

**Initial Graft Tension and ACL Surgery**

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**ClinicalTrials.gov identifier: NCT00434837**

**Updated: 09/10/2019 (after NIH funding received for 15-year follow-up; R01-AR074973)**

## SPECIFIC AIMS

**The primary objective of this prospective, randomized, double-blinded, controlled study is to assess OA progression following ACL reconstruction (ACLR), and to determine how the initial tension applied to the graft at the time of surgery may influence disease progression.** ACLR is commonly performed to restore joint function and to decrease the risk of post-traumatic osteoarthritis (OA) in the ACL-deficient knee. However, clinical studies suggest that the outcome is highly variable, and that OA often progresses despite ACLR. The tension applied to the graft at the time of ACLR fixation (“initial graft tension”) affects knee kinematics and the distribution and magnitude of contact stress, which in turn, is thought to influence articular cartilage damage. The effects of low- and high-initial graft tensions on graft healing and articular cartilage degeneration following ACLR are unknown and are currently under investigation in this study. Over the past funding cycle, ACL-injured subjects (108 patients) and matched controls (60 subjects) were recruited and enrolled. Short-term ( $\leq 84$  months) post-surgical evaluations have been performed. The objective of this update is to prospectively obtain valuable long-term (15 year) follow-ups on this captured patient/control population. We intend to follow these patients a minimum of 15 years. These long-term data will allow us to establish not only the incidence of OA after ACLR following an isolated ACL tear, but whether changing the initial graft tension can decrease this risk.

**This study is designed to compare two common initial graft tension protocols for ACLR that influence joint contact mechanics.** The first treatment group consists of patients whose grafts were tensioned to restore the normal anterior-posterior displacement of the tibia relative to the femur (“AP laxity”) at the time of surgery (i.e. AP laxity equal to that of the contralateral normal knee; the “low-tension” treatment). The second treatment group consists of patients whose grafts were tensioned to over-constrain the joint (i.e. AP laxity 2mm less than that of the contralateral knee; the “high-tension” treatment). In the last funding cycle, we have shown that the initial joint contact conditions between these two groups are significantly different in cadavers<sup>39</sup>, and that the associated laxity differences in patients are different *in vivo*. The two treatment groups are being compared to a third matched control group. Fifty-four subjects were enrolled into each group. With this update, they will be followed 180 months after surgery. We are planning to follow these patients for a minimum of 15 years. Significant changes in cartilage integrity are expected within this long-term time frame in this patient population<sup>26,35,50</sup>.

**Radiographic assessment of joint space narrowing is the only validated indicator of structural change used to evaluate OA progression in clinical studies, and it will continue to be the primary outcome measure of cartilage damage<sup>67</sup>.** MR images of the articular cartilage and associated knee joint structures will provide secondary structural biomarkers for the early detection of OA<sup>31</sup>. MRI is being used to directly measure changes in cartilage thickness in the load bearing regions<sup>11,12</sup>, while joint integrity will be assessed using the Whole Organ Magnetic Imaging Score (WORM score)<sup>56</sup>. Using these imaging-based outcome measures, we will test the primary hypothesis:

- *Tibiofemoral joint space width (via radiography) and cartilage thickness (via MRI) in the reconstructed knees of the “high-tension” treatment group will be equal to that of the control group, while the joint space width and cartilage thickness in the “low-tension” treatment group will be significantly less than that of the control group 15 years after surgical reconstruction of the anterior cruciate ligament.*

**Surgical outcome will also be assessed via: 1) patient-oriented outcome scores<sup>59,76</sup>, 2) AP laxity (an indicator of graft integrity<sup>6,44</sup> and knee kinematics<sup>23</sup>), 3) isokinetic strength (an indicator of dynamic knee function<sup>16</sup>), and 4) clinical outcome scores<sup>48,78</sup>.** Analysis of primary and secondary outcomes will enable us to determine the long-term effects of initial graft tension on cartilage status and knee joint function, and to evaluate the relationships between longitudinal changes that occur in tibiofemoral (TF) joint space (x-ray), cartilage thickness (MRI), general MRI scores (WORM score), knee laxity (KT-1000), strength (Biodex strength test, 1 legged hop test) and patient-oriented outcome scores (SF-36, Knee Osteoarthritis Outcome Score). In the past funding cycle, data were obtained from ACL-reconstructed patients pre-operatively, immediately post-operatively, and after 6, 12, 36, and 84 months of healing. From the control group data were obtained at the time of recruitment and at 12, 36, and 84 months. In this update, additional evaluations will be performed 144 and 180 months in the ACLR and control subjects, a time frame in which cartilage damage should become prevalent in the ACLR patient population. We intend to follow these patients for a minimum of 15 years.

## RESEARCH DESIGN AND METHODS

### 1. Overview of Research Design

**This investigation is designed as a prospective, randomized, double-blinded clinical study evaluating the effects of two different initial tension conditions applied to an ACL graft at the time of fixation on healing using biomechanical, clinical, and patient-oriented outcome measures.** The primary outcome is evaluating the progression of OA via objective radiographic measurements of joint space narrowing. We are also assessing temporal changes in cartilage thickness, and the integrity of various knee joint structures using MRI. We will test the hypothesis that tibiofemoral (TF) joint space width (via radiography) and cartilage thickness (via MRI) in the reconstructed knees of the “high-tension” treatment group will be equal to that of the control group, while the joint space width and cartilage thickness in the “low-tension” treatment group will be significantly less than that of the control group 15 years after surgical reconstruction of the ACL. We intend to follow these patients for a minimum of 15 years.

**Surgical outcome will also be assessed via: 1) patient-oriented outcome scores<sup>59,76</sup>, 2) AP laxity (an indicator of graft integrity<sup>6,44</sup> and knee kinematics<sup>23</sup>), 3) isokinetic strength (an indicator of dynamic knee function<sup>16</sup>), and 4) clinical outcome scores<sup>48,78</sup>.** Analysis of primary and secondary outcomes will enable us to determine the long-term effects of initial graft tension on cartilage status and knee joint function, and to evaluate the relationships between the longitudinal changes that occur in TF joint space narrowing (x-ray), cartilage thickness (MRI), general MRI scores (WORM score), knee laxity (KT-1000), thigh strength (Biodex strength test, 1 legged hop test) and patient-oriented outcome scores (SF-36, Knee Osteoarthritis Outcome Score). In the past funding cycle, data were obtained prospectively from ACLR patients and matched control subjects from the time of recruitment (pre-operative) through 84 months of healing. In this update, additional evaluations will be performed 144 and 180 months, a time frame in which cartilage damage should become more pronounced in this patient population. These analyses will shed light on potential factors that may play a role in the degenerative process and long-term outcome.

### 2. Subjects

**108 ACL-injured patients, who required ACLR, were recruited during the first three years of the initial funding cycle.** It was our intent to identify patients with isolated ACL injuries while minimizing confounding variables. To do this, all patients who came through the sports medicine clinics of University Orthopaedics Inc between 02/09/2004 and 02/08/2007 were considered for the study. All who met the pre-operative inclusion criteria and did not meet the exclusion criteria (Table 1) were asked to participate and provide their informed consent. Additional “intra-operative” inclusion/exclusion criteria were then evaluated at the time of surgery (Table 1). If the patient remained eligible, minimum likelihood allocation was used to randomly assign each subject to one of the two initial graft tension groups<sup>1</sup>. Randomization was performed to achieve balance between the treatment groups for characteristics that would influence long-term outcome and cartilage health; age, gender, race, and activity level (Tegner score). The number of patients who injured their ACL and choose ACLR within the clinical practice was documented, and the reasons for excluding subjects were recorded.

**60 “matched” control subjects, who had no known history of knee injury or symptoms of arthritis, were recruited from the hospital campus, local colleges, and Providence community.** They were selected to match the frequency of individuals by age ( $\pm 5$  years), gender, race, and activity level (Tegner score  $\pm 1$  point). The subjects' knees were evaluated by clinical exam at a screening visit. Subjects were not included in the control group if they have a side-to-side difference in AP laxity greater than or equal to 2-mm (KT-1000), a Tegner activity score less than 5<sup>69</sup>, or if they meet any of the other exclusion criteria (Table 1). It was our intent to establish a control group that matched the characteristics of the population at risk to ACL injury.

### 3. Research Design

**This study is designed as a prospective, randomized, double-blinded controlled trial comparing the outcome of two different initial tension conditions applied to the ACL graft at the time of surgery, and to determine the relationship between factors that may predict who will be risk for OA.** The project statistician and the operating surgeon initially knew a patient's assignment at the time of surgery, however, the

surgeon was not allowed to review the assignment once the surgery was completed, and the statistician was not allowed to review the assignments until after all the subjects were enrolled. The patient, the therapist performing the follow-up assessments, the AP laxity and isokinetic strength testing, the engineer performing the radiographic joint space width and cartilage thickness measurements, and the radiologist performing the WORM scoring will continue to be blinded from the subject's group assignment throughout the study. An intent-to-treat protocol is being utilized. All subjects randomized to each group are being followed, and all available data will be analyzed even if the graft fails, if the subject is unwilling to perform a particular follow-up test (missing data), or if a subject completely drops out of the study.

**Table 1.** Inclusion/exclusion criteria for patient enrollment.

<b>Treatment Groups (Hi- and Lo-tension)</b>	
Inclusion Criteria	Male or female subjects between the ages of 15 and 50 years with unilateral ACL injury.
	Candidates for ACLR using bone-PT-bone or four-stranded hamstring tendon autograft.
	A Tegner activity score <sup>69</sup> $\geq 2$ .
	Minor tears of the menisci that require minimal treatment ( $<1/3$ ).
Exclusion Criteria	An ACL tear occurring more than 12-months prior to the 1st office visit.
	Previous injury to either knee.
	Increased clinical laxity of the MCL, LCL, or PCL as compared to the control knee.
	Evidence of degenerative arthritis on radiographs.
	Women who are pregnant.
	Diseases that predispose a patient to articular cartilage damage.
	Moderate sized fissures or lesions in articular cartilage.
	Meniscal tears requiring partial meniscectomy involving more than 1/3 of meniscus.
<b>Control Group</b>	
Inclusion Criteria	Male or female subjects between the ages of 18 and 50 years.
	A Tegner activity score <sup>69</sup> $\geq 2$ .
Exclusion Criteria	Previous injury to either knee.
	Increased laxity of the MCL, LCL, or PCL compared to the control knee.
	Evidence of degenerative arthritis on radiographs
	Women who are pregnant.
	Diseases that predispose a patient to articular cartilage damage (e.g. rheumatoid arthritis, osteoporosis, metabolic diseases).

**Patients were included in the study if they were candidates for autogenous ACLR with either a bone-patellar tendon-bone or a 4-stranded hamstring tendon graft.** Due to the popularity of these graft types, both were included to extend the recruitment base. It should be noted that we initially proposed to include only bone-patellar tendon-bone grafts in the study. However, the recent surge in popularity of the hamstring tendon graft and the need to extend our recruitment based convinced us to include this procedure after eight months of recruiting candidates for patellar tendon autograft only. This was justified since recent biomechanical studies have shown that the structural properties of the patellar tendon autograft are equal to that of the 4-stranded hamstring tendon autograft <sup>79</sup>. Likewise, the in-situ forces, the passive load-displacement response, and dynamic kinematics of reconstructed knees with patellar tendon and 4-stranded hamstring tendon grafts are equivalent <sup>68,82</sup>. Recent prospective randomized clinical trials comparing these two graft types have shown that functional and patient-oriented outcomes are equivalent <sup>2,3,19,33,34,41,42,49,62,64</sup>. Finally, the two graft tension procedures in this study produced the same AP laxity values between graft types. Other than graft type, all surgically related parameters were standardized across surgeons. The same surgical instrumentation within each graft type was used to ensure that intra-articular graft placement was similar between patients. "Aperture" fixation interference screws were used to standardize graft fixation. Another variable, which could possibly affect outcome, is the rehabilitation program prescribed following surgery <sup>8</sup>. Recent data comparing commonly used rehabilitation protocols has shown that rehabilitation with either an "accelerated" or "non-accelerated" program would produce the same clinical, functional and patient oriented outcomes <sup>5,8</sup>. Nonetheless, all

subjects were required to follow the same “accelerated” rehabilitation program, which was geared to get patients back to sport within 6-months.

#### **4. Independent variable (Initial graft tension condition based on AP laxity)**

**Two initial graft tension conditions are being compared; 1) a graft tension that restored the AP laxity of the ACLR knee to that of the contralateral ACL intact knee (the “low-tension” treatment), and 2) a graft tension that reduced the AP laxity by 2mm in comparison to the contralateral ACL-intact knee (the “high-tension” treatment) at the time of surgery.** Thus, a graft tensioning protocol that is based on the AP laxity at the time of graft fixation (“laxity-based” approach) was selected for this study instead of a “tension-based” approach<sup>39</sup>. It has been shown that the graft tension immediately after fixation is dependent on the knee angle and magnitude of tension applied immediately prior to fixation and that an increase in graft tension reduces knee laxity<sup>17,38,39,81</sup>. The laxity-based approach implies that the tension in the graft is adjusted to produce an AP laxity value that is equal to or less than that of the contralateral normal knee, depending on a subject’s group assignment. A tension-based approach (e.g. 20 N, 40 N, etc) was not used for this study because the amount of force required to restore AP laxity would be subject specific<sup>15</sup>, and prone to other sources of error<sup>40,75</sup>. Although a laxity-based tensioning approach may require a variety of tension levels to be applied across patients within a treatment group, the tension applied to the graft in an effort to recreate normal AP laxity would be less than that required to over-constrain the joint, hence the terminology of “low-tension” versus “high-tension”. It is known that AP laxity values are significantly less when the graft is tensioned at 30° in comparison to full extension (0°), thus it is easy to control AP laxity by tensioning the graft at different knee flexion angles. The two initial tension treatments were controlled as follows. For the “low-tension” treatment, the tension was applied to the graft with the knee at 0° flexion (full extension). After an initial tension level was selected, the knee was flexed to 20° and an AP laxity test was performed (using the KT-1000S). The tension was adjusted iteratively until the AP laxity of the ACLR knee matched that of the contralateral limb ( $\pm 1.0$  mm). For the “high-tension” treatment, the tension was applied with the knee at 30° of flexion. The tension was adjusted until the AP laxity value at 20° of flexion is 2mm ( $\pm 1.0$  mm) less than the contralateral limb. The graft was then fixed with an interference screw, and the laxity value rechecked to ensure that the initial tension condition was maintained during fixation. The difference in knee flexion angle at which the tension was applied between the high-tension treatment as compared to the low-tension treatment assists in producing a lower AP laxity value at 20°. Thus, higher forces are produced in the graft across the full range of knee flexion angles<sup>17,38,81</sup>. Another advantage of using AP laxity at the time of graft fixation to control graft tension was that changes in AP laxity can be measured at the post-operative follow-up visits as well. It would not be possible to directly measure graft forces immediately after graft fixation and at the follow-up visits if a tension-based approach was utilized. In our pilot analysis we demonstrated that it is possible to restore normal laxity (at  $\pm 90$  N shear force) and to reduce AP laxity by at least 1.5mm (at  $\pm 90$  N shear force) compared to the normal side using these initial graft-tensioning protocols. For the patients enrolled in the current study, the mean ( $\pm$  standard deviation) laxity difference at 133 N (reconstructed knee – control knee) for the high-tension group was -2.1 ( $\pm 0.69$ ) and -0.3 ( $\pm 1.29$ ) mm for the high- and low-tension groups, respectively, with the “manual maximum” test<sup>23</sup>. The required difference in AP laxity at the time of graft fixation between tensioning techniques (the independent variable) was achieved.

#### **5. Outcome Measures (dependent variables)**

**In this comprehensive evaluation of the effects of initial graft tension on ACLR, five sets of outcomes are under examination: 1) Imaging assessment of OA progression; 2) Patient-oriented outcomes; 3) Knee kinematics; 4) Dynamic joint function; and 5) Clinical outcome.** Within each category (Tables 2&3), at least one test will be performed. In those categories featuring two or more tests, the first will be considered the primary test of that category.

##### **5.1. Imaging assessment of OA progression**

**Joint Space Narrowing (radiography):** Measurement of joint space narrowing via radiographs is the current validated standard for quantifying the progression of OA in clinical studies<sup>67</sup>, and is serving as the primary imaging outcome measure<sup>54</sup>. Joint space width measurements are obtained from radiographs based on the semi-flexed metatarsophalangeal (MTP) view as originally described Buckland-Wright<sup>14</sup>. The



**Subjective grading (radiography):** The overall condition of the joint via radiographs will be graded using the system developed by Daniel et al <sup>26</sup>. Weightbearing A-P, lateral and tunnel radiographs of the knees are taken before surgery and at the final follow-up visit. A grade of 0 (normal) to 3 (severe) will be assigned to six different radiographic factors: osteophyte formation, subchondral sclerosis, femoral condyle flattening, subchondral cysts, ligament calcification, and joint space narrowing. Each factor will be subdivided within regions of the knee. For example, osteophytes will be graded according to size (0=no osteophyte; 1=1- to 3-mm; 2=4- to 6-mm, and 3=>6-mm) in eight different sites; the medial femoral and tibial condyles, the lateral tibial and femoral condyles, femoral notch, tibial spine, femoral aspect of the patellofemoral joint, and the patella. A total radiographic score of 83 is possible, which represents severe damage. A zero represents no damage. A radiologist (GAT), who is blinded to the subject number and the subject's group assignment, evaluates all of the films.

**Table 4:** The scanning sequences being utilized for the MRI examinations (3T). The protocol was designed to provide the data to perform cartilage thickness measurements and the WORM scores while limiting MRI time to 1 hour per visit.

Sequence	Outcome
Sagittal T1-weighted water-excitation (WE) three-dimensional (3D) fast low-angle shot (WE-3D FLASH): 20/7.6 [TR msec/ TE msec]; 12° [flip angle]; 160 mm [field of view, FOV]; 1.5 mm/0 [slice thickness/interslice gap]; 80 slices per slab; 130 hz/pixel [bandwidth, BW]; 512x512 [matrix]; right/left [phase encoding axis]; one average of two excitations. This sequence will cover all articular cartilage plates in the knee.	Volume; Thickness; WORM score
Coronal Intermediate-weighted turbo-spin echo (TSE): 3850/29; 7 [echo train length]; 140 mm; 3mm/0mm; 41 slices; 352 hz/pixel; 307x384; right/left; one average.	WORM score
Sagittal* T2*-weighted WE-3D double echo steady state (WE-3D DESS): 16.3/4.7; 25°; 140 mm; 0.7mm/0mm; 185 hz/pixel; 307x384; anterior/posterior; one average.	WORM score
Sagittal Intermediate-weighted TSE with fat-saturation: 3200/30; 5 ETL; 160 mm; 3mm/0mm; 248 hz/pixel; 313x448; superior/inferior; one average.	WORM score

\*From the sagittal T2\*-weighted WE-3D FLASH sequence, additional MR images will be reconstructed in both the transverse axial and coronal planes.

**Cartilage Thickness (MRI):** Magnetic resonance (MR) imaging of both knees will be performed on a 3T whole-body scanner (Siemens TIM Trio; Erlangen, Germany) using a commercially available circularly-polarized knee surface coil to measure temporal changes in cartilage thickness <sup>11,12</sup>. Scans were obtained at the time of recruitment and after 36 and 84 months of healing and will be taken at the 144- and 180-month follow-up visits. The cartilage thickness calculations will be based on the sagittal water-excitation T1-weighted 3D FLASH sequence (Table 4). A trained technologist, under the direction of the radiologist, will perform manual segmentations on all slices (1.5mm) for each knee using Mimics software <sup>11</sup>. MRI's will be segmented in pairs and blinded to sequence. Segmented slices will then be grouped to generate a 3-D mesh to represent the volumetric shape <sup>11,12,65</sup>. Once segmented, the cartilage structure will be registered between the multiple scans of the same subject taken at 0, 36, 60 and 84 months, the change in the shape of the cartilage will be characterized, and the shape and its change will be averaged and normalized across subjects. The segmented cartilage will be considered as unorganized point clouds, and intra-subject registration will be based on closest point algorithm <sup>20-22,53,60</sup>. This will enable alignment of the cartilage between time points (0, 36, 60 and 84 months) with a point-wise description of change. We will then focus our thickness measurements to the cartilage regions of the tibiofemoral joint with the greatest load bearing requirements. A cylinder will be fit to the bone-cartilage interface of the femoral cartilage of the reconstructed images. The notch marking the junction between the TF and patellofemoral joints on the lateral condyle is easy to identify on the sagittal MR view. A line will then be drawn from the notch (0°) to the center of the cylinder <sup>12</sup>. Each condyle of the TF joint will then be divided at 40°, 70°, 100°, and 130° from the notch point toward the posterior aspect of the condyles to create 6 patches of cartilage (3 medial, 3 lateral); the width of each patch will be 20% of the overall width of the femoral cartilage and centered about the midline of each condyle (Fig. 6). Two patches on the tibial cartilage (1 medial, 1 lateral) will also be defined by calculating the centroid of each compartment and the inertial axes of the medial compartment using MATLAB (The Mathworks, Inc., Natick, MA). The inertial axes will serve as a coordinate system, and the patch in each compartment will be defined as the area ±20% of the overall depth (A-P) and ±15% of the overall width (M-L) from the centroid <sup>12</sup>. The average thickness of each patch will be calculated by the closest point. The cartilage volume will be quantified for the

tibia and femur by the numerical integration of the number of voxels contained within the segmented regions for each bone<sup>32</sup>. The cartilage volumes will be normalized by the surface area of underlying bone from the Time 0 data set (pre-operative visit) in order to increase the construct validity of the measurement<sup>47</sup>. Subjects will be labeled as having OA if they exhibit a cartilage volume loss exceeding 2.5% per year over the study period. This value was selected because patients without OA have been shown to have changes of 0.5% per year while those with OA lose approximately 4-6% per year<sup>43</sup>. Although the changes in the cartilage volume for the femur will be assessed, the focus will be on the volume changes of the tibial condyles where OA is easiest to detect<sup>18</sup>, and most affected by ACL injury<sup>36</sup>. **Note: Due to problems with artifact, this outcome measure was discontinued. The other imaging outcome measures were performed as originally planned.**

**Whole Organ Magnetic Imaging Score (secondary MRI measure):** The general status of the knee will be independently assessed by an expert musculoskeletal radiologist (G. Tung) and the PI using the semi-quantitative WORM score<sup>56,71,77</sup>. The scoring utilizes four MR sequences (Table 5). The images are scored with respect to 14 independent features<sup>56</sup>. Cartilage signal and morphology (8-point scale), subarticular bone marrow abnormality (4-point scale), subarticular cysts (4-point scale), subarticular bone attrition (4-point scale), and marginal osteophytes (8-point scale) will be evaluated in 15 regions (2 in the patella, 6 in the femur, 7 in the tibia). The regions are subdivided by distinct anatomical landmarks as described by Peterfy<sup>56</sup>. In addition, the menisci (5-points), cruciate and collateral ligaments (2-points each), synovitis (4-points), loose bodies (4-points), and periarticular cysts (3-points) are scored. A total of 332 points per knee is possible. WORM scores are calculated for each feature in each compartment and for all features combined. The musculoskeletal radiologist assessing the WORM scores has the expertise in doing so for ACL injured patients<sup>28,73,74</sup>.

## 5.2. Patient-reported outcomes

**The Knee Injury and Osteoarthritis Outcome Score (KOOS) and the Medical Outcomes Study Short Form-36 (SF-36)** will be used to assess patient-oriented outcomes. The KOOS addresses knee performance and was designed and validated to monitor changes in outcome and the progression of OA following ligament and meniscal injuries<sup>59</sup>. The KOOS is a self-administered questionnaire that evaluates treatment outcomes within 5-categories: 1) pain, 2) symptoms, 3) activities of daily living, 4) sports and recreation function, and 5) knee related quality of life. All questions within each category are scored on a 5-point scale. The scores within each category are added to produce a scoring profile (on a scale of 100 for each of the five categories) that can be followed over time. A 15-point decrease in the KOOS is equivalent to the difference between a “mild” and “moderate” deficit<sup>59</sup>. Although all five scores are evaluated, those that are most sensitive to change after ACLR are the KOOS-quality of life and the KOOS-sports<sup>59</sup>. These are expected to provide the greatest insight into the patient-oriented outcome of our patients. The SF-36 is a validated, self-administered instrument that is commonly used to monitor general health and to evaluate treatment effects in clinical studies<sup>76</sup>. It assesses physical function, role limitations due to physical health issues, bodily pain, vitality, social functioning, mental health, and reported health transition.

## 5.3. Knee kinematics

**A-P laxity:** Passive laxity measurements<sup>24,27</sup>, that are obtained with the leg muscles relaxed, are an important outcome since they assess ligamentous and capsular function, are predictive of the graft material properties<sup>6,44</sup>, and correlate with radiographic change in ACL-deficient knees<sup>26</sup>. The KT-1000 is the most reliable of the commercially available knee laxity measurement devices<sup>37,66</sup>, and is used by the clinical coordinator to document A-P laxity. For this study, A-P laxity is defined as the amount of A-P directed translation of the tibia (relative to the femur) between the shear load limits of -90 N (posterior) and 133 N (anterior). A-P laxity (instead of anterior laxity) was selected since variability is reduced when sagittal plane laxity is referenced to a posterior shear load rather than zero load<sup>23,37</sup>.

## 5.4. Dynamic joint function

**Isokinetic strength testing** is performed to assess the strength of the quadriceps muscles. Isokinetic strength of the quadriceps has been shown to be a predictor of the peak external flexion moments that is produced during jogging ( $r^2 = 0.83$ )<sup>16,55</sup>. The clinical coordinator administers the tests using the Biodex System 3 (Biodex Medical Systems, Inc. Shirley NY) located in our research facility. The subjects are positioned on the



device with its axis of rotation aligned with the transepicondylar axis of the femoral condyles. The subjects perform the tests at 60°/sec<sup>16</sup>. Averaging the peak torques of five repetitions and normalizing these values with respect to bodyweight and height quantifies peak quadriceps strength. Both knees are tested. **Note: The isokinetic testing system failed after the 84-month follow-ups were completed. The system was not replaced and thus will not be used for the 12 and 15-year follow-up assessments.**

**One-leg hop test** is also performed to assess function<sup>61,78</sup>. The subject performs the one-leg hop test for distance independently on each leg. Three trials for each are recorded and averaged. The difference in distance between the reconstructed and the normal knee is calculated.

## 5.5. Clinical outcome

**Clinical outcome will be assessed using the International Knee Documentation Committee (IKDC) knee rating scale**<sup>23,48</sup>. The IKDC rating has been validated for ACLR<sup>48</sup>. The IKDC scores evaluate four categories: 1) the patient's subjective assessment of function, 2) symptoms, 3) range of knee motion, and 4) clinical examination. The IKDC score rates knees as normal, nearly normal, abnormal, and severely abnormal, which can be transformed to an ordinal scale of 1 (normal) to 4 (severely abnormal). The final IKDC rating is then based on the score of the worst category<sup>48</sup>. In addition, height, weight, body mass index, thigh circumference (6cm above joint line) and the number of recurrent injury episodes is recorded. A sports medicine physician and a physical therapist will continue to independently perform all of the pre- and post-operative clinical examinations.

## 6. Controlled Variables

**Investigators have shown that the initial graft tension level required to restore normal knee laxity is specific to the graft material, cross-sectional area of the graft, and the free length of the graft between fixation sites<sup>15</sup>, and these were controlled in this study.** Initially, subjects undergoing ACL reconstruction using a bone-patellar tendon-bone autograft were recruited to control the variability due to graft type. However, there has been a recent surge in the popularity of the 4-stranded hamstring tendon graft. Thus, we elected to recruit patients who were candidates for ACL reconstruction with 4-stranded hamstring autografts to increase our population base. This was justified because recent biomechanical studies have demonstrated that the structural properties of the patellar tendon autograft are equal to that of the 4-stranded hamstring tendon autograft<sup>79</sup>. Likewise, the in-situ forces, the passive load-displacement response, and dynamic kinematics of reconstructed knees with patellar tendon and 4-stranded hamstring tendon grafts are similar<sup>68,82</sup>. Finally, recent prospective randomized clinical trials have shown that functional outcome following ACL reconstruction with 4-stranded hamstring or patellar tendon autografts are equivalent<sup>2,3,19,33,34,41,42,49,57,62,64</sup>.

**The intra-articular position of the graft has been shown to affect the graft forces post-operatively, and was standardized in this study<sup>10,17,25,38,46</sup>.** A 2 mm deviation in femoral graft placement has been shown to have a pronounced effect on the graft elongation pattern<sup>45</sup>. A graft that is placed too far anterior on the femur will cause it to get tight in flexion and slack in extension. Likewise, a graft that is placed in the "over-the-top" position will get tight in extension and slack in flexion. Thus, intra-articular graft position may influence the healing response<sup>9,70</sup>. However, all the surgeons utilized the same drill guide system and anatomical landmarks to standardize graft position across subjects. Although variation may still exist, we have previously shown that they are equally distributed within each treatment group<sup>9</sup>.

**Another standardized variable, which could possibly affect outcome, is the rehabilitation program prescribed following surgery<sup>8</sup>.** Recent data comparing commonly used rehabilitation protocols suggest otherwise. We have shown that rehabilitation with either an "accelerated" or "non-accelerated" program produces the same outcome with respect to AP knee laxity, clinical assessment, patient satisfaction, functional performance, strength, and proprioception<sup>5,8</sup>. In the current study, all subjects were required to follow the "accelerated" rehabilitation program. They received supervised post-operative physical therapy for a minimum of 16 weeks. Because the patients were randomly assigned to each treatment group, we feel that any deviation from the rehabilitation program (either produced by the patient's inability to keep up with the program, or the patient's unwillingness to follow the prescribed rehabilitation) was equally distributed between the two groups.

## 7. Protocol Summary

**When a subject (either surgical or control) consents to continue their participation in the study, 144- and 180-month follow-up assessments will be performed.** All patients have been previously enrolled into the study. However, the lay summary consent forms were based on an 84-month follow-up. Therefore, the subjects will need to be re-consented in order to participate in the extended study. The clinical coordinator will consent the patients after contacting them via mail with a phone call follow-up. Within the initial contact letter, a card will be provided so that the subject can let us know if they do not want us to contact them by phone.

**The clinical examinations will occur at the sports medicine clinic of University Orthopaedics Inc.** At the first visit (144 month), the subject will meet with the clinical coordinator to finalize the consent forms. Once the subject has granted informed consent, an X-ray technician will acquire the radiographs for the joint space width measurements. These will be obtained under the direction of the clinical coordinator who will make sure all the necessary steps required to reposition the patient relative to the x-ray system are taken. A research physical therapist will independently perform the clinical exam (IKDC). At this time, the clinical coordinator will administer the questionnaires (SF-36; KOOS; Tegner), the A-P laxity exam (KT-1000) and the functional assessment (One-leg hop). The clinical coordinator will also schedule the MRI examination, which will be performed at another site.

**The MRIs will be performed at the MRI Research Facility at Brown University under the guidance of a certified MR technician.** The scans (Table 4) will be performed using the TIMS Trio scanner. The scans will be WORM scored by a board-certified radiologist with expertise in musculoskeletal MR.

**All subjects will be contacted by the clinical coordinator via phone each year that a visit is not scheduled.** The primary reason for this will be to keep all of the subjects engaged in the study.

## 8. Statistical analyses

**Treatment Comparisons - Primary Outcome Measure:** Repeated measures analysis of variance will be used to evaluate differences among treatment groups with respect to temporal changes in joint space width (i.e. joint space narrowing). The statistical model will include fixed factors representing treatment group ("low-tension", "high-tension" and "control"), limb (operative vs. contra-lateral or two controls), location (medial vs. lateral), time (baseline, 12-, 36-, 60-, and 84-month), and their interactions. If significant interactions are detected, simple effects will be compared using the Student-Newman-Keuls procedure based on the appropriate error terms<sup>80</sup>. Because one of the repeated factors (i.e. time) is quantitative, orthogonal polynomial will be used to partition the time effect into its individual quantitative components (i.e. linear and quadratic). The significance of these orthogonal contrasts will be used to evaluate the linearity (or non-linearity) of the temporal trend associated with degeneration. Analyses will be performed using SAS, PROC MIXED<sup>52</sup> that allows for covariance structures other than compound symmetry (e.g. unstructured, autoregressive, spatial power law). It is expected that the variability across subjects may increase across time due to only a subset of individuals exhibiting degeneration, which would violate the standard homogeneity of variance assumptions. The normality assumption will be examined based on residuals using normal probability plots and the Wilk-Shapiro test. If necessary, data will be transformed prior to analysis in order to satisfy the distributional assumptions.

**Treatment Comparisons - Secondary Outcome Measures:** Repeated measures analyses of variance will also be used to test for differences in secondary outcome measures corresponding to knee kinematics, dynamic function, patient reported outcomes, and clinical outcomes. For measures that are performed on each limb (e.g. A-P laxity), the statistical model will include fixed factors representing treatment group, limb, and time, along with their interactions. Repeated measures analyses on secondary outcome that are not limb-specific (e.g. KOOS and SF36) will include only treatment, time, and their interaction as factors. Post hoc analyses involving tests of simple effects and orthogonal polynomials will be similar to methodology previously described for joint space width. Because specific secondary outcome measures are assessed more frequently in the two experimental arms than in the control group (Tables 2&3), direct post hoc comparisons involving the two tension groups and examination of temporal trend in these group will utilize the additional assessments.

**Relationship between A-P Laxity and Progression of OA:** The longitudinal relationship between A-P laxity and progression of OA as measured by joint space narrowing (both radiographically and using MRI) will be examined in the context of hierarchical linear modeling<sup>13</sup>, also known as random coefficient modeling. Using data obtained from the experimental subjects, SAS PROC MIXED will be employed to examine the association between individual subjects' changes in A-P laxity with their changes in joint space width (radiography) or cartilage thickness (MRI). This will be accomplished by considering A-P laxity as a covariate (predictor) that would potentially change over time with joint space width and cartilage thickness being considered as the dependent measures. Individual subjects are modeled based on unique intercepts and slopes corresponding to time and the covariate. Across subject factors such as tension group, gender, graft type, and age will also be considered. A similar analysis will be performed to establish the relationship between isokinetic strength, KOOS, functional testing and OA progression.

**Missing Visits and Subject Loss to Follow-up:** Unlike traditional software used for repeated measures analyses (e.g. SAS PROC GLM and BMDP -2V), PROC MIXED appropriately handles incomplete data due to missed visits without completely excluding subjects from the analysis. The pattern of missing data is assumed to be random, which in-practice, is likely to be violated to some degree. We will test for differences in the rate of missed visits across treatment groups and across time using categorical repeated measures (SAS, PROC CATMOD). The proportion of subjects that are loss to follow-up will be compared across treatment and control arms using a chi square test. Though we are finding that missed visits are infrequent and most likely equally distributed across treatment groups, we will examine whether specific baseline characteristics that may be predictive of outcome are also associated with missed visits using logistic regression. We recruited 54 subjects per group in an effort to have 46 assessable subjects per group at the three-year follow-up visit based on the estimated 15% dropout rate. We have more than met this goal (3% drop out in our treatment groups and 15% drop out in our control group at 3 years. For the proposed 180-month follow-up, we expect that we will have at least 35 patients/subjects in each group (20% drop out rate of subjects currently enrolled).

**Justification of Sample Size based on Primary Outcome Measure:** The estimated sample size of 35 assessable subjects per group through the 84-month study period will result in having sufficient power ( $1-\beta=0.80$  using  $\alpha=.05$ ) to detect a mean difference between groups of 0.25 mm in joint space narrowing over the 84-month study period. This estimated difference is based on the following rationale. Previous studies have shown that patients with primary OA exhibit an estimated 0.3-mm change in joint space width per year<sup>51,63</sup>. Since we will be studying patients at the time of OA onset, we will assume that patients who undergo initial changes will exhibit an average joint space narrowing of 0.1 mm per year, or a total of approximately 0.6 mm over the 84 months. This estimate was conservatively adjusted based on the study by Johma et al, who found that only 50% of the subjects that undergo ACL reconstruction after injury exhibit early degenerative changes following surgery<sup>50</sup>. After taking into account that only a subset of subjects randomized may exhibit OA, the resulting mean difference is decreased to be 0.25-0.30 mm over the 84-month study period. An additional consequence of only a subset of the patients that are randomized exhibiting degeneration is an increase in the variability encountered across subjects with respect to joint space narrowing. The variability estimate used in our computations ( $\sigma_{\Delta}=0.35$  mm) resulted from increasing the estimate derived from the literature for a group of subjects with OA in order to reflect our expected mixture of two subsets of subjects. Based on each subset having  $\sigma_{\Delta}=0.20$ , with 50% of the patients exhibiting narrowing a total of 0.6 mm and 50% showing no degeneration, the resulting overall estimated  $\sigma_{\Delta}=0.35$ . Assuming joint space width at baseline is approximately 4.5 mm<sup>30</sup>, this detectable mean difference (0.25 mm) represents an approximate 5% change between the treatment groups in the mean rate of degeneration. We recruited 54 subjects per group in an effort to have 46 assessable subjects per group at the three-year follow-up visit based on the estimated 15% dropout rate<sup>4,7</sup>. We have more than met this goal (3% drop out in our treatment groups and 15% drop out in our control group at 3 years). For the proposed 180-month follow-up we expect that we will have at least 35 patients/subjects in each group (20% drop out rate of subjects currently enrolled).

**Power for Secondary Outcome Measures:** Having determined the number of subjects needed to have sufficient power to detect expected differences in joint space narrowing, we computed the magnitude of the detectable difference for the main secondary outcome measures. These estimates are based on our previous data and values found in the literature. When the estimates were based on cross-sectional data from the literature (i.e. isokinetic strength), moderate correlation across time was assumed ( $r=0.50$ ). The following mean differences correspond to the estimated power=0.80 and  $\alpha=.05$  with the proposed sample sizes: A-P laxity =

1.25 mm (a 16% change relative to the normal A-P laxity value <sup>72</sup>); isokinetic knee strength = 18.5 Nm (a 12% change relative to normal, a “mild” deficit <sup>16</sup>); KOOS- QOL score = 10.5 (a 10% change relative to full scale, considered less than a mild deficit <sup>59</sup>); KOOS-sports score = 10.1 (a 10% change relative to full scale, considered less than a mild deficit <sup>59</sup>), and IKDC score =.50 (a 12% change relative to normal <sup>48</sup>).

Note (9/29/2017): The 7 year data were completed and published in the American Journal of Sports Medicine in January 2016 (<http://www.ncbi.nlm.nih.gov/pubmed/27159308>). The study was extended to 12 and 15 years and the data collection for these time points is currently underway.

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