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MRI Volume and Signal Intensity of the ACL Graft Predicts Clinical, Functional and Patient Oriented Outcome Measures Following ACL Reconstruction

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Abstract

Background—Clinical, functional and patient-oriented outcomes are commonly used to evaluate the efficacy of treatments following ACL injury; however, these evaluation techniques do not directly measure the biomechanical changes that occur with healing.

Purpose—To determine if the magnetic resonance (MR) image-derived parameters of graft volume and signal intensity (SI), which have been used to predict the biomechanical (i.e., structural properties) of the graft in animal models, correlate with commonly used clinical (anteroposterior (AP) knee laxity), functional (1-leg hop) and patient-oriented outcome measures (KOOS) in patients 3- and 5-years after ACL reconstruction.

Study Design—Descriptive Laboratory Study

Methods—Using a subset of participants enrolled in an ongoing ACL reconstruction clinical trial, AP knee laxity, 1-legged hop test, and KOOS were assessed at 3- and 5-year follow-up. 3-D T1-weighted MR images were collected at each visit. Both the volume and median SI of the healing graft were determined and used as predictors in a multiple regression linear model to predict the traditional outcome measures.

Results—Graft volume combined with median SI in a multiple linear regression model predicted 1-legged hop test at both the 3-year and 5-year follow-up visits ($R^2=.40$, $p=.008$ and $R^2=.62$, $p=.003$, respectively). Similar results were found with 5-year follow up for the KOOS quality of life ($R^2=.49$, $p=.012$), sport_function ($R^2=.37$, $p=.048$), pain ($R^2=.46$, $p=.017$) and symptoms ($R^2=.45$, $p=.021$) sub-scores, though these variables were not significant at 3 years. The multiple linear

regression model for AP knee laxity at 5-year follow-up approached significance ($R^2=.36$, $p=.088$).

Conclusion—The MR parameters (volume and median SI) used to predict *ex vivo* biomechanical properties of the graft in an animal model have the ability to predict clinical or *in vivo* outcome measures in patients at 3- and 5-year follow-up.

Keywords

MRI; ACL; clinical assessment; patient outcome; biomechanics

Introduction

Current clinical, functional and patient-oriented outcome assessments for evaluating the success of anterior cruciate ligament (ACL) treatments include hop testing, knee arthrometry and patient-oriented outcome questionnaires. These assessment techniques have been useful in many clinical studies as a standardized way to evaluate the success of the treatment.¹¹ However, because these evaluation techniques are an indirect measure of graft health or integrity, they require large numbers of patients to provide sufficient power and to detect differences between treatment groups. The lack of sensitive outcome measures for clinical studies may be one reason why no improvements have been found in many clinical trials comparing outcomes of different ACL reconstruction techniques (e.g., comparisons of graft type,²¹ graft position,¹ rehabilitation,² or graft tension¹¹). Furthermore, most of these knee specific outcome measures may not be sensitive enough to detect biomechanical changes in the graft itself during healing. As a result *ex vivo* animal models are frequently used to determine the biomechanics of a reconstructed graft to directly evaluate graft healing.^{12,23} However, *ex vivo* approaches require destructive testing and are not suitable for longitudinal *in vivo* use. This limitation makes a reliable, quantitative, *in vivo*, method for determining the biomechanical performance of a graft during healing highly desirable in both research and clinical settings.

Magnetic resonance (MR)-derived measures of volume^{13,15} and signal intensity (SI)^{3,34} have been found to be independent predictors of graft or ligament failure properties. More specifically, the linear combination of graft volume and median SI has been found to correlate to the biomechanical properties measured via *ex vivo* mechanical testing and offers a more complete evaluation of ligament or graft integrity than either MR-derived variable alone.^{3,34} While a method that directly relates these MR-derived parameters to the graft biomechanical properties is an important finding, determining the relationship between a graft's MR parameters and a patient's knee specific traditional outcomes will offer a graft specific assessment to complement the existing clinical evaluation tools.

The objective of this study was to determine if the MR parameters (volume and SI), which have been used to predict the biomechanical properties of the graft,^{3,4} will predict clinical (AP knee laxity), functional (1-leg hop for distance) and patient-oriented outcome measures (Knee Osteoarthritis Outcome Scores) at 3- and 5-years after ACL reconstruction.¹¹ We hypothesize that the MR-derived parameters of graft volume and median signal intensity will significantly predict these clinical, functional and patient-oriented outcomes in an ACL

reconstructed cohort. Results from this study will provide a translational link between *ex vivo* animal model data of graft healing and commonly used clinical assessment tools. Furthermore, these data could help in the development of a more objective test to determine the appropriateness of timing for athletes to return to sports.

Methods

Patient population

A subset of participants enrolled in an ongoing Institutional Review Board (IRB) approved study, investigating the effects of initial graft tension on long-term outcome of ACL reconstruction with autograft, was used for this analysis (NCT00434837).¹¹ Patients received either a high-tension or low-tension graft following an isolated unilateral ACL injury as previously described.¹¹ Postoperatively, all patients followed a standardized rehabilitation program designed to get them back to sport within 6 months. The primary study results at 3-year follow-up found no significant differences in the clinical, functional and patient-oriented outcome measures between the high- and low-tension treatment groups.¹¹ Subsequently, all patients with complete traditional outcomes and MR scans were pooled for this analysis. Of the 90 patients enrolled in the original clinical study,¹¹ 64 completed an onsite visit to obtain the clinical and functional outcomes at the three year follow-up. Of those 64, 50 MR images were collected. Of the 50 patients with complete traditional outcomes and MR scans, 29 of those scans were confounded by metal artifact in the immediate area of the graft and were omitted as it was not possible to obtain accurate volume and SI measurements. The study group at 3 years (23 total; 10 men, 13 women) had a mean age of 23 ± 9 years at time of surgery. Seventeen patients received bone–patellar tendon–bone autograft obtained from the central third of the ipsilateral patellar tendon and 6 received a 4-stranded autograft created from the semitendinosus and gracilis tendons. Ten received a low-tension graft and 13 received a high-tension graft. Of the 23 patients with complete traditional outcomes and MR images obtained at 3 years, 17 returned for an onsite follow-up at 5 years. Of these 17, 16 underwent MR imaging and none were excluded due to artifact. At 5 years the study group (16 total; 6 men, 10 women) had a mean age of 24 ± 10 years at time of surgery. Eleven received bone–patellar tendon–bone autografts and 5 received 4-stranded autografts. Seven received a low-tension graft and 9 received a high-tension graft.

Traditional Outcomes

Clinical, functional and patient-oriented outcomes were used to assess overall patient knee function and patient outcome and to establish the relationships with the MR parameters of graft healing.

Clinical Outcome—AP knee laxity values for both knees were measured using an arthrometer (KT-1000; MEDmetric Corp, San Diego, CA) at 3- and 5-year follow-up. Anterior-directed shear loads were applied in succession to find the neutral position of the knee. Three manual maximum tests were then performed and the displacement readings between -90 Newtons of posterior shear load and the manual maximum anterior shear load were averaged. The AP knee laxity score was reported as the difference in displacement

between the injured knee and the uninjured contra-lateral knee (APlaxity difference). One examiner, with more than 6 years of experience, performed all of the arthrometer measurements.

Functional Outcome—At each follow-up visit, patients performed the 1-legged hop test for distance independently 3 times, and the trials were averaged.²⁹ The mean hop distance of the injured knee was normalized to that of the uninjured contralateral knee to determine the patient's hop score (hop%).

Patient-Oriented Outcome—The KOOS³⁰ was implemented to assess patient-oriented outcomes of the cohort at both time points. The KOOS evaluates 5 domains: knee-related quality of life (KOOS-qol), sports and recreation function (KOOS-spt), pain (KOOS-pain), symptoms (KOOS-sym), and activities of daily living (KOOS-adl).³⁰

MRI ligament outcomes

The MR parameters (volume and median SI), which have been used to predict the biomechanical properties of the graft,^{3,4} were used to quantify graft integrity. All MR images were acquired 3- and 5-years post-operatively using a surface knee coil on the same 3T scanner (Siemens TIM Trio, Erlangen, Germany) using standardized protocol and acquisition parameters. A 3-D T1-weighted FLASH sequence (TR_TE_FA, 20_7.6_ 12°; FOV, 160 mm; matrix 512X512, slice thickness_gap, 1.5mm_0; avg 1; bandwidth, 130) was used. Scans with confounding metal artifact due to magnetic susceptibility effects in the immediate proximity to the graft were omitted from analysis. These artifacts were most likely generated from the metallic drill bits used for tunnel placement during the reconstruction procedure. Some patients did receive a metallic fixation screw but in all cases the screw was sufficiently far from the intra-articular space to avoid direct issues with artifact and the ACL. Each ACL graft was then manually segmented from the MR image stacks and 3-D models of the graft were created using commercially available software (Mimics 16.0; Materialize, Ann Arbor, MI).³ Summing the total number of ACL graft voxels provided an estimate of the whole graft volume (6.94 voxels equaled one mm³). The median graft SI (grayscale value) was calculated for each patient and was normalized to the subject-specific SI of femoral cortical bone to minimize inter-scan variability.^{3,31} All graft segmentations, for both 3- and 5-year scans, were done by one examiner with more than 5 years of experience. The images were randomly processed within a six month time period. Prior to beginning the study, the intra-examiner reliability was tested using seven repeated scans of a human cadaveric knee and four repeated scan of a porcine reconstructed knee and a coefficient of variation of less than 5.8% was observed for both volume and signal intensity measures.

Data Analysis

Because median graft SI values were not normally distributed, values were log transformed (Base 2) prior to analysis as previously reported.³ Both volume and median graft SI were included as independent variables in a first order multiple linear regression model to predict the traditional outcome measures (i.e. knee laxity (APlaxity difference)), hop score (hop%), knee-related quality of life (KOOS-qol), sports and recreation function (KOOS-spt), pain

(KOOS-pain), symptoms (KOOS-sym), and activities of daily living (KOOS-adl)). In addition to reporting the individual slope coefficients and the significance of the two predictors (volume and SI), the model R^2 is also presented as a measure of overall model performance.^{9,24} Regression diagnostics based on residual plots were used to evaluate the appropriateness of the linear model.⁹ Randomness of residuals was accepted for all variables except KOOS-adl, which was due to the limited range of patient scores (most patients had perfect KOOS-adl scores). Additionally, multi-collinearity between volume and SI in the multiple regressions was assessed using the variance inflation factor (VIF) at both 3 and 5-year time points. VIF values were 1.01 for 3-year and 1.11 for 5-year time points and were well below the recommended limit of 10, as stated in the literature.^{20,25} A VIF of 1 indicates a stable regression. Statistical analyses were performed using SAS statistical software (SAS Institute, Cary, NC).

Results

Clinical Outcomes

Graft volume combined with median graft SI in a multiple linear regression model did not predict APlaxity difference at 3-year follow-up (Table 1). Likewise, the combination of volume and median SI did not predict APlaxity difference at 5-year follow up; however, it did approach significance ($R^2=0.36$, $p=0.088$) (Figure 1, Table 1).

Functional Outcomes

Volume combined with median graft SI in a multiple linear regression model predicted hop % at 3-year follow-up ($R^2=0.40$, $p=0.008$) (Figure 2a, Table 1). The combination of volume and SI also predicted hop% at 5-year follow up ($R^2=0.62$, $p=0.003$) (Figure 2b, Table 1).

Patient-Oriented Outcomes

At 3-year follow-up, volume combined with median graft SI in a multiple linear regression model did not predict KOOS-qol, KOOS-spt, KOOS-pain, KOOS-sym, KOOS-adl (Table 1). However, at 5-year follow-up, the combination of volume and SI predicted KOOS-qol ($R^2=0.49$, $p=0.012$) (Figure 3), KOOS-spt ($R^2=0.37$, $p=0.048$), KOOS-pain ($R^2=0.46$, $p=0.017$), KOOS-sym ($R^2=0.45$, $p=0.021$) (Table 1). At 5-year follow-up, the linear combination of volume and median SI did not predict KOOS-adl (Table 1).

Discussion

Knee arthrometry, hop testing, and patient-oriented outcome questionnaires have been useful for many clinical studies as a standardized way to evaluate overall patient knee outcome following ACL treatment;¹¹ however, these evaluation techniques are knee specific measures of joint and patient health but may lack the sensitivity to determine the biomechanical properties of the graft. A more specific measure of graft integrity would therefore be a useful complement to the already existing set of treatment evaluation tools. Using patients from an ongoing ACL reconstruction study¹¹ we were able to show that the same MR parameters (volume and median SI) used to directly predict *ex vivo* biomechanical

properties of the graft in an animal model^{3,4} have the ability to predict overall knee health in terms of functional and patient-oriented outcome measures in patients.

In general, for traditional outcomes at 5-year follow-up, larger grafts with lower median SI values were associated with better knee performance and surgical outcome (Figure 4). For the functional outcome at 5-year follow-up, patients with higher hop% (higher percent score reflects better knee function),²⁸ tended to have larger grafts with lower median SI (Figure 2). Similarly, for the KOOS-spt, KOOS-pain, KOOS-qol, and KOOS-sym sub-scores at 5-year follow-up, patients with larger graft volumes and lower SI had higher sub-scores (higher scores indicate better knee function) (Figure 3).⁶ At 5-year follow-up, patients with higher APlaxity difference scores (i.e., more surgical knee laxity than the contra-lateral control),⁵ while not significant tended to have grafts with smaller volume and higher median SI (Figure 1). Previous research has shown larger graft or ligament volume^{3,13,15} and lower graft or ligament SI^{3,34} are correlated to higher strength or biomechanical properties. These results show that MR parameters that relate to graft biomechanical performance are also predictive of overall patient knee health and ACL reconstruction surgical outcomes.

At 3-year follow-up, the MR variables of volume and median SI were unable to predict clinical (APlaxity difference) and patient-oriented outcomes (KOOS sub-scores). These non-significant predictions at the 3-year follow-up paired with lower observed standard deviations in both volume at the 3-year compared to the 5-year follow-up (Volume: 618 vs 711 mm³; SI: 0.39 vs 0.43, respectively) suggest that there may not be enough variability^{7,18} in patient graft volume and SI to predict traditional outcomes at this earlier time point. However, at 3-year follow-up the prediction for hop% was significant. Additionally, we saw an increase in prediction between the 3- and 5-year hop% data as indicated by increasing R² values (3-year R²=0.40, 5-year R² = 0.62). Considering this increase in R² and the significant 5-year prediction of APlaxity difference and the KOOS sub-scores (KOOS-spt, KOOS-pain, KOOS-qol, and KOOS-sym sub scores), these results suggest that patient graft volume and SI are more heterogeneous at the 5-year follow-up time, and may indicate that the graft is still remodeling at 3 years. The linear combination of graft volume and median graft SI were unable to predict the KOOS-adl sub-score at either 3- or 5-year follow-up. These results support previous research showing that the KOOS-adl sub-score has been reported to be the least indicative of patient surgical outcome.^{6,11}

The relative contribution of the independent variables of graft volume and median graft SI were assessed with individual p-values in the linear regression.¹⁹ Median graft SI significantly contributed to the predictions for all 5-year traditional outcomes (all p < 0.048, Table 1), except the APlaxity difference and KOOS-adl. SI was also significant at 3-year follow up for the hop test. Median graft or ligament SI has shown to be a significant predictor of *ex vivo* biomechanical properties in an animal model,^{3,34} further indicating graft integrity as represented by median SI may reflect surgical outcomes. Graft volume was only a significant contributor for the hop test at 5-year follow up and approached significance for the KOOS sport 5-year follow up. Despite being a significant predictor in *ex vivo* models,^{3,13,15} graft volume may not be as strong of a predictor in this study due to variations in patient graft type.

ANOVA's were used to test for differences between patient graft type for both volume and SI. No significant differences were found with graft volume or SI between graft types. Additionally, ANOVA's were used to test for differences between the high tension and low tension group for both volume and SI. No significant differences were found with volume and SI between the tension groups. This finding reflects the lack of differences in the tension groups for the original clinical study.¹¹

SI has been used in prior clinical studies to evaluate ACL graft health and maturation following ACL reconstruction surgery.^{10,16,22,27,32} More specifically, it was found that four years after ACL reconstruction semi-quantitative clinician graded scores based on graft SI appearance were unable to predict knee laxity or the International Knee Documentation Committee clinical outcome score. The lack of correlation found in this prior study could be due to the semi-quantitative nature of the clinician-based grading system,^{17,27,32} which may lack the specificity needed to detect subtle differences in graft integrity. Furthermore, the authors cited a study selection bias³² where patient recruitment was done after ACL reconstruction surgery, which may have limited the patient population to those with positive surgical outcomes, limiting the variability in the treatment outcomes.

This study was limited by the use of the SI variable, which can vary depending on scanner hardware and MRI acquisition parameters.⁸ To address this concern we used the same MR imaging parameters and manufacturer (Seimens, 3T Trio) throughout the study. Furthermore, we normalized the graft SI values to that of cortical bone within each image to minimize concerns of variability between scan sessions.^{3,31} Another limitation was the metal artifact identified in some of the follow-up MR scans. To address this limitation, we omitted scans with confounding metal artifact. However, metal artifact is not uncommon in MR images of patients' knees following ACL reconstruction.^{14,33} The problem could be minimized in part with the use of non-metallic fixation screws and flushing the joint to flush residual debris prior to closure. It was assumed the MR parameters (volume and median SI) used to directly predict *ex vivo* biomechanical properties of the graft in an animal model^{3,4} would directly translate to a human clinical population. However, *ex vivo* failure testing of the graft is not possible in a clinical population. Therefore, this study was built on the research performed in a porcine model.²⁶ For this study, we assumed that graft volume and SI were the only MR variables affecting patient outcome. However, it is possible that MR analyses to directly quantify fiber alignment and orientation could bolster the predictions of patient outcomes. Also, finding that graft volume and SI were predictive of traditional outcomes does not imply causality. It is possible that poor patient surgical outcome caused graft changes that are then detected through MRI rather than graft MR appearance affecting patient traditional outcomes. Further research would be necessary to clarify this point. Finally, at this point it is unknown how time would affect the relationships between the independent variables (volume, SI) and traditional outcomes, as 3 and 5 years following ACL reconstruction may not be the ideal time to evaluate the healing process. Future studies will focus on earlier time points when the graft is expected to be actively remodeling. If the relationship between volume and SI and traditional outcomes are found to hold at earlier time points, it could allow clinicians to determine graft specific health to determine if the graft is healed enough to return to sport.

Despite these limitations, the results from this study provide a valuable translational link between *ex vivo* animal model data and patient data collected in a clinical context. With further development these data could be used as a more objective test to determine the appropriateness of timing for the athletes return to sports.

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Clinical Relevance

Results from this study may enhance clinical evaluation of graft health by relating the MR parameters of volume and median SI to traditional outcome measures and could potentially aid researchers in determining the appropriate timing for athletes to return to sport.

Figure 1.

The patient graft prediction plane for knee APlaxity difference as a function of graft volume and median SI at 5-year follow-up ($R^2 = 0.36$, $p=0.088$). The grafts with the higher volume and lower SI tended to have lower APlaxity difference scores (injured minus contra-lateral).

Figure 2.

The patient prediction planes for hop score as a function of graft volume and median SI at A) 3-year follow-up ($R^2 = 0.40$, $p=0.008$) and B) 5-year follow-up ($R^2 = 0.62$, $p=0.003$). The grafts with the higher volume and lower SI tended to have higher hop scores (% injured vs contra-lateral).

Figure 3.

The patient prediction plane for KOOS-qol sub-score, as a function of graft volume and median SI at 5-year follow-up ($R^2 = 0.49$, $p=0.012$). The grafts with the higher volume and lower SI tended to have higher KOOS-qol sub-scores (100 being perfect knee function). Similar plots were found for the KOOS-spt, KOOS-pain and the KOOS-sym 5-year follow-up prediction models.

Figure 4.
Example A) low and B) high SI for patient grafts on one sagittal slice of the MR image stack.

Table 1

Summary of the patient outcome prediction equations for both the 3- and 5-year follow up as a function of graft volume and SI in terms of median grayscale value (log base 2 transform). Stars indicate significance.

Traditional Outcome	Dependent Variable	Independent Variable	3-year			5-year				
			Coefficient	p-value	Model R ²	Model p-value	Coefficient	p-value	Model R ²	Model p-value
Clinical	AP Laxity difference	Intercept Volume SI	0.821	0.213	0.12	0.294	-4.0	0.304	0.36	0.088
			-0.0012 1.067	0.426			0.0007 2.1	0.099		
Functional	I-Leg Hop	Intercept Volume SI	135.5	0.652	0.40	0.008*	134.5	0.050*	0.62	0.003*
			-0.002 -17.4	0.002*			0.006 -19.1	<0.001*		
Patient-Oriented	KOOS-qol	Intercept Volume SI	110.5	0.580	0.09	0.396	160.4	0.137	0.49	0.012*
			0.005 -17.8	0.245			0.011 -40.4	0.004*		
	KOOS-spt	Intercept Volume SI	126.5	0.592	0.14	0.232	122.2	0.054	0.37	0.048*
			-0.003 -15.9	0.097			0.013 -23.8	0.033*		
	KOOS-pain	Intercept Volume SI	101.1	0.739	0.01	0.842	123.6	0.163	0.46	0.017*
			-0.001 -3.5	0.609			0.004 -15.4	0.006*		
	KOOS-sym	Intercept Volume SI	97.8	0.997	0.03	0.770	136.6	0.211	0.45	0.021*
			0 -5.9	0.479			0.006 -26.1	0.007*		
	KOOS-adi	Intercept Volume SI	101.4	0.823	0.02	0.808	110.3	0.322	0.141	0.372
			0.001 -3.2	0.569			0.004 -9.2	0.213		