSION

The study findings support our hypothesis that sex significantly affects the graft structural properties and AP knee laxity after ACL reconstruction, with female pigs having weaker and less vascular grafts and more lax knees. In addition, the female pigs had greater knee cartilage damage than their male counterparts, a difference that was ameliorated with the addition of an extracellular matrix-based scaffold loaded with autologous PRP. The results highlight the importance of further optimization of the current treatments to better fit each sex instead of a “one fits all” approach. This may in turn lead to improved surgical outcomes, decreased incidences of graft failure and reinjury, and a decreased risk of posttraumatic OA after ACL injury and reconstruction, especially among women.

ACKNOWLEDGMENT

The authors thank Patrick Vavken from Boston Children’s Hospital for helping with surgical procedures; Matthew Shalvoy, Alison Biercevicz, David Paller, Sarath Koruprolu, and Ryan Rich (Rhode Island Hospital Orthopaedic Foundation) for their assistance with mechanical testing; and Henry Feldman (Clinical Research Center at Boston Children’s Hospital) and Harvard Catalyst (Harvard Clinical and Translational Science Center) for helping with the statistical analysis.

REFERENCES


