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Predictors of Healing Ligament Size and MR Signal Intensity at 6 months after Bridge-Enhanced ACL Repair

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Abstract

Background: Primary repair of the ACL augmented with a tissue engineered scaffold to facilitate ligament healing is a technique under development for patients with ACL injuries. The size (the amount of tissue) and signal intensity (the quality of tissue) of the healing ligament as visualized on MRI have been shown to be related to its strength in large animal models.

Hypothesis: It was hypothesized that both modifiable and non-modifiable risk factors could influence the size and signal intensity of the repaired ligament in patients at six months after surgery.

Study Design: Case Series.

Methods: Sixty-two patients (mean age=19.4 years; range 14 to 35 years) underwent MR imaging of the knee six months after ACL repair augmented with an extracellular matrix scaffold. The signal intensity (normalized to cortical bone) and average cross-sectional area of the healing ligament was measured from the MR image stack obtained using a gradient echo sequence. Associations between these two measures and subject characteristics, which included demographic, clinical and anatomic features, were determined using multivariable regression analysis.

Results: A higher cross-sectional area of the repaired ligament at six months was associated with male sex, older age and the performance of a larger notchplasty ($p < 0.05$ for all associations). A lower signal intensity at six months, indicating greater similarity to normal ligament, was associated with a lower tibial slope and greater side-to-side difference in quadriceps strength three

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months post-surgery. Other factors, including preoperative BMI, mechanism of injury, tibial stump length, and Marx activity score, were not significantly associated with either MR parameter at 6-months.

Conclusions: Modifiable factors, including surgical notchplasty and slower recovery of quadriceps strength at 3 months, were associated with a larger cross-sectional area and improved signal intensity of the healing ACL after bridge-enhanced ACL repair in this preliminary study. Further studies to determine the optimal size of the notchplasty and the most effective post-operative rehabilitation strategy after ACL repair augmented by a scaffold are justified.

Keywords

ACL; repair; MRI; biomechanics; outcome; research

INTRODUCTION

Primary repair of the ACL augmented by a tissue engineered scaffold is a new surgical technique to treat ACL injuries that is currently in development. In its current form, the procedure consists of a specific bioengineered scaffold that is saturated with autologous blood,^{21,22} and then placed in the gap between the torn ligament ends at the time of surgical repair. The blood-laden scaffold provides a space and structure that facilitates healing of the ligament.²⁸ The safety and effectiveness of this procedure have been evaluated in preclinical models,^{16,21,27,32} and in an early clinical cohort study.²² However, patient and surgical factors that may influence the size or quality of the repaired ligament remain unknown.

Magnetic resonance (MR) imaging has been demonstrated to be useful for predicting the size and mechanical properties of the healing ACL in a large animal model.^{5-7,12,34} Cross-sectional area of the ligament, an indicator of the amount of tissue, and signal intensity, an indicator of the quality of the tissue, can be combined into equations to predict the maximum failure load and linear stiffness of the porcine ACL after scaffold-augmented ACL repair.⁵⁻⁷ A higher cross-sectional area of the healing ACL is predictive of a higher maximum load and linear stiffness, and a lower signal intensity (i.e., darker appearance) on a gradient echo sequence is also predictive of a higher ACL maximum load and linear stiffness values. It is likely that both MR parameters would be predictive of a higher maximum load and/or stiffness of the healed ligament in human patients. Furthermore, these MR parameters have been shown to be related to histological features indicative a maturing ligament in animal models of scaffold augmented ACL repair and ACL reconstruction.^{7,34}

In this study, 6-month post-operative MR images of patients who had undergone scaffold-enhanced ACL repair were analyzed to evaluate anatomical and surgical factors that could influence MR parameters known to reflect healing.^{7,34} It was hypothesized that there would be subject, surgical and post-operative rehabilitation characteristics associated with the size and signal intensity of the healing ACL. The pre-operative characteristics included sex, age, BMI, mechanism of injury, Marx activity score, femoral stump length, tibial stump length, and posterior tibial slope. Notchplasty size was considered as an intra-operative characteristic. The post-operative characteristics included the side-to-side difference in

quadriceps strength at three months, which was selected as an indicator for rehabilitation progression.

METHODS

Patients

IRB (Boston Children's Hospital, P00021470) and FDA approval (IDE G150268) were obtained prior to the start of the study, and the study was registered on clinicaltrials.gov (NCT02664545). All patients granted their informed consent. All patients presenting to the clinics of the participating surgeons were screened and, if they met enrollment criteria, were offered participation in the study. Sixty-five patients, ages 14 to 35, who presented with a complete ACL tear, who were less than 45 days from injury, who had closed physes and who had at least 50% of the length of the ACL attached to the tibia (as determined from a pre-operative MR image) underwent a scaffold-augmented ACL repair (Bridge-Enhanced® ACL Repair or BEAR®) procedure as part of the BEAR II trial (IDE G150268, IRB#P00021470, NCT02664545). Patients were excluded from enrollment if they had a history of prior knee surgery, history of prior infection in the knee, or had risk factors that might adversely affect ligament healing (nicotine/tobacco use, corticosteroids in the past six months, chemotherapy, diabetes, inflammatory arthritis). Patients were also excluded if they had a displaced bucket handle tear of the medial meniscus requiring repair; however, all other meniscal injuries were included. Patients were also excluded if they had a full thickness chondral injury, a Grade III MCL injury, a concurrent complete patellar dislocation, or an operative posterolateral corner injury. Three patients were excluded for the current report due to loss to follow-up, or artifact or blurry images in the MRI, leaving 62 for analysis. Patient recruitment was completed over an 11-month period.

Extracellular Matrix Scaffold

The extracellular matrix scaffold (BEAR® scaffold, Boston Children's Hospital, Boston MA) was manufactured from bovine tissue. The tissue was processed into a slurry of extracellular matrix proteins, with collagen as the most abundant protein in the slurry. The collagen concentration of the slurry was adjusted to a minimum of 10 mg/ml. Lyophilization of the slurry was used to produce a scaffold with an outer diameter of 22 mm and length of 30 mm. The scaffolds were packaged, terminally sterilized and stored at room temperature until use.

Surgical Procedure (Fig. 1; Supplemental Fig. S1)

After the induction of general anesthesia, an examination was performed to verify the positive pivot shift on the injured side and to record the Lachman test, range of motion and pivot shift exam results on both knees. A tourniquet was then applied to the surgical limb. A knee arthroscopy was performed, and any meniscal injuries were treated if present. A tibial aimer (ACUFEX Director Drill Guide; Smith and Nephew, Andover, MA) was used to place a 2.4mm guide pin through the tibia and the tibial footprint of the ACL. The pin was over-drilled with a 4.5 mm reamer (Endoscopic Drill; Smith & Nephew, Andover, MA). A notchplasty was performed using a combination of shaver and curette to facilitate visualization of the femoral footprint. A guide pin was then placed in the femoral ACL

footprint, drilled through the femur and then over-drilled with the 4.5 mm reamer. A 4 cm arthrotomy was made at the medial border of the patellar tendon and a whip stitch of #2 absorbable braided suture (Vicryl; Ethicon, Cincinnati, OH) was placed into the tibial stump of the torn ACL. Two #2 non-absorbable braided sutures (Ethibond; Ethicon, Cincinnati OH) were looped through the two center holes of a cortical button (Endobutton; Smith & Nephew, Andover, MA). The free ends of a #2 absorbable braided suture from the tibial stump were passed through the cortical button, which was then passed through the femoral tunnel and engaged on the lateral femoral cortex. Both looped sutures of #2 non-absorbable braided (four matched ends) were passed through the scaffold, and 10 cc of autologous blood obtained from the antecubital vein was added to the scaffold. The scaffold was then passed up along the sutures into the femoral notch and the non-absorbable braided sutures were passed through the tibial tunnel and tied over a second cortical button on the anterior tibial cortex with the knee in full extension. The remaining pair of suture ends coming through the femur were tied over the femoral cortical button to bring the ACL stump into the scaffold using an arthroscopic surgeon's knot and knot pusher. The arthrotomy was closed in layers and the tourniquet deflated. Sterile dressings, followed by a cold therapy unit (Polar Care, Breg, Carlsbad, CA) and locking hinge knee brace (T-scope, Breg, Carlsbad, CA) were applied. No surgical drain was used.

MR Imaging

MR images were acquired pre-operatively and from all operated knees six months after surgery. Using a 3T scanner (Tim Trio, Siemens, Erlangen Germany) and a 15-channel knee coil, the following sequences were obtained: sagittal and coronal Proton Density Fast Spin Echo (PD FSE; TR/TE = 3000/9.7, 16 cm FOV, 3 skip 0.3 slice/gap and 284×384 (phase x frequency) matrix, 4 ETL), and a 3D Constructive Interference in Steady State (CISS; TR/TE = 14/7, FA = 35, 16 cm FOV, $100 \times 384 \times 284$ (slice x frequency x phase)). Images of the surgical and contralateral knees from the CISS sequence were used to measure notchplasty in 56 of 62 subjects (Table 1; Supplemental Figure S2). One subject had no contralateral image obtained and five had contralateral images obtained but not used because the contralateral knee had undergone ACL reconstruction (n=4) or the image was too noisy (n=1). It was assumed that the contralateral notch width represented the pre-operative notch width of the surgical knee.

Candidate Independent Variables (Predictor Variables)

Pre-operatively, the patients' sex, age, BMI and mechanism of injury were recorded. All patients completed questionnaires to determine the International Knee Documentation Committee (IKDC) Subjective Score (<https://www.sportsmed.org/AOSSMIMIS/members/downloads/research/IKDCEnglishUS.pdf>) and Marx Activity Score (<https://www.aaos.org/uploadedFiles/PreProduction/Quality/Measures/pdf-MARX%20SCALE-%20english.pdf>). The pre-operative MR images were used to measure the femoral stump length, tibial stump length, and posterior tibial slope (Table 1; Supplemental Fig. S2).

Three months post-operatively, the quadriceps and hamstring strengths for both the surgical and contralateral control legs were measured by a physical therapist using a hand-held dynamometer (Microfet 2; Hoggan Scientific LLC, Salt Lake City, UT). The quadriceps

strength was measured with the subject seated and the knee supported at 90 degrees of flexion. The dynamometer was placed at the distal tibia and the patient was instructed to extend the knee with maximum effort. The hamstring strength was measured with the subject prone and the knee in 90° of flexion. The dynamometer was placed at the ankle and the patient was instructed to pull the foot toward the hip with maximum effort. Muscle strength values were presented as the percent of the contralateral uninjured control leg.

MRI Measurements (Dependent Variables)

The measurements of cross-sectional area and signal intensity were obtained from the 3D CISS (Constructive Interference in Steady State) sequence (Table 1) obtained at six months after bridge-enhanced ACL repair (Supplemental Fig. S2). The average cross-sectional area of the ligament was calculated by manually segmenting the ACL in 3D and dividing the volume by the ACL length measured from the 3D model.⁴ The median ACL signal intensity was calculated from the segmented ACL mask and then normalized to the subject-specific signal intensity of the posterior cortex of the femoral shaft to minimize interscan variability.⁴ The intraclass correlation coefficients (ICCs) between two independent observers for the normalized signal intensity and average cross-sectional area measurements were .909 and .959 respectively.

Statistical Analysis

Subject characteristics and MRI measurements were summarized with descriptive statistics. In unadjusted analyses, the associations between the independent variables (subject, anatomic and surgical factors) and the dependent variables (ligament cross-sectional area and signal intensity) were evaluated with two-sample t-tests and simple linear regression. Factors with p-values <0.10 in unadjusted analysis were considered for inclusion in multivariable linear regression models for the adjusted analysis. Two-sided p-values are reported and considered significant when $p < 0.05$ (5% Type I error rate). A retrospective power calculation shows that if the true correlation between cross-sectional area or signal intensity and a predictor is at least ± 0.35 , corresponding to an R^2 of at least 12.3%, our sample size of $N=62$ provides an 80% or larger chance of finding a significant association (80% power). Analyses were conducted using SAS® software, version 9.4.

RESULTS

Patient Findings

Demographic and clinical subject characteristics of the cohort are provided in Table 2. Females in the study were on average younger than males [mean($\pm$ SD) age: 17.6($\pm$ 3.1) vs 21.9($\pm$ 6.1), $p=.001$]. In the examination under anesthesia, 16% of the patients exhibited hyperextension of the injured knee (Table 2). All subjects had a positive pivot shift exam (glide, clunk or gross).

The MRI features from the pre-operative and six months post-operative scans are summarized in Table 3 (Supplemental Fig. S3 & Fig. S4). The amount of notchplasty performed ranged from 0 to 6.1mm.

Univariate Analyses

The associations for each subject characteristic with ligament cross-sectional area and signal intensity of the healing ligament are reported in Table 4, and the anatomic characteristics measured from the MR images and their association with ligament cross-sectional area and signal intensity are presented in Table 5. For subject characteristics, male sex and older age were associated with a larger average cross-sectional area of the healing ACL, while lower quadriceps strength was associated with a lower signal intensity, indicating more similarity to normal ligament. For tear characteristics, longer femoral stump length and greater posterior notchplasty were associated with a larger average cross-sectional area and a lower lateral or medial tibial slope and a larger femoral stump, measured as a percentage of the total ACL length, were associated with a lower signal intensity, indicating more similarity to normal ligament.

Adjusted Analyses

Multivariable regression models for prediction of cross-sectional area of the healing ligament are presented in Table 6. The most promising factors from the unadjusted (univariate) analyses (age, sex, size of the notchplasty and femoral stump length) were used as the starting point. The non-modifiable factor column does not include notchplasty size in the model, as notchplasty is potentially modifiable, where the “All Factors” model includes notchplasty as well. Femoral stump length was excluded from the models because in preliminary modeling its estimated association with cross-sectional area was greatly attenuated and non-significant after adjusting for age and sex. When adjusted for sex, age appears to be less of an influence on healing ligament cross-sectional area, and posterior notchplasty size has a significant association with cross-sectional area that is independent of age and sex (Table 6).

Regression models for prediction of signal intensity of the healing ligament are presented in Table 7. The most promising factors from the unadjusted analyses (lateral and medial tibial slope, femoral stump length and quadriceps strength difference at three months) were used as the starting point. Lateral tibial slope was retained in the models, although replacing this with medial tibial slope led to very similar results. Femoral stump length measured in mm and as a percentage of ACL length also had similar strengths of association with signal intensity. The statistical models were run using femoral stump length percent. The non-modifiable factor column does not include quadriceps strength difference in the model, as that is potentially modifiable, where the “All Factors” model includes the quadriceps strength difference measurement as well. Even when adjusted for lateral tibial slope and femoral stump length percent, the quadriceps strength difference at three months remains significantly associated with the signal intensity of the healing ligament (Table 7).

DISCUSSION

The most important finding of this study is that anatomical and surgical factors were shown to be associated with the mean cross-sectional area and normalized signal intensity of the healing ACL. In this analysis, both modifiable and non-modifiable risk factors were considered. While some of the factors associated with an increased cross-sectional area or

lower signal intensity of the healing ligament were non-modifiable (age, sex) or only modifiable (tibial slope) with an invasive surgical procedure (tibial osteotomy), both notchplasty and early quadriceps strength deficits represent potentially modifiable factors that can increase the cross-sectional area of the healing ligament and reduce signal intensity values (i.e., better tissue quality), respectively. The MR measurements of cross sectional area and signal intensity have been previously shown to reflect the overall integrity of the healing ligament and/or graft^{5,7,34} without the complications of external factors that have previously been shown to significantly influence clinical outcomes (including activity choices^{1,8} and psychological factors¹⁰). Thus, MRI represents an important tool to provide insight into surgical parameters (e.g., notch width) or patient anatomy (e.g., tibial plateau geometry) that may influence the intrinsic mechanical properties of the healing ligament, and may be used to accelerate our understanding of what anatomic features may predict a poorly healing ligament or which surgical modifications may lead to an improved MR appearance at six months after surgery.

Notchplasty has been used historically in the setting of ACL reconstruction to minimize impingement of the graft on the notch, particularly for hamstring quadruple bundle autograft where the graft may be larger than the native ACL or placed such that impingement occurs particularly in full extension.^{14,33} Previous studies have reported concerns that a notchplasty increases post-operative blood loss;^{9,25} however, the differences in post-operative blood loss were minimal (60 cc over 24 hours, with a drop in hematocrit of 2.3%²⁵) and not clinically significant in a healthy, athletic population. These same studies reported no effect of notchplasty on range of motion of the knee at one month after surgery,⁹ and no effect on patient reported outcomes (IKDC, Lysholm) or anteroposterior laxity (KT testing) one year post ACL reconstruction surgery.²⁵ In this current study, the notchplasty was performed to facilitate visualization of the femoral stump from the lateral portal. This allowed for more accurate placement of the femoral tunnel and adequate visualization for placement of the whip stitch suture in the ACL stump and placement of the scaffold. The degree of notchplasty varied from patient to patient (ranging from 0 to 6.1 mm) based on their anatomy, surgeon preference and the placement of the viewing portal. The MR measurements of the actual amount of notchplasty performed revealed that for every 1 mm of notchplasty performed, the cross-sectional area of the ACL increased by 2.4mm² (approximately 4.1%). As a larger cross-sectional area is also associated with a higher maximum load of a structure, surgeons may wish to consider performing a notchplasty at the time of bridge-enhanced ACL repair.

A larger quadriceps strength deficit at 3 months was associated with a lower signal intensity of the healing ligament at 6 months. Normal ligaments have a very low signal intensity, while more disorganized scar tissue typically has a higher signal intensity.⁷ Thus, patients who had a more complete recovery of quadriceps strength at 3 months after surgery had a ligament with a signal intensity that was more like scar tissue, whereas those who had less recovery of the quadriceps strength on the surgical knee had a signal intensity that was similar to that of the normal ACL. In the BEAR II trial, all subjects followed a physical therapy protocol where range of motion was restricted from 0 to 50 degrees for two weeks, however subjects were allowed ambulation with the brace unlocked. One hypothesis as to why a more incomplete quadriceps recovery at 3 months was potentially beneficial is that

patients who protected the knee in the early healing stages, either by voluntarily limiting activity or by utilizing crutches for a longer period, may have had a larger post-operative deficit in quadriceps strength. This finding may suggest that less quadriceps activity may be helpful during the early period of ligament repair. Further studies to evaluate the effect of various rehabilitation protocols on ACL healing after bridge-enhanced ACL repair are needed.

Interestingly, there were several factors we hypothesized would have a significant association with either cross-sectional area or signal intensity of the healing ligament but were not found to be associated with either parameter. For example, tibial stump length has been hypothesized to be predictive of a ligament tear pattern associated with “repairability” and a greater propensity for successful healing;²⁰ however, in this study, tibial stump length was not found to be predictive of either healing ligament size or tissue quality.

Signal intensity measures, which reflect the “maturation” of graft healing, have been used to evaluate outcomes and the factors that may influence outcomes following ACL reconstruction.^{17–19,23,24,29–31} In a cohort of ACL reconstructed patients, Li et al showed significant correlations between signal intensity and physical activity, and between signal intensity and time from surgery, both of which were sex dependent.¹⁸ Rose et compared two types of allografts for ACL reconstruction using signal intensity. They determined that “graft maturity” was dependent on the position of the tibial tunnel and the sagittal plane orientation of the graft, though there were no differences between the two graft types (hamstring tendon vs tibialis anterior).²⁹ Signal intensity measures have also been used to compare graft types,^{19,31} tunnel placement,^{17,30} and biologic augmentation.^{23,24} It is difficult to directly compare signal intensity values across studies as the signal intensity magnitude is dependent of the hardware, sequence, sequence parameters and the normalization process selected,⁶ which vary across studies. This is a limitation of using signal intensity as an outcome measure, particularly for multicenter studies. Work is currently under way to implement and optimize relaxometry methods (e.g., T_2^* relaxation time),^{2,3,6,7} which are theoretically less dependent on hardware and post-processing and would provide consistency across platforms, institutions and trials.⁶ Nonetheless, normalized signal intensity measures obtained using the same hardware and sequence within a study provides insight into the integrity of the healing ligament or graft.

There are several other limitations to consider. The follow-up period for these subjects was only six months; whether the findings of increased cross-sectional area and decreased signal intensity are predictive of ACL function or other clinical outcomes at longer time points requires further study. We have previously shown that both of these MR parameters of a healing graft are associated with clinical, functional, and patient-oriented outcome measures 3 and 5 years after ACL reconstruction.⁴ In addition, the current study only evaluated potential factors that we selected for assessment at 6-month follow-up. It is possible that we missed other important risk factors. Additional studies to verify the identified risk factors in a randomized control trial of notchplasty vs no notchplasty or conservative vs more aggressive rehabilitation strategies following enhanced ACL repair are needed to completely answer these questions.

In conclusion, multiple factors (age, sex, performance of a notchplasty) influenced the cross-sectional area of a healing ligament. Other factors (tibial slope, quadriceps strength deficit) influenced the quality of the healing ACL tissue as measured by the MR signal intensity. Further work to determine the optimal size of notchplasty to perform or the best approach for rehabilitation after ligament repair are needed to potentially improve the overall results of bridge-enhanced ACL repair.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1:

Stepwise demonstration of the “Bridge-Enhanced ACL repair” technique using the extracellular matrix scaffold. In this technique, the torn ACL tissue is preserved (A). A whip stitch of #2 Vicryl (purple suture) is placed into the tibial stump of the ACL. Small tunnels (4 mm) are drilled in the femur and tibia and an Endobutton with two #2 Ethibond sutures (green sutures) and the #2 Vicryl ACL sutures attached to it is passed through the femoral tunnel and engaged on the proximal femoral cortex. The Ethibond sutures are threaded through the scaffold, tibial tunnel and secured in place with an extracortical button. The scaffold is then saturated with 5 mL of the patient’s blood (B), and the tibial stump pulled up into the saturated scaffold (C). The ends of the torn ACL then grow into the scaffold and the ligament reunites (D). Used with permission from Murray et al, OJSM 2016.²²

Table 1:

MR sequences and technique used to measure each imaging variable (Supplemental Fig. S2)

Variable	Sequences	How measured
Femoral Stump Length	Pre-operative Sagittal Proton Density (PD) Fast Spin Echo (FSE). The location of the tear was also confirmed in T2 Fat Saturate (FS) sequence.	Linear distance from the center of the femoral attachment site to the most distal fibers of the femoral remnant. ¹¹ Stump length was also expressed as a percentage of the total ACL length.
Tibial Stump Length	Pre-operative Sagittal Proton Density (PD) Fast Spin Echo (FSE). The location of the tear was also confirmed in T2 Fat Saturate (FS) sequence.	Linear distance from the center of the tibial attachment site to the most superior fibers of the tibial remnant. ¹¹ Stump length was also expressed as a percentage of the total ACL length.
Lateral Tibial Slope	6 Months Post-operative Sagittal Proton Density (PD) Fast Spin Echo (FSE)	The angle between a line that joined the peak points on the anterior and posterior rims of the plateau in a sagittal slice at the center of lateral plateau and a line perpendicular to longitudinal axis of the tibia. ^{13,15}
Medial Tibial Slope	6 Months Post-operative Sagittal Proton Density (PD) Fast Spin Echo (FSE)	The angle between a line that joined the peak points on the anterior and posterior rims of the plateau in a sagittal slice at the center of medial plateau and a line perpendicular to longitudinal axis of the tibia. ^{13,15}
Medial Tibial Depth	6 Months Post-operative Sagittal Proton Density (PD) Fast Spin Echo (FSE)	The perpendicular distance between a line connecting the anterior and posterior rims of the medial tibial plateau and the deepest point of the medial plateau in the same slice that the medial slope was measured. ¹³
Notchplasty	6 Months Post-operative Coronal Proton Density (PD) Fast Spin Echo (FSE)	Notch width was measured with knee at full extension, as positioned for MR imaging, parallel to a line along the most inferior aspects of the femoral condyles in a coronal slice corresponding to the back of the notch. Notch width was measured at multiple locations from middle to the bottom of the notch and the maximum value was used as notch width. Notchplasty was defined as the difference between the notch width in the surgical knee and contralateral ACL-intact knee. ²⁶
Cross Sectional Area	6 Months Post-operative 3D CISS	The ACL was manually segmented in 3D. Average cross-sectional area was calculated by dividing the volume by its length measured from the 3D model. ⁴
Signal Intensity	6 Months Post-operative 3D CISS	Median ACL signal intensity was calculated from the segmented ACL mask and then normalized to the subject-specific signal intensity of the posterior cortex of the femoral shaft to minimize interscan variability. ⁴

Table 2.

Demographic and clinical subject characteristics. N=62 except as indicated below*.

Subject Characteristic	no. (%), or mean ($\pm$ SD)
Sex	
Male	26 (42%)
Female	36 (58%)
Age at Surgery, years	19.4 ($\pm$ 5.1)
BMI at Study Entry, kg/m ²	24.7 ($\pm$ 3.8)
Injury by Contact	17 (27%)
Days Injury to Surgery	35 ($\pm$ 8)
Hyperextension Under Anesthesia	10 (16%)
IKDC pre-operative score	50 ($\pm$ 17)
Marx pre-operative score	14.1 ($\pm$ 3.2)
Hamstring Strength at 3 mos, % contralateral	91.9 ($\pm$ 15.7)
Quadriceps Strength at 3 mos, % contralateral	91.7 ($\pm$ 13.5)

* N=62 except IKDC and Marx (N=61).

Table 3.Mean MRI measurements. N=62 except notchplasty (N=56)^{*}

Measurement	Mean ($\pm$ SD)
<i>Predictor Variables</i>	
Femoral Stump Length, mm	16.6 ($\pm$ 4.1)
Tibial Stump Length, mm	22.1 ($\pm$ 5.8)
Femoral Stump Length ^{**} , %	40.6 ($\pm$ 8.8)
Tibial Stump Length ^{**} , %	54.5 ($\pm$ 12.6)
Lateral Tibial Slope, °	6.53 ($\pm$ 3.06)
Medial Tibial Slope, °	5.34 ($\pm$ 2.67)
Medial Tibial Depth, mm	1.68 ($\pm$ 0.62)
Posterior Notchplasty, mm	1.62 ($\pm$ 1.77)
<i>Dependent Variables</i>	
Cross-Sectional Area, mm ²	56.2 ($\pm$ 11.7)
Signal Intensity ^{***}	1364.5 ($\pm$ 229.3)

^{*} Six contralateral MR images were not used. See Methods.

^{**} Femoral and tibial stump percentages are normalized to the ACL length.

^{***} Signal Intensity $\times$ 1000 (e.g., the mean is actually 1.3645)

Table 4.

Unadjusted association between each of cross-sectional area and signal intensity and subject characteristics. β is regression slope, representing change in the outcome per unit change in the characteristic.

Subject Characteristic	N	R ² (%)	Cross-Sectional Area			MRI Outcome		
			Mean ($\pm$ SD), or			Signal Intensity*		
			β	(95% CI)	p-value	R ² (%)	β	(95% CI) p-value
All	62		56.2	($\pm$ 11.7)			1364.5	($\pm$ 229.3)
Sex		13.1			0.004	3.8		
Male	26		61.1	($\pm$ 12.0)			1312.3	($\pm$ 250.6)
Female	36		52.6	($\pm$ 10.3)			1402.2	($\pm$ 208.0)
Age, years	62	7.3	0.63	(0.05, 1.20)	0.03	2.8	-7.5	(-19.1, 4.0)
BMI, kg/m ²	62	2.7	0.50	(-0.28, 1.28)	0.20	1.2	6.5	(-8.8, 21.9)
Injury by Contact		1.1			0.41	0.6		
Yes	17		58.2	($\pm$ 11.0)			1392.4	($\pm$ 258.0)
No	45		55.4	($\pm$ 12.0)			1354.0	($\pm$ 219.7)
Injury to Surgery, days	62	0.7	0.13	(-0.25, 0.51)	0.51	0.1	-0.8	(-8.3, 6.7)
Hyperextension Under Anesthesia		<0.1			0.92	0.6		
Yes	10		55.8	($\pm$ 12.6)			1404.0	($\pm$ 115.9)
No	52		56.2	($\pm$ 11.7)			1356.9	($\pm$ 245.2)
IKDC Score at study entry	61	0.5	0.05	(-0.13, 0.23)	0.58	1.1	1.4	(-2.1, 5.0)
Marx Score at study entry	61	<0.1	-0.04	(-0.97, 0.90)	0.94	<0.1	-1.4	(-20.1, 17.3)
Hamstring Strength at 3 mos, %	62	<0.1	-0.02	(-0.21, 0.18)	0.87	0.2	0.6	(-3.1, 4.4)
Quadriceps Strength at 3 mos, %	62	0.5	-0.06	(-0.28, 0.16)	0.59	18.9	7.4	(3.4, 11.3)

*Signal Intensity $\times$ 1000. Regression coefficients are 1000 $\times$ change in Signal Intensity per unit change in subject characteristic.

Table 5.

Unadjusted association between each of cross-sectional area and signal intensity and other MRI measurements. β is regression slope, representing change in the outcome per unit change in the measurement. N=62 except posterior notchplasty (N=56).

Measurement	MRI Outcome							
	Cross-Sectional Area				Signal Intensity*			
	R ² (%)	β	(95% CI)	p-value	R ² (%)	β	(95% CI)	p-value
Femoral stump, mm	6.9	0.74	(0.04, 1.45)	0.04	4.7	-11.9	(-25.9, 2.0)	0.09
Tibial stump, mm	0.1	0.07	(-0.46, 0.59)	0.80	<0.1	-0.2	(-10.4, 10.1)	0.98
Femoral stump, %	1.3	15.4	(-18.9, 49.6)	0.37	9.6	-810.2	(-1451.6, -168.7)	0.01
Tibial stump, %	1.0	-9.1	(-33.0, 14.8)	0.45	0.5	133.9	(-335.0, 602.8)	0.57
Lateral Tibial Slope, °	2.7	0.6	(-0.4, 1.6)	0.21	11.3	25.2	(7.0, 43.4)	0.008
Medial Tibial Slope, °	5.0	1.0	(-0.1, 2.1)	0.08	11.8	29.5	(8.7, 50.3)	0.006
Medial Tibial Depth, mm	0.3	1.0	(-3.8, 5.9)	0.68	0.4	24.4	(-70.6, 119.3)	0.61
Posterior Notchplasty, mm	11.3	2.3	(0.5, 4.0)	0.01	0.2	-5.6	(-40.9, 29.6)	0.75

* Regression coefficients for Signal Intensity are $1000 \times$ change in Signal Intensity per unit change in subject characteristic.

Table 6.

Adjusted analyses of Cross-Sectional Area. β is regression slope, representing change in the outcome per unit change in the characteristic.

Measurement	Non-Modifiable Factors ($R^2=14.7\%$)			All Factors ($R^2=22.4\%$)		
	β	(95% CI)	p-value	β	(95% CI)	p-value
Age, years	0.33	(-0.29, 0.95)	0.29	0.07	(-0.58, 0.72)	0.84
Female Sex	-7.1	(-13.3, -0.8)	0.03	-7.5	(-14.1, -1.0)	0.02
Posterior Notchplasty, mm				2.3	(0.5, 4.0)	0.01

Table 7.

Adjusted analyses of Signal Intensity. β is regression slope, representing change in the outcome per unit change in the characteristic.

Measurement	Non-Modifiable Factors($R^2=22.9\%$)			All Factors($R^2=32.5\%$)		
	β	(95% CI)	p-value	β	(95% CI)	p-value
Lateral Tibial Slope, °	27.4	(10.2, 44.7)	0.002	23.1	(6.6, 39.6)	0.007
Femoral stump, %	-893	(-1493, -294)	0.004	-675	(-1262, -88)	0.02
Quadriceps Strength at 3 mos, %				5.5	(1.7, 9.3)	0.006