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SYMPOSIUM: SEX DIFFERENCES IN MUSCULOSKELETAL DISEASE AND SCIENCE

Biomechanical Outcomes of Bridge-enhanced Anterior Cruciate Ligament Repair Are Influenced by Sex in a Preclinical Model

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Abstract

Background Despite the well-established role of sex on the anterior cruciate ligament (ACL) injury risk, its effects on ACL surgical outcomes remain controversial. This is particularly critical when developing novel surgical techniques to treat the injury because there are limited data existing on how these procedures will respond in each sex. One such approach is bridge-enhanced ACL repair, in which primary suture repair of the ACL is augmented with a bioactive scaffold saturated with autologous blood. It has shown comparable biomechanical outcomes to ACL reconstruction in preclinical models.

Questions/purposes We asked (1) whether sex affects the biomechanical outcomes of bridge-enhanced ACL repair; and (2) if suture type (absorbable or nonabsorbable), used to repair the torn ACL, can minimize the potential sex discrepancies in outcomes after 15 weeks of healing in a large animal preclinical model.

Methods Seventeen (eight males, nine females) Yorkshire pigs (Parson's Farms, Hadley, MA, USA) underwent bilateral ACL transection and received bridge-enhanced ACL repair with an absorbable suture (n = 17) on one side and with a nonabsorbable suture (n = 17) on the other side. The leg receiving the absorbable suture was randomized within each animal. ACL structural properties and AP knee laxity for each knee were measured after 15 weeks of healing. Mixed linear models were used to compare the biomechanical outcomes between sexes and suture groups.

Results When treated with absorbable suture, females had a lower ACL linear stiffness (females, 11 N/mm [range, 8–42]; males, 31 N/mm [range, 12–56]; difference, 20 N/mm [95% confidence interval {CI}, 4–36]; p = 0.032), ACL yield (females, 121 N [range, 56–316]; males, 224 N [range, 55–538]; difference, 103 N [95% CI, 6–200]; p = 0.078), and maximum load (females, 128 N [range, 63–332]; males, 241 N [range, 82–538]; difference, 114 N

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Each author certifies that his or her institution approved the animal protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research.
This work was performed at the Sports Medicine Research Laboratory, Department of Orthopaedic Surgery, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA, and the Department of Orthopaedics, Rhode Island Hospital, Providence, RI, USA.

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[95% CI, 15–212]; p = 0.052) than males after 15 weeks of healing. Female knees treated with absorbable suture had a lower linear stiffness (absorbable, 11 N/mm [range, 8–42]; nonabsorbable, 25 N/mm [range, 8–64]; difference, 14 [95% CI, 2–26] N; p = 0.054), ACL yield (absorbable, 121 N [range, 56–316]; nonabsorbable, 230 N [range, 149–573]; difference, 109 N [95% CI, 56–162]; p = 0.002), and maximum load (absorbable, 128 N [range, 63–332]; nonabsorbable, 235 N [range, 151–593]; difference, 107 N [95% CI, 51–163]; p = 0.002) along with greater AP knee laxity at 30° (absorbable, 9 mm [range, 5–12]; nonabsorbable, 7 mm [range, 2–13]; difference, 2 mm [95% CI, 1–4]; p = 0.034) than females treated with nonabsorbable suture. When repaired using nonabsorbable suture, the biomechanical outcomes were similar between female and male knees (p > 0.10).

Conclusions Females had significantly worse biomechanical outcomes than males when the repairs were performed using absorbable sutures. However, the use of nonabsorbable sutures ameliorated these differences between males and females.

Clinical Relevance The current findings highlight the critical role of sex on the biomechanical outcomes of bridge-enhanced ACL repair in a relevant large animal model. Better understanding of the mechanisms responsible for these observations using preclinical models and concomitant clinical studies in human patients may allow for additional development of sex-specific surgical and rehabilitative strategies with potentially improved outcomes in women.

Introduction

Injuries to the anterior cruciate ligament (ACL) are common [31]. Women are at increased risk (up to 10-fold) for ACL injury in comparison to men when playing the same sport [29]. Despite reasonable success of ACL reconstruction, the current gold standard of treatment, in restoring the gross stability of the ACL-deficient knee, it fails to restore normal joint kinematics and kinetics [8, 22, 24, 25, 43, 52]. Moreover, ACL reconstruction is associated with reduced activity level [5], an increased rate of secondary injury [48], and high risk of posttraumatic osteoarthritis (OA), up to 74%, even with advanced anatomic reconstruction techniques [13, 32, 33, 40, 50, 56]. The associated complications with ACL reconstruction, in addition to the advent of functional tissue engineering, precipitated a move in ACL research from improving replacement techniques to developing procedures for biologically augmented repair of the ligament. One such approach, bridge-enhanced repair [34], has shown comparable biomechanical outcomes to ACL reconstruction in preclinical models [34, 35, 54]. This emerging surgical technique uses a combination of an extracellular matrix (ECM)-based scaffold saturated with autologous blood along with sutures to repair the torn ACL [34]. Most importantly, bridge-enhanced ACL repair has resulted in a substantial reduction of posttraumatic OA compared with ACL reconstruction in a 1-year followup preclinical study in a porcine large animal model [35].

The rapid rise in the incidence of ACL injuries among women, particularly in the young active population, has generated a substantial interest in studying the sexual dimorphism in the outcomes of ACL surgery [46, 53]. Despite recent findings of worse functional and biomechanical outcomes in women compared with men after ACL reconstruction [1, 9, 15, 17, 23, 41, 42, 44], the role of sex on the outcomes of recently developed surgical techniques such as bridge-enhanced ACL repair is not yet known. A clear understanding of how sex may affect the outcomes of such surgical techniques can help further optimize these approaches with improved outcomes for each sex. This is also necessary to comply with the current National Institutes of Health recommendations to study sex disparities in medical research and the inclusion of female animals in preclinical research to minimize the sex bias and further facilitate the translation from the preclinical stage to human trials [14].

Thus, the current study was designed (1) to investigate the effect of sex on biomechanical outcomes of bridge-enhanced ACL repair; and (2) to determine if suture type (absorbable versus nonabsorbable) used to repair the torn ACL can alleviate the potential sex discrepancies in measured outcomes after 15 weeks of healing in a well-established porcine model with similar sex-specific knee anatomical and biomechanical properties as the human knee [30]. We hypothesized that there are sex differences in the biomechanical outcomes of bridge-enhanced ACL repair with lower ACL structural properties and greater AP knee laxity in females than males and that the choice of suture type used to repair the torn ACLs would affect the observed sex differences in measured biomechanical outcomes.

Materials and Methods

Experimental Design

Seventeen (eight males, nine females) Yorkshire pigs (Parson's Farms, Hadley, MA, USA; age, 4 ± 1 months; weight, 28 ± 2 kg) underwent bilateral ACL transection and received bilateral bridge-enhanced ACL repair using an ECM-based bioactive scaffold (MIACH; Boston Children's Hospital, Boston, MA, USA). This large animal model has been widely used in preclinical studies of ACL surgery [18–21, 27, 33, 35–37, 54, 55] and has recently been validated as a sex-specific large animal surrogate model to study the human knee [30]. The bridge-enhanced ACL repair procedures were performed using an absorbable suture stent (Vicryl®; Ethicon Inc, Somerville, NJ, USA; n = 17) on one hindlimb and using a nonabsorbable suture stent (Ethibond; Ethicon Inc; n = 17) on the other hindlimb. The animals were randomly selected. The legs receiving absorbable and nonabsorbable sutures within each animal were alternated across animals. This method of randomization was used to ensure equal distribution of suture type within the study population. Both knees were then harvested and subjected to biomechanical testing. ACL structural properties and AP knee laxity were measured and compared between males and females. Institutional Animal Care and Use Committee approvals were obtained before initiating this study.

Surgical Procedure

After general anesthesia, a medial arthrotomy was made to expose the ACL. The ACL was isolated and transected at its proximal third (Fig. 1A). The knee was irrigated with 500 mL saline solution. A Lachman test was performed to verify functional loss of the ACL. For all knees, a Kessler suture using No. 1 Vicryl® was placed in the tibial stump of the ACL to repair the transected ligament [20, 36, 37]. Femoral (4.5 mm) and tibial (2.4 mm) tunnels were then drilled in standard positions for ACL reconstruction with the tibial tunnel exiting in the center of the tibial attachment and the femoral tunnel placed at the center of the femoral ACL attachment site. An EndoButton (Smith & Nephew, Andover, MA, USA) loaded with three No. 1 sutures was passed through the femoral tunnel and flipped on the lateral cortex to provide femoral fixation of the sutures (Fig. 1B). Two of these three sutures were used to create the suture stent, which were either Vicryl® (absorbable) or Ethibond (nonabsorbable) based on the study group. The suture stent was then threaded through the ECM-based MIACH scaffold and the scaffold was introduced into the notch until femoral contact was visually verified (Fig. 1C). The suture stent was then passed through the tibial tunnel and tied over a button in front of the tibia with the knee at full extension. The remaining third suture (Vicryl®) from the femoral tunnel/EndoButton was tied to the Kessler suture in the tibial ACL stump to position the remaining ACL tissue in its anatomic orientation (Fig. 1D). Subsequently, the scaffold was saturated in situ with up to 5 mL of autologous blood (Fig. 1E). The knee was kept immobilized for 10 minutes to allow the implanted blood to clot in the scaffold before the incisions were closed in layers.

All animals were housed in individualized pens for 15 weeks postsurgery. The animals were allowed ad libitum activity during the 15-week postoperative period. They were then euthanized, and the hindlimbs were harvested and immediately frozen at −20 °C until the biomechanical evaluation.

Biomechanical Testing

The knees were thawed to room temperature 24 hours before the biomechanical testing. Specimens were

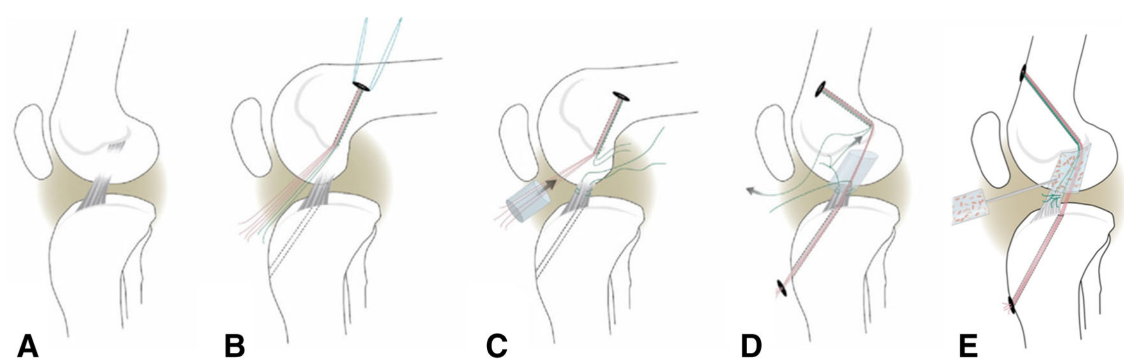

Fig. 1A–E (**A**) ACL injury was simulated by cutting the ACL in the midsubstance. (**B**) Femoral and tibial tunnels (dashed lines) were drilled and an EndoButton pulled through the femoral tunnel and engaged on the proximal femoral cortex. The EndoButton was loaded with three sutures, resulting in six free ends. (**C**) A Kessler suture was placed in the tibial ACL stump, and the MIACH scaffold was threaded onto four of the strands, which served as the suture stent (red). (**D**) The four suture strands running through the scaffold (red) were then passed through the tibial tunnel. (**E**) The transtibial sutures (red) were tightened and tied over an extracortical button. The scaffold was then saturated with 5 mL of autologous blood and placed into the notch. The free ends of the ACL suture pulley (green) were tied to secure the ACL stump in the blood-scaffold composite. Adapted and modified from Vavken P, Fleming BC, Mastrangelo AN, Machan JT, Murray MM. Biomechanical outcomes after bioenhanced anterior cruciate ligament repair and anterior cruciate ligament reconstruction are equal in a porcine model. *Arthroscopy.* 2012;28:672–680, with permission from Elsevier.

sectioned at the proximal femur and distal tibia with all soft tissues external to the joint capsule removed. The distal tibia and proximal femur were potted for rigid attachment to the testing frame (MTS 810; Material Testing Systems, Prairie Eden, MN, USA) [21]. The joints were wrapped in towels saturated with physiologic saline to minimize dehydration before testing.

AP Knee Laxity

AP knee laxity values were measured at 30°, 60°, and 90° of knee flexion angle using a custom fixture within the testing frame (Fig. 2A) [18, 19]. With knees locked at each prespecified flexion angle, axial tibial rotation was constrained in the neutral position, whereas tibial translation/rotation remained unconstrained in the coronal plane [21]. The knees were subjected to 12 sinusoidal cycles of ± 40 N AP-directed shear loads at each knee flexion angle and the AP displacements were measured. The first three cycles were used to precondition the knees, whereas the data from the remaining nine cycles were averaged for final measurements. AP knee laxity was defined as the total femoral translation in the sagittal plane, with respect to the tibia, within the AP shear load limits of ± 30 N [19, 21].

Anterior Cruciate Ligament Structural Properties

The structural properties of the repaired ACLs were determined using a tensile test to failure as previously described (Fig. 2B) [21]. After the laxity assessment, all remaining soft tissues were dissected from the joint leaving the femur-repaired ACL-tibia construct intact. All knees were grossly assessed for repair tissue integrity and the presence of remaining suture material within the repaired

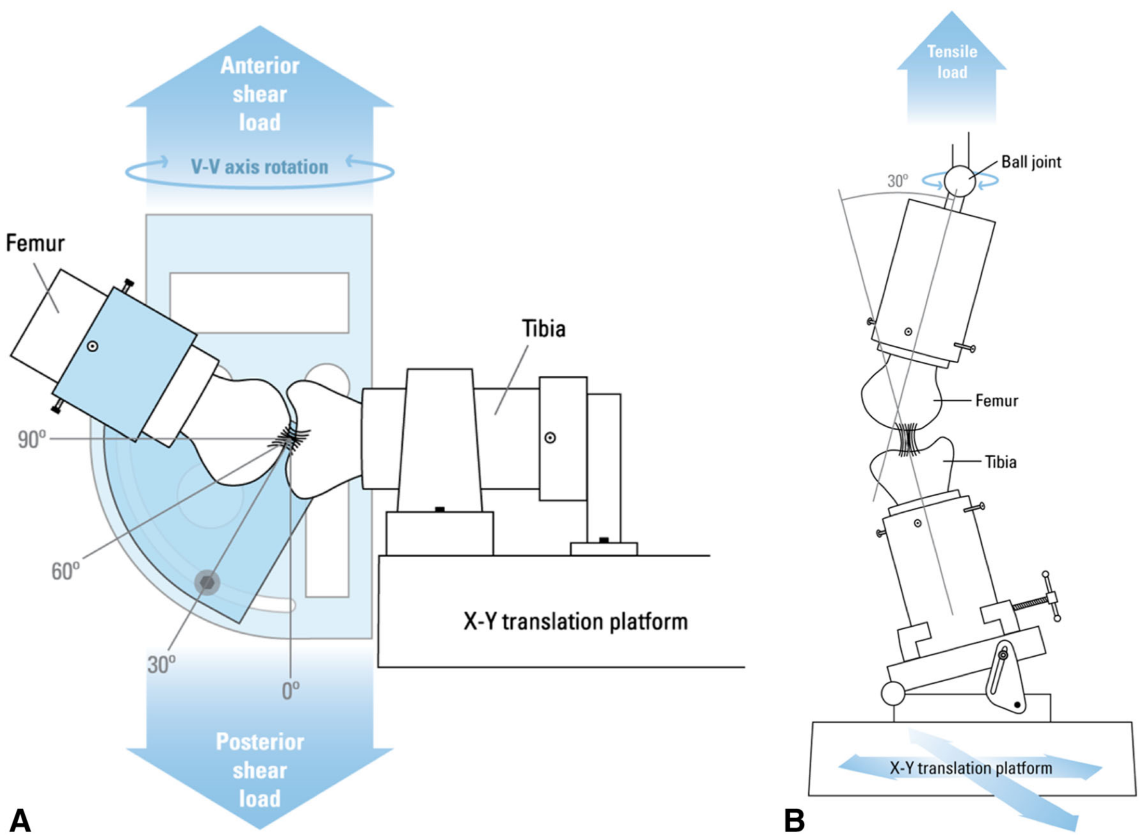

Fig. 2A–B (**A**) AP knee laxity was measured with the a prescribed knee flexion angle, constrained axial tibial rotation in the neutral position, and the unconstrained translations in the coronal plane during the application of the cyclic AP shear loads. Adapted from Murray MM, Palmer M, Abreu E, Spindler KP, Zurakowski D, Fleming BC. Platelet-rich plasma alone is not sufficient to enhance suture repair of the ACL in skeletally immature animals: an in vivo study. *J Orthop Res.* 2009;27:639–645, with permission from John Wiley and Sons. (**B**) ACL structural properties were assessed with the knee flexion angle set at 30° initially. The tibia was mounted to the base of the MTS through a sliding X-Y platform while the femur was unconstrained to rotations so that the specimen could seek its own position to ensure that the load was distributed over the entire ACL cross-section. Adapted from Fleming BC, Spindler KP, Palmer MP, Magarian EM, Murray MM. Collagen-platelet composites improve the biomechanical properties of healing anterior cruciate ligament grafts in a porcine model. *Am J Sports Med*. 2009;37:1554–1563, with permission from Sage.

ACL during the dissection was noted. The femur-ACL-tibia constructs were secured in a custom-designed tensile testing fixture such that the mechanical axis of the ACL was collinear with the load axis of the test frame [21]. The femoral rotation was unconstrained with a ball joint and the tibia was connected to the test frame through a sliding X-Y table to enable the specimen to seek its own physiologic position as the tensile load was applied. Specimens were then loaded in tension to failure at 20 mm/min. This loading rate was adapted from previously established protocols for testing the tensile properties of bone-ligament-bone constructs in porcine and canine models [21, 26, 28, 57]. Linear stiffness, yield, and maximum loads of the repaired ACL were determined from the load displacement data [26, 28]. Energy to failure was also calculated as the area under the load displacement curve for each knee.

Statistical Analysis

All quantified outcomes were grouped and compared based on sex (between subject) and suture type (within subject). Comparisons were conducted using multiple mixed linear models with hindlimb side as the repeating factor. Probability values were adjusted for multiple comparisons using post hoc Bonferroni correction. Results are reported as mean (range) and mean differences (95% confidence intervals); $p \leq 0.05$ was considered statistically significant. Analyses were conducted using SPSS statistical package (Version 22.0; IBM Corp, Armonk, NY, USA).

Animal Welfare

All animals recovered well from surgery and survived the full 15-week followup with no signs of infections or other complications. Weightbearing status was achieved within 72 hours after surgery. All nonabsorbable sutures had ruptured by the 15-week time point with ruptures occurring in the distal half of the intraarticular portion. No residual suture material was found in any of the knees repaired with absorbable sutures as assessed by macroscopic evaluation before tensile testing.

Results

All the ACL ruptures occurred at the ligament midsubstance with no signs of bony avulsions. For knees undergoing bridge-enhanced ACL repair with an absorbable suture stent, females had a significantly lower ACL linear stiffness than their male counterparts after 15 weeks of healing (females, 11 N/mm [range, 8–42]; males, 31 N/mm [range, 12–56]; difference, 20 N/mm [95% confidence interval {CI}, 4–36]; $p = 0.032$). Females also had lower ACL yield (females, 121 N [range, 56–316]; males, 224 N [range, 55–538]; difference, 103 N [95% CI, 6–200]; $p = 0.078$) and maximum loads (females, 128 N [range, 63–332]; males, 241 N [range, 82–538]; difference, 114 N [95% CI, 15–212]; $p = 0.052$) compared with males, which approached statistical significance (Fig. 3). No differences were observed in ACL energy to failure and AP knee laxity between male and female knees treated with bridge-enhanced ACL repair with absorbable suture ($p \geq 0.70$ for all comparisons; Table 1). For knees repaired with nonabsorbable sutures, there were no significant differences between males and females in any of the measured biomechanical outcomes ($p > 0.10$ for all outcomes; Table 1).

Female knees treated with absorbable suture had a significantly lower ACL yield (absorbable, 121 N [range, 56–316]; nonabsorbable, 230 N [range, 149–573]; difference, 109 N [95% CI, 56–162]; $p = 0.002$) and maximum loads (absorbable, 128 N [range, 63–332]; nonabsorbable, 235 N [range, 151–593]; difference, 107 N [95% CI, 51–163]; $p = 0.002$) than female knees repaired with nonabsorbable suture (Fig. 4A). There was a strong trend that female ACLs repaired with absorbable suture had a lower linear stiffness (absorbable, 11 N/mm [range, 8–42]; nonabsorbable, 25 N/mm [range, 8–64]; difference, 14 [95% CI, 2–26] N; $p = 0.054$) and failure energy (absorbable, 733 Nmm^2 [range, 173–1452]; nonabsorbable, 1230 Nmm^2 [range, 742–2021]; difference, 497 Nmm^2 [95% CI, 27–967]; $p = 0.08$) than those treated with nonabsorbable suture (Fig. 4A). Female knees repaired with absorbable suture also had a significantly greater AP knee laxity at 30° of knee flexion (absorbable, 9 mm [range, 5–12]; nonabsorbable, 7 mm [range, 2–13]; difference, 2 mm [95% CI, 1–4]; $p = 0.034$) compared

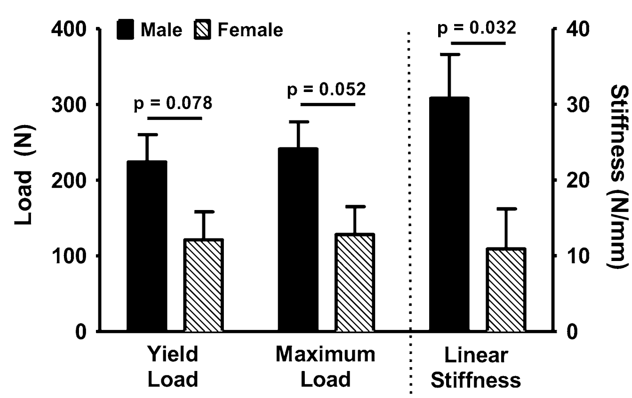

Fig. 3 ACL structural properties for knees treated with bridge-enhanced ACL repair using absorbable suture were compared between sexes after 15 weeks of healing in a porcine model.

Table 1. Quantified ACL structural properties and AP knee laxity in both the male (M) and female (F) pigs treated with absorbable (AB) and nonabsorbable (NA) sutures

Parameter	Mean (Range)				Mean difference (95% CI)			
	Absorbable		Nonabsorbable		p value*			
	Male	Female	Male	Female	AB (M versus F)	NA (M versus F)	M (AB versus NA)	F (AB versus NA)
Yield load (N)	224 (55–538)	121 (56–316)	235 (84–450)	230 (149–573)	103 (6–200) p = 0.078	11 (−45 to 67) p = 1.000	5 (−88 to 97) p = 1.000	109 (56–162) **p = 0.002**
Maximum load (N)	241 (82–538)	128 (63–332)	275 (123–469)	235 (151–593)	114 (15–212) p = 0.052	40 (−54 to 134) p = 0.772	33 (−25 to 92) p = 0.480	107 (51–163) **p = 0.002**
Linear stiffness (N/mm)	31 (12–56)	11 (8–42)	39 (21–75)	25 (8–64)	20 (4–36) **p = 0.032**	14 (−2 to 29) p = 0.166	8 (−5 to 21) p = 0.410	14 (2–26) p = 0.054
Energy to failure (Nmm^2)	950 (272–1901)	733 (173–1452)	1194 (494–2268)	1230 (742–2021)	216 (−358 to 792) p = 0.888	36 (−516 to 588) p = 1.000	244 (−237 to 725) p = 0.588	497 (27–967) p = 0.08
Laxity at 30° (mm)	8 (1–14)	9 (5–12)	9 (5–12)	7 (2–13)	1 (−3 to 4) p = 1.000	2 (0–5) p = 0.158	1 (−1 to 3) p = 0.780	2 (1–4) **p = 0.034**
Laxity at 60° (mm)	14 (9–19)	15 (8–20)	12 (11–14)	14 (8–21)	1 (−1 to 4) p = 0.700	2 (−1 to 4) p = 0.422	2 (0–4) p = 0.216	1 (−1 to 3) p = 0.416
Laxity at 90° (mm)	10 (7–14)	10 (8–14)	9 (7–11)	10 (7–12)	0 (−2 to 2) p = 1.000	1 (−1 to 3) p = 0.544	1 (−1 to 3) p = 0.454	0 (−2 to 2) p = 1.000

*Significant differences ($p \leq 0.05$) are shown in bold; ACL = anterior cruciate ligament.

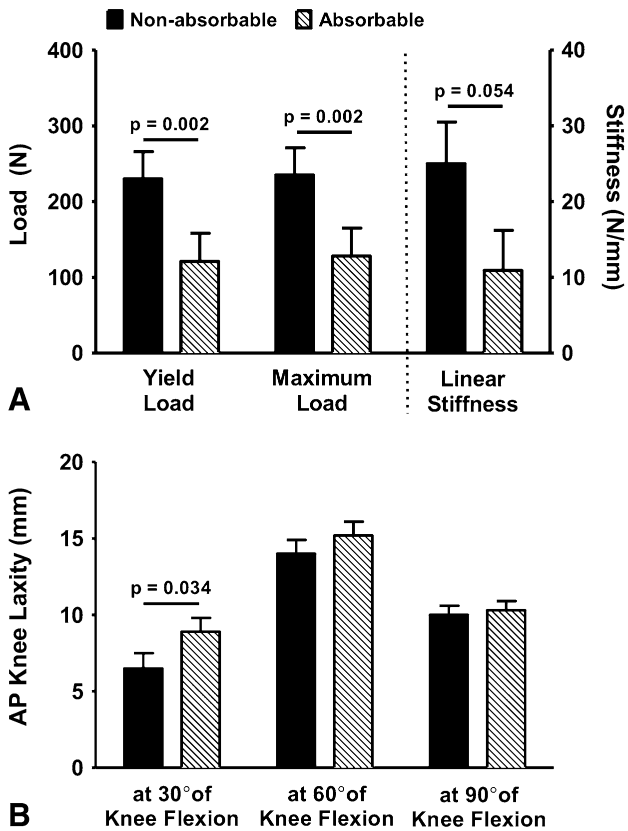

Fig. 4A–B (**A**) Biomechanical outcomes in female pig knees using absorbable suture were compared with those treated with nonabsorbable suture with regard to (A) ACL structural properties and (B) AP knee laxity after 15 weeks of healing.

with female knees treated with nonabsorbable suture (Fig. 4B). No differences were observed in AP knee laxity at 60° and 90° of flexion between females treated with absorbable or nonabsorbable sutures ($p > 0.20$ for all comparisons; Table 1). All measured biomechanical outcomes were similar between male knees treated with either absorbable or nonabsorbable suture stents ($p > 0.20$ for all comparisons; Table 1).

Discussion

Despite reported sex differences in ACL reconstruction outcomes [1, 9, 15, 17, 23, 41, 42, 44], no data exist on potential sexual dimorphism in outcomes of recently developed surgical treatments for ACL injuries such as bridge-enhanced ACL repair. In this study we examined the effect of sex on the biomechanical outcomes of bridge-enhanced ACL repair in a validated sex-specific large animal preclinical model. We also investigated whether the choice of suture type affects the sex differences in biomechanical outcomes after 15 weeks of healing. Female knees showed worse outcomes than males with regard to ACL structural properties when repaired with absorbable suture; however, the use of nonabsorbable suture resulted in a significant improvement in the biomechanical outcomes of the repairs in females, to the point where there was no longer a significant difference in outcomes between the male and female knees after 15 weeks of healing. The choice of suture type did not have any effect on the biomechanical outcomes of bridge-enhanced ACL repair among male pigs.

Our study has several limitations to consider. The pig is a quadruped and postoperative rehabilitation is difficult to control. It therefore does not fully represent the human condition. However, similar anatomical and biomechanical features between pigs and humans have been noted in terms of biomechanics of the knee, hematology, and wound healing [11, 45, 58]. Moreover, the porcine large animal model has been previously shown to be a valid surrogate model for the human knee in the study of sex disparities thought to increase risk for ACL injury [30]. The investigation was conducted on juvenile, skeletally immature pigs. Although they were sexually immature at the time of surgery, they were approximately 7 months old and sexually mature [10] at the time the biomechanical analyses were performed. Thus, the observed sex differences may have been influenced as well by hormonal factors specific to adolescence. These findings underscore the need for further investigation of the mechanisms through which sex affects the biomechanical outcomes of ACL surgeries including hormonal influences in maturing and sexually mature animals. Future studies are essential to determine whether the current findings also translate to older animals (adolescents and adults). The two-factor study design (ie, sex and suture type) with a sample size of eight or nine per group may limit the statistically significant differences in some of the biomechanical outcomes. However a post hoc power analysis, using a fixed-effects F-test, indicated a power of 0.80, 0.83, 0.90, and 0.87 for ACL yield load, maximum load, linear stiffness, and failure energy, respectively, with a nominal α of 0.05 based on observed mean values for all four groups. Assuming a clinically relevant minimal detectable difference of 3 mm in AP knee laxity [38, 49, 54], the study was powered to 0.89, 0.81, and 0.91 at 30°, 60°, and 90°, respectively. To reduce the potential for bias, all investigators were blinded to the sex during surgeries (MMM), harvest (MMM, BCF), and mechanical testing (BCF). Future studies with higher sample sizes and a more specific study design, focused on the sex effect, are required to address these limitations and build on the current findings.

Another shortcoming of this study is that the ACL injuries were produced in the midsubstance of the ligament using a surgical blade, which does not truly replicate a clinical tear. This may have affected the outcomes of ACL repair; however, it is less likely that the observed sex differences in this study would be affected by this limitation because all animals received the same injury. Additionally, animals underwent bilateral surgery, which may have resulted in lower repaired ACL structural properties compared with a unilateral procedure in which the contralateral knee remains intact and the animal can better protect the healing knee [54]. However, because animals in both groups had bilateral procedures, it is less likely that this variation in healing ACL properties significantly affected the observed sex differences in the biomechanical outcomes of ACL repair. Future studies using a unilateral approach are required to further address this issue. Lastly, animals were followed for only 15 weeks after surgery. However, our prior studies in this model suggest that the initial 15 weeks are when the greatest improvements in ligament biomechanical properties occur [12, 16, 27, 35] and this time point has shown to be a reasonable predictor of long-term healing response in the porcine model [20]. Further investigations are required to determine whether the sex differences in the outcomes of bridge-enhanced ACL repair exist in later stages of ACL healing.

Although no frank ligament failures were noted among the pigs after surgical repair in the current study, female pigs repaired with absorbable suture showed a lower mean ACL linear stiffness than males (by 65%) after 15 weeks of healing (Fig. 2). A poorly healed ACL can present with inferior structural properties with no signs of gross failure, which can lead to lowered functional outcomes. This is in consistent with prior reports of higher rates of graft failure [41] and worse patient-reported outcomes [1, 17, 23, 42] in women compared with men after ACL reconstruction. In a recent study of 375 patients, Teitsma and colleagues [53] have shown time-dependent differences in clinical outcomes between males and females for up to 12 months after ACL surgery. Significantly worse outcomes were reported in females when measured using the Knee Injury and Osteoarthritis Outcome Score, Lysholm score, and Tegner score at several intervals within the first 9 months after ACL reconstruction, whereas both sexes showed comparable outcomes at 12 months [53]. These findings along with the observed sex differences in the current work suggest that there are sex differences in ACL (or graft) healing rates with slower healing in females. Interestingly, in the current study, the use of nonabsorbable suture stents was able to diminish these sex differences.

The use of a nonabsorbable suture stent (as opposed to a absorbable suture stent) significantly improved the structural properties of the healing ACL in females with a 56% increase in ACL linear stiffness and 2 mm decrease in AP knee laxity. The fact that all sutures were already disrupted at 15 weeks after surgery makes it less likely that the reported differences are the result of retained suture material. The suture stent used in the bridge-enhanced ACL repair procedure provides initial biomechanical stability and mechanical protection, in particular in early phases of ACL healing and remodeling [55]. Although both the absorbable and nonabsorbable sutures used in this study have similar structural properties at time zero [39], their stress shielding and mechanical protection for repaired ACL may vary as a result of the absorption rate or time until suture failure. Ethibond is a nonabsorbable, braided poly-(ethylene, terephthalate) suture, which does not lose strength as long as it remains intact. In contrast, Vicryl® is an absorbable, polyglactin suture that loses approximately 25% of its strength each week after implantation and completely dissolves in almost 63 days [47, 51]. This may result in exposure of the repaired tissue to higher loads at earlier stages of healing than the nonabsorbable Ethibond suture. It is noteworthy to mention that excessive stress shielding of a healing ligament could also be detrimental and lead to lower outcomes [4]. Furthermore, suture absorption results in release of breakdown products such as glycolic acid (from polyglycolic acid) or lactic acid (from polylactic acid), which reduce tissue pH and inhibit cell growth [2, 3, 6, 7], thus potentially affecting tissue healing. All of these may in turn preclude the repaired ACL to heal properly.

The findings support our hypothesis that sex significantly affects the biomechanical outcomes of bridge-enhanced ACL repair. Inferior mechanical properties were found for females after 15 weeks of repair using absorbable sutures. Surprisingly, the use of nonabsorbable sutures significantly improved outcomes in female knees. Although more research is needed, these results highlight the potential need to further define sex-specific healing patterns to aid in the development of sex-specific surgical and rehabilitative interventions to match the sex-specific healing requirements.

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