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Stability and early detection of osteoarthritis (OA) following anterior cruciate ligament (ACL) rupture and reconstruction with or without a lateral extraarticular tenodesis (LET)

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1.1 Abstract

Purpose: Graft failure rates following anterior cruciate ligament reconstruction (ACLR) are inadequate in young, active patients. Recently, the STABILITY 1 Study provided level 1 evidence that augmenting hamstring ACLR with a lateral extra-articular tenodesis (LET) reduces graft failure. Further evidence regarding outcomes after LET and in those with specific risk factors is required.

Methods: This thesis includes three studies. In study 1, we used logistic regression to determine predictors of persistent rotatory laxity and graft failure in young, active patients two-years post-ACLR. In study 2, we investigated a subgroup of patients with lateral meniscal posterior root tears (LMPRT) at the time of ACLR to determine how the injury affected their outcome postoperative. In study 3, we performed magnetic resonance imaging on a consecutive subgroup of patients at two-years postoperative to determine whether augmenting ACLR with LET affects articular cartilage quality in the lateral compartment of the knee.

Results: In study 1, adding an LET was significantly associated with 60% lower odds of graft rupture, while younger age, increased tibial slope, high-grade preoperative knee laxity, and earlier RTS were associated with higher odds of graft rupture. Adding an LET and increasing graft diameter significantly reduced persistent rotatory laxity. In study 2, we found that patients with a LMPRT have similar outcomes to patients without LMPRT, regardless of treatment performed. In study 3, we found that T1rho relaxation was slightly elevated in the lateral compartment for the ACLR + LET group. Cartilage relaxation values increased as meniscal tear size increased when the meniscus was excised, while relaxation times were relatively stable after repair.

Conclusion: Our findings confirm the protective nature of the LET while identifying other predictors of clinical failure and graft rupture. Our results suggest clinicians are skilled at deciding when LMPRTs need to be repaired, and that the meniscus should be repaired, where possible, to prevent changes in cartilage relaxation. This study confirms the need for long-term follow-up of STABILITY 1 patients to determine whether the LET provides short-term stability without increasing increased risk of OA development.

Keywords

Anterior cruciate ligament, lateral extra-articular tenodesis, instability, graft failure, cartilage, osteoarthritis, magnetic resonance imaging.

Summary for Lay Audiences

The anterior cruciate ligament (ACL) is commonly torn in young, active people. ACL tears result in an unstable knee that people cannot trust, so it needs to be replaced with surgery. Adding an extra piece, called a lateral extra-articular tenodesis (LET), to the outside of the knee during ACL surgery leads to a more stable knee and lower chance of injuring the ACL again. This thesis contains three studies using patients from the STABILITY 1 study who underwent ACL surgery with or without LET, to get more information on how patients do after surgery. The goal of the first study is to see which patient and injury characteristics are related to injuring the ACL again after surgery. The second and third projects are magnetic resonance imaging (MRI) studies. MRI lets us see inside the knee to look at damage. The second study takes patients who had a specific injury at the same time as their ACL, called a lateral meniscal posterior root tear (LMPRT), and looks at how the injury was treated and how these patients do after surgery. The last study takes a group of patients from one site to see how adding an LET affects knee cartilage, which protects the knee during activity. When cartilage is injured, it begins to wear down and stops protecting the knee, which can lead to pain and difficulty with activity. MRI can be used to compare cartilage after ACL surgery with or without the LET, to help us think about how these patients will do ten- or twenty-years later. Overall, these studies will help show how specific risk factors relate to results of ACL surgery and whether adding an LET has any effect on knee cartilage.

Co-Authorship Statement

With the support of my supervisors (Dr. Dianne Bryant and Dr. Alan Getgood), we conceptualized three studies for this thesis. I, Andrew Firth, was the first author on all three studies. The STABILITY 1 Study Group co-authored Chapter 3, as data was collected at multiple sites and the principal investigators reviewed the manuscript and offered feedback. Dr. Satyen Jesani co-authored Chapter 4, as he assessed radiographs and provided feedback on the original draft of the manuscript. Dr. Stephany Pritchett, Jaques S. Milner, and Dr. David Holdsworth co-authored Chapters 4 and 5. They were essential to the quantitative and semi-quantitative MRI outcomes used in both studies.

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Table of Contents

List of Tables

List of Figures

List of Appendices

List of Abbreviations

ACL - Anterior cruciate ligament

ACLOAS – Anterior cruciate ligament osteoarthritis score

ACLR - Anterior cruciate ligament reconstruction

ALL – Anterolateral ligament

ANCOVA – Analysis of covariance

AUC – Area under the curve

BMI – Body mass index

BML – Bone marrow lesion

BTB – Bone-patellar tendon-bone

CFMM – Center for Functional and Metabolic Mapping

CI – Confidence Interval

FKSMC – Fowler Kennedy Sport Medicine Clinic

HRHL – High-risk, high-level sport

HRLL – High-risk, low-level sport

HT – Hamstrings

ICRS – International Cartilage Repair Society

IKDC – International Knee Documentation Committee

ITB – Iliotibial band

IQR – Interquartile range

KOOS – Knee injury and Osteoarthritis Outcome Score

LCL – Lateral collateral ligament

LEFS – Lower extremity functional scale

LET - Lateral extra-articular tenodesis

LFC – Lateral femoral condyle

LMPRT – Lateral meniscus posterior root tear

LOWESS – Locally weighted scatterplot smoothing

LRHL – Low-risk, high-level sport

LRLL – Low-risk, low-level sport

LSI – Limb symmetry index

LT – Lateral tibia

MCL – Medial collateral ligament

MOON - Multicenter Orthopaedic Outcomes Network

MRI - Magnetic resonance imaging

MSK - Musculoskeletal

OA – Osteoarthritis

OR – Odds ratio

P4 – 4-Item Pain Intensity Measure

PCL – Posterior cruciate ligament

qMRI - Quantitative magnetic resonance imaging

RCT – Randomized controlled trial

RD – Risk difference

ROC – Receiver operating characteristic

RPE – Relative percentage extrusion

RTS - Return to sport

SD - Standard deviation

SE – Standard error

VIF – Variance inflation factor

Chapter 1

2 Introduction: Background and Rationale

Anterior cruciate ligament (ACL) injury is one of the more common orthopedic knee injuries, with an incidence of approximately 69 per 100,000 person-years.[1] As of 2009, an estimated 250,000 ACL injuries and 100,000 ACL reconstructions (ACLR) occurred per year in Canada and the United States alone.[2] The incidence of ACL injuries and procedures is increasing[3], which, after factoring in the significant costs associated with surgery and rehabilitation, requires greater healthcare utilization for both the patient and society.[4-7] The direct and indirect costs associated with ACL injury and rehabilitation are estimated to be 7 billion dollars annually.[8]

ACL tears predominantly occur in younger individuals, as the incidence peaks from 14- to 18-years of age in females, and 19- to 25-years of age in males.[1] A number of studies have found that females are at higher risk of injury than males, with an incidence rate approximately 1.5-times higher than males, particularly after adjusting for type of sport and exposure time.[9-12] One reason tears are most prevalent in younger individuals is the increased risk of injury that comes with participation in high-level pivoting sports.[8-10] In a recent systematic review, Gornitzky et al.[10] estimated the risk of ACL injury in high school-aged athletes was 0.7% per season for females, and 0.4% per season for males. Greater risk of injury has been identified in female soccer and basketball players, and male football players.[9-11]

Many studies have investigated the mechanism of ACL injury, particularly during sports participation. ACL tears primarily occur through a non-contact mechanism[8, 13], where the foot is planted and the tibia is externally rotated as the knee moves into valgus in early flexion.[14, 15] Hyperextension injuries were also reported.[14] These movement patterns commonly occur when decelerating and changing direction or landing from a jump.[14] Patients often hear a ‘pop’ at the time of injury and may feel the knee give way, followed by rapid swelling post-injury.[16] The ACL is a primary stabilizer of the knee thus, an ACL injury compromises normal knee function. The ACL is comprised of both an anteromedial and posterolateral bundle that function to primarily resist anterior translation of the tibia[17-19] and help prevent internal rotation of the tibia as well.[19] ACL tears can be diagnosed clinically using the pivot shift test, where a clinician supports the heel of the patient and moves their knee into flexion and internal rotation while applying a valgus stress, to detect rotational laxity.[20] While a good patient history and other clinical tests may also contribute to diagnosis, the pivot shift is the most specific test for confirmation of a torn ACL.[21]

Whilst ACL tears can be an isolated injury, they are often associated with damage to other structures in the knee, including menisci and cartilage.[22-24] In a cohort of over 5000 patients (mean age = 30 years, range = 9 to 69) undergoing ACLR, meniscal tears requiring treatment occurred in approximately 50% of patients, including 27.1% with a medial meniscal tear and 29.1% with a lateral meniscal tear.[25] While 35.7% of patients had articular cartilage damage, just 3.1% had cartilage lesions with an ICRS grade of 3+. Data from a younger group of patients participating in the Multicenter Orthopaedic Outcomes Network (MOON) cohort (mean age = 26.8 years) showed the prevalence of medial and lateral meniscal tears was 40% and 46% respectively, while grade 3+ cartilage lesions, according to the International Cartilage Repair Society (ICRS) criteria, were present in roughly 28% of patients.[22] The menisci also contribute to the stability of the knee. In cadaveric studies, a compromised medial meniscus has shown to increase anterior translation of the knee[26], while a compromised lateral meniscus has been associated with greater rotatory laxity.[26, 27] Clinically, meniscus injuries have been associated with high-grade laxity following ACL injury.[28-30]

The primary goal of surgical intervention after ACL injury is to restore the normal kinematics of the knee.[16, 31] ACLR is routinely performed, particularly for young, active patients returning to pivoting sports[16, 31], despite a lack of evidence to support better outcomes than non-operative treatment.[32, 33] The results of two studies where patients were randomized to early ACLR versus rehabilitation and optional delayed ACLR showed conflicting results on patient reported outcomes however, approximately 50% of patients in the optional delayed group of either trial underwent surgery.[32-34] These findings suggest surgical reconstruction may be the logical choice if patients are likely to undergo an operation eventually, particularly if ACLR is the patients' preferred treatment option.[35] In other studies, delaying surgery has been shown to increase the risk of high-grade laxity pre-operatively[28, 36], and cartilage and meniscus damage[25, 36-39], supporting the decision for reconstruction within a few months post-injury.

Anterior cruciate ligament reconstructions have been well-studied. Many trials have compared different surgical techniques, such as graft type[40-44], tunnel position[45, 46], and single versus double bundle grafts[47-49] in an attempt to improve patient outcomes after surgery. Patients and clinicians must consider both short- and long-term outcomes when discussing surgical reconstruction of the ACL. Short-term postoperative complications that can affect recovery include stiffness, infection, meniscal re-tear, while the greatest concerns long-term are graft failure and the development of osteoarthritis.[50, 51] Overall ACLR graft failure rates are suspected to be somewhere between 2% and 6%[52] however, they have shown to be much higher in young, active patients.[53-57] In 2016, Wiggins et al. performed a systematic review and meta-analysis to determine graft failure rates specific to younger patients.[58] They found that 10% of individuals under the age of 25 re-tore their ACL and, overall, 23% of patients under 25 who returned to high-level sport suffered another ACL injury on either knee.[58] The MOON group showed similar results in a cohort of high school and college-aged athletes (mean age = 17 years, range: 14 to 22), as roughly 9% of patients required revision ACLR and 20% underwent ACLR on either knee during the six-year follow-up period. Moreover, several meta-analyses have demonstrated that current ACLR techniques fail to adequately restore rotational stability, as high positive pivot shift test rates were found post-operatively.[59, 60] High pivot shift rates, and thus rotatory laxity of the knee, are concerning as they have been found to correlate with poor functional outcomes following ACLR.[61]

Persistent rotatory laxity following ACLR has led to renewed interest in the anterolateral ligament (ALL), another structure thought to contribute to rotational stability of the knee. The ALL is part of the complex anatomy on the lateral side of the knee, and lies just anterior to the fibular collateral ligament and inferior to the iliotibial band (ITB).[62] It helps prevent internal rotation of the tibia[63, 64] and acts as the primary restraint to this motion above 35º of flexion.[63] The ALL provides less resistance in early flexion where the ACL is commonly injured, as other anterolateral structures, such as the ITB and Kaplan fibers, play a larger role.[64, 65] Regardless, biomechanical studies have demonstrated that rotatory laxity persists after ACLR and that augmentation of ACLR with a lateral procedure better restores the normal kinematics of the knee.[19, 64, 66-68] The potential role of a lateral procedure following ACL injury is not a new concept, as lateral extra-articular procedures were popular in the 1980s before surgeons shifted back to intra-articular reconstruction techniques.[69, 70]

Prior to 2015, several randomized controlled trials had compared ACLR alone to ACLR with a lateral procedure[71-77], yet a systematic review by Hewison et al. found these studies lacked methodological rigor and were significantly underpowered.[78] More participants and greater evidence, including level one randomized controlled trials (RCTs), were needed. In 2019, we completed the STABILITY 1 Study, an international, multicenter, pragmatic randomized controlled trial comparing single-bundle hamstring autograft ACLR with or without an LET in young, active patients at high-risk of graft failure.[79] Six-hundred and eighteen patients were randomized at nine centers (7 in Canada, 2 in Europe) and followed for two-years post-operatively. Eligible patients were skeletally mature patients 25-years of age or younger with an ACL-deficient knee, who met two of the three following criteria: 1) participation in competitive pivoting sports, 2) grade 2+ pivot shift pre-operatively, or 3) generalized ligamentous laxity (Beighton score of 4+) or genu recurvatum >10º. Patients were ineligible if they had previous ACLR on either knee, a multi-ligament injury requiring surgical treatment, a symptomatic articular cartilage defect requiring treatment other than debridement, asymmetric varus >3º, or unwillingness to commit to two years of follow-up. The primary outcome was ACLR clinical failure, defined as either persistent rotatory laxity or graft rupture. Numerous secondary outcomes were collected, including patient-reported outcome measures (PROMs), functional tests, and imaging. The results showed that, compared to ACLR alone, ACLR + LET significantly reduced the rate of clinical failure (25% versus 40%, p< 0.0001) and graft rupture (4% versus 11%, p <0.001).[23, 80] No difference in functional outcomes was found between the two groups.[81]

Other smaller RCTs and non-randomized studies published around the same time demonstrated similar potential for ACLR combined with a lateral procedure to reduce post-operative laxity.[82-84] A recent prospective, non-randomized study by Sonnery-Cottet et al. (2017) compared bone-patellar tendon-bone (BTB) graft, quadrupled hamstring tendon (HT) graft, and hamstring tendon graft combined with anterolateral ligament reconstruction (HT + ALL) graft in 541 patients. Patients had a mean age of 22.4 years (range = 16 to 30), and between group differences in age, sex, and sport participation were found at baseline, which required adjustment at the time of analysis. A total of 502 patients were available at final follow-up (mean = 38.4, range = 24 to 54 months) and 40 patients had suffered a graft rupture during the study period. Graft rupture was significantly lower in the HT + ALL group (4%), compared with the HT (11%) and BTB (16%) groups (p = 0.034). No differences were found between groups in terms of return to sport rates or reoperation post-operative (p>0.05). While these findings suggest lateral augmentation of HT ACLR may be protective of graft failure, this study was underpowered and considered level two evidence.

Two studies each randomized over 100 male patients (mean age = 26 years) to ACLR with or without ALL reconstruction.[82, 83] Ibrahim et al. found no difference between groups in the proportion of patients with abnormal pivot-shift test (ACL = 88.0%, ACL + ALL = 90.6%, p = 0.89), Lachman test (ACL = 90.0%, ACL + ALL = 92.5%, p = 0.88), anterior drawer test (ACL = 86.0%, ACL + ALL = 88.7%, p = 0.91), or graft rupture at 27-months post-operative however, there was a statistically significant difference in the proportion of patients with abnormal knee laxity on KT-1000 arthrometer testing (ACL = 16.0%, ACL + ALL = 9.4%, p <0.001).[82] Hamido et al. (2020) found there was no difference between groups in anterior drawer testing and Lachman testing at 5-years follow-up however, a statistically significant difference in abnormal pivot shift rates (ACL = 17.3%, ACL + ALL = 4.0%, p < 0.001) and graft failure (ACL = 9.6%, ACLR + ALL = 0%, p < 0.001). Porter and Shadbolt (2020) randomized 55 patients (mean age =

22 years) undergoing primary ACLR with no meniscal repair and residual laxity after ACLR to ACLR alone or ACLR with a lateral procedure using a modified IT band tenodesis (MITBT). At two-years follow-up there was a statistically significant difference in favor of the ACL + lateral tenodesis group in terms of KOOS sport scores (ACLR = 91.5, ACLR + lateral = 95.3, $p = 0.02$), Lysholm scores (ACLR = 92.5, ACLR + lateral = 96.8, $p = 0.004$), Tegner activity scores (ACLR = 7, ACLR + lateral = 8, $p = 0.03$), and the proportion of patients that suffered graft rupture (ACLR = 14.8%, ACLR + lateral = 0%, $p < 0.001$). There was no difference between groups for IKDC scores or the KOOS quality of life subscale. While these three studies demonstrate that the addition of a lateral procedure may improve knee stability, the evidence is limited by few events and a lack of generalizability, as all studies were performed at a single center[82-84] and two only included male patients.[82, 83] With more evidence now available, recent systematic reviews and meta-analyses have shown that the addition of a lateral procedure to ACLR significantly decreases both the risk of post-operative rotatory laxity and graft rupture.[85, 86]

Despite biomechanical evidence and growing clinical evidence that augmentation of ACLR with a lateral procedure provides better knee stability, surgeons lack clear indications for when these procedures should be performed.[87, 88] Recently, two independent groups published consensus statements including criteria for when lateral augmentation should be considered. In 2017, the Anterolateral Ligament Expert Group suggested decisive criteria for a lateral procedure include ACL revision surgery, high-grade pivot shift, presence of Segond fracture, high level athletes returning to pivoting sport, and hyperlax joints.[88] They also suggested if multiple secondary criteria were present, including contralateral ACL rupture, Lachman test > 7mm, deep lateral femoral notch sign, and age < 25 years old, a lateral procedure should be performed. A year later, a second independent group of experts, the Anterolateral Complex Consensus Group, released a statement recommending augmentation of ACL with a lateral procedure for patients with high grade pivot shift, generalized ligamentous laxity/genu recurvatum, for young patients returning to pivoting sport, and for revision ACLR.[87] These statements represent level V evidence, and recommendations were based on populations where

ACLR failure rates are high, rather than groups where augmenting ACLR with lateral procedures had shown to be beneficial. Recent studies have begun to show better outcomes with a lateral procedure in these populations[23, 82-84] however, further clinical evidence is needed to identify when lateral procedures are warranted.

While lateral augmentation of ACLR demonstrates the potential to reduce rotatory laxity, there are concerns that these procedures could lead to higher risk of osteoarthritis long-term.[89] There is limited evidence that ACLR reduces the risk of osteoarthritis after ACL injury[90-92], with OA rates ranging from 25% to 75% a minimum of 10-years post-surgery.[92-94] Some authors have posited that high osteoarthritis rates after ACLR may be due to the inability to control persistent rotatory laxity with current ACLR techniques.[90] High rates of OA have been found in high-level athletes[92] and soccer players over 10-years post-ACLR[95, 96], and the majority of female patients in one study reported symptoms of knee OA were affecting their quality of life.[95] Biomechanical studies have demonstrated overconstraint of the knee joint following combined ACLR and lateral procedures[19, 66, 97-99], which could lead to greater contact pressures and may increase the risk of developing OA.[100, 101] In 2017, Devitt et al. performed a systematic review to assess the risk of osteoarthritis after ACLR combined with a lateral procedure.[93] Follow-up data from two RCTs and several cohorts were included, but the authors concluded there was insufficient evidence to claim that augmenting ACLR with a lateral procedure increases OA risk. Since that review, Castoldi et al. (2020) published long-term follow-up data from a randomized study of 120 patients randomized to ACLR with a BTB graft (n = 61) or BTB ACLR with a modified-Lemaire LET (n = 60).[102] At approximately 20-years post-surgery, 66% of patients (n = 79 patients, 80 knees) completed the IKDC and Lysholm questionnaires however, just 43 (36%) were available for imaging and clinical examination. The authors found no difference in graft failure rates (BTB = 29%, LET = 13%, $p = 0.10$), IKDC scores (BTB = 81.1, LET = 82.4, $p = 0.70$), Lysholm scores (BTB = 86.6, LET = 90.3, $p = 0.2$) or sports participation ($p>0.99$) between groups, despite significantly higher risk of lateral compartment osteoarthritis in the LET group (BTB = 22%, LET = 59%, $p = 0.02$). While the high attrition rate could bias their results, higher risk of lateral knee OA in the LET group is concerning. Further evidence is clearly needed to understand the potential effects of performing ACLR combined with lateral procedures on the lateral compartment of the knee.

All told, unacceptable outcomes after ACLR, my work on the STABILITY 1 Study, and the need for further evidence following augmentation of hamstring ACLR with an LET provided the motivation for my doctoral research. I worked on the STABILITY 1 Study from 2016 to 2019, recruiting patients and collecting follow-up data at the Fowler Kennedy Sport Medicine Clinic (FKSMC). This thesis paper includes three secondary analyses using data from the STABILITY 1 cohort designed to address the following aims:

1) Identify demographic and surgical predictors of persistent rotatory laxity and graft rupture in patients from the STABILITY 1 Study.
2) Assess outcomes in a sub-group of patients that had concomitant lateral meniscus posterior root tear (LMPRT) identified at surgery.
3) Compare articular cartilage quality following ACLR alone versus ACLR with LET at two-years post-operative to determine whether lateral procedures lead to overconstraint and early degenerative changes in the lateral compartment of the knee.

To identify predictors of persistent rotatory laxity and graft failure, we considered demographic and surgical variables shown to be associated with outcomes following ACLR in the literature and formed clinical hypotheses about variables collected during our study. We used multivariable logistic regression to model the relationships between those variables and our definitions of graft failure from our STABILITY 1 cohort. We used the resulting models to suggest certain factors and scenarios where surgeons may want to consider augmenting ACLR with an LET to reduce the risk of graft failure. We presented the results of this study to a diverse team of health care professionals at FKSMC and circulated our findings to orthopedic surgeons at each participating STABILITY 1 site to elicit their feedback. This study was published in the American Journal of Sports Medicine in February 2022.[80]

For studies two and three, I led the collection of MRI scans for patients at FKSMC participating in the LMPRT subgroup or the two-year cohort. I scheduled MRIs at one- and two-years post-operative at the Centre for Functional and Metabolic Mapping (CFMM) and brought patients to and from these appointments. I collaborated with researchers at the Robarts Research Institute and a musculoskeletal radiologist at the London Health Sciences Centre to evaluate the qualitative and quantitative results of patients' MRI scans. I, along with an orthopedic surgical fellow, measured meniscal extrusion for patients in the LMPRT subgroup. Additionally, I was responsible for segmentation of the processed T1rho and T2 maps to determine cartilage relaxation times in the regions of interest.

The STABILITY 1 Study showed that the addition of an LET significantly reduces failure and has the potential to change clinical practice. This research will identify specific patients where augmentation of ACLR with an LET may significantly reduce graft failure, will describe the impact of secondary injuries on recovery trajectory following ACLR, and will identify whether adding a LET has any detrimental effects on the lateral compartment of the knee. The implications for clinical practice changes are enormous and will affect change not only in Canada but worldwide.

2.1 Thesis Outline

This thesis is comprised of five chapters including this introduction (Chapter 1). Chapter 2 is a published case-control study investigating demographic and surgical predictors of ACLR graft failure in the STABILITY 1 cohort. The intention of this study was to identify variables related to poor outcomes in our cohort of young active patients and provide evidence for potential indications were augmentation of ACLR with an LET may be warranted.

Chapter 3 focuses on a subgroup of patients that had LMPRT identified at the time of surgery in the STABILITY 1 cohort. The purpose of this study was to assess how an LMPRT affects recovery trajectory and joint health at one- and two-years post-surgery in our patients.

Chapter 4 is an MRI-based study of a subgroup of STABILITY 1 patients at two-years post-surgery. The purpose of this study is to determine whether adding an LET affects articular cartilage quality in the lateral compartment of the knee at two-years post-operative. To our knowledge, it is the first study to use quantitative MRI to compare articular cartilage between patients who underwent ACLR alone versus ACLR with LET.

Chapter 5 is a discussion regarding our findings and how future research can make use of our graft failure model and establish stronger evidence regarding the effect of lateral procedures on osteoarthritis risk after ACLR.

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Chapter 2

3 Predictors of Graft Failure in Young, Active Patients Undergoing Hamstring Autograft Anterior Cruciate Ligament Reconstruction with or without an LET: The Stability Experience

3.1 Abstract

Background: Anterior cruciate ligament reconstruction (ACLR) has higher failure rates in young, active patients returning to sport compared with older, less active individuals. Augmentation of ACLR with an anterolateral procedure has been shown to reduce failure rates; however, indications for this procedure have yet to be clearly defined. The purpose of this study was to identify predictors of ACL graft failure in high-risk patients and determine key indications for when hamstring (HT) ACLR should be augmented by lateral extra-articular tenodesis (LET).

Hypothesis: We hypothesized that different pre-operative characteristics and surgical variables may be associated with graft failure characterized by asymmetric pivot shift and graft rupture.

Study Design: Case-control study

Methods: Data was obtained from the Stability 1 Study, a multicenter, randomized controlled trial of young active patients undergoing autologous HT ACLR with or without LET. We performed two multivariable logistic regression analyses with asymmetric pivot shift and graft rupture as the dependent variables. LET, age, sex, graft diameter, tear chronicity, pre-operative high-grade knee laxity, pre-operative hyperextension on the contralateral side, medial meniscal repair, medial meniscal excision, lateral meniscal repair, lateral meniscal excision, posterior tibial slope angle, and RTS exposure time and level were included as predictors.

Results: Of the 618 patients in the Stability 1 Study, 568 patients with a mean age of 18.8 years (292 females, 51.5%) were included in this analysis. Asymmetric pivot shift occurred in 152 patients (26.8%) and graft rupture occurred in 43 (7.6%). The addition of a LET (odds ratio (OR) = 0.56, 95% confidence interval (CI): 0.37 to 0.83) and increased graft diameter (OR = 0.62, 95%CI: 0.44 to 0.87) were significantly associated with lower odds of asymmetric pivot shift. The addition of a LET (OR = 0.40, 95%CI: 0.18 to 0.91) and older age (OR = 0.83, 95%CI: 0.72 to 0.96) significantly reduced the odds of graft rupture, while greater tibial slope (OR = 1.15, 95%CI: 1.01 to 1.32), pre-operative high-grade knee laxity (OR = 3.27, 95%CI: 1.45 to 7.41), and greater exposure time to sport (i.e., earlier return to sport) (OR = 1.18, 95%CI: 1.08 to 1.29) were significantly associated with greater odds of rupture.

Conclusion: The addition of a LET and larger graft diameter were significantly associated with reduced odds of asymmetric pivot shift. Adding a LET was protective of graft rupture, while younger age, greater posterior tibial slope, high-grade knee laxity, and earlier return to sport are associated with increased odds of graft rupture. Orthopedic surgeons should consider supplementing HT autograft ACLR with a LET in young, active patients with morphological characteristics that make them at high risk of re-injury.

Firth AD, Bryant DM, Litchfield R et al. Predictors of Graft Failure in Young Active Patients Undergoing Hamstring Autograft Anterior Cruciate Ligament Reconstruction With or Without a Lateral Extra-Articular Tenodesis: The Stability Experience. American Journal of Sports Medicine. 2022;50(2)384-394. Copyright © 2021 The Author(s). DOI: 10.1177/03635465211061150

3.2 Introduction

There are many studies detailing the successful outcome of anterior cruciate ligament reconstruction (ACLR); however, there are also many reports of unsatisfactorily high rates of failure, particularly in the younger aged athlete.[1,25,28,54,59] A systematic review by Wiggins et al. showed athletes under the age of 25 who return to sports following ACLR have a reported ipsilateral failure rate between 7% and 14%.[61] Age has been shown to be a significant predictor of ACLR failure in multiple studies.[26,29,50,54] The Multicentre Orthopaedic Outcome Network (MOON) knee group showed that the odds of ACLR failure decrease by 9% for every year increase in age.[24] Webster et al.[59] also showed that patients younger than 20 had a 30% cumulative risk of ACLR re-injury, or contralateral knee ACL injury in the first two years following reconstruction. Other risk factors for ACLR failure have included increased posterior tibial slope[58], meniscus deficiency[43], graft size[29], and graft choice.[32]

Anterolateral based procedures, such as lateral extra-articular tenodesis (LET), or the newer anterolateral ligament (ALL) reconstruction techniques, have emerged as surgical methods to attempt to reduce persistent anterolateral rotatory laxity and ACL graft failure, particularly in patients who may be at high risk of graft failure. A number of theories have been postulated as to why an anterolateral procedure can reduce graft failure. The reduction of persistent rotatory laxity is the most obvious. However, as shown by Engebretsen et al.[10] and more recently Moram et al.[33], the addition of an LET results in reduced graft forces post-ACLR. This may provide some protection during the graft healing and maturation phases. Unfortunately, there is a paucity of literature regarding the indications for adding an anterolateral procedure during ACLR. Two recent consensus papers have outlined potential indications for the augmentation of ACLR with an anterolateral procedure.[11,51] The first included revision ACLR, increased posterior tibial slope, generalized ligamentous laxity (or knee hyperextension greater than 10 degrees), young age and return to contact pivoting sport.[51] The second targeted revision ACLR, high-grade pivot shift, Segond fracture, participation in pivoting sport, and hyperlaxity as primary criteria, and contralateral ACL rupture, Lachman >7mm, deep lateral femoral notch sign, and age younger than 25 as secondary criteria.[11] However, both papers were based upon level V evidence and would suggest that nearly all patients undergoing ACLR should have an anterolateral procedure augmentation. Consequently, given the lower level of evidence behind these position statements and therefore the potentially erroneous conclusions that have been made regarding the addition of anterolateral procedures, higher level of evidence studies are necessary to determine the appropriate indications for lateral augmentation during ACLR. It is clear that more robust evidence is required to guide surgeons and patients as to when an anterolateral augmentation of ACLR is required.

We recently performed a multicenter, randomized clinical trial in which young patients aged 25 and under, who were deemed as being at high risk of re-injury, were treated with hamstring tendon autograft ACLR with or without LET (Stability 1 Study).[12] At two-years post-operative, the addition of the LET resulted in a 60% relative risk reduction of graft failure compared to the ACLR alone.[14] The purpose of the present study was to:

1. Identify pre-operative variables associated with persistent rotatory laxity or graft rupture in high-risk patients from the Stability 1 Study.
2. Determine key indications to inform surgeons when hamstring autograft ACLR should be supplemented with a LET.

The hypothesis of this study was that different patient characteristics and surgical variables may be associated with graft failure characterized by asymmetric pivot shift or graft rupture.

3.3 Methods

3.3.1 Data Collection

Data for this analysis was obtained from the Stability 1 Study (ClinicalTrials.gov: NCT02018354). Six-hundred and eighteen (618) patients between the ages of 15 and 25 years old were recruited from nine centres (7 in Canada, 2 in Europe), then followed for two-years post-operatively. Patients underwent clinical assessment and completed patient-reported outcome measures at 3-, 6-, 12-, and 24-months post-operative. The study was approved by the Western University Research Ethics Board and local Research Ethics Boards at each institution. A detailed study protocol and results are published.[12–14]

3.3.2 Outcomes

The primary outcome in the Stability 1 Study was clinical failure of the ACLR, defined as 1) persistent grade 1 pivot shift at multiple visits; 2) grade 2 pivot shift or greater at any visit; or 3) graft rupture confirmed arthroscopically or on magnetic resonance imaging (MRI).[2] The pivot shift test, which has shown to be specific (97% to 99%, sensitivity 14% to 48%) for detection of ACL rupture,[47] was completed at each visit by a trained, blinded member of the surgical team and graded according to the International Knee Documentation Committee (IKDC) form.[19] A positive pivot shift test has been shown to correlate with worse functional outcome[3,27], and is widely accepted as a marker of failed ACLR.[34–36]

3.3.3 Predictors

We selected 12 predictors for our analyses based on previous findings and clinical hypotheses. These included age[26,29,50], sex[32], treatment group (ACLR alone or ACLR + LET)[14], pre-operative knee hyperextension on the contralateral side[8], graft diameter[29], posterior tibial slope[58], time from injury to surgery (months)[49], pre-operative high-grade knee laxity[30,31], and meniscal treatment status (medial repair, medial excision, lateral repair, lateral excision).[43]

Patients reported age, sex, and date of injury on a patient demographic questionnaire pre-operatively. Tear chronicity was calculated as the time interval, in months, between the date of injury and date of surgery. Passive hyperextension >10 degrees was measured on both knees pre-operatively as part of the Beighton score. Because the degree of hyperextension between uninjured knees is highly correlated and the surgical knee in some patients was locked or otherwise unable to demonstrate pre-injury extension, we used the measurement from the non-operative knee. Pivot shift and Lachman tests were performed under anaesthesia at the time of surgery by the operating surgeon according to the International Knee Documentation Committee guidelines.[19] Presence of a grade 3 Lachman (>10mm difference compared to the other side) or grade 3 pivot shift (+++ gross) were used to define high-grade knee laxity similar to previous research by the MOON group.[30,31] Posterior tibial slope for all patients was measured on a true lateral x-ray taken pre-operatively by one fellowship-trained orthopedic surgeon according to the technique used by Webb et al.[58]

Patients were randomized intra-operatively to ACLR alone or ACLR + LET. The type of procedure performed, ACL graft diameter, and the presence and treatment of meniscal tears were documented on the standardized surgical report forms by the operating surgeon.

3.3.4 Confounding Variables

Patients reported their primary sport and participation level (none, recreational, competitive, varsity, elite) pre-operatively. Post-operatively, patients were given a return to sport (RTS) questionnaire and asked to indicate when they returned to sport and whether it was at a higher, similar or lower level. We classified those who returned to competitive, varsity, or elite sport as high level, those returning to recreational sport as low level, and identified those who did not return at all. Patients were also classified based on their primary sport as high or low risk. High risk sports were defined as those sports requiring cutting, pivoting, or landing from jumps (e.g. soccer, basketball, volleyball, etc.) while low risk sports did not (e.g. swimming, running, etc.). Exposure time, the number of months that patients were playing sports during the study period, was determined by subtracting the post-operative RTS month from the total follow-up period of 24-months. For example, a patient who returned to sport 6-months post-operative would have an exposure time of 18-months and a patient who did not return to sports would have an exposure time of zero-months. Early return to knee-strenuous sports and higher activity level have previously been shown to be related to increased risk of graft failure.[2,5,24]

3.3.5 Statistical Analysis

Statistical Analysis: The primary outcome variable was separated into two distinct groups; those with asymmetric pivot shift (i.e. a grade 1+ pivot shift at multiple visits or a grade 2+ pivot shift at any visit that did not meet the definition of graft rupture) and those with graft rupture, as different factors may be associated with each event. We performed multivariable logistic regression to predict asymmetric pivot shift and graft rupture using the all-enter method with 11 of 12 predictors. Radiographs were not available for 55 patients therefore tibial slope was added in a second step to show the effect of removing these patients and adding slope to the analysis. The graft rupture model was adjusted for the number of months post-operative that patients returned to sport and the level at which they returned. Potential interactions were evaluated between treatment group and other predictors to determine whether they impacted the effectiveness of adding a LET.

To check the assumptions for logistic regression, locally weighted scatterplot smoothing (LOWESS) curves were used to assess linearity between continuous predictors and the log odds. The variance inflation factor (VIF) was used to detect multi-collinearity between predictors. A VIF >2 required investigation and a VIF >10 required the removal of predictors causing multi-collinearity.[18] Outliers and influential points were identified using DFbeta values >0.10[6], with planned sensitivity analyses to determine whether removing influential points changed the contribution of each predictor.

We pared the models down to include only important predictors, removing variables where p>0.30 and presented odds ratios (ORs) and 95% confidence intervals (CIs) for each model. The Hosmer-Lemeshow goodness of fit test and area under the curve (AUC) for a receiver-operating characteristic (ROC) curve were used to assess model fit and its ability to correctly classify individuals. To inform our second objective to patients for whom the addition of a LET may be most beneficial, predictors that could not be measured pre- or intra-operatively (i.e. RTS level and time) were removed. The relationship between these predictors and the addition of a LET were further explored by calculating the risk ratio of graft rupture for different thresholds of each variable by treatment group. Lastly, the predicted probabilities of graft rupture for patients from the Stability 1 study were determined and presented in graphical form for ease of interpretation. All statistical analyses were performed using Stata 15.1.[56]

3.4 Results

Six-hundred and eighteen patients were recruited for the Stability 1 Study and 587 patients (95.0%) had outcome data available at two-years post-operative. Nineteen (3.2%) of the remaining patients were missing predictor variables and were removed from this analysis. The demographic characteristics of the 568 patients we included are presented in Table 2.1.

Table 3.1 Demographic characteristics of Stability 1 patients included in this analysis

Patient demographic characteristics	Stability 1 Cohort (n = 568)
LET group, n (%)	282 (49.6)
Age, years (SD)	18.8 (3.2)
Female, n (%)	292 (51.5)
Knee hyperextension, n (%)	192 (33.8)
Tear chronicity, months (IQR)*	5 (5.7)
Graft diameter, mm (%)	8.1 (0.6)
Medial meniscus repair, n (%)	188 (33.1)
Medial meniscus excision, n (%)	55 (9.7)
Lateral meniscus repair, n (%)	91 (16.0)
Lateral meniscus excision, n (%)	130 (22.9)
Posterior tibial slope, degrees (SD)	9.0 (2.7)
Pre-operative high-grade knee laxity, n (%)	120 (21.1)
Exposure time, months (SD)	11.2 (6.0)
RTS Level	
None	74 (13.1)
Low risk	98 (17.1)
High risk, low level	152 (26.7)
High risk, high level	244 (43.0)

*LET = lateral extra-articular tenodesis; mm = millimetres; SD = standard deviation; RTS = return to sport; IQR = interquartile range; * = median and interquartile range*

Of the available patients, one-hundred and fifty-two patients (26.8%) had asymmetric pivot shift and 43 patients (7.6%) had graft rupture. Adding tibial slope to the 11 predictors in the asymmetric pivot shift model removed 55 patients from the analysis due to missing data; the effect of this decision on predictor estimates and precision in the full model is provided in Table 2.2.

Table 3.2. Odds ratios and standard errors for the original asymmetric pivot shift model before and after including tibial slope

	Excluding Tibial Slope (n=568)		Including Tibial Slope (n = 513)	
Predictor variable	Odds Ratio	SE	Odds Ratio	SE
ACL + LET	0.57	0.11	0.57	0.12
Age	0.95	0.03	0.95	0.03
Female sex	0.99	0.23	1.00	0.24
Knee hyperextension	1.24	0.25	1.38	0.30
Graft diameter	0.60	0.11	0.62	0.12
Medial meniscus repair	1.17	0.25	1.33	0.30
Medial meniscus excision	1.75	0.54	1.58	0.55
Lateral meniscus repair	1.27	0.32	1.34	0.34
Lateral meniscus excision	1.25	0.28	1.18	0.29
High-grade knee laxity	0.87	0.21	0.85	0.22
Tibial slope	---	---	1.08	0.04

SE = standard error, ACL = anterior cruciate ligament, LET = lateral extra-articular tenodesis

The model met all assumptions, and three outliers were identified; however, removing them did not change the model estimates or statistical significance. All VIF values were < 2 indicating no multi-collinearity between predictors and no significant interaction terms were identified between treatment and other predictors. The pared down model with odds ratios (ORs) and 95% confidence intervals (CIs) for important predictors that remained is presented in Table 2.3.

Table 3.3 Predictors of asymmetric pivot shift after paring down the model using p<0.30

Predictor variable	Odds Ratio	95% CI	p-value
ACL + LET	0.56	0.37 to 0.83	**0.004***
Age	0.95	0.89 to 1.02	0.14
Knee hyperextension	1.39	0.91 to 2.10	0.13
Graft diameter	0.62	0.44 to 0.87	**0.005***
Medial meniscus repair	1.30	0.85 to 1.99	0.23
Medial meniscus excision	1.55	0.79 to 3.06	0.19
Tibial slope	1.07	1.00 to 1.15	0.06

*ACL = anterior cruciate ligament, CI = confidence interval; LET = lateral extra-articular tenodesis; age in years, graft diameter in mm; tibial slope in degrees; * = statistically significant*

Adding a LET (OR = 0.56, 95%CI: 0.37 to 0.83) and increasing graft diameter (OR = 0.62, 95%CI: 0.44 to 0.87) significantly decrease the odds of an asymmetric pivot shift. Increasing age remained in the model and was associated with decreased odds of positive pivot shift, though it was not statistically significant (p>0.05). Knee hyperextension, medial meniscus repair, medial meniscus excision and greater tibial slope were associated with increased odds of asymmetric pivot, although none of these variables were statistically significant (p>0.05). The Hosmer-Lemeshow test returned a non-significant result (p=0.52) indicating adequate model fit, and the AUC for the ROC curve was 0.64.

The model for graft rupture, including the 12 factors adjusted for RTS time and level, was performed. Sport risk and level were combined into five categories: 1) No return to sports, 2) Low risk, low level (LRLL), 3) Low risk, high level (LRHL), 4) High risk, low level (HRLL), and 5) High risk, high level (HRHL). Very few patients returned to low-risk sport, so categories 2 and 3 were condensed to one low risk (LR) category. The effect of adding tibial slope and deleting 55 cases from the full model is shown in Table 2.4.

Table 3.4 Odds ratios and standard errors for the original graft rupture model before and after including tibial slope, adjusted for return to sport time and level

	Excluding Tibial Slope (n=557)		Including Tibial Slope (n = 507)	
Predictor variable	Odds Ratio	SE	Odds Ratio	SE
ACL + LET	0.31	0.12	0.34	0.15
Age	0.83	0.06	0.85	0.07
Female sex	0.97	0.31	1.30	0.46
Knee hyperextension	0.80	0.34	0.93	0.45
Graft diameter	0.80	0.24	0.75	0.26
Medial meniscus repair	0.97	0.36	1.11	0.45
Medial meniscus excision	1.74	0.74	2.03	0.97
Lateral meniscus repair	0.95	0.47	0.78	0.44
Lateral meniscus excision	1.12	0.46	0.94	0.45
High-grade knee laxity	3.12	1.19	3.56	1.54
Exposure time	1.22	0.04	1.11	0.05
RTS Level				
None (reference level)	---	---	---	---
Low risk	1.41	1.66	1.12	1.42
High risk, low level	1.73	1.81	1.58	1.61
High risk, high level	1.81	2.17	1.58	1.99
Tibial slope	---	---	1.15	0.08

SE = standard error; ACL = anterior cruciate ligament; LET = lateral extra-articular tenodesis; RTS = return to sport

All assumptions were checked identifying 10 potential outliers; however, removing these observations did not change the model estimates or affect statistical significance. The pared down model with ORs and 95% CIs for important predictors of graft rupture is presented in table 2.5.

Table 3.5 Predictors of graft rupture after paring down the model using p<0.30

Predictor variable	Odds Ratio	95% CI	p-value
ACL + LET	0.40	0.18 to 0.91	**0.03***
Age	0.83	0.72 to 0.96	**0.01***
Tibial slope	1.15	1.01 to 1.32	**0.049***
High-grade knee laxity	3.27	1.45 to 7.41	**0.004***
Medial meniscus excision	1.88	0.64 to 5.50	0.25
Exposure time	1.18	1.08 to 1.29	**0.001***

*ACL = anterior cruciate ligament; CI = confidence interval; LET = lateral extra-articular tenodesis; age in years; tibial slope in degrees; Exposure time in months; * = statistically significant*

The LET procedure was significantly associated with 60% lower odds (95%CI: 0.18 to 0.91) of graft rupture, and a one-year increase in age was associated with 17% lower odds of rupture (95%CI: 0.72 to 0.96). A one degree increase in posterior tibial slope was significantly associated with 15% higher odds (95%CI: 1.01 to 1.32) of rupture. Patients with high-grade pre-operative knee laxity were at 3.27 times (95%CI: 1.45 to 7.41) higher odds of graft rupture. Exposure time remained in the model as a significant predictor, with each additional month of exposure time, indicating an earlier return to sport, increasing the odds of rupture by 18% (95%CI: 1.08 to 1.29). The Hosmer-Lemeshow test returned a non-significant result (p=0.91) and the AUC for the ROC curve was 0.78.

Predicted probabilities of graft rupture for the two continuous predictors, age and posterior tibial slope, are presented graphically by group (Figure 2.1 and 2.2), as well as overall (Figure 2.3).

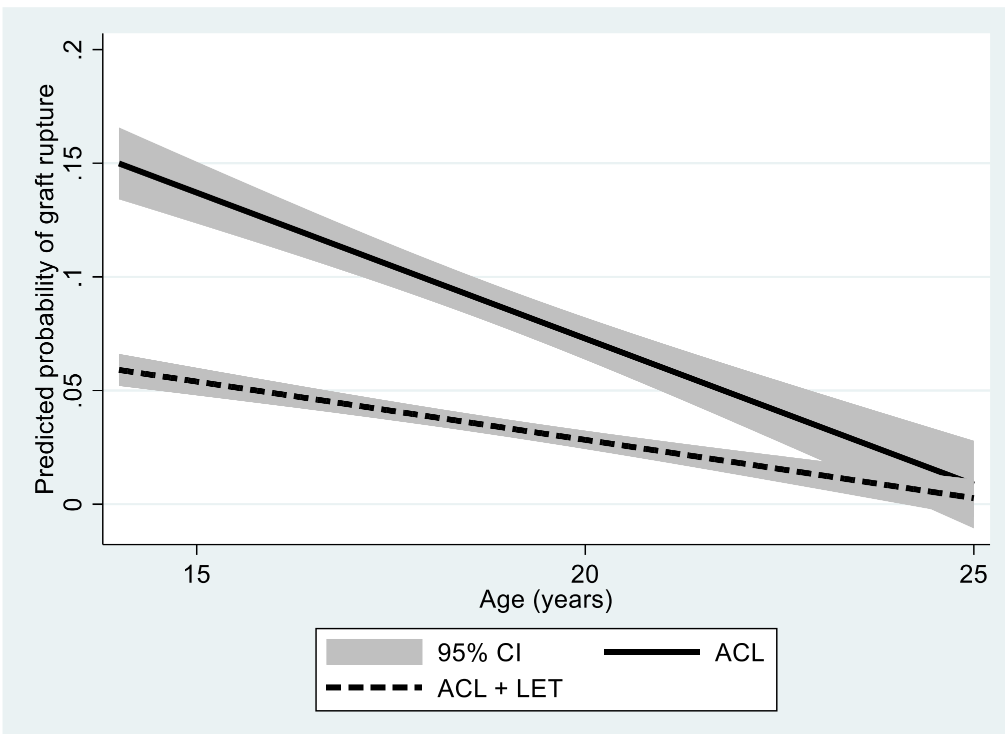

Figure 3.1 Predicted probability of graft rupture by age with and without the addition of a LET for patients in the Stability 1 Study, adjusted for tibial slope angle, medial meniscus deficiency, high-grade knee laxity, and time of return to sport

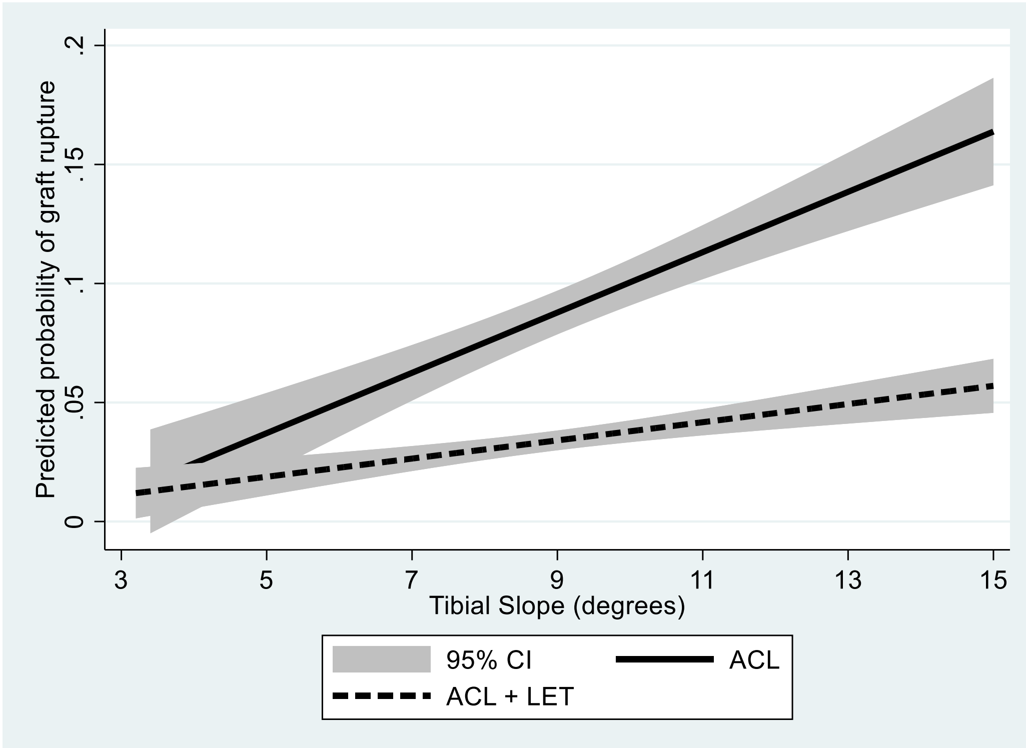

Figure 3.2 Predicted probability of graft rupture by tibial slope angle with and without the addition of a LET for patients in the Stability 1 Study, adjusted for age, medial meniscus deficiency, high-grade knee laxity, and time of return to sport

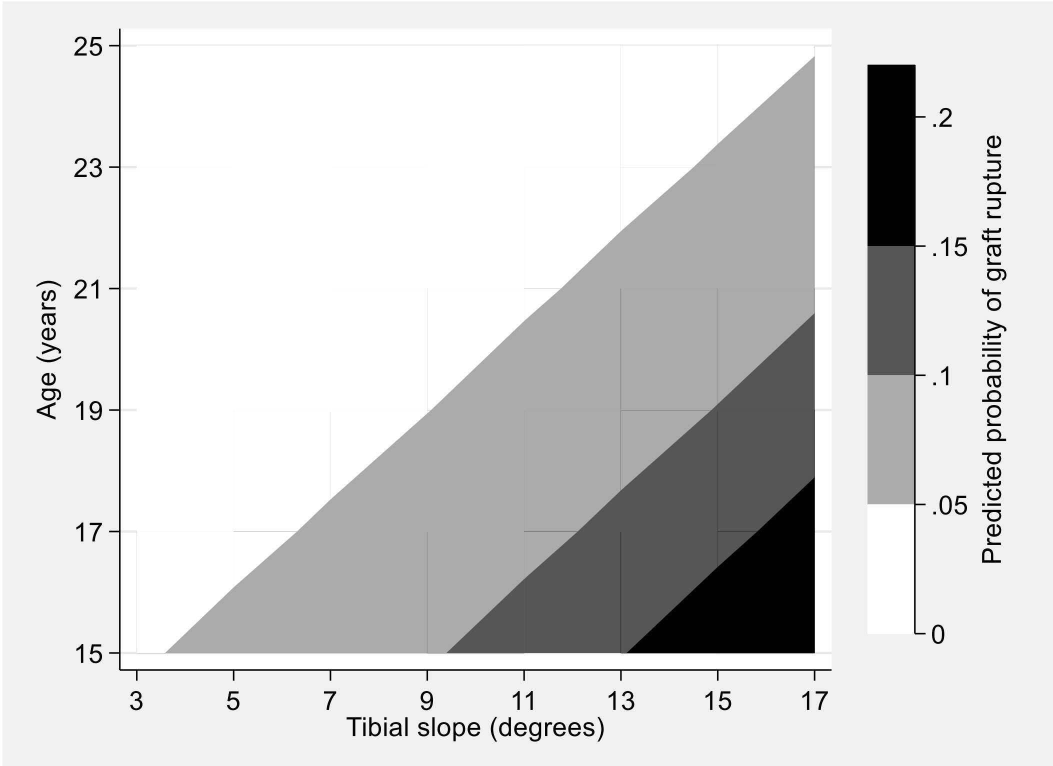

Figure 3.3 Contour plot showing predicted probabilities of graft failure for patients in the Stability 1 Study by age and tibial slope, adjusted for the addition of LET, high-grade knee laxity, time returned to sport and deficient medial meniscus. This shows the predicted probability of ACLR rupture from the Stability 1 Study as a function of tibial slope angle and patient age. Predicted probabilities range from approximately 0% to 25%, with greater probability of failure indicated by areas with darker shading.

Important predictors that contributed to the final models (p<0.30), and thus may be potential indications for LET based on the goal of the procedure in young high-risk patients, are summarized in Table 2.6.

Lastly, we performed a sensitivity analysis using an ROC curve to determine the optimal threshold of the posterior tibial slope variable that best identified those at greater risk of graft failure. The optimal threshold for tibial slope was 9.4-degrees (AUC = 0.62), and patients with slope greater than 9.4-degrees were at 2.7-times greater odds (95%CI: 1.28 to 5.76) of graft rupture than patients with a slope below this threshold.

Table 3.6 Pre-operative and operative indications that adding a LET to hamstring autograft may be warranted to reduce the odds of asymmetric pivot shift or graft rupture

Variable	Asymmetric Pivot	Rupture
Younger age	X	X*
Knee hyperextension	X	
Small graft diameter	X*	
Medial meniscus repair	X	
Medial meniscus excision	X	X
Greater tibial slope	X	X*
High-grade knee laxity		X*
Earlier return to sport		X*

*** = statistically significant**

3.5 Discussion

This multivariable analysis has identified pre-operative patient characteristics and surgical variables that are associated with persistent rotatory laxity and graft rupture within the Stability 1 Study randomised clinical trial. The most important finding was that augmentation of a hamstring tendon autograft ACLR with LET reduces the odds of graft rupture by 60% and post-operative asymmetric pivot shift by 46% after adjusting for other confounding factors.

Age was tightly constrained within our cohort, as only skeletally mature patients who were 25 years of age or younger at the time of surgery were included. Regardless, younger age was associated with higher odds of asymmetric pivot shift and significantly higher odds of graft rupture after adjusting for return to sport time (exposure) and level. In the Stability 1 Study, 37 of the 45 graft ruptures occurred in the 355 patients under the age of 20 (10.4%). Previous studies have also shown that younger patients are at higher risk of graft failure[24,59]. Webster et al. observed that the incidence of ACL failure in patients under 20 was 30% at 2 years when ipsilateral and contralateral injuries were combined.[59] In a study from the MOON group, Kaeding at al. also demonstrated that young age was associated with ACL reinjury, with a 9% decrease in risk for every year gained in age.[24] In a more recent study from the MOON group, college athletes under the age of 23 were shown to have an incidence of 19.7% of ACL rupture of either knee by 6 years post-operative.[54] Furthermore, patients treated with a HT autograft were found to have a 2.1 times higher odds of rupture than those treated with a bone patella tendon bone (BTB) autograft.

In the Stability study, posterior tibial slope was also found to be a significant predictor of graft rupture and contributed to the model for asymmetric pivot shift. The mean tibial slope in our study was 9 degrees (SD = 2.7), which is similar to the mean slope from the case-control study by Webb et al. (males = 9.3 [SD = 2.4], females = 8.5 [SD = 2.3]) that found an association between slope and re-injury.[58] The same group studied the association of tibial slope and age, demonstrating the ‘catastrophic’ effect of young age and increased posterior tibial slope, with an 11 times increase in risk of graft rupture if under 18 years old with a tibial slope greater than 12 degrees at 2 years post-operative.[46] Our data showed that patients with a tibial slope above approximately 9.5-degrees had over twice the odds of graft rupture compared to a patient with slope below that threshold, though the risk difference between patients receiving ACLR alone and ACLR + LET was similar at all levels of tibial slope (Appendix B). If the effectiveness of LET does not change with tibial slope (i.e. LET is equally protective at all slope angles), this suggests LET may contribute to a different mechanism than tibial slope. While tibial slope is modifiable through osteotomy procedures, surgeons may first want to consider using less aggressive procedures known to reduce risk of graft rupture, such as an

LET[14,53] or a different graft choice such as bone-patella tendon-bone autograft[54], even if these factors work independently.

Understanding the significantly increased risk of age and tibial slope to ACLR failure, we investigated the effectiveness of adding a LET visually. We plotted the predicted probability of graft rupture with 95% CIs across the range of tibial slope values and patients' age within the Stability study, adjusting for other important predictors. The graphs suggest that adding a LET to a hamstring tendon autograft ACLR significantly reduces the probability of failure in patients under the age of 23 and with a tibial slope greater than 6 degrees, as the CIs no longer overlap at these proposed thresholds. Tables showing graft rupture between groups (Appendix B) demonstrate a similar relative risk at all values of slope and age, with the addition of a LET being 3- to 4- times more protective than a hamstring autograft ACLR alone.

In this study, lateral meniscus repair or excision had no effect on either outcome and therefore were excluded from the model. While medial meniscus tears requiring treatment at the time of surgery were not statistically significant in either model, they did remain as potential contributing variables; medial meniscus repair was retained in the model for asymmetric pivot shift while medial meniscal excision was retained for both asymmetric pivot shift and graft rupture.

In the asymmetric pivot shift model, the odds of residual laxity were slightly greater when meniscal excision (OR = 1.55, 95%CI: 0.79 to 3.06) was performed compared to meniscal repair (OR = 1.30, 95%CI: 0.85 to 1.99) in relation to no treatment of the medial meniscus. The menisci are understood to behave as secondary stabilizers to anterior translation and anterolateral subluxation in the ACL deficient knee.[37] Recently, Jacquet et al. found a statistically significant association between meniscal treatment and high-grade residual laxity at 3.5 years post-operative.[21] While they included meniscal treatment as a whole rather than assess the medial and lateral compartments separately, they demonstrated the odds of residual laxity were 3.3 times greater in patients undergoing meniscal repair compared to non-repair, and 2.7 times greater in patients undergoing meniscectomy compared to repair.

Medial meniscal excision, while non-significant, was associated with 1.9 times (95%CI: 0.64 to 5.50) higher odds of graft rupture in our model. More specifically, 14/181 (7.7%) patients who had a medial meniscus repair suffered graft rupture, compared with 6/55 (10.9%) of patients who underwent medial meniscus excision. Despite suggestions that repair of a medial meniscus tear may lead to poor outcomes[60], this evidence supports the need for meniscal preservation during ACLR as a deficient medial meniscus may be more problematic. Robb et al. prospectively followed 124 patients undergoing primary ACLR over the course of two years and performed a survival analysis to determine prognostic factors of graft survival.[43] Eighteen patients (14.5%) in the study suffered graft failure, and they found that medial and lateral meniscal deficiency were associated with the risk of failure, and the risk of failure was over 4 times higher for those with medial meniscus deficiency.[43] Research from the MOON group on concomitant meniscal tears at the time of ACL surgery found that while medial and lateral repairs fail at a similar rate by 6-years post-operative, medial repairs fail earlier in follow-up (medial re-tear= mean 2.1 years, lateral re-tear= mean 3.7 years).[60] The SANTI Group found that in 383 patients followed for between two and five years, the addition of an anterolateral ligament (ALL) reconstruction at the time of ACLR is protective of medial meniscus repair, as the failure rate was two times lower in the ACLR and ALL group compared to the ACL alone group.[52] As such, anterolateral procedures such as LET or ALL reconstruction may therefore not only be protective of ACL graft rupture, but also of meniscus repair failure, which in turn may have a combined effect on ACLR outcomes. In contrast, there are concerns that the addition of an anterolateral procedure may over-constrain the knee joint, potentially leading to an increased risk of osteoarthritis (OA) development in the long-term.[42] A 2016 systematic review of eight studies and 421 patients by Devitt et al. showed low incidence of OA in the first 11-years post-operative following combined ACLR and LET however, two studies with >24-months follow-up demonstrated OA rates of greater than 50%.[9] Further evidence of long-term outcomes is required, thus surgeons should weigh the potential risks and benefits when deciding whether to augment ACLR with an LET.

Unsurprisingly, increased exposure time (i.e., earlier return to sport) was also associated with graft rupture. Multiple studies have demonstrated the negative effects of an early return to sport.[5,16,20,39] This may be secondary to reduced neuromuscular conditioning[40] as well as lack of ACL graft maturity.[17] In a recent narrative review, Nagelli and Hewett posed the question of whether return to sport should be delayed until at least 2 years post-operative to allow for appropriate healing and rehabilitation.[38] Whilst this may not be a plausible option for many young athletes, it does highlight the need for better return to sport assessment and functional testing prior to release of patients back to full activity. Understanding these factors warrants a conversation with the patient regarding the addition of LET, but also to determine their post-operative goals, particularly surrounding their desire and intended timing of return to high-risk sport. Despite the lack of retention in the model, our analysis showed that return to a higher risk sport carried greater risk than return to a lower risk sport (Table 2.4).

Graft diameter has previously been shown to be predictive of failed HT ACLR. Magnussen et al. demonstrated that a graft size less than 8mm was associated with failure, whilst a follow up study demonstrated that a 0.5mm increase in graft diameter was associated with a 14% to 18% reduction in the likelihood of revision surgery.[48,55] Graft diameter was not related to graft rupture in our study, likely in part due to specific efforts made to control for graft size intra-operatively by tripling semitendinosus if a 4 strand semitendinosus/gracilis construct was less than 8mm. However, even with these measures in place, we did find that a 1.0mm increase in graft diameter was associated with 38% lower odds of asymmetric pivot shift test.

Knee hyperextension was also found to contribute to the model for persistent rotatory laxity, although was not predictive of graft rupture. Because hyperextension is linked with mechanisms that can increase graft laxity, such as impingement[23], superficial laceration[45], and increased tension on the ACL[22], it is not surprising that hyperextension is predictive of rotational instability but not rupture. Several biomechanical and cadaveric studies have assessed the impact of knee hyperextension on impingement and graft tension. Jagodzinksi et al. (2000) performed MRI scans of 15 knees and found strong correlation (r = 0.67, p = 0.006) between the degree of hyperextension and graft impingement.[23] Goss et al. (1997) took five fresh-frozen cadaveric knees and assessed contact pressure and graft tension for three different tibial tunnel positions; they found higher contact pressures between the ACL graft and the intercondylar notch as hyperextension increased, and increasing graft tension as the degree of hyperextension was greater, regardless of tunnel placement.[15] Clinical research studies have shown conflicting results. Several studies have shown an association between knee hyperextension and pre-operative instability[4,44] post-operative instability[51], and graft failure[8], while others report no relationship between hyperextension and risk of laxity or rupture.[7]

High-grade pre-operative knee laxity as determined by either a grade 3 Lachman or pivot shift test was significantly associated with 3-times greater odds of graft rupture within the Stability 1 study, though it was not retained in the asymmetric pivot shift model. The Stability 1 cohort intentionally included high-risk patients with significant pre-operative laxity[12], including 62% of patients with grade 2 Lachman and 76% of patients with grade 2 pivot shift. Thus, the low-grade vs. high-grade variable is largely a comparison of grade 2 vs grade 3 laxity. Our findings suggest patients with high-grade laxity have similar odds of residual rotational laxity as those with low-grade laxity, while high-grade laxity does contribute to the risk of graft rupture. In contrast, Jacquet et al.[21] recently showed that high-grade pre-operative laxity was predictive of residual laxity in a cohort of 266 patients, though their cohort was older (age range: 18 to 50) and predominantly male (71.3%). Magnussen et al. previously showed an association between high-grade laxity and graft rupture in the MOON cohort at 2- and 6-years post-operative.[30,31] They also showed that high-grade laxity was not associated with the risk of contralateral ACL tear, suggesting that high-grade laxity was related to injury-specific rather than patient-specific factors.[30]

This study has limitations, particularly in relation to the patient sample included in the analysis. First, the sample was part of an RCT of young, active patients at high risk of re-tear that underwent ACLR with a HT autograft, exhibiting specific criteria that put them at higher risk of failure. As such, this cohort is not representative of the overall ACLR population or those receiving other graft types for ACLR. It is also not clear whether the addition of a LET to a BTB autograft would provide the same level of protection, as was found in the previously mentioned MOON study, and is undergoing further investigation in our ongoing study 'Stability 2' (ClinicalTrials.gov: NCT03935750). Second, while the pivot shift test was scored by experienced members of the surgical team (i.e. orthopedic surgeons or orthopedic surgical fellows), this was a multicenter study thus various members of the surgical team performed the pivot shift assessment. While the assessment was performed according to the IKDC scoring system and the trial methodology required multiple grade 1 pivot shift tests for the primary outcome to reduce the effect of measurement variability, there may be some differences in how the pivot shift was graded.

Third, surgical variables such as tunnel placement have also been identified as predictors of ACLR failure in previous studies but were not controlled for in the Stability 1 trial. Furthermore, due to the relatively low number of graft ruptures (n=45) we are at risk of overfitting the rupture model, as logistic regression requires at least 10 events per predictor to be adequately powered.[41] Validation outside the study sample is particularly important for a model with few events; however, the predictors identified by this analysis do coincide with clinical hypotheses for graft rupture.[11,51]

3.6 Conclusion

The addition of a LET to hamstring autograft ACLR was significantly associated with 60% lower odds of graft rupture, while younger age, increased tibial slope, high-grade preoperative knee laxity, and early RTS were associated with higher odds of graft rupture. Younger age, knee hyperextension, increased tibial slope, and medial meniscal repair or excision were all related to higher odds of asymmetric pivot shift, while adding a LET and increasing hamstring autograft diameter significantly reduced asymmetric pivot shift in our high-risk cohort from the Stability 1 Study. Orthopaedic surgeons should consider supplementing hamstring autograft ACLR with a LET in young active patients with morphological characteristics that make them at high risk of reinjury, as the LET was protective when adjusted for other variables in this analysis.

3.7 References

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Chapter 3

4 Meniscal Root Repair Healing at 2-years Following Anterior Cruciate Ligament Reconstruction with or without a Lateral Extra-Articular Tenodesis

4.1 Abstract

Purpose: The purpose of this study is to describe the prevalence of lateral meniscal posterior root tears (LMPRTs) and assess the healing on magnetic resonance imaging (MRI) 1- and 2-years post-surgery in a young, active population following anterior cruciate ligament reconstruction (ACLR).

Methods: Patients were included from the Stability 1 Study, a multi-centre randomized controlled trial of 618 patients undergoing ACLR with or without a lateral extra-articular tenodesis (LET). Patients with LMPRTs were identified at the time of surgery and tear information was documented on the surgical information form. A subset of 20 patients with LMPRT at one study site (FKSMC) underwent bilateral 3T MRI 1- and 2-years post-surgery, and root tear healing was assessed on MRI by a musculoskeletal radiologist. Secondary outcomes included IKDC and KOOS patient-reported outcomes, coronal plane meniscal extrusion, quantitative analysis of lateral tibial cartilage and degree of OA as per the ACLOAS.

Results: LMPRTs were identified during arthroscopy in 6.8% (42/618) of patients and 11.2% (22/196) of patients at FKSMC. Twenty patients (15 root repair, 1 partial excision with repair, 3 excision and 1 untreated) participated in the MRI portion of the study. Complete healing occurred on MRI for 75% (12/16) of repaired tears. The tear was no longer visible on the MRI for 100% (4/4) of non-repaired/non-excised tears at 2-years. There were no significant differences in IKDC and KOOS scores between the root tear cohort and patients without a root tear, or tibial cartilage morphology between the involved and uninvolved knees, at either time point. Relative percentage meniscal

extrusion and relaxation times were similar between those that underwent root repair and those that did not.

Conclusion: Patients with LMPRT demonstrated good outcomes on MRI and patient-reported outcomes out to two years post-operative. There was no difference in outcomes between patients who had LMPRT repaired versus those that were left alone or underwent partial excision. This suggests surgeons are good at identifying which LMPRTs need to be repaired, and in no way suggests root repair is unnecessary.

4.2 Introduction

Lateral meniscus posterior root tears (LMPRTs) have been reported to occur in approximately 7-12% of patients that suffer an anterior cruciate ligament (ACL) tear[1] and are classified by avulsion of the meniscal root or a radial tear within 9mm of the attachment point.[2] The majority of lateral meniscus injuries happen during sports participation, particularly sports that involve pivoting and contact. LMPRTs at the time of ACL injury may be associated with a concomitant medial meniscal damage, increased rotatory laxity, and meniscal extrusion.[3, 4] The meniscal root anchors the meniscus to the tibia, allowing the meniscus to distribute forces throughout the compartment protecting the underlying cartilage and bone.[5] The biomechanical impact of root tears on the tibiofemoral joint is concerning, as cadaveric studies have shown root tears compromise meniscal integrity and function.[2, 6, 7] In two studies that specifically assessed the effect of LMPRTs on tibiofemoral biomechanics, the authors found that root avulsion and nearby radial tears result in decreased contact areas and greater mean and peak contact pressures.[2, 7] Repairing the LMPRTs restored contact pressures to the normal state[2, 7], though Schillhammer et al. found reduced contact area persisted.[7] The lateral posterior root has shown greater mobility than the medial root, which suggests it contributes less to the stability of the knee. Regardless, cadaveric studies have shown high-grade rotatory laxity in combined ACL and LMPRT injury[8-11] and suggest that ACL reconstruction

(ACLR) alone is insufficient to restore normal rotation.[8, 9] Furthermore, while studies with long-term follow-up have shown patients with combined ACL and meniscus tears may have a higher risk of developing knee osteoarthritis (OA).[12, 13] Common treatment options have included non-operative treatment and partial meniscectomy depending on tear severity[14]; however, posterior root repair is currently recommended to restore normal kinematics and prevent the onset of cartilage degeneration.[15] Quantitative magnetic resonance imaging (qMRI) techniques, such as T1rho and T2 mapping, can detect early changes in articular cartilage microstructure[16], which is made up of largely water and an organized extracellular matrix (ECM) that contains collagen, proteoglycans (PGs), and chondrocytes.[17, 18] Early arthritic changes first affect the structure of the cartilage, disrupting organization of collagen, reducing the PG content and increasing water content of the tissue.[17] T1rho and T2 relaxation times are sensitive to changes in the proteoglycan content[19] and water content of the cartilage respectively, with longer relaxation times indicative of degenerative changes.[20, 21] Elevated T1rho and T2 relaxation times have been shown in patients at baseline following acute ACL injury[19, 22-25] and at a minimum of six months post-operative.[19, 22, 26-31] Several studies have found that elevated relaxation times may be related to articular cartilage injury[32] or meniscal tears[19, 26, 33, 34] adjacent to the articular cartilage following ACLR, with the type of repair potentially having an effect as well.[22]

The purpose of this study was to assess articular cartilage health in the lateral compartment of the knee using quantitative MRI at one- and two-years post-operative for a sub-group of patients from the Stability 1 Study that had a LMPRT at the time of surgery. Secondary objectives include describing the incidence of LMPRTs in the study, investigating meniscal extrusion and tear healing, and presenting patient-reported outcome scores for the cohort. Our hypothesis was that repair of the LMPRT would result in similar cartilage quality and outcomes between patients with LMPRT and those without LMPRT at two-years post-operative.

4.3 Methods

4.3.1 Patients:

Patients participating in the Stability Study, a 1:1 randomized controlled trial comparing single bundle hamstring ACLR with or without a lateral extra-articular tenodesis (LET), underwent arthroscopic examination at surgery. The presence of LMPRT was documented, as were patient demographics and a knee examination under anaesthetic. Patients were skeletally mature, aged 25 years and under, had an ACL-deficient knee, and were followed at standardised time points out to two years post-operative.

4.3.2 Surgical Intervention

All patients underwent anatomic, single-bundle ACLR with a hamstring autograft with or without a LET according to the study protocol.[35] Meniscal status was diagnosed arthroscopically and tear characteristics (i.e. type, location, size, etc.) were documented by the operating surgeon. LMPRTs were treated at the time of ACLR according to surgeon preference.

4.3.3 Patient-Reported Outcomes:

All patients enrolled in the Stability 1 Study completed two region-specific questionnaires, the International Knee Documentation Score (IKDC) Questionnaire and the Knee Injury and Osteoarthritis Outcome Score (KOOS), pre-operatively and at each follow-up visit. The IKDC is a patient-reported region-specific functional outcome score that has demonstrable discriminative properties following ACLR and has excellent test-retest reliability and good construct validity for a number of conditions at the knee.[36, 37] The KOOS is a region-specific patient-reported questionnaire divided into five sub-categories that has demonstrated reliability, validity and responsiveness in patients following ACLR.[38]

4.3.4 Imaging Protocols:

MR images of the knee were obtained for each patient at one- and two-years post-operative at one participating site (Fowler Kennedy Sport Medicine Clinic, University of Western Ontario). Baseline scans were retrieved retrospectively for those that underwent MRI for clinical purposes. Patients underwent MRI using a 3T Siemens Magnetom Trio magnet, and a 15-channel Siemens PRISMA knee coil (Siemens Medical Solutions, New Jersey, USA).

Quantitative MRI pulse sequences consisted of a Sagittal Multi-Echo Spin Echo T2 Mapping sequence, and a 16-shot Gradient Echo T1rho Mapping sequence. The T2 Mapping sequence included the following parameters: repetition time = 2700ms, echo times = every 11.1ms out to 77.7ms, field of view = 120mm, matrix size = 384x270, slice thickness = 3.0mm, intersection gap = 0.15mm, bandwidth (Hertz/pixel) = 250, iPat = 2. The T1rho sequence had the following parameters: excitation repetition time = 6.3ms, echo time = 3.2ms, excitation flip angle = 10 degrees, field of view = 160mm, matrix size = 256x256, slice thickness = 3.0mm, view per segment = 512, time of recovery = 4.0 seconds, time of spin lock = 10/20/30/40ms, frequency of spin lock = 500Hz.

Clinical sequences included a proton density (PD) SPACE fat-saturated (FS) sagittal view, a PD turbo spin echo (TSE) FS axial view, a T1 TSE coronal view, and a PD TSE sagittal ACL oblique view. Quantitative sequences were repeated on the contralateral side.

4.3.5 Radiological Assessment:

A fellowship trained musculoskeletal radiologist (SP) reviewed all MRI scans. The site of the LMPRT was visualized and the posterolateral root was identified as being intact or showing signs of residual or recurrent tear. The radiologist also evaluated the entire knee-joint using the ACL OsteoArthritis Score (ACLOAS)[39], a semi-quantitative MRI-based score of total knee health that incorporates assessment of cartilage, ligaments and grafts, bone marrow lesions, synovitis and other features.

Meniscal extrusion was measured on each scan by two independent raters (AF and SJ). A standard mid-coronal slice was selected at the point where the tibial eminence was widest. Meniscal extrusion was measured using the method described by Verdonk et al.[40] and is shown in Figure 3.1.

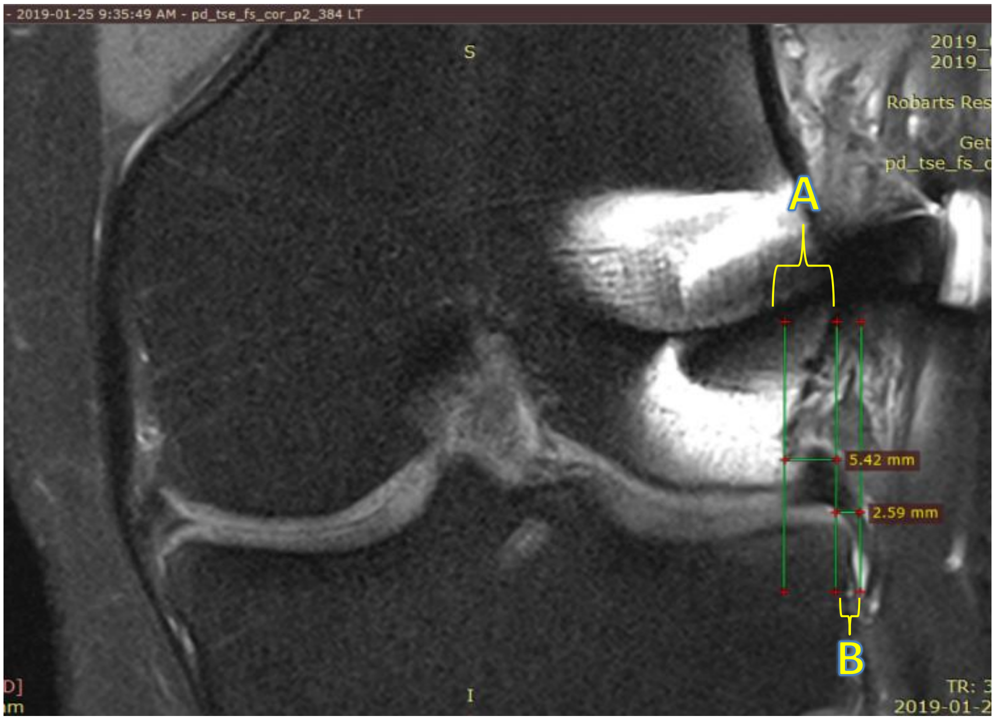

Figure 4.1 Depiction of relative percentage extrusion measurement. The ratio of the lateral meniscus outside the joint over the total width of the meniscus was used to calculate the relative percentage extrusion

Three parallel vertical lines were placed: (A) at the innermost edge of the lateral meniscus; (B) touching the lateral edge of the tibial eminence, and; (C) touching the outermost edge of the lateral meniscus. Two horizontal lines were drawn perpendicular to the vertical lines to measure the distance between A and C (total width of the lateral meniscus), and B and C (lateral meniscus lying outside the joint line). Relative percentage extrusion (RPE) was calculated using the equation:

RPE= ((distance from B to C) / (distance from A to C))*100.

Quantitative Analysis of Articular Cartilage: T1rho and T2 relaxation maps were generated using software developed by an imaging scientist (JSM) at Robarts Research Institute. Maps were created by fitting image intensities of the T1rho and T2 weighted images pixel-by-pixel to the equation $S(TE) \propto \exp(-TE/T2)$ using a Levenberg-Marquardt mono-exponential fitting algorithm. Free software (3D Slicer version 4.10.1; http://www.slicer.org) was used to manually segment articular cartilage according to the method used by Li et al[19]: femoral cartilage was segmented into five sections and tibial cartilage was segmented into three sections in both the medial and lateral compartments using the meniscus as landmarks (Table 3.1) (Figure 3.2).

Table 4.1 Segmentation of knee articular cartilage based on anatomical landmarks in the lateral compartment

	Lateral Cartilage Segmentation
Compartment	Compartment Definition
LT-1	Beneath the anterior horn of the meniscus
LT-2	Between the anterior and posterior horns
LT-3	Beneath the posterior horn of the meniscus
LFC-1	Anterior to the anterior horn
LFC-2	Above the anterior horn of the meniscus
LFC-3	Between the anterior and posterior horns of the meniscus

LFC-4	Above the posterior horn of the meniscus
LFC-5	Posterior to the posterior horn

LT = lateral tibia; LFC = lateral femoral condyle

Medial and lateral slices were selected for segmentation by starting at the center of the joint and moving outwards until three consecutive slices of weight-bearing articular cartilage were found. Each slice was manually segmented, then slices were merged and averaged to provide values for each section. One reader (AF) performed segmentation on each image to quantify articular cartilage quality, then repeated manual segmentation of ten images to determine intra-rater reliability. A second, independent reader performed manual segmentation of ten images to determine inter-rater reliability. We hypothesized that differences in cartilage relaxation may be found in regions adjacent to the posterior horn of the meniscus, such as LT-3 and LFC-4. Given LaPrade's findings of increased contact pressures in deep flexion,[2] we hypothesized elevated relaxation times may also be seen in LT-2 and LFC-5. We also expected these differences may be more prevalent in patients who underwent partial excision compared with root repair.

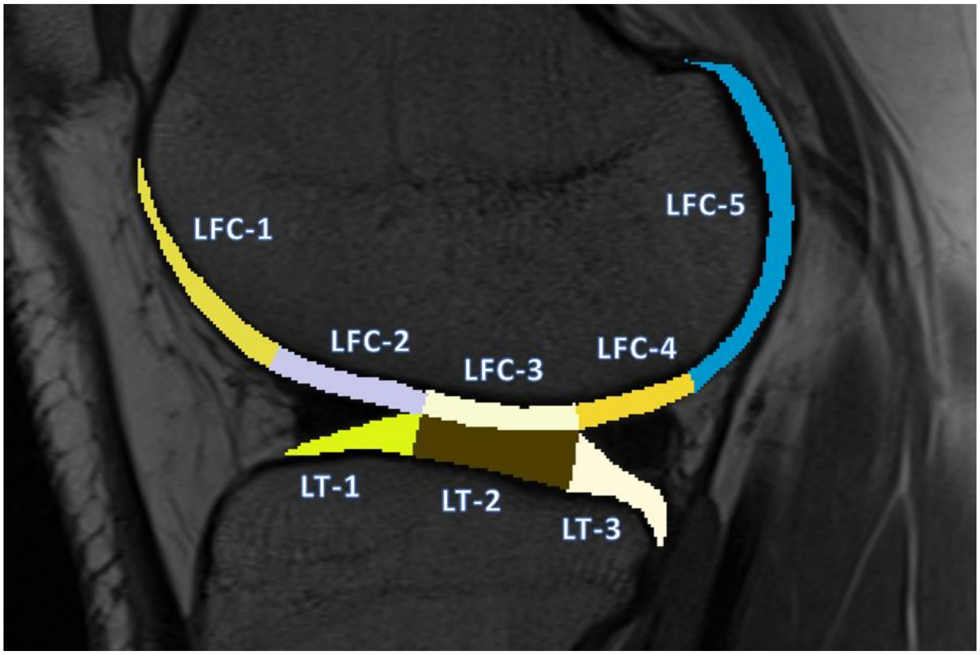

Figure 4.2 Cartilage segmentation of lateral compartment articular cartilage into three tibial regions and five femoral regions.

4.3.6 Statistical Analysis:

Baseline characteristics were presented for patients at all sites within the Stability Study diagnosed with LMPRTs, and patients with LMPRTs participating in the MRI cohort at FKSMC. Continuous variables were summarized using means and standard deviation, while proportions were used to summarize categorical variables. Dependent t-tests were used to compare cartilage relaxation times in the MRI subgroup between the involved and uninvolved knees, and relaxation times, mean differences, and associated 95% confidence intervals (CIs) were reported for each compartment. A Mann-Whitney U test was used to compare the degree of meniscal extrusion in patients where the tear was still visible on MRI versus those that had healed. Inter-rater reliability for meniscal extrusion measurements and qMRI segmentation was assessed using a single-rating, 2-way mixed-effects model, intra-class correlation coefficient (ICC (3, 1), which was interpreted according to the criteria of Koo and Li[41]: <0.50 = poor, 0.50 to 0.75 = moderate, 0.75 to 0.90 = good, >0.90 = excellent. T-tests of unequal variance were used to compare IKDC and KOOS scores between patients in the Stability study without a LMPRT and those patients with an LMPRT. The proportion of patients demonstrating meniscal healing, along with a summary of ACLOAS scores by compartment, were presented for patients at one- and two-years postoperative. Statistical significance was set at $p<0.05$ and all analyses were performed in Stata 16 (StataCorp LLC, 2019).[42]

4.4 Results

4.4.1 Patient and Treatment Characteristics:

A total of 618 patients were enrolled in the Stability study between January 2014 and March 2017 (Figure 3.3).

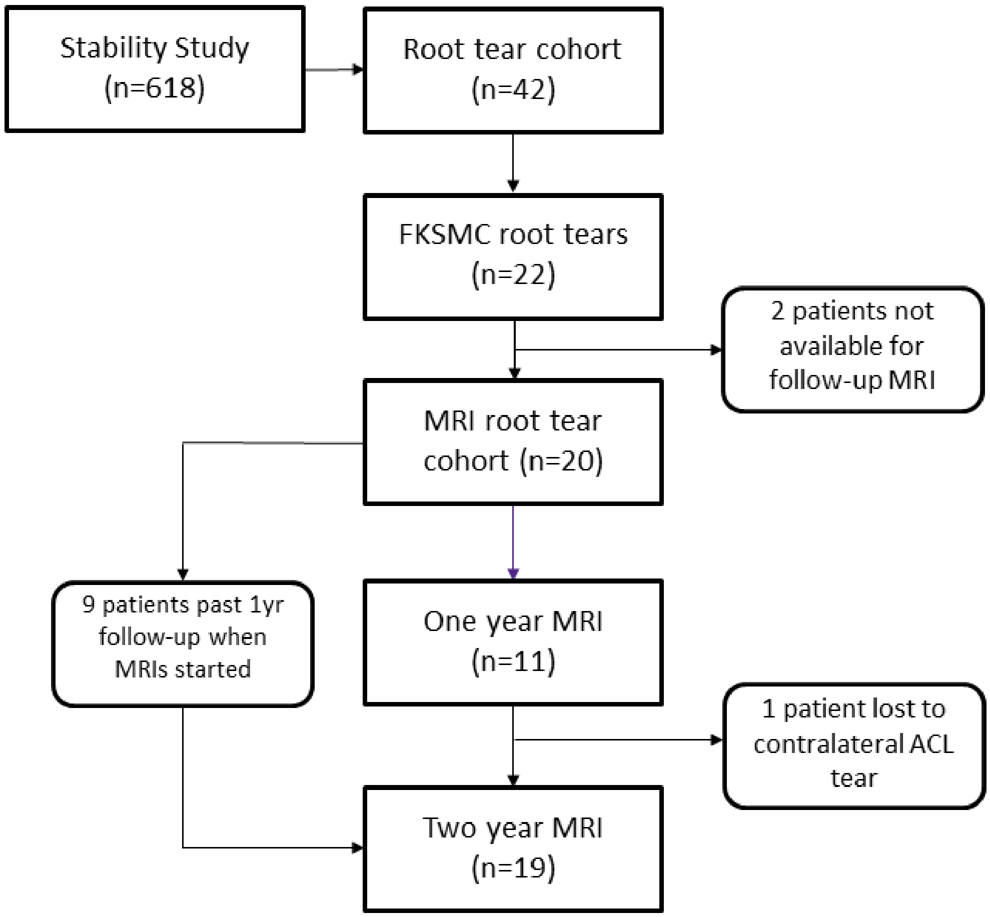

Figure 4.3 Flow diagram of patients in the STABILITY 1 Study with LMPRT, those at FKSMC, and those that agreed to undergo MRI as part of this sub-study

LMPRTs were identified in 42 of 618 (6.8%) patients during arthroscopy at the time of ACLR. Baseline characteristics are shown for the entire Stability 1 cohort, patients at all sites with LMPRT, and the LMPRT sub-group that participated in the MRI sub-study (Table 3.2). Most patients with an LMPRT (95%, 40/42) had a grade 2 pivot shift test or greater at the time of surgery.

Table 4.2 Demographic characteristics of all patients participating in the Stability 1 Study, a sub-group of patients with a lateral meniscus posterior root tear (LMPRT), and the cohort with LMPRT that underwent magnetic resonance imaging (MRI) at one clinical site.

Demographic characteristics	Stability Study (n=618)	Lateral root tear cohort (n=42)	FKSMC MRI cohort (n=20)
Sex, n (%)			
Male	302 (48.9)	18 (42.9)	6 (30)
Mean age (yrs) ± SD	18.9 ± 3.5	18.2 ± 3.3	17.9 ± 2.9
Mean BMI (kg/m^2) ± SD	21.3 ± 3.8	24.5 ± 4.1	23.3 ± 2.7
Mean time from injury to surgery (mos) ± SD	8.4 ± 17.8	7.0 ± 8.3	6.5 ± 6.1
Pre-operative pivot shift grade, n (%)			
Grade 1	59 (9.7)	2 (4.8)	
Grade 2	460 (75.4)	34 (81.0)	
Grade 3	73 (12.0)	6 (14.3)	
Sport participation at time of injury, n (%)	577 (93.4)	40 (95.2)	19 (95)
Soccer	219 (35.4)	9 (22.5)	8 (42.1)
Basketball	84 (13.6)	8 (19.5)	3 (15.8)
Football	53 (8.6)	7 (17.1)	3 (15.8)
Other	221 (38.3)	16 (38.1)	5 (26.3)
Patient-reported injury mechanism, n (%)			
Non-contact	351 (55)	23(57.1)	9 (45)
Concomitant injury, n (%)			
Medial meniscus tear	289 (46.7)	17 (40.5)	9 (45)
Second lateral meniscus tear	---------	10 (23.8)	8 (40)
Chondral defect	179 (29.0)	14 (33.3)	4 (20)
Partial or complete meniscal tear, n (%)			
Complete	---------	26 (62)	16 (80)
Mean tear length (mm) ± SD	---------	7.7 ± 3.5	8.4 ± 4.1
Treatment of LMPRT, n (%)			
None	---------	4 (9.5)	1 (5)

Excision	---------	12 (28.6)	4 (20)
Root repair	---------	26 (61.9)	15 (75)

BMI = body mass index; kg = kilograms; m = metres; mm = millimetres; mos = months; SD = standard deviation; yrs = years; FKSMC = Fowler Kennedy Sport Medicine Clinic; MRI = magnetic resonance imaging

Meniscal root repair was performed on 26 of 42 (61.9%) patients with a LMPRT. Of the patients that did not undergo root repair (16 patients), 12 underwent partial excision/debridement and 4 were left untreated.

4.4.2 Quantitative MRI:

Of the patients in the MRI sub-group, four underwent no treatment or excision while 16 underwent root repair. Within the whole subgroup, there was no difference in lateral tibial cartilage T1rho or T2 relaxation times between the involved and uninvolved side at one-year and two-years post-operative. T2 relaxation times in the lateral femoral cartilage were significantly elevated in two compartments (LFC-1 and LFC-2) and significantly decreased in two compartments (LFC-3 and LFC-4) at 1- and 2-years post-operative (Table 3.3), while T1rho relaxation times were similarly elevated in LFC-2 at 2-years and decreased in LFC-4 at both post-operative timepoints (Table 3.4). T1rho and T2 relaxation times were similar between those repaired and those untreated/excised at all timepoints ($p>0.05$). Inter-rater reliability for cartilage segmentation between the two raters was good (ICC(3,1) = 0.86 (95%CI: 0.83 to 0.88)).

Table 4.3 Comparison of T2 relaxation times between the involved and uninvolved limb in the lateral compartment of the knee at 1- and 2-years post-operative

Compartment	Visit	Involved Mean ± SE	Uninvolved Mean ± SE	Mean diff. (95%CI)	p-value

LT-1	1yr	38.9 ± 0.6	39.4 ± 0.8	-0.5 (-3.1 to 2.0)	0.66
	2yr	38.6 ± 0.7	38.2 ± 0.8	0.4 (-1.6 to 2.4)	0.68
LT-2	1yr	39.0 ± 0.8	39.9 ± 0.4	-0.9 (-2.8 to 1.1)	0.35
	2yr	38.5 ± 0.7	39.8 ± 0.7	-1.2 (-3.0 to 0.7)	0.19
LT-3	1yr	42.9 ± 1.0	42.7 ± 0.9	0.2 (-2.7 to 3.0)	0.90
	2yr	44.1 ± 1.0	43.1 ± 0.9	1.0 (-1.1 to 3.1)	0.34
LFC-1	**1yr**	**53.8 ± 1.7**	**48.4 ± 1.3**	**5.4 (0.7 to 10.1)**	**0.03**
	2yr	**53.6 ± 1.0**	**46.9 ± 0.9**	**6.7 (3.5 to 9.9)**	**<0.001**
LFC-2	**1yr**	**43.9 ± 1.2**	**40.2 ± 1.1**	**3.7 (0.3 to 7.2)**	**0.04**
	2yr	**42.8 ± 0.8**	**38.0 ± 1.0**	**4.7 (2.0 to 7.5)**	**0.002**
LFC-3	**1yr**	**43.9 ± 1.2**	**47.6 ± 1.3**	**-3.7 (-7.3 to -0.2)**	**0.04**
	2yr	**42.6 ± 0.8**	**45.6 ± 0.9**	**-3.0 (-5.5 to -0.5)**	**0.02**
LFC-4	**1yr**	**44.8 ± 2.0**	**50.1 ± 1.3**	**-5.3 (-8.9 to 1.6)**	**0.009**
	2yr	**44.2 ± 0.9**	**49.5 ± 0.9**	**-5.2 (-6.8 to -3.6)**	**<0.001**
LFC-5	1yr	50.0 ± 1.2	47.4 ± 0.6	2.6 (-0.4 to 5.6)	0.08
	2yr	47.7 ± 0.6	46.6 ± 0.7	1.1 (-0.4 to 2.6)	0.14

CI = confidence interval, LFC = lateral femoral condyle, LT = lateral tibia, SE = standard error

Table 4.4 Comparison of T1 relaxation times between the involved and uninvolved limb in the lateral compartment of the knee at 1- and 2-years post-operative

Compartment	Visit	Involved Mean ± SE	Uninvolved Mean ± SE	Mean diff. (95%CI)	p-value
LT-1	1yr	37.7 ± 1.9	37.8 ± 0.9	-0.2 (-4.0 to 3.7)	0.92
	2yr	36.3 ± 1.0	35.2 ± 1.1	1.1 (-2.4 to 4.6)	0.52
LT-2	1yr	35.7 ± 1.9	37.9 ± 0.8	-2.3 (-6.1 to 1.6)	0.22
	2yr	35.9 ± 0.9	35.7 ± 1.3	0.1 (-3.2 to 3.5)	0.93
LT-3	1yr	41.2 ± 1.5	41.3 ± 0.5	-0.1 (-3.3 to 3.2)	0.97

	2yr	41.2 ± 1.1	41.6 ± 1.1	-0.4 (-4.0 to 3.1)	0.80
LFC-1	1yr	55.1 ± 1.8	52.2 ± 2.7	2.9 (-3.1 to 8.8)	0.31
	2yr	55.8 ± 1.1	52.3 ± 1.5	3.5 (-0.5 to 7.6)	0.09
LFC-2	1yr	41.1 ± 1.6	40.2 ± 1.2	0.9 (-2.6 to 4.4)	0.58
	2yr	**44.0 ± 1.2**	**39.1 ± 0.9**	**4.9 (1.5 to 8.3)**	**0.008**
LFC-3	1yr	37.3 ± 1.8	40.8 ± 1.3	-3.5 (-8.4 to 1.4)	0.15
	2yr	39.5 ± 1.0	39.3 ± 1.4	0.2 (-3.4 to 3.8)	0.92
LFC-4	**1yr**	**39.6 ± 1.4**	**44.3 ± 1.2**	**-4.6 (-8.8 to -0.5)**	**0.03**
	2yr	**39.6 ± 1.1**	**43.8 ± 0.9**	**-4.2 (-6.9 to -1.5)**	**0.005**
LFC-5	1yr	48.0 ± 1.5	48.6 ± 1.6	-0.5 (-4.4 to 3.3)	0.76
	2yr	45.6 ± 1.3	48.7 ± 1.5	-3.1 (-6.9 to 0.7)	0.11

CI = confidence interval, LFC = lateral femoral condyle, LT = lateral tibia, SE = standard error

4.4.3 ACLOAS Total Joint Score:

Median (Interquartile range - IQR) total joint ACLOAS scores were similar (15 (11 to 17) versus 15 (11 to 24)) for participants in the MRI sub-group at 1- and 2-years, respectively. The overall score and sub-score joint characteristics are summarized in Table 3.5.

Table 4.5 Overall ACLOAS and sub-category scores for patients with a LMPRT in the Stability I Trial at one- and two-years post-operative

ACLOAS Sub-category	1-year Scores (n = 11)	2-year Scores (n = 19)
Overall scores		
Median (IQR)	15 (11 to 17)	15 (11 to 24)
Cartilage lesions, N (%)		

Medial femur	2 (18.2)	4 (21.1)
Medial tibia	0 (0)	0 (0)
Lateral femur	3 (27.3)	5 (26.3)
Lateral tibia	0 (0)	0 (0)
Patella	2 (18.2)	2 (10.5)
Degenerative BMLs		
Number of lesions (%)		
0	5 (54.6)	13 (68.4)
1	4 (27.3)	4 (21.1)
2	0 (0)	2 (10.5)
3	2 (18.2)	0 (0)
Compartment		
Patellar	1 (10)	3 (37.5)
Medial	4 (40)	0 (0)
Lateral	3 (30)	2 (25.0)
SS tibia	2 (20)	3 (37.5)
Osteophytes, N (%)		
Medial compartment	7 (63.6)	8 (42.1)
Lateral compartment	2 (18.2)	1 (5.3)
Patellar compartment	1 (9.1)	3 (15.8)
Meniscus morphology		
Medial score, median (IQR)	3 (0 to 4)	3 (0 to 6)
Lateral score, median (IQR)	5 (5 to 7)	5 (5 to 7)
Ligament score, N (%)		
ACL		
0	3 (27.3)	4 (21.1)
1	8 (72.7)	14 (73.7)
2	0 (0)	1 (5.3)

PCL grade 1+	0 (0)	0 (0)
MCL grade 1+	3 (27.3)	1 (5.3)
LCL grade 1+	1 (9.1)	1 (5.3)
Effusion-Synovitis, N (%)	5 (45.5)	9 (47.4)
Hoffa's Fat Pad	8 (72.7)	19 (100)

IQR = interquartile range, BML = bone marrow lesion, SS = subspinous, ACL = anterior cruciate ligament, PCL = posterior cruciate ligament, MCL = medial collateral ligament, LCL = lateral collateral ligament

4.4.4 Meniscal Status:

Postoperatively, a partial root tear was still visible on 2 of 11 (18.2%) 1-year MRIs and 7 of 19 (36.8%) 2-year MRIs. All patients with visible partial tears at 1- and 2-years underwent root repair, rather than excision or no treatment. Measurement of lateral meniscal extrusion found 45.5% (5/11) of patients had no extrusion at one-year and 42.1% (8/19) had no extrusion at two-years. The median RPE was 9% (IQR = 0 to 22) and 14% (IQR = 0 to 24) at one- and two-years, respectively. There was no statistically significant difference in median (IQR) RPE between patients who underwent no treatment or partial excision and those that underwent root repair at one-year (13 (IQR = 4.5 to 27) versus 0 (IQR = 0 to 22), p = 0.55) or two-years (5 (IQR = 0 to 15.5) versus 14 (IQR = 0 to 26), p = 0.22) respectively. Interrater reliability for extrusion measurements performed by the two raters was excellent (ICC (3,1) = 0.91, 95%CI: 0.82 to 0.96).

4.4.5 Patient-Reported and Clinical Outcomes:

There was no difference in mean (± standard error (SE)) patient-reported outcome scores between the LMPRT cohort and the other Stability I patients for the IKDC (1yr: 83.5 ± 2.2 versus 83.7 ± 0.6, p=0.93; 2yr: 86.5 ± 0.6 versus 87.4 ± 1.8, p=0.63) or KOOS (1yr: 95.5 ± 1.1 versus 95.6 ± 0.3, p=0.87; 2yr: 96.3 ± 0.9 versus 95.9 ± 0.3, p=0.72) at 1- or 2-years post-operative.

In the overall Stability cohort, 35.7% (15/42) of patients with LMPRT had a grade 2 or greater pivot shift at one visit, or a grade 1 pivot shift at multiple study visits within the two-year post-operative period. Rotatory laxity occurred in 37.5% (6/16) patients that underwent no treatment or excision, and 34.6% (9/26) patients that underwent root repair ($p = 0.92$). There was no statistically significant difference between those that underwent ACLR alone (9/20, 45%) and those that underwent ACLR + LET (7/22, 30%) ($p = 0.32$). There was no difference in clinical failure between patients with a root tear and the rest of the Stability 1 cohort ($p = 0.45$), or between those who underwent root repair and the rest of the Stability 1 cohort ($p = 0.78$).

Six patients with LMPRTs required another operation (3 in the root repair group and 3 in the no treatment or partial excision group). Two patients in the root repair group suffered ACL graft rupture and one required surgery to treat a failed medial meniscal repair, while two patients in the no treatment/excision group tore their contralateral ACL and one had post-operative stiffness requiring manipulation.

4.4.6 Outcome Comparison for Patients with 1- and 2-year MRI:

Ten patients underwent MRI at both 1- and 2-years post-operative. Relaxation times corresponding to the region above and below the posterior aspect of the lateral meniscus, ACLOAS scores, and RPE at each timepoint are shown in Table 3.6 for each patient. Cartilage and meniscal status appear to be relatively stable between the two timepoints as no clear pattern was found, regardless of treatment performed.

Table 4.6 Cartilage, meniscus, and joint outcomes at one- and two-years postoperative for patients in the MRI subgroup that underwent scans at both timepoints

ACLOAS = ACL osteoarthritis score; RPE = relative percentage extrusion; LT = lateral tibia; LFC = lateral femoral condyle

					LT-3		LFC-4	
Patient	Treatment	Visit	ACLOAS Score	RPE	T1rho	T2	T1rho	T2
1	Repair	1-year	16	22%	35.0	41.7	39.9	49.0
		2-years	16	26%	36.4	39.5	37.6	47.0
2	Repair	1-year	28	0%	43.4	42.0	46.9	48.9
		2-years	16	0%	44.4	46.7	46.3	49.0
3	Repair	1-year	15	0%	36.1	50.1	33.0	41.4
		2-years	26	0%	34.7	44.2	32.3	42.3
4	Excision	1-year	11	9%	42.2	45.0	45.7	52.1
		2-years	11	10%	41.0	45.9	39.8	50.2
5	Repair	1-year	32	0%	39.9	41.7	35.1	41.8
		2-years	45.5	0%	36.0	43.5	40.7	47.6
6	No Treatment	1-year	11	17%	40.8	44.5	42.2	52.6
		2-years	12	21%	37.3	46.4	42.3	51.6
7	Repair	1-year	17	0%	42.3	41.0	41.4	53.0
		2-years	11	0%	44.6	39.9	45.4	48.7
8	Repair	1-year	11	16%	39.6	40.4	33.4	42.9
		2-years	15	14%	37.9	48.8	36.0	43.0
9	Repair	1-year	16	50%	50.7	36.5	41.3	37.2
		2-years	10	50%	46.1	33.1	44.8	39.7
10	Excision	1-year	13.5	0%	47.3	43.5	37.6	34.0
		2-years	13	0%	41.5	40.4	31.0	35.3

4.5 Discussion

In this study, we followed a cohort of patients with concomitant LMPRT at the time of ACLR to assess clinical outcomes at 1- and 2-years post-operative. Our findings show statistically significant side-to-side differences in T2 and T1rho relaxation times in the lateral femoral compartment between scans performed at one and two years post operative. Differences ranged from three to six milliseconds depending on region, with higher relaxation times in anterior compartments (LFC-1 and LFC-2) and lower relaxation times in the central and posterior segments (LFC-3 and LFC-4). These findings are inconsistent with our *a priori* hypotheses, as we expected regions adjacent to the posterior horn to demonstrate increased relaxation times if LMPRTs were not properly repaired (e.g., extrusion following repair, or meniscal excision).

A biomechanical study by Perez-Blanca et al. compared eight cadaveric knees with the lateral root intact, avulsed, repaired, and excised.[43] They found that root avulsion significantly decreased contact area in the lateral condyle and root repair was able to restore them at lesser angles, but at greater angles the differences persisted. Our study may contradict these findings since our findings, that posterolateral relaxation times in LFC-3, LFC-4, and LFC-5 were maintained, and in some cases better than the contralateral side, would indicate successful treatment and preservation of cartilage integrity out to two years.

We found no differences in cartilage relaxation or any other outcomes between those who underwent root repair compared with excision; however, this analysis included a small number of patients. In a biomechanical study, Tang et al. showed that partial meniscectomy of LMPRT restores knee biomechanics after ACLR, which also supports our inability to detect differences between the two at an early timepoint.[8] It is important to highlight that our findings are in no way meant to suggest whether surgeons should or should not repair LMPRTs at the time of ACL surgery. Instead, these findings more likely demonstrate the validity of the criteria surgeons in our study used to decide when LMPRTs need to be repaired. Recently, Shumborski et al. published 15-year follow-up data from 52 patients with stable LMPRT that went untreated at surgery and 440 patients with intact lateral meniscus.[44] The authors suggest that while not repairing stable root tears led to a statistically significant effect of increased frequency and severity of pain, and lower IKDC scores compared to patients without lateral meniscal damage, the small effect size was not clinically significant. It is unclear what criteria our surgeons used to determine the treatment of tears that were left alone or partially excised. It may be that these were stable with continuity of the root insertion, hence further evidence of the tear was not visible on MRI at 1 and 2 years follow up. As the numbers of non-repaired LMPRTs in our study and that of Shumborski are small, additional level I and II evidence is required before clinicians accept stable LMPRTs do not need to be repaired.

Traumatic bone marrow lesions often occur in the lateral compartment at the time of ACL injury[45], in the area that corresponds with LFC-2. Traumatic impaction compresses the articular cartilage and could have lasting effects on cartilage composition and quality. In this study, we were unable to account for bone bruising at surgery as patients did not undergo preoperative MRI, thus it is possible these injuries are contributing to the differences seen in the anterolateral knee compared to the contralateral side. Other factors could also be at play. Nakamae et al.[46] (2018) studied predictors related to progression of articular cartilage damage in 174 patients who underwent ACLR and second-look arthroscopy 18-months post-surgery. They found that partial meniscectomy and post-operative anterior laxity compared to the contralateral side were associated with progression of articular cartilage damage in the lateral compartment. While differences were seen in lateral femoral cartilage, relaxation times in the lateral tibia were no different to the uninvolved knee, suggesting cartilage composition is preserved in patients with a LMPRT out to two-years post-operative. Previously, Hirose et al.[32] found patients with posterior horn lesions of the medial meniscus exhibited significantly higher T1 values in weight bearing regions of tibiofemoral cartilage compared to control subjects while patients without medial meniscus injury did not. Koo et al. showed medial meniscus posterior horn tears are more likely to be degenerative and associated with meniscal extrusion than lateral tears[47], which might explain why lateral tears were not associated with worsening cartilage quality in our study.

We also found that complete healing was present in 81.8% (9/11) and 63.2% (12/19) of knees at 1- and 2-years respectively. While seven patients required a second operation, none were specifically to repair the LMPRT. Studies evaluating healing after posterior meniscal root tears have predominantly focused on the medial side.[14] There is some evidence that patients with LMPRTs have better outcomes than those with MMPRTs following surgical repair.[48] Zhuo et al.[49] investigated a series of 31 patients undergoing pull-out repair for LMPRT to assess healing on MRI and at second-look arthroscopy at a minimum of two-years post-operative. On MRI, 28/31 (90.3%) of patients had complete healing and the other three demonstrated partial healing. Anderson et al.[50] performed a retrospective review of 24 patients that underwent repair of radial tears and posterior horn detachment at the time of ACLR to assess outcomes at a minimum of two-years follow-up. Five of their 16 patients (31.3%) required a second operation; however, like our findings, most re-operations were not related to lateral posterior horn injury. One patient suffered a knee injury while skiing and was found to have a detached lateral posterior horn of the meniscus that could not be repaired because of the damage.

While partial healing was visible for some patients on MRI, it appears to have little effect on their patient-reported outcome scores. We found patients with concomitant ACLR and LMPRT had similar IKDC and KOOS scores to other participants without LMPRTs at 1- and 2-year follow-up. Previous studies have similarly shown that good patient-reported outcomes can be expected two-years following root repair.[50, 51] LaPrade et al.[52] reviewed outcomes for 50 patients over the age of 18 that underwent anatomic transtibial pull-out repair for posterior meniscal root tears. The cohort that underwent lateral root repair (n = 14) demonstrated statistically significant improvements on the Lysholm score, the Western Ontario and McMaster Universities Osteoarthritis Index, the Short-Form Health Survey Physical Component Score, and Tegner scores at a minimum of two-years post-operative (range = 2.0 to 4.5). Krych et al.[48] retrospectively reviewed 141 patients with posterior root tears, including 30/141 (21.3%) with occurrence in the lateral compartment. Patients with LMPRTs were younger (mean age = 24.6 years) and more likely to have concurrent ACL injury (26/30, 86.7%) than those with medial root tears, and that root repair results in good patient-reported outcomes at a minimum of two-years post-operative.

In the Stability study, 35.7% (15/42) of patients with a LMPRT had the primary outcome of clinical failure in the post-operative period, a composite measure of asymmetric rotatory laxity and graft rupture. In the group that underwent root repair, 9 of 27 (33%) patients demonstrated clinical failure. This is slightly higher than the clinical failure rate of 31.6% (173/547) in study participants without an LMPRT. Two recent biomechanical studies assessing the role of the lateral meniscus as a secondary-stabilizer of the knee found greater tibial translation during the pivot shift test with a deficient lateral meniscus[11] or detached posterior root.[53] While the goal of root repair is to restore normal biomechanics to the knee, there is the potential that patients with LMPRT are at higher risk of persistent rotatory laxity post-surgery. Additionally, 45% (17/42) of patients in the LMPRT group had a concomitant medial meniscus tear at the time of surgery. The lateral meniscus is more mobile than the medial meniscus, which suggests the medial side contributes more to knee stability.[47] A biomechanical study by Musahl et al.[11] (2010) demonstrated an association between medial meniscus deficiency and the amount of anterior translation for the standardized Lachman test. The combination of LMPRT and medial meniscus pathology could be related to the slightly increased risk of rotatory laxity following ACLR.

We found that just over 50% (10/18) of patients with an LMPRT at the time of surgery demonstrated meniscal extrusion at two-years post-operative, which appears high compared to the published literature. Previous studies have shown that extrusion of the meniscus occurs less often in patients with LMPRTs compared to those with medial root tears. Brody et al.[54] retrospectively reviewed 264 patients undergoing ACLR and identified 26 lateral and 8 medial meniscal root tears. They found extrusion occurred in 6 of 26 (23%) lateral tears and 7 of 8 (87.5%) medial tears. Ahn et al.[55] followed 25 patients who underwent all-inside LMPRT for a minimum of 1-year post-operative, of which 40% (10/25) had extrusion at baseline. Eighteen patients underwent follow-up MRI, and the authors found no significant difference in meniscal extrusion in the coronal plane (p = 0.096) however, extrusion was significantly reduced on sagittal scans (p = 0.007). Proper meniscal repair is critical to the restoration of meniscal function; Schillhammer et al.[7] demonstrated meniscal repair of LMPRT significantly reduces contact pressures on the lateral side in eight cadaveric knees, while contact pressures were much higher in the sectioned (i.e. meniscus deficient) model.

Our study has strengths and limitations. The STABILITY 1 study was a multi-center study large enough to identify 42 patients with LMPRT despite an incidence rate below 7%. The MRI sub-study, however, was only performed at one study site which meant that we were unable to include roughly half the patients with an LMPRT in our analyses. We were able to follow these patients prospectively and collect numerous outcomes to assess their functional outcomes, articular cartilage health, meniscal status, and healing. Unfortunately, baseline quantitative MRI was not included in the study protocol thus we were unable to measure meniscal extrusion or complete the ACLOAS score preoperatively. This prevents us from commenting on baseline damage, along with the longitudinal effect of meniscal treatment on joint changes from the time of injury through the follow-up period. Lastly, two years is a relatively short follow-up period to detect degenerative changes, even with the use of qMRI to detect early biochemical signs of OA, hence future studies should focus on longer-term follow-up of patients with an LMPRT.

4.6 Conclusion

Patients in the Stability study with LMPRT demonstrated good outcomes on MRI and patient-reported outcomes out to two years post-operative. There was no difference in outcomes between patients who had LMPRT repaired versus those that were left alone or underwent partial excision. This suggests surgeons are good at identifying which LMPRTs need to be repaired, and in no way suggests root repair is unnecessary.

4.7 References

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Chapter 4

5 Quantitative Evaluation of Lateral Articular Cartilage Quality on Magnetic Resonance Imaging at 2-years following Anterior Cruciate Ligament Reconstruction with or without a Lateral Extra-Articular Tenodesis

5.1 Abstract

Introduction: Concerns have arisen that the addition of a lateral extra-articular tenodesis (LET) to anterior cruciate ligament reconstruction (ACLR) may accelerate the development of post-traumatic osteoarthritis (OA) in the lateral compartment of the knee.

Hypothesis/Purpose: The purpose of this study is to evaluate whether augmentation of ACLR with an LET affects articular cartilage quality on magnetic resonance imaging (MRI) two years post-operatively in a young, active population. We hypothesized there would be no difference in T1rho and T2 relaxation times in the lateral compartment if an LET was added to ACLR.

Methods: A consecutive sub-group of patients at the Fowler Kennedy Sports Medicine Clinic participating in the STABILITY 1 Study, which compares ACLR Alone to ACLR + LET, underwent bilateral 3T MRI at two-years post-surgery. The primary outcome was T1rho and T2 relaxation times. Articular cartilage was manually segmented on three consecutive slices, and values were averaged for three regions on the tibia and five regions on the femur in the lateral compartment. Analysis of covariance (ANCOVA) was used to compare relaxation times between groups for each compartment, adjusted for lateral meniscus tears and treatment, the presence of cartilage and bone marrow lesions, and relaxation times on the contralateral side. An effect size (ES) (Cohen's d) was calculated to estimate the magnitude of the standardized difference between groups for each compartment (<0.2 = trivial, 0.2 to 0.5 = small, 0.5 to 0.8 = moderate, >0.8 = large). The Anterior Cruciate Ligament OsteoArthritis Score (ACLOAS) was completed by a musculoskeletal radiologist.

Results: Ninety-five participants (44 ACL, 51 ACL+LET) with a mean age of 18.8 years (59.8% female, 58/97) underwent MRI 2-years post-operative (range = 20 to 36 months). Means and standard errors (SE) were calculated for T1rho and T2 relaxation times (ms) for each compartment. T1rho relaxation times were significantly elevated for the ACLR + LET group in LT-1 (ACLR = 34.1 ± 0.8, ACLR+LET = 37.3 ± 0.7, p = 0.005) and LFC-2 (ACLR = 34.7 ± 0.8, ACLR+LET = 37.3 ± 0.7, p = 0.007) demonstrating moderate effect sizes, while T2 relaxation times were significantly elevated for the ACLR+LET group in LFC-1 (ACLR = 34.7 ± 0.8, ACLR+LET = 37.3 ± 0.7, ES = moderate) and LFC-4 (ACLR = 34.7 ± 0.8, ACLR+LET = 37.3 ± 0.7, ES = moderate) demonstrating small effect sizes. There was no difference in ACLOAS scores between groups (p = 0.99). Quadriceps and hamstring strength asymmetry were weakly correlated with elevated relaxation times in LT-1 and LFC-1. Relaxation times were not associated with patient-reported outcomes at two-years postoperative.

Conclusions:

Increased relaxation times demonstrating small-to-moderate effect sizes suggest early biochemical changes in the articular cartilage of the anterolateral compartment in patients who underwent ACLR + LET compared to patients that underwent ACLR alone. Higher relaxation times in the anterolateral tibia and femur were associated with quadriceps and hamstring asymmetry, however, there was no association between relaxation times and patient-reported outcomes. Poor model fit, and findings inconsistent with *a priori* hypotheses, puts the clinical significance of these findings into question. Further evidence and long-term follow-up are needed to better understand the association between these results and the risk of development of OA in our patient cohort.

5.2 Introduction

Anterior cruciate ligament reconstruction (ACLR) is a highly-recommended treatment option for those with ACL deficiency, particularly for those keen to return to pivoting or cutting sports.[54] Recently, a greater focus has been placed on the anterolateral complex (ALC) and its role in reducing graft failure due to its function as a secondary stabilizer of the knee.[81,86] Many biomechanical studies have shown augmenting ACLR with an anterolateral procedure leads to better restoration of knee stability compared to ACLR alone[18,25,38,92]; however, several studies also demonstrated over constraint of the lateral compartment of the knee.[25,37,38,72,92] Concerns surrounding over constraint continue to be equated to increased load in the lateral compartment of the knee, which in turn has been suggested to be associated with the development of osteoarthritis (OA).[6,73] Evidence from early clinical studies, where lateral extra-articular tenodesis (LET) was performed in isolation rather than concomitantly with ACLR, demonstrated progressively worse outcomes and high rates of osteoarthritis more than ten years after surgery.[3,69] However, more recent level I and II studies comparing ACLR with lateral augmentation to ACLR alone have demonstrated reduced rates of postoperative rotatory laxity[28] and graft failure[28,77,78] with no evidence of over constraint[90]. Long-term follow-up data from these trials is not yet available. In contrast, Castoldi et al. (2020) recently published long-term follow-up data of a randomized controlled trial comparing bone-patellar tendon-bone (BTB) ACLR with or without an LET.[15] While just 43 of 120 patients (36%) were available for clinical follow-up, they found the LET group had significantly higher risk of lateral compartment OA (BTB = 22%, LET = 59%, $p = 0.02$). Determining whether augmentation of ACLR with LET affects the risk of osteoarthritis is paramount, as patients undergoing ACLR are already at high risk of developing osteoarthritis long-term.[24,52]

Early detection of biochemical changes in articular cartilage, a precursor to visible radiographic degradation and osteoarthritis, is possible using quantitative magnetic resonance imaging (qMRI).[10,30] Two popular compositional imaging techniques are T1rho and T2 imaging.[30] Changes in T1rho relaxation times are associated with changes in extracellular matrix (ECM) and proteoglycan content[20,44], while changes in T2 relaxation times relate to both collagen orientation and content, and water content in the ECM.[19,51,59] Longer T1rho and T2 relaxation times have shown to be associated with worsening cartilage quality.[19,30,43,46,66,68] Many studies have used compositional imaging to assess articular cartilage after ACL injury[11,12,31,61,62,83,88] and ACLR.[5,29,33,40,47-49,63,64,76,82,83,87,88,91,93] Changes in tibiofemoral cartilage relaxation times have been detected using T1rho and T2 qMRI within the first two postoperative years following ACLR.[49,82,87,91] To our knowledge, no studies have compared the effect of augmenting ACLR with LET on cartilage matrix composition compared to ACLR alone.

Therefore, the purpose of this study is to evaluate whether augmentation of ACLR with an LET affects articular cartilage quality on qMRI compared to ACLR alone at two years postoperatively in a young, active population from the STABILITY 1 Study. We hypothesized there would be no difference in T1rho and T2 relaxation times in the lateral compartment of knees undergoing ACLR alone compared to ACLR with LET at two-years postoperative. If there was a difference in lateral compartment cartilage relaxation due to adding an LET, we expected to find it in the central or posterior tibia and femur, as previous biomechanical studies have demonstrated over constraint after augmenting ACLR with an LET anywhere from 15 to 90 degrees of flexion.[25,42,60]

5.3 Methods

5.3.1 Patient Recruitment

Patients in this MRI cohort were participants in the STABILITY 1 Study, a multicenter, pragmatic, randomized controlled trial comparing anatomic hamstring autograft ACLR with or without an LET.[26] A total of 618 patients were recruited and randomized 1:1 to ACLR alone or ACLR + LET, then followed for two-years postoperative. Patients were eligible to participate in the Stability 1 Study if they were skeletally mature and 25-years of age or younger, with an ACL-deficient knee, and were considered at high-risk of re-injury based on two of the following criteria: 1) participation in competitive pivoting sports, 2) presence of a grade 2 pivot shift or greater, 3) generalized ligamentous laxity (Beighton score of 4 or greater) or genu recurvatum greater than 10º. Patients were excluded if they had: previous ACLR on either knee, a multi-ligament injury, a symptomatic articular cartilage defect requiring treatment other than debridement, asymmetric varus greater than 3º, or unwillingness to complete two years of follow-up. Results from the Stability 1 Study have been published.[23,27,28]

A consecutive sub-group of patients at one clinical site, the Fowler Kennedy Sport Medicine Clinic (FKSMC), were recruited to participate in this sub-study. These patients underwent 3T MRI at the Centre for Functional and Metabolic Mapping (CFMM) at the Robarts Research Institute at their two-year follow-up visit.

5.3.2 Surgical Approach

All patients underwent anatomical autograft hamstring ACLR. The presence of cartilage lesions or meniscus tears, and concomitant procedures, were documented at the time of surgery by the operating surgeon. A Modified-Lemaire LET was performed for all patients randomized to ACLR + LET.[26] A 5cm oblique skin incision was made between the lateral epicondyle and Gerdy's tubercle. A strip of iliotibial band measuring 1cm x 8cm was taken without removing it from the Gerdy's tubercle attachment, which was then tunneled under the fibular collateral ligament and attached to the femur with a Richards' staple (Smith & Nephew). The LET was attached with the knee at 70º flexion in neutral rotation and with minimal tension applied.

5.3.3 Quantitative MRI

The primary outcome for this study was T1rho and T2 relaxation times at two-years postoperative determined using qMRI. Patients underwent bilateral 3T MRI on a Siemens Magnetom Trio magnet, and a 15-channel Siemens PRISMA knee coil (Siemens Medical Solutions, New Jersey, USA) at or after the two-year visit. Pulse sequences included a 16-shot Gradient Echo T1rho Mapping sequence and a Sagittal Multi-Echo Spin Echo T2 Mapping sequence (Table 4.1). In-house software was used to generate T1rho and T2 relaxation maps. Image intensities of the T1rho and T2 weighted images were fit pixel-by-pixel to the equation $S(TE) \propto \exp(-TE/T2)$ using a Levenberg-Marquardt mono-exponential fitting algorithm.

Table 5.1 Quantitative magnetic resonance imaging sequences and parameters

Sequence and Parameter	
T2 mapping sagittal 7-echo RT	
Repetition time/echo times (ms)	2700/11.1, 22.2, 33.3, 44.4, 55.5, 66.6, 77.7
Field of view (mm)	120
Matrix size	384 x 270
Slice thickness (mm)	3.0
Intersection gap (mm)	0.15
Bandwidth (Hz/px)	250
iPat	2
T1rho 16shot tr4000 40ms RT	
Excitation repetition time/echo time (ms)	6.3/3.2
Excitation flip angle (deg)	10
Field of view (mm)	160
Matrix size	256 x 256
Slice thickness (mm)	3.0
View per segment	512
Time of recovery (sec)	4.0
Time of spin lock (ms)	10, 20, 30, 40
Frequency of spin lock (Hz)	500

Ms = milliseconds; mm = millimetres; Hz = Hertz; sec = seconds

Cartilage was segmented manually by one assessor (AF) using free 3D Slicer software (version 4.10.1, https://www.slicer.org/). Processed T1rho and T2 maps were registered in Slicer and overlaid with MR images that demonstrated cartilage contours. Relaxation times less than 0ms and greater than 100ms were filtered from the T1rho and T2 maps used for segmentation to remove artificially high or low relaxation times from the articular cartilage region. Manual segmentation was performed on the cartilage image using three consecutive slices in the lateral compartment of the joint similar to the method used by Li et al.[49] Articular cartilage was separated into three regions on the tibia and five regions on the femur, in the lateral compartment of the knee (Table 4.2) (Figure 4.1).

Table 5.2 Segmentation of knee articular cartilage based on anatomical landmarks in the lateral compartment

Lateral Cartilage Segmentation	
Compartment	Compartment Definition
LT-1	Beneath the anterior horn of the meniscus
LT-2	Between the anterior and posterior horns
LT-3	Beneath the posterior horn of the meniscus
LFC-1	Anterior to the anterior horn
LFC-2	Above the anterior horn of the meniscus
LFC-3	Between the anterior and posterior horns of the meniscus
LFC-4	Above the posterior horn of the meniscus
LFC-5	Posterior to the posterior horn

LT = lateral tibia, LFC = lateral femoral condyle

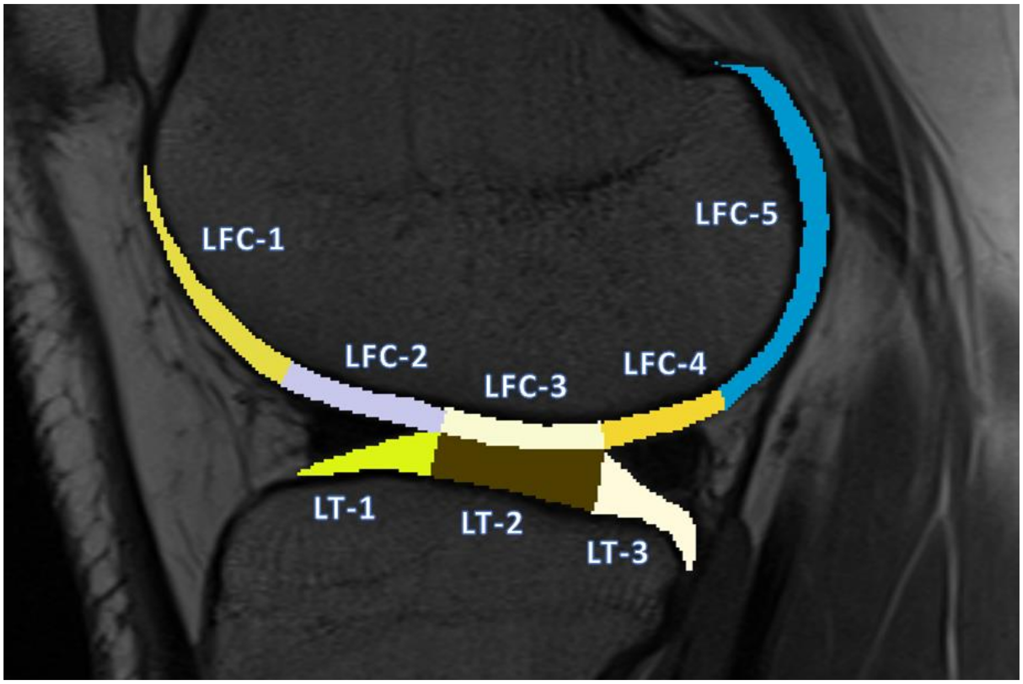

Figure 5.1 Diagram showing manual articular cartilage segmentation into three tibial regions and five femoral regions in the lateral compartment of the knee

5.3.4 Qualitative MRI

Additional MRI sequences were available for qualitative assessment, including a proton density (PD) SPACE fat-saturated (FS) sequence, a PD turbo spin echo (TSE) FS axial view, a T1 TSE coronal view, and a PD TSE sagittal ACL oblique view. A modified version of the Anterior Cruciate Ligament OsteoArthritis Score (ACLOAS) was used to assess joint health at two-years postoperative. The ACLOAS is a semi-quantitative scoring system designed to assess longitudinal knee joint health in patients following ACL injury that involves assessment of bone marrow lesions (BMLs), cartilage morphology, osteophytes, cruciate and collateral ligaments, the ACL graft, meniscal tears and extrusion, and effusion-synovitis.[70] The ACLOAS has previously been shown to have good intra- and inter-rater reliability for most features in patients out to five-years post-ACLR.[70] Patients included in this study did not undergo baseline MRI, thus the ACLOAS represents cross-sectional joint health at two-years, rather than longitudinal change from the time of injury. All scans were scored by one experienced musculoskeletal (MSK) radiologist (SP). We were unable to blind the radiologist to the LET procedure due to the presence of artifact in the lateral compartment from the titanium staple used to anchor the tenodesis.

5.3.5 Patient-Reported Outcome Measures and Functional Testing

As part of the STABILITY 1 Study, patients completed questionnaires at the two-year timepoint. We included the International Knee Documentation Committee (IKDC) score, the Knee injury and Osteoarthritis Outcome Score (KOOS), Lower Extremity Functional Scale (LEFS), and the 4-Item Pain Intensity Measure (P4) in this analysis. The IKDC is an 18-item questionnaire that asks patients about symptoms, sports activities, and function following a knee injury. Higher scores on the IKDC indicate better knee function. The IKDC has been shown to be useful for describing patient function after ACLR.[34,39] The KOOS is a 42-item questionnaire with five subscales related to pain, symptoms, activities of daily living, sports, and quality of life. The KOOS is scored from 0 (extreme limitations) to 100 (no limitations), and has shown to be reliable and valid in patients following ACLR.[71] The LEFS is a regional questionnaire that includes 20-items scored from zero to four on a five-point Likert-scale. The items ask about limitations with activity, and the total score ranges from 0 (no limitations) to 80 (extreme difficulty). It is reliable and valid for patients with lower extremity injuries and after ACLR.[2,9] The P4 includes four items that ask patients to score their pain from 0 (no pain) to 10 (worst pain imaginable) in the morning, afternoon, night, and during activity over the past two days. The total score ranges from 0 (no pain) to 40 (worst possible pain), and the P4 has shown to be valid and responsive in patients with musculoskeletal conditions.[80]

Functional testing included the hop test and isokinetic strength testing. Both tests are explained in detail in a previous publication.[27] Hop test was expressed as a limb symmetry index (LSI), where performance on the involved limb was expressed as a percentage of the contralateral side. The average peak torque (Newton meters) was recorded for the quadriceps and hamstrings of each limb. Quadriceps and hamstring strength were expressed as a percentage of the contralateral side by dividing the involved average peak torque by the contralateral value.

5.3.6 Plan for Analysis

An *a priori* sample size calculation was not performed as this was a sub-study of a larger trial. We approached a consecutive sample of participants from the STABILITY 1 Study to undergo MRI at their final follow-up visit. Based on a previous systematic review by Atkinson et al. effect sizes of 0.68 to 0.72 for T2 relaxation times exist between those at risk of OA and controls in the lateral compartment. Thus, expecting an effect size of 0.7, and assuming a type 1 error rate of 5% (alpha = 0.05) and 80% power (beta = 0.20), we would require approximately 32 participants per group. Patient characteristics were summarized for both groups using means and standard deviations for continuous variables and proportions for categorical variables. Total ACLOAS scores and sub-group scores were summarized for each group using the median and interquartile range (IQR). We used an analysis of covariance (ANCOVA) to determine the adjusted mean T1rho and T2 relaxation times for each group in the lateral compartments of the knee, adjusted for surgical repair or excision of the lateral meniscus, visible cartilage and bone marrow lesions, and contralateral relaxation times within the same compartment. Meniscal tear length was included as a continuous covariate, while meniscal repair or excision were treated as dichotomous. A standardized effect size (Cohen's d) was calculated following ANCOVA to estimate the effect attributable to adding an LET, which we interpreted using Cohen's suggested criteria[17]: <0.2 = trivial, 0.2 to 0.5 = small, 0.5 to 0.8 = medium, >0.8 = large. We planned to perform sensitivity analyses where we remove any patients who suffered a graft rupture or contralateral ACL tear prior to the two-year MRI to test the robustness of the effect attributed to LET itself.

Lastly, we assessed the correlation between T1rho and T2 relaxation times and secondary outcomes from the STABILITY 1 Study, including the IKDC, KOOS, LEFS, P4, hop test LSI, quadriceps average peak torque indices, and hamstrings average peak torque indices. We used Spearman's rho to determine the magnitude and direction of the correlation, which we interpreted according to Cohen's criteria:[17] <0.10 = no correlation, 0.10 to 0.30 = weak correlation, 0.30 to 0.50 = moderate correlation, >0.50 = strong correlation. Statistical significance was set to $p<0.05$ and all analyses were performed in Stata version 17 (StataCorp LLC).

5.4 Results

Ninety-seven patients at FKSMC agreed to undergo MRI at two-years postoperative (range: 20 to 36 months postoperative). One patient failed pre-screening and was unable to undergo MRI due to the presence of metal shrapnel in their body. One patient that underwent MRI was excluded from this analysis as significant motion artifact rendered the scan unusable (Figure 2). All 95 patients completed patient-reported outcome measures at two-years, while 88 patients completed strength and 72 completed hop testing.

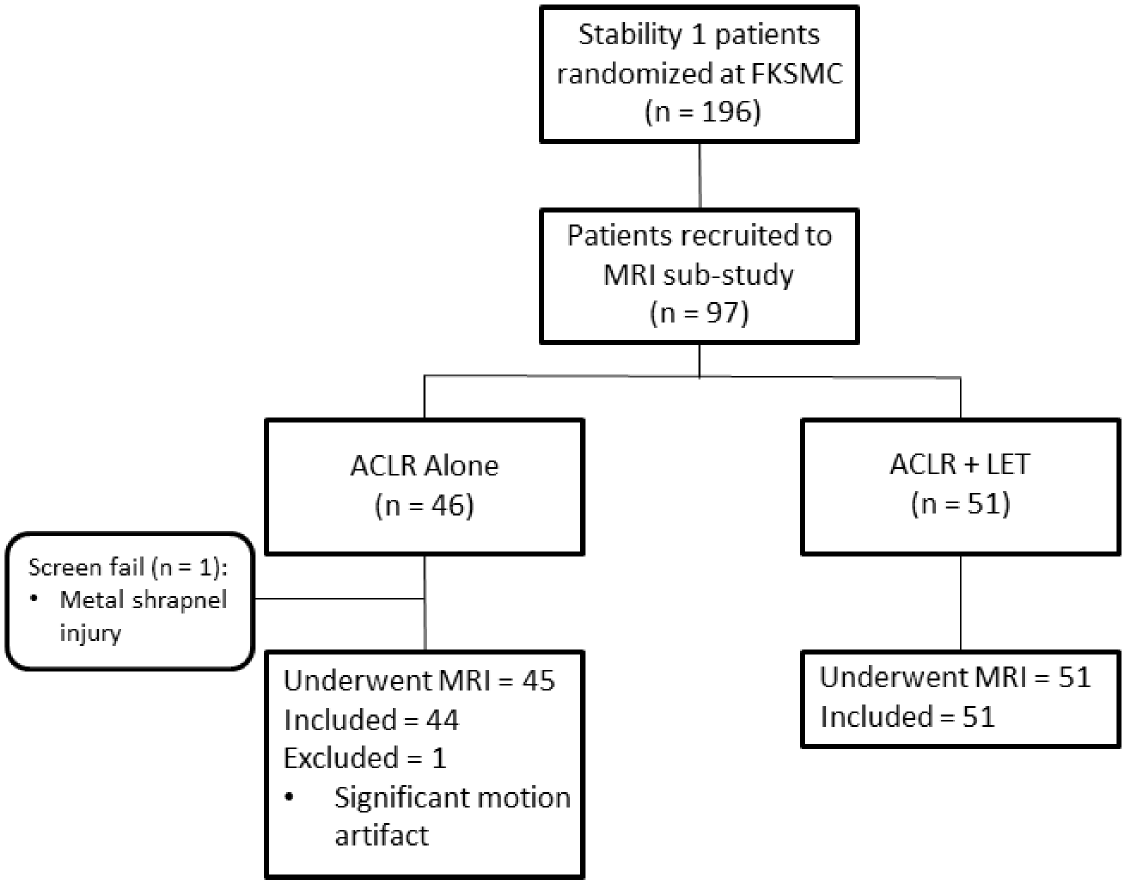

Figure 5.2 Flow diagram of STABILITY 1 patients recruited for participation in the MRI sub-study at the Fowler Kennedy Sport Medicine Clinic

Demographic and surgical characteristics for those included in this study were similar between groups (Table 4.3). Slightly more patients underwent lateral meniscus repair or excision in the ACLR Alone group, but these differences were not statistically significant.

Table 5.3 Demographic and surgical characteristics of patients included in the MRI subgroup

Characteristic	ACLR Alone (n = 44)	ACLR + LET (n = 51)	P-value
Age (years), mean ± SD	19.0 ± 3.3	18.6 ± 3.2	0.51
Female sex, n (%)	26 (59.1)	32 (62.7)	0.77
Contact injury, n (%)	18 (40.9)	24 (47.1)	0.49
Height (in), mean ± SD	68.1 ± 3.8	67.2 ± 3.5	0.25
Weight (kg), mean ± SD	71.2 ± 15.5	72.2 ± 14.8	0.75
Body mass index (kg/m^2), mean ± SD	23.6 ± 3.4	24.6 ± 3.4	0.18
Beighton score	3.5 ± 2.7	3.2 ± 3.3	0.61
Knee hyperextension, n (%)	18 (40.9)	19 (37.3)	0.63
Posterior tibial slope, mean ± SD	9.6 ± 2.6	9.2 ± 2.8	0.49
Tear chronicity (months), mean ± SD	6.5 ± 8.9	9.8 ± 17.2	0.26
Meniscal status, n (%)			
Medial meniscus repair	21 (47.7)	18 (35.3)	0.22
Medial meniscus excision	1 (2.3)	3 (5.9)	0.62
Lateral meniscus repair	13 (29.5)	9 (17.6)	0.17
Lateral meniscus excision	8 (18.2)	6 (11.8)	0.38

Cartilage lesions at surgery, n (%)	7 (15.9)	7 (13.7)	0.77
Lateral tibia	1 (2.3)	0 (0)	
Lateral femur	6 (13.6)	4 (7.8)	
Postoperative sport demand, n (%)			0.80
No return to sport	3 (6.8)	5 (9.8)	
Low risk, low level sport	5 (11.4)	8 (15.7)	
Low risk, high level sport	6 (13.6)	4 (7.8)	
High-risk, low-level sport	9 (20.5)	12 (23.5)	
High-risk, high-level sport	21 (47.7)	21 (41.2)	
Exposure time postoperative (months), mean ± SD	12.1 ± 5.9	11.5 ± 5.4	0.60

**Indicates statistical significance at p<0.05; SD = standard deviation; in = inches; kg = kilograms; high risk sport = cutting, pivoting or landing from jumps; low risk sport = none of these movements; high level sport = competitive, varsity, or elite; low level = recreational.*

Adjusted mean T1rho and T2 relaxation times were calculated for each compartment on the lateral side using contralateral relaxation times and the presence of cartilage lesions as covariates (Table 4.4). Contralateral relaxation times were associated with relaxation times on the surgical side in many compartments ($p<0.05$). Cartilage and BML covariates were not significantly associated with T1rho relaxation times. Interaction terms were found between meniscal tear length and meniscal treatment for T1rho relaxation in LFC-1 ($p = 0.03$), and T2 relaxation in LFC-3 ($p = 0.12$), LFC-4 ($p = 0.02$), and LFC-5 (p =

0.06). In all cases, as meniscal tear length increased, meniscal repair was associated with lower cartilage relaxation times compared to meniscal excision (Figure 4.3). BMLs, and visible cartilage lesions were not associated with a difference in T2 relaxation times (p>0.05).

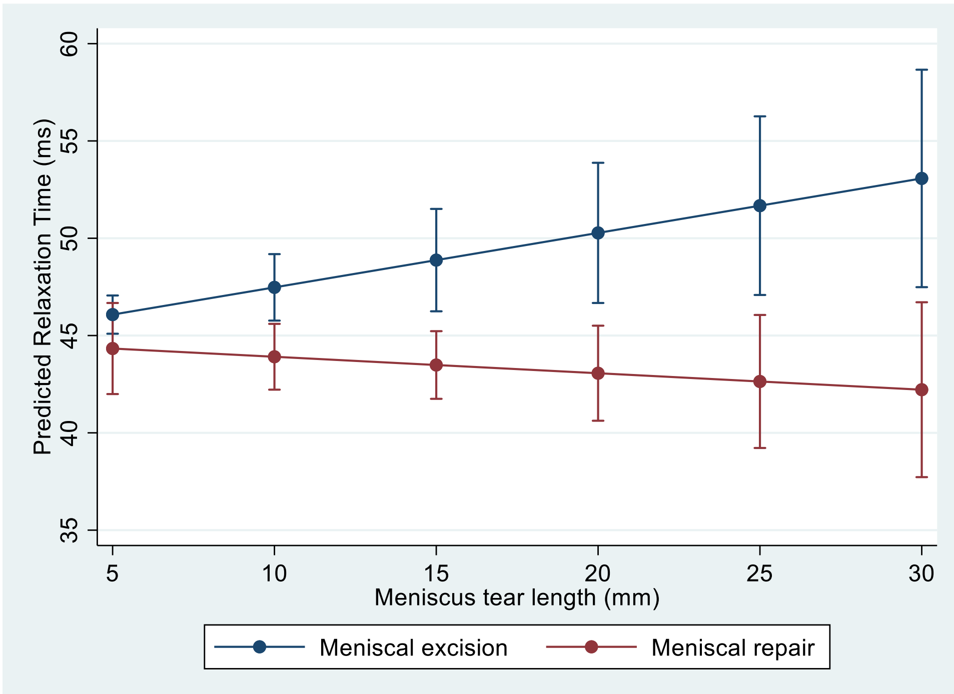

Figure 5.3 Margins plot demonstrating the interaction effect (p = 0.02) between meniscal tear length and treatment on T2 relaxation in LFC-4. Larger meniscal tears are associated with increased relaxation times two-years postoperative if patients undergo meniscal excision, while meniscal repair results in lower relaxation times regardless of tear length.

We found that for the ACLR+LET group, adjusted T1rho relaxation times were statistically significantly higher in LT-1 and LFC-2, with both differences representing a medium effect size between groups. T2 relaxation times were statistically significantly higher for the ACLR+LET group in LFC-1 and LFC-4, though the effect size was small.

Table 5.4 Comparison of adjusted mean T1rho and T2 relaxation times between the ACLR Alone and ACLR+LET groups in the lateral compartment of the knee

Region	Scan	ACLR Alone	ACLR + LET	P-value	Effect Size Interpretation	Adjusted R^2
LT-1	**T1rho**	**34.1 ± 0.8**	**37.3 ± 0.7**	**0.005***	**Medium (0.69)**	**0.10**
	T2	37.2 ± 0.5	37.3 ± 0.4	0.89	Trivial (0.03)	0.05
LT-2	T1rho	34.3 ± 0.9	36.6 ± 0.8	0.07	Small (0.40)	0.08
	T2	38.0 ± 0.4	38.9 ± 0.3	0.07	Small (0.38)	0.14
LT-3	T1rho	41.7 ± 0.8	41.0 ± 0.7	0.52	Trivial (0.13)	0.00
	T2	42.9 ± 0.6	43.8 ± 0.5	0.24	Small (0.24)	0.06
LFC-1	T1rho	53.4 ± 0.8	53.8 ± 0.7	0.72	Trivial (0.08)	0.02
	T2	**49.1 ± 0.7**	**51.2 ± 0.7**	**0.03***	**Small (0.44)[a]**	**0.13**
LFC-2	**T1rho**	**40.1 ± 1.0**	**43.9 ± 0.9**	**0.007***	**Medium (0.54)**	**0.03**
	T2	40.2 ± 0.6	40.4 ± 0.5	0.80	Trivial (0.05)	0.06
LFC-3	T1rho	37.3 ± 1.0	39.5 ± 0.9	0.09	Small (0.34)	0.00

	T2	41.8 ± 0.6	42.6 ± 0.5	0.30	Small (0.22)	0.10
LFC-4	T1rho	39.4 ± 0.8	40.1 ± 0.7	0.52	Trivial (0.13)	0.00
	T2	**44.2 ± 0.6**	**45.9 ± 0.5**	**0.04***	**Small (0.46)**	**0.33**
LFC-5	T1rho	46.4 ± 1.2	43.9 ± 1.1	0.051	Small (0.44)	0.08
	T2	47.4 ± 0.5	48.4 ± 0.4	0.16	Small (0.33)	0.15

**Indicates statistically significant differences; [a]indicates statistically significant differences disappeared when patients who suffered an injury to either ACL postoperative were removed; LT = lateral tibia; LFC = lateral femoral condyle. Interpretation of Cohens d: <0.2 = trivial, 0.2 to 0.5 = small, 0.5 to 0.8 = moderate, >0.8 = large.*

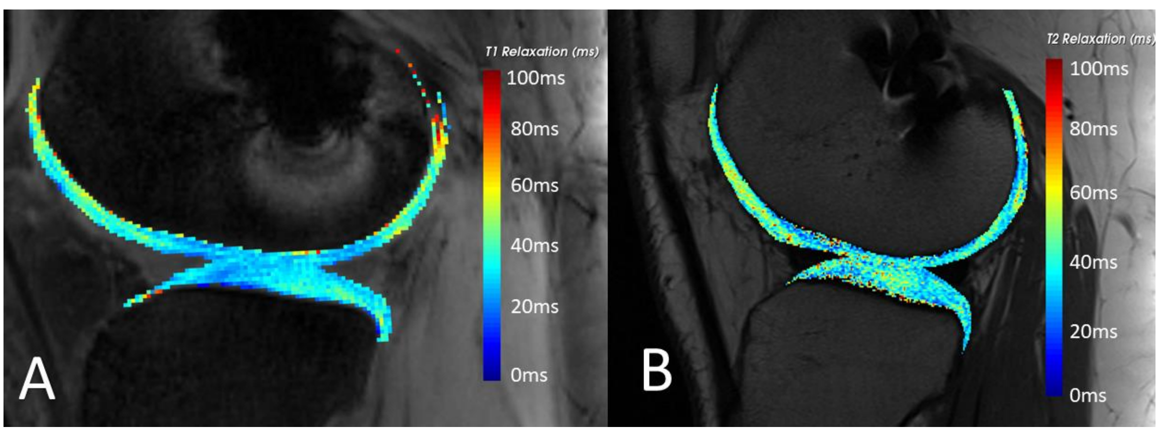

Figure 5.4 Cartilage heat map of A) T1rho and B) T2 relaxation times in the lateral compartment of the knee for a patient in the ACLR + LET group, where relaxation times range from 0ms (blue) to 100ms (red). The presence of metal artifact from the titanium staple.

Total ACLOAS scores and subcategory scores are summarized for each group in Table 4.5. There were no significant differences between groups for overall ACLOAS score (z = -0.01, p = 0.99), and there was no difference in cartilage integrity, bone marrow lesion, osteophyte development, or ACL graft score between groups (p>0.05). There were few visible cartilage lesions in the tibia for either group, while lesions were most common in the central and posterior regions of the lateral compartment. A higher proportion of patients in the ACLR + LET group had an ACL graft that was hypointense with regular thickness, though this difference was not statistically significant. The distribution of meniscal scores on the ACLOAS was similar between groups, however there was a significant difference in the posterolateral compartment. Median meniscal scores were higher for the ACLR Alone group (median = 3, IQR = 5) at two-years compared to the ACLR + LET group (median = 0, IQR = 1).

Table 5.5 Anterior Cruciate Ligament OsteoArthritis Scores overall and for each sub-category between groups for patients in the STABILITY 1 MRI sub-study

ACLOAS Category	ACLR Alone	ACLR + LET	p-value
Overall score, *median (IQR)*	10 (9.5)	11 (11)	0.99
Cartilage integrity score, *median (IQR)*	0 (0)	1 (3)	0.10
Anterolateral tibia, *n (%)*	0 (0)	0 (0)	
Centrolateral tibia, *n (%)*	0 (0)	0 (0)	
Posterolateral tibia, *n (%)*	0 (0)	1 (2.0)	
Anterolateral femur, *n (%)*	1 (2.3)	2 (3.9)	
Centrolateral femur, *n (%)*	8 (18.2)	6 (11.8)	
Posterolateral femur, *n (%)*	2 (4.5)	5 (9.8)	
Bone marrow lesion score, *median (IQR)*	1 (1)	1 (1)	0.50
Anterolateral tibia, *n (%)*	0 (0)	4 (7.8)	

Centrolateral tibia, *n (%)*	0 (0)	4 (7.8)	
Posterolateral tibia, *n (%)*	3 (6.8)	3 (5.9)	
Anterolateral femur, *n (%)*	0 (0)	1 (2.0)	
Centrolateral femur, *n (%)*	4 (9.1)	1 (2.0)	
Posterolateral femur, *n (%)*	2 (4.5)	0 (0)	
Presence of osteophytes, *n (%)*	16 (36.4)	22 (43.1)	0.50
Osteophyte score, *median (IQR)*	0 (1.5)	0 (1)	0.59
ACL graft score, *n (%)*			0.19
Hypointense, regular thickness	15 (34.1)	27 (52.9)	
Hyperintense, regular thickness	24 (54.5)	22 (43.1)	
Thinned or elongated graft	3 (6.8)	1 (3.9)	
Graft failure, complete discontinuity	2 (4.5)	1 (2.0)	
Meniscal Scores, *median (IQR)*	5 (7.5)	3 (8)	0.30
Anterolateral meniscus, *median (IQR)*	0 (0)	0 (0)	0.99
Lateral meniscus body, *median (IQR)*	0 (1)	0 (0)	0.99
Posterolateral meniscus, *median (IQR)*	3 (5)	0 (1)	0.02

ACLOAS = Anterior Cruciate Ligament OsteoArthritis Score; IQR = interquartile range

We performed two sensitivity analyses to determine the robustness of our findings. First, we removed seven patients who had suffered either a contralateral ACL tear (n = 2, ACLR Alone = 1, ACLR+LET = 1) or graft rupture (ACLR Alone = 4, ACL + LET = 0) during the postoperative period. Second, we removed an additional four patients who re-tore their meniscus during the postoperative period (ACLR Alone = 2, ACLR+LET = 2).

Neither sensitivity analysis led to changes in our findings for T1rho or T2 mapping. The difference in posterolateral meniscus scores on the ACLOAS was no longer significant once patients who suffered a secondary injury were removed.

Mean (± standard error) patient-reported outcome scores, including the IKDC (ACLR Alone = 88.9 ± 1.6, ACLR + LET = 91.0 ± 1.5, $p = 0.34$), KOOS (ACLR Alone = 86.6 ± 1.7, ACLR + LET = 88.9 ± 1.5, $p = 0.33$) , LEFS (ACLR Alone = 75.8 ± 1.1, ACLR + LET = 76.3 ± 0.9, $p = 0.72$), and median (interquartile range) P4 scores (ACLR Alone = 0 (0 to 2), ACLR + LET = 0 (0 to 1), $p = 0.39$) were similar between groups. Functional testing scores, including the average peak torque quadriceps indices (ACLR Alone = 90.9 ± 1.9, ACLR + LET = 91.0 ± 1.4, $p = 0.95$), hamstring indices (ACLR Alone = 91.3 ± 1.2, ACLR + LET = 88.1 ± 1.9, $p = 0.23$), and hop test LSI (ACLR Alone = 98.8 ± 0.8, ACLR + LET = 99.4 ± 0.6, $p = 0.50$) were also similar between groups. There were no significant correlations between relaxation times and patient-reported outcomes at the two-year timepoint within any region of the lateral compartment ($p > 0.05$). Several weak, negative correlations were found between relaxation times and functional testing results. Higher T1rho ($r_s = -0.22$, $p = 0.047$) and T2 ($r_s = -0.26$, $p = 0.04$) relaxation times within LT-1 were associated with lower hamstrings average peak torque symmetry, while higher T2 relaxation times in LFC-1 were associated with reduced quadriceps average peak torque symmetry ($r_s = -0.27$, $p = 0.03$). Functional testing was not significantly correlated with relaxation times in any other region.

5.5 Discussion

In this study, we found that quantitative 3T MRI using T1rho and T2 mapping demonstrated elevated relaxation times for the ACLR + LET group in the anterolateral tibia, and in three regions of the femur at two-years postoperative. However, the clinical impact of these changes is unclear due to their anatomical location and the small magnitude of differences. Because of the damage to articular surfaces during the original ACL rupture, we expected to observe evidence of OA development in LT-2 and -3, and

LFC-3 and -4. Because a LET has been shown to be associated with over constraint between 15 and 90 degrees of flexion[1,25,42,60], we expected to find greater evidence of OA development in these same locations for patients who underwent LET compared with those who did not. This is not consistent with what we observed. The majority of differences between groups were found in the anterior region (i.e., LFC-1, LFC-2, and LT-1) of the lateral knee. With respect to meniscal injury at the time of ACL rupture, we expected worse relaxation times in patients who had undergone an excision. In fact, we were able to show that the effect of meniscal tear length on femoral cartilage degradation depends on whether the tear was treated with repair or partial excision. Meniscal repair led to relatively stable cartilage relaxation regardless of tear length, while partial excision of increasingly large meniscal tears was associated with greater femoral cartilage relaxation values compared to repaired tears of the same size. Interestingly, previous studies have shown there may be an association between meniscal deficiency and LET in the anterolateral knee. A recent cadaveric study by Shimakawa et al.[75] showed that the center of pressure was observed to move more anterior on the tibia following LET in a lateral meniscus deficient knee, which could help explain our findings. While small to moderate effect sizes were found to exist within these regions of the lateral compartment, the clinical significance of these findings is uncertain. Atkinson et al. recently performed a systematic review and meta-analysis to compare relaxation times between those at risk for knee OA and healthy controls.[4] Large T2 effect sizes differentiated between patients who were either classified as at-risk or healthy, in the LFC and LT, while moderate T1rho effect sizes differentiated between groups in LFC. Conversely, T1rho relaxation was unable to differentiate between those at-risk and healthy controls in the LT. Only one finding from our study, a moderate difference in T1rho relaxation for LFC-2, approaches these thresholds. Furthermore, there was no association between cartilage relaxation times and patient-reported outcomes at the two-year follow-up. While early biochemical changes may not be affecting patients’ quality of life and function at the two-year timepoint, this cohort will be followed long-term to monitor these differences and determine whether differences at two-years are associated with later osteoarthritis development.

Greater effect sizes were detected using T1rho mapping, which may be especially sensitive for the detection of proteoglycan depletion in early OA.[31,53] We found that T1rho and T2 relaxation times were not similarly elevated within each region, which suggests different mechanisms of cartilage degeneration within different regions of the lateral knee. Both proteoglycan depletion and disorganization of the collagen matrix are known to occur with early OA, and it is possible that detection of, or advancement, of these processes differs by region within the lateral knee. To our knowledge, this is the first study to compare the effect of different ACLR techniques on cartilage integrity and specifically in those who underwent ACLR with or without an LET.

The proposed advantage of quantitative mapping techniques is the ability to detect changes in cartilage biochemistry before structural changes become evident.[7,50,66] Therefore, it is not surprising that we found small to moderate effect sizes between groups using qMRI, whilst there was no difference in terms of visible joint damage on the ACLOAS ($p = 0.99$). Most visible damage in our young, active population was related to meniscal procedures performed at the time of ACLR rather than early signs of osteoarthritis. Overall, patients within our study demonstrated few visible cartilage lesions at two-years follow-up. Lesions were most common within the centrolateral femur, as they were present in 14.7% (14/95) of patients. Potter et al. found that LT and LFC were the two most common regions for cartilage lesions at the time of ACL injury in a longitudinal study monitoring the progression of cartilage injuries long-term.[65] The authors graded cartilage integrity using the Outerbridge score and found mean scores of approximately 2.5 in the LFC and 3.5 in the LT for the ACLR group by two-years post-injury. Our patients fared better in terms of cartilage integrity at two-years, as median ACLOAS scores were 0 and 1 for the ACLR and ACLR + LET groups respectively. While this is encouraging, Potter et al. did show that cartilage loss accelerates by 7-years postinjury, with the risk of cartilage loss in the LFC soaring to 50-times higher than baseline by seven-years post-injury. While low-grade cartilage lesions were not associated with relaxation times in any compartment, this may be due to signal heterogeneity, where both high and low signal are found within the lesion.[43] The variance in relaxation times may make it difficult to detect cartilage degeneration within these low-grade lesions using T1rho and T2 mapping alone.

Additionally, BMLs present at two-years were not significantly associated with increased relaxation times in our study, though others have shown bone bruising at the time of injury are associated with both chondral injury, greater cartilage relaxation values postoperative, and development of OA.[22,88] A lack of baseline imaging limits our ability to control for bone bruising at the time of surgery. Bone bruises relate to the mechanism of injury and are quite common in the lateral compartment[36,74,89], particularly in regions that correspond with LFC-2 and LT-3 in our study. Little damage was seen in the anterolateral part of the joint at two-years postoperative yet, we found a difference between the ACLR + LET and ACL Alone groups in this area, contrary to our *a priori* hypotheses. This could help explain our findings given the association between BMLs and cartilage degeneration. In a study of 15 patients, Su et al.[82] found the LT was the most common region for BMLs at the time of ACL injury, as 93.3% of patients (14/15) had a lesion on baseline imaging. Both the volume and presence of BMLs significantly decreased throughout follow-up, as only four patients had BMLs at two-year follow-up.[82] Overall, the proportion of patients with BMLs at two-years postoperative, and the BML score on the ACLOAS were not significantly different throughout the lateral compartment between groups ($p = 0.50$).

We also found that both groups had elevated relaxation times in LT-3 compared to the rest of the lateral tibia, which suggests that cartilage degeneration in this segment is unrelated to the addition of an LET. Higher LT-3 relaxation times have been shown previously following ACLR and may be related to recovery from damage suffered at the time of injury.[12,82] Patients did not undergo baseline imaging thus we were unable to assess longitudinal changes in articular cartilage biochemistry; however, we did assess and control for visible damage at the two-year timepoint. Within our study, most damage occurred in the posterolateral regions of the knee, which could contribute to increased relaxation times in the region. While many patients had meniscal tears overlying this region of the knee, these tears seemed to have a greater impact on lateral femoral cartilage. The interaction term between meniscal tear size and treatment suggests one cannot interpret the effect of increasingly large meniscal tears on cartilage relaxation without first knowing whether the meniscus was repaired or partially excised. and the consequences of partial meniscal excision in the lateral femoral condyle. Repair of lateral meniscal tears, when possible, results in similar cartilage relaxation regardless of tear size, while performing excision is associated with increasingly higher relaxation times as tear size increases. This relationship was found in multiple regions of the femoral condyle and aligns with clinical hypotheses that the meniscus should be preserved[67] as lateral meniscectomy is associated with increased risk of OA.[16] Previous studies have demonstrated an association between meniscal damage at the time of ACL injury and biochemical changes in cartilage at follow-up.[11,45] Su et al. found baseline meniscal injury was significantly associated with increased T1rho relaxation times in the medial femur and tibia, however, these associations were not found on the lateral side. Elevated relaxation times could also be due to biomechanical changes that occur following ACLR.[11,33] Bolbos et al.[11] found higher T1rho relaxation times in the posterolateral compartment of the femur and tibia, that correspond with LFC-4 and LT-3 in our study, compared to healthy controls.

All of the STABILITY 1 patients randomized to ACLR + LET received a modified-Lemaire tenodesis.[26] At this time, there is little consensus regarding which anterolateral procedure best restores rotational stability without over constraining the knee.[25,37,38,57,72,92] Growing evidence shows that these procedures prevent persistent rotatory laxity and graft failure compared to ACLR alone.[8,28,55,78] It has been proposed that the LET works by protecting the ACLR in the early postoperative phase by reducing the strain placed on the graft[41], as biomechanical research has shown the LET reduces intra-articular ACL graft strain by over 40%.[21] Our findings suggest that adding an LET helps maintain graft integrity out to two-years postoperative, as a higher proportion of patients in the ACLR + LET group had a hypointense, regular thickness ACL graft (27/51, 53%) on the ACLOAS compared to the ACLR Alone group (15/44, 34%), though these differences were not statistically significant. These findings correlate with the primary outcome data from the STABILITY 1 Study, which found that ACLR + LET significantly reduced persistent rotatory laxity and graft rupture compared to HT ACLR alone.[28]

Mean adjusted T1rho and T2 relaxation times ranged from 30 to 55ms in our study, similar to previous studies of patients who underwent ACLR.[49,53,82]. While comparing between studies is of interest, numerous factors limit the validity of these comparisons.[4] Previous studies have shown that acute loading of the knee is associated with decreased relaxation times.[32,56,58,79,84,85] Knee loading from activities of daily living[85], walking[32], and running[84], all significantly affect relaxation time values thus, standardizing the unloading protocol prior to MRI is important. To reduce patient burden and limit time away from work or school, we scheduled the two-year visit and the MRI scan on the same day. While we were able to have patients undergo MRI prior to performing any of the functional testing, scheduling up to four patients on the same day meant we were unable to have all patients undergo scans at the same time of day. Given the young, active nature of our cohort, this potentially means some patients may have participated in sports or activity prior to their visit to the clinic. To account for differences in timing and unloading, along with other factors that could impact cartilage relaxation times such as return to activity and exposure time, we adjusted our analysis using contralateral relaxation times as an internal control. While the surgical limb may not respond to stress in the same way as the patients' healthy limb, contralateral times were significantly correlated with relaxation times on the involved limb and adjustment improved the precision of our estimates.

The relationship between early cartilage matrix changes and early patient function needs to be better understood. Currently, there is limited evidence showing an association between relaxation times and patient-reported outcomes or functional testing after ACLR.[13,48,63,64] In our study, we found that increased cartilage relaxation in the anterolateral tibia and femur were associated with lower hamstring and quadriceps symmetry at two-years postoperative. In the STABILITY 1 Study, the ACLR + LET group was found to have lower quadriceps torque and average power at the 6-month timepoint.[27] While these differences resolved by the 1-year timepoint, early strength deficits may be associated with articular cartilage quality in both the short- and long-term. Hipsley et al.[35] looked at cartilage volume in the medial tibia, lateral tibia, and patella of 51 patients 2-years following ACLR and associated quadriceps strength. They found that lower cartilage volume was associated with greater quadriceps torque between 40º and 60º when adjusted for age, sex, and body mass index (BMI), suggesting that weaker quadriceps muscles may be associated with decreased proteoglycan density in the ECM.[14] The strength of this relationship is uncertain; however, as 18 other models comparing other extensor strength measurements and cartilage volumes returned non-significant results.[35] Postoperative quadriceps deficits at the time of return to sport may also have long-term implications on cartilage matrix quality. Brunst et al.[13] found patients with quadriceps symmetry <85% at the time of return to sport had increased T2 relaxation times 5-years later compared to patients with quadriceps symmetry ≥ 90% however, significant results came from a sub-group analysis of superficial and deep articular cartilage in 12 regions from a sample of 27 patients. While strength was associated with T1rho and T2 relaxation at the two-year timepoint, dynamic knee stability was not. Previous studies have shown some association between early postural imbalance, measured through Y-Balance Test performance, and cartilage degeneration at two-years[48], perhaps due to increased contact pressures in the knee. Hop test limb symmetry may be a better predictor long-term, though further research is needed to fully understand which modifiable functional limitations are associated with early biochemical changes in articular cartilage after ACLR.

Our study has strengths and limitations. We are one of the first studies to compare relaxation times between patients who underwent two different ACLR techniques. Additionally, we were able to recruit 95 participants for this sub-study, which is one of the larger studies to use qMRI after ACLR. The patients included this MRI cohort were participants in the STABILITY 1 Study and thus, were randomly allocated to treatment group. Randomization, coupled with similar patient characteristics in this subgroup, decreases the potential for selection bias to impact our findings. As noted previously, our study was limited by the lack of baseline imaging and difficulty standardizing both the timing and the unloading protocol of the imaging. Our models, particularly for T1rho values, demonstrated poor fit as they explained little variance in relaxation times (adjusted R^2 range = 0 to 0.10), compared to the T2 models (adjusted R^2 range = 0.05 to 0.33). Three of these T1rho models found a significant difference between group, though the poor model fit suggests we are unable to account for other predictors that may explain significant variance in relaxation times. Additionally, neither the qualitative or quantitative assessors were blinded when segmenting or scoring the scans, which could lead to performance and detection bias. Metal artifact from the titanium staple used to perform the LET was occasionally visible in the cartilage space of the lateral compartment, so having an unblinded third party conceal the staple would not have fully blinded the raters. Furthermore, it is unclear what impact the staple had on lateral compartment relaxation times.

To mitigate the risk of bias, the MSK radiologist completing ACLOAS assessment followed the specified scoring instructions[70], and rules for segmentation were determined *a priori* to standardize the process. Lastly, the MRI cohort was a sub-group of study patients recruited from one clinical site in the STABILITY 1 network, which reduces the external validity of our findings. While comparing relaxation times between sites may be difficult due to issues regarding standardization and reliability of qMRI protocols[4], recruiting patients from all sites would have increased the generalizability of this study. Future studies should include patients from multiple sites and include imaging at baseline and follow-up. Longer follow-up that includes imaging at the five- or ten-year timepoints is necessary to confirm whether these differences persist and whether differences in relaxation times between groups are associated with the development of osteoarthritis long-term in our sample.

5.6 Conclusion

Increased relaxation times demonstrating small-to-moderate effect sizes suggest early biochemical changes in the articular cartilage of the anterolateral compartment in patients who underwent ACLR + LET compared to patients that underwent ACLR alone. Higher relaxation times in the anterolateral tibia and femur were associated with quadriceps and hamstring asymmetry, however, there was no association between relaxation times and patient-reported outcomes. Poor model fit, and findings inconsistent with *a priori* hypotheses, puts the clinical significance of these findings into question. Further evidence and long-term follow-up are needed to better understand the association between these results and the risk of development of OA in our patient cohort.

5.7 References

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Chapter 5

6 Summary and Discussion

This chapter will summarize the main findings of this dissertation and will discuss the clinical implications and limitations of my research. Additionally, I will discuss the potential for future research to expand upon these findings.

6.1 Summary

The overarching goal of this thesis was to improve clinical and patient-reported outcomes in young, active patients following ACLR. We developed a model that predicts persistent rotatory laxity and graft rupture, provided evidence of good outcomes in a sub-group of patients with meniscal tears that increase rotational laxity, and investigated the effect that adding an LET to hamstring ACLR has on articular cartilage at two years postoperative.

Chapter 2 (Study 1)

This study identified predictors of persistent rotatory laxity and graft rupture in a cohort of young, active patients randomized to hamstring ACLR alone versus hamstring ACLR + LET. Our final regression models showed that adding an LET and increased graft diameter were predictors of persistent rotatory laxity, while younger age, adding a LET, increased posterior tibial slope, preoperative high-grade knee laxity, and earlier return to sport were predictors of graft rupture. We suggested that these factors may be indications for when augmentation of hamstring ACLR with LET may be warranted.

Chapter 3 (Study 2)

Study 2 focused on the incidence and postoperative outcomes of a subgroup of STABILITY 1 patients with concomitant posterolateral meniscal root tear (PLMRT) at the time of ACLR. We monitored this group closely, as they underwent MRI at one- and two-years post-operative. We found that these patients demonstrated outcomes similar to the full STABILITY 1 cohort at one- and two-years postoperative, whether they underwent meniscal root repair or excision. This suggests that surgeons are skilled at deciding whether they need to repair the meniscus to achieve a good outcome for their patient.

Chapter 4 (Study 3)

Study 3 showed that quantitative MRI incorporating T1rho and T2 relaxation times were elevated in the lateral compartment of patients that underwent ACLR + LET compared to those that underwent ACLR alone at two-years postoperative. We also discovered interaction terms that suggest repair of larger lateral meniscal tears is associated with lower cartilage relaxation in specific compartments compared to excision of these increasingly larger tears. While increased relaxation times are thought to be an early biomarker for risk of OA development, the clinical significance of these differences is uncertain as our findings were impacted by poor model fit resulting in inconsistency with our *a priori* hypotheses. Continued follow-up of patients in the STABILITY 1 study is important to determine whether augmenting hamstring ACLR with an LET affects osteoarthritis development long-term.

6.2 Implications and Future Directions

Graft failure rates remain high in young, active patients following ACLR. The results of study 1 support recent findings that augmentation of hamstring ACLR with LET reduce graft failure while also identifying other preoperative and surgical variables associated with failure in these patients. Our second study demonstrates good outcomes in a subgroup of patients with LMPRT at the time of ACLR.

Ideally, our predictive model would be used to determine when hamstring ACLR is augmented with LET however, our model requires extensive validation to be clinically useful.[1] First, retrospective validation on an external dataset, where patients have undergone ACLR with or without LET, would be necessary to ensure model fit and generalizability outside of the study sample. Next, a prospective study, where we enter preoperative and surgical variables to determine the predicted treatment, then compare those receiving the expected graft versus a different one to see if it improved postoperative outcomes. Lastly, a randomized trial, where patients were randomized to graft selection by the model versus an orthopedic surgeon, would need to show that use of the model outperforms surgeons' choice in terms of graft failure. Realistically, the findings from this study will be used to inform stakeholders about patient risk profiles and the implications of graft selection for patients undergoing ACLR. Risk calculators, designed as app- or web-based interactive dashboards, are growing in popularity as a patient-friendly knowledge translation tool.[2, 3] The MOON Knee Group website provides patients with information about ACL graft ruptures, and hosts a risk calculator where patients can enter their information to understand their risk of re-tear with different graft types (https://acltear.info/acl-reinjury-risk/). Patient information for predictive variables can be entered directly into the platform, from which probabilities are calculated and returned to communicate the expected risk of each treatment option. Interactive risk calculators are an excellent way to demonstrate the clinical implications of a model and educate patients on their own personal risk. Given the utility of risk calculators, we developed a prototype for our study in R Shiny, which is shown in Figure 5.1.

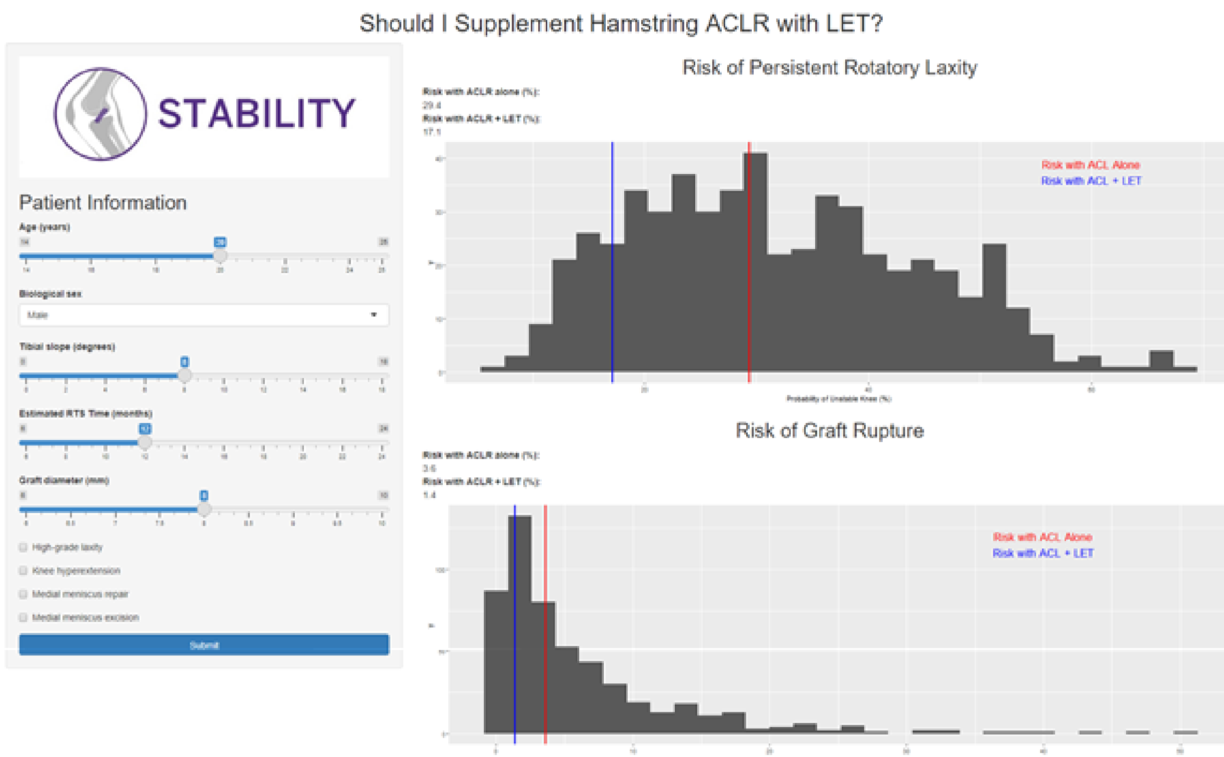

Figure 6.1 A prototype risk calculator developed in R Shiny to communicate the results of the STABILITY 1 Predictors paper. The interactive dashboard takes patient information entered on the left and calculates the probability of failure if ACLR or ACLR+LET is performed based on the model from the predictors paper.

The predicted probability of persistent rotatory laxity and graft rupture for each procedure are returned on the main page, overlying histograms that show the risk distribution for patients in the STABILITY 1 Study.

The LET was so protective in our study that any risk calculation will demonstrate lower risk of graft failure for ACLR + LET for all patients, regardless of demographic or injury characteristics. A relative risk reduction of 50% or an absolute risk difference exceeding 5% could be utilized as a threshold of importance that would be required to determine that ACLR should be augmented with LET. The MOON Group set arbitrary thresholds using absolute risk differences (RD), where: RD <3% indicates either graft could be chosen, 3% to 5% RD indicates the lower risk graft should be favored, while RD > 5% means the higher risk graft should be eliminated as an option. Adding more graft choice options could also improve the utility of the model. The STABILITY 2 Study (https://clinicaltrials.gov/ct2/show/NCT03935750), which compares quadriceps graft ACLR to bone-patellar tendon-bone (BTB) graft ACLR with or without an LET, is currently in the recruitment and data collection phase. Combining the data from STABILITY 1 and STABILITY 2 to develop a predictive model, where the model differentiates between three grafts (hamstring, quadriceps, BTB) with or without LET, could be extremely useful as a shared decision-making tool for patients and surgeons to optimize surgical decision making.

While our predictive model demonstrated several predictors were associated with composite clinical failure and graft rupture in the STABILITY 1 Study, we found that patients with a LPMRT at the time of surgery had similar outcomes to other patients in the trial at two-years postoperative. Patients did well whether they had their tear surgically repaired or partially excised; however, this does not suggest that repair or excision can be done interchangeably with good results. Rather, this suggests that surgeons are skilled at deciding whether tears can be repaired or excised at the time of surgery. The novel use of qMRI to assess articular cartilage relaxation in patients with concomitant LMPRT led to results inconsistent with *a priori* hypotheses, as cartilage relaxation was elevated in the anterolateral femur (LFC-1 and LFC-2) and lower in the centrolateral femur (LFC-3 and LFC-4) compared to the contralateral side in patients with LMPRT at the time of ACLR. Long-term follow-up is likely needed to determine whether cartilage relaxation is associated with the development of OA, and thus a valid surrogate outcome measure in this population. Future studies, with larger samples, may be able to better differentiate the impact of LMPRT repair versus excision, as we were limited by small numbers, particularly in our MRI sub-group.

While evidence is mounting that augmenting hamstring ACLR with LET improves short-term outcomes, the long-term implications need to be better understood. Our results showed elevated relaxation times in some regions of the lateral compartment; however, the clinical significance of these changes is unclear. Early changes in articular cartilage biochemistry may serve as a surrogate biomarker for OA development, thus these findings confirm that STABILITY 1 patients should be followed long-term. Outcome data collected ten- to twenty-years postoperative will provide a more complete story around the effects of augmenting ACLR with an LET on OA, as roughly half of patients that undergo ACLR have been shown to develop OA by that time.[4, 5] Future research should prioritize long-term follow-up of patients who underwent ACLR + LET, whether that data comes from registries or randomized clinical trials. Challenges associated with long-term follow-up are well understood. Many long-term follow-up studies demonstrate attrition[6-9], as patients' circumstances or contact information change, and they are unable to return for research follow-up. As little as 5% attrition has the potential to bias study results[10, 11], while >20% attrition is associated with high-risk of bias. Currently, five-, seven-, and ten-year follow-up of STABILITY 1 patients is ongoing at FKSMC. Patients undergo clinical and radiographic assessment, complete PROMs at each visit, and undergo MRI at the 7-year time point. Collection of this data will allow investigators to determine whether differences in relaxation times persist, and whether they correlate with visible OA at later timepoints. If investigators can limit LTF and collect long-term data on patients from multiple participating sites, this data has the potential to greatly contribute to the literature on long-term effect of LET. Understanding whether augmenting HT ACLR with an LET impacts OA development will allow for better treatment algorithms, as surgeons can weigh the potential benefits of short-term knee stability against any potential long-term risks.

6.3 Summary

High failure rates after ACLR in young, active patients have led investigators to re-focus on supplementing ACLR with LET. The predictive model outlined in this dissertation confirms the protective nature of the LET while also identifying other variables associated with higher or lower failure rates in this cohort. This model could be used to educate patients or guide treatment decisions in young, active patients. Our findings showed that patients with lateral meniscal posterior root tears demonstrate similar outcomes to the rest of the STABILITY 1 cohort at two-years postoperative. Outcomes were similar regardless of whether meniscal repair or excision was performed, though our sample was small. This suggests that surgeons are skilled at determining whether LMPRTs need to be repaired or excised at the time of surgery. Our two-year MRI findings confirm that long-term follow-up of STABILITY 1 patients is necessary to determine whether the LET provides short-term benefits without long-term risk of osteoarthritis development.

Appendices

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Article	**Predictors of Graft Failure in Young, Active Patients Undergoing Hamstring Autograft Anterior Cruciate Ligament Reconstruction with or without an LET**
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Author(s)	**Andrew Firth, Dianne Bryant, Alan Getgood, Robert Litchfield, Robert McCormack, Mark Heard, Peter MacDonald, Tim Spalding, PETER VERDONK, Devin Peterson, Davide Bardana, Alex Rezansoff, Stability 1 Study Group**

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Signing Author:	Alan Getgood (electronic signature)
Date:	11 November 2021

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Appendix B: Supplementary Tables - Risk at Different Thresholds of Age and Tibial Slope (Study 1)

Table 1 Relative risk of graft rupture by group below or at and above each threshold of tibial slope in patients from the Stability I Study

Slope	Cat	ACL Intact	ACL Rupture	LET Intact	LET Rupture	Risk Ratio
5	<5	17	2	19	0	-
	5+	245	31	261	11	0.36
6	<6	35	3	41	0	-
	6+	227	30	239	11	0.38
7	<7	62	5	55	1	0.24
	7+	200	28	225	10	0.35
8	<8	87	5	84	1	0.22
	8+	175	28	196	10	0.35
9	<9	118	8	133	2	0.23
	9+	144	25	147	9	0.39
10	<10	154	11	171	4	0.35
	10+	108	22	109	7	0.36
11	<11	177	15	200	6	0.38
	11+	85	18	80	5	0.34
12	<12	202	17	227	7	0.39
	12+	60	16	53	4	0.33

13	<13	220	21	241	7	0.32
	13+	42	12	39	4	0.42
14	<14	228	22	250	7	0.31
	14+	34	11	30	4	0.48
15	<15	236	23	252	8	0.35
	15+	26	10	28	3	0.35

Table 2 Relative risk of graft rupture by group below or at and above each threshold of patient age in patients from the Stability I Study

Age	Cat	ACL Intact	ACL Rupture	LET Intact	LET Rupture	Risk Ratio
15	<15	7	1	11	0	-
	15+	254	32	267	11	**0.35**
16	<16	31	7	40	3	**0.38**
	16+	238	8	250	26	**0.32**
17	<17	79	16	75	4	**0.30**
	17+	182	17	203	7	**0.39**
18	<18	113	23	114	7	**0.34**
	18+	148	10	164	4	**0.38**
19	<19	138	25	143	9	**0.39**
	19+	123	8	135	2	**0.24**
20	<20	158	27	160	10	**0.40**
	20+	103	6	118	1	**0.15**

21	<21	181	30	184	10	**0.36**
	21+	80	3	94	1	**0.29**
22	<22	201	31	198	10	**0.36**
	22+	60	2	80	1	**0.38**
23	<23	215	32	223	10	**0.33**
	23+	46	1	55	1	**0.84**
24	<24	225	32	241	11	**0.35**
	24+	35	1	37	0	**-**

Appendix C: Letter of Information and Ethics Approval

FOWLER KENNEDY
SPORT MEDICINE CLINIC

LETTER OF INFORMATION

Title of Research:
Multicenter Randomized Clinical Trial comparing Anterior Cruciate Ligament Reconstruction With and Without Lateral Extra-articular Tenodesis in Individuals Who Are At High Risk of Graft Failure.

Lead Researchers:

Dr. Alan Getgood
Fowler Kennedy Sport Medicine Clinic, Western University
London, Ontario, Phone: [redacted]

Dr. Dianne Bryant
Elborn College, Western University
London, Ontario, Phone: [redacted]

Study Sponsors:

International Society of Arthroscopy, Knee Surgery and Orthopaedic Sports Medicine (ISAKOS)
Orthopaedic Research and Education Foundation (OREF)

Information:
You are being invited to participate in a research study because your surgeon has determined that you have a torn anterior cruciate ligament (ACL) and you have elected to undergo surgery to reconstruct this ligament. The purpose of this letter is to provide you with information required for you to make an informed decision regarding participation in this research.

The purpose of this study is to compare outcomes (function, strength, range of motion and quality of life) between patients who receive the usual anterior cruciate ligament (ACL) reconstructive surgery to patients who receive anterior cruciate ligament reconstructive surgery with a lateral extra-articular tenodesis. A lateral extra-articular tenodesis is the creation of a new ligament-like structure using a piece of the Iliotibial (IT) band on the outside of the knee. The usual standard of care for an ACL tear is ACL reconstruction without this lateral extra-articular tenodesis (new ligament-like structure). Some studies have shown high graft failure rates (ACL re-tear) in young individuals who return to pivoting contact sports following ACL reconstruction. This study is designed to look at whether or not adding this extra structure reduces the risk of graft failure in this population. To determine whether one procedure is better than the other, we must randomize (like flipping a coin) you into one of the surgery groups. Six hundred (600) patients will take part in this study at different centres around the world. This centre will recruit one hundred (200) patients; approximately 100 per group.

Eligibility:

To participate in this study you must be 25 years of age or younger. You cannot have had previous ACL reconstruction on either knee. You cannot have a multi-ligament injury (two or more ligaments requiring surgery). If you are currently participating in another research study, you must inform your surgeon and the research assistant.

Explanation of the Study Procedures:

The goal of anterior cruciate ligament reconstruction surgery is to replace the torn ACL with a tissue graft to provide stability to the knee. This is done through a surgical procedure that is performed arthroscopically (with a camera). Either spinal or general anesthesia is used. Small screws are placed into the bone to hold the tissue graft in place.

If, during the surgery, your surgeon determines that your knee does not meet the requirements for the study i.e. other ligaments are found to be torn, or it cannot be treated using the surgical procedure defined in the study protocol, he/she will withdraw you from the study and you will be treated according to standard practice of your surgeon.

Description of the Study:

The total time commitment of the study is two years. Visits for this study will coincide with follow-up visits that you would already attend with your surgeon after your surgery. Each visit with the surgeon will take approximately 40 minutes of your time. Before your surgery, you will be asked to complete ten questionnaires along with a strength assessment, hop test and range of motion measurement. Following your surgery you will receive instructions to undergo standardized physical therapy. You will be given a Rehabilitation Guide to give to your physical therapist.

After surgery, you will come in for an appointment with your surgeon at 3 months, 6 months, 1 year and 2 years where you will be asked to complete the same nine questionnaires. At that time, we will also measure your range of motion. Completing these questionnaires will take approximately 15 - 20 minutes of your time and collection of range of motion measurements, strength and hop testing will take approximately 45 minutes.

At 6 months, 1 year and 2 years post - surgery, we will measure your strength and assess your ability to perform a series of simple jumping tasks. Strength tests will be performed by bending and extending your knee 3 times to measure your strength

against resistance. This is done using a computerized machine called an isokinetic dynamometer. During each test session, you will be seated with your back against a backrest with a seat belt securing you into place.
If you have undergone a posterior meniscal root repair we will schedule you for Magnetic Resonance Imaging (MRI) testing at or after your 1 year appointment. MRI is a common medical diagnostic tool that uses a strong magnetic field, a low frequency magnetic field and a radio frequency field. The purpose of the MRI is to evaluate the healing of your meniscus following its repair. The MRI will take approximately 2 hours of your time and we will schedule and confirm the time and location with you beforehand.

The jumping tests are subdivided into functional tests and biomechanical assessment. The functional tests include a single hop for distance, a timed 6 metre hop test, a triple hop for distance and a crossover hop for distance. The biomechanical assessment will use motion analysis equipment and a clinician rated scale to look at the mechanics of your knee as you perform a vertical jumping task.

The single hop for distance test is performed by having you stand on your leg to be tested, and hop forward on the same leg. The timed 6 metre hop test is performed by having you perform large one - legged hops in series over the 6 metres. The triple hops for distance test is performed by having you stand on one leg and perform three hops in a row on the same leg, landing as far away as possible. The crossover hop for distance is performed by having you hop forward three times while making a "Z' pattern.

The biomechanical assessment will take place in the Wolf Orthopaedic Biomechanics Laboratory (WOBL) at the Fowler Kennedy Sports Medicine Clinic. The task will require you to jump onto a force plate while sensors monitor your movements and muscle activity. These sensors will be placed on your skin over your feet, knees, hips, arms and shoulders using double-sided tape. You will be asked to wear dark (black or navy) shorts and a dark (black or navy) T-shirt or tank top to limit identifiable features and assist with the placement of the sensors. Although the sensors are easily removed, the tape may cause some pulling of hair therefore we may ask to shave some areas with a plastic disposable razor in order to limit discomfort.
After becoming familiarized with the instrumentation we will ask you to perform a double leg drop vertical jump. This task will require you to drop/hop off a box (at an elevated height of 31cm) and land with both legs on a force plate outlined on the ground, following which you will immediately jump vertically as high as you can, as if rebounding a basketball. As you are performing this task, a clinician and a researcher will use a Clinician Rated Drop Vertical Jump Scale to evaluate your landing. Additionally, we will videotape your jump so that the same clinician and researcher can later review the video and re-rate your jump, which will help us determine whether the evaluation of your landing is similar whether it is done in-person or using a video. Only your torso and lower body will be visible in the video. You will be asked

to return to WOBL approximately two weeks after this 6 month visit to again perform the double leg drop vertical jump. The purpose of this second visit is to determine whether the Clinician Rated Drop Vertical Jump Scale gives the same results when no change has occurred.

Alternatives to Participation:
If you do not choose to participate in this study, you will receive the usual ACL reconstructive surgery provided by your surgeon.

Risks:
You could fall, injure or re - injure yourself while performing tests, however, the risks are no greater than those encountered with typical postoperative rehab protocols.

Your participation in this study may involve an MRI. No X-rays are used. As with any technology there is a risk of death or injury. For MRI the risk of death is less than 1 in 10 million and the risk of injury is less than 1 in 100,000. These risks do not arise from the MRI process itself but from a failure to disclose or detect MRI incompatible objects in or around the body of the subject or scanner room. It is therefore very important that you answer all questions honestly and fully on the MRI screening questionnaire.

Almost all the deaths and injuries related to MRI scans have occurred because the MRI operator did not know that surgically implanted metal hardware (such as a cardiac pacemaker) was present inside the subject during the MRI scan. Other Remote risks involve temporary hearing loss from the loud noise inside the magnet. This can be avoided with ear headphone protection that also allows continuous communication between the subject and staff during the scan. For comparison, the risk of death in an MRI is similar to travelling 10 miles by car, while the risk of injury during an MRI is much less than the risks associated with normal daily activities for 1 hour.

If you have any history of head or eye injury involving metal fragments, if you have ever worked in a metal shop or been a soldier, if you have some type of implanted electrical device (such as a cardiac pacemaker), if you have severe heart disease (including susceptibility to arrhythmias), if you are wearing metal braces on your teeth, or [for women] if you could be pregnant, or have an intrauterine device, you should not have an MRI scan.

If you undergo a posterior meniscus root repair and are unable to have an MRI scan you will still be allowed to continue participating in the rest of this study.

There are no other known health risks associated with this study.

Benefits:
There are no direct benefits to you for participating in this study; however your

participation will help inform surgeons and physiotherapists as to which surgical procedure offers patients who undergo ACL reconstruction the best outcome.

Cost/Compensation:
You will not be compensated for your participation in this study. You will be responsible for the cost of parking.

Voluntary Participation:
Your participation in this study is voluntary. You may refuse to participate, refuse to answer any questions or withdraw from the study at any time with no effect on your future care. Should you choose to withdraw from this study, we will keep all data obtained up to the point that you chose to withdraw.

Participation in this study does not prevent you from participating in any other research studies at the present time or future. If you are participating in another research study, we ask that you please inform of us of your participation. You do not waive any legal rights by signing the consent form.

Request for Study Results:
Should you decide to participate and want to receive a copy of the study results, please provide your contact information on a separate piece of paper. Once the study has been published, a copy will be mailed to you. Please note that the results of this study are not expected for at least 5 years. Should your mailing information change, please let us know.

Confidentiality:
All information will be kept confidential to the best of our ability. The company that takes care of the research database is EmPower Health Research. Your identifying information (name, mailing address, phone number, email address, date of birth) is being collected as part of your participation in this study. Your data is protected by a username and password. It travels in a scrambled format to a server (storage computer) that is located in Montreal, Quebec, Canada. The company that houses the server is a professional company (Netelligent) with extremely high standards of physical and virtual security. We want to let you know however, that even with this high level of security, there is always a remote chance that your information could be accessed or "hacked" by someone who is not supposed to have your information. The chance that this information will be accidentally released is small. In any publication, presentation or report, your name will not be used and any information that discloses your identity will not be released or published. We wish to make you aware that Dr. Bryant, who is one of this study's investigators, is the Director of EmPower Health Research. However, Dr. Bryant is not paid a salary by EmPower.

Study data will be kept for seven years. Representatives of The University of Western Ontario Health Sciences Research Ethics Board may contact you or require access to your study-related records to monitor the conduct of the research.

Questions:
If you have questions about the conduct of the study or your rights as a research participant, you may contact [redacted], Scientific Director, Lawson Health Research Institute [redacted]d.

If you have questions or concerns about your surgery or physiotherapy, please contact your orthopaedic surgeon or physiotherapist. If you have any questions about this research, please contact Andrew Firth at [redacted] or your orthopaedic surgeon.

This letter is yours to keep.

Sincerely,

Dr. Alan Getgood, MD
Dr. Dianne Bryant, PhD
Stacey Wanlin
Andrew Firth, MSc
Ryan Pinto, MSc

FOWLER KENNEDY
SPORT MEDICINE CLINIC

CONSENT FORM

<u>Title of Research:</u>
Multicenter Randomized Clinical Trial comparing Anterior Cruciate Ligament Reconstruction With and Without Lateral Extra-articular Tenodesis in Individuals Who Are At High Risk of Graft Failure.

I have read the letter of information, have had the nature of the study explained to me, and I agree to participate in the study. All questions have been answered to my satisfaction. I will receive a copy of the Letter of Information and this signed consent form.

_______________________	_______________________	________________
Printed Name of the Participant	Signature of the Participant	Date
_______________________	_______________________	________________
Printed Name of the Parent or Legally Authorized Representative (if required)	Signature of the Parent or Legally Authorized Representative (if required)	Date
_______________________	_______________________	________________
Printed Name of the Person Responsible for Obtaining Informed Consent	Signature of the Person Person Responsible for Obtaining Informed Consent	Date

FOWLER KENNEDY
SPORT MEDICINE CLINIC

☐ I would like to receive a copy of the results of this study.
Please mail to:

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Western Research

Research Ethics

Use of Human Participants - Initial Ethics Approval Notice

Principal Investigator: Dr. Alan Getgood
File Number:104524
Review Level: Full Board
Protocol Title: Multicenter Randomized Clinical Trial comparing Anterior Cruciate Ligament Reconstruction With and Without Lateral Extra-articular Tenodesis in Individuals Who Are At High Risk of Graft Failure.
Department & Institution: Schulich School of Medicine and Dentistry\Surgery,Western University
Sponsor:
Ethics Approval Date: February 07, 2014
Ethics Expiry Date: September 30, 2023

Documents Reviewed & Approved & Documents Received for Information:

Document Name	Comments	Version Date
Other	12 Month Clinical Assessment (Received Oct.11/13)	
Other	24 Month Clinical Assessment (Received Oct.11/13)	
Other	3 Month Clinical Assessment (Received Oct.11/13)	
Other	6 Month Clinical Assessment (Received Oct.11/13)	
Other	Baseline Clinical Assessment (Received Oct.11/13)	
Instruments	International Knee Documentation Committee (IKDC) Subjective (Received Oct.11/13)	
Instruments	Lower Extremity Functional Scale (LEFS)(Received Oct.11/13)	
Instruments	4-Item Pain Intensity Measure (P4)(Received Oct.11/13)	
Instruments	Return to Sport (Received Oct.11/13)	
Instruments	EQ-5D VAS (Received Oct.11/13)	
Instruments	Hop Testing (Received Oct.11/13)	
Instruments	Range of Motion (Received Oct.11/13)	
Instruments	Strength (Received Oct.11/13)	
Instruments	SF-12 Health Survey (Received Oct.11/13)	
Instruments	Knee injury and Osteoarthritis Outcome Score (Received Oct.11/13)	
Instruments	MARX Activity Rating Scale (Received Oct.11/13)	
Instruments	Mohtadi Anterior Cruciate Ligament Quality of Life Questionnaire (Received Oct.11/13)	
Western University Protocol	Original (received Oct 11/13)	
Letter of Information & Consent	Clean updated LOI and Consent	2013/11/30
Recruitment Items	Poster	

This is to notify you that the University of Western Ontario Health Sciences Research Ethics Board (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced study on the approval date noted above. The membership of this HSREB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the University of Western Ontario Updated Approval Request form.

Member of the HSREB that are named as investigators in research studies, or declare a conflict of interest, do not participate in discussions related to, nor vote on, such studies when they are presented to the HSREB.

The Chair of the HSREB is Dr. Joseph Gilbert. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number [redacted]

Signature

Ethics Officer to Contact for Further Information

[redacted]

This is an official document. Please retain the original in your files.

Western University, Research, Support Services Bldg., Rm. 5150
London, ON, Canada N6A 3K7 [redacted] www.uwo.ca/research/services/ethics

Appendix D: Curriculum Vitae

Andrew Firth

PhD(can.), MSc, BSc

EDUCATION:

Western University Sept. 2018 – Present

PhD Candidate | Measurement and Methods in Health Rehabilitation Sciences

• Thesis: *Improving Outcomes Following Anterior Cruciate Ligament Reconstruction*

Western University Sept. 2014 – Aug. 2016

Master of Science| Integrated Biosciences in Kinesiology

• Thesis: *Reliability and Validity Parameters of the Star Excursion Balance Test for Patients with Chronic Patellar Instability*

University of British Columbia Sept. 2009 - Apr. 2014

Bachelor of Science | Kinesiology

TEACHING EXPERIENCE:

Lecturer | Western University Fall 2020 & Fall 2021

HS 9788: Advanced Quantitative Methodology

• Taught 30 graduate students quantitative research methodology and critical appraisal of the literature.

Guest Lecturer | Western University Jan. 2021 & Feb. 2022

MSK 9100: Musculoskeletal Health Research B

• Taught clinical research design and interpretation to 30 graduate students from a multitude of disciplines.

Guest Lecturer | McMaster University Jan. 20, 2020

HS 3G03: Appraisal of the Medical Literature

• Lecture on the measurement properties of outcome measures for a class of 200 undergraduate students.

Guest Lecturer | Western University Jan. 21, 2019

KIN 9620: Coaching and the Injured Athlete, Prof. Greg Alcock

• Present/discuss critical appraisal of a prognosis/risk study with 20 graduate students

Guest Lecturer | Western University Jan. 23, 2017

KIN 9620: Coaching and the Injured Athlete, Prof. Greg Alcock

• Present/discuss critical appraisals of published research with 20 graduate students

Teaching Assistant | Western University 2018-19 & 2019-20

HS 9788: Advanced Quantitative Research Methods

• Graded critical appraisals and discussed methodology pertaining to different study types

Teaching Assistant | Western University 2018 to 2020
PT 9600: Introduction to Quantitative Research Methods
• Taught basic concepts and provided additional information and discussion with students

Teaching Assistant | Western University 2014-15 & 2015-16
Kin 2222: Anatomy and Physiology
• Organized and taught laboratory sessions on the musculoskeletal system using 3D models

RELATED WORK EXPERIENCE:
Program Evaluator | Western University School of Physical Therapy Dec. 2021 - Present
• Contracted by the School of Physical Therapy to perform data entry, analysis, and formatting of documents related to program evaluation for the Physiotherapy Education Accreditation Canada review. I organized course documentation and demonstrated alignment between course objectives and the core competencies of the Physiotherapy Association of Canada

Content Developer | Vice-Provost Commissioned Quantitative Working Group Jul. 2020 – Jan. 2021
• Contracted as an expert in quantitative statistics to contribute to an initiative proposed by the provost to offer a university wide series of online, interactive, research methods modules to graduate students.

PUBLICATIONS:
Peer-Reviewed:
Khan M, Bedi A, Degen RM, **STABLE Study Group**, Gamez-Banos F. A pilot multicenter randomized controlled trial comparing Bankart repair and remplissage with the Latarjet procedure in patients with subcritical bone loss (STABLE): study protocol. *Pilot and Feasibility Studies*. 2022;8(1). doi:10.1186/s40814-022-01020-4.

Almasri M, Simunovic N, Heels-Ansdell D, Ayeni OR, **FIRST Investigators**. Osteochondroplasty Benefits the Pragmatic Patient with Femoroacetabular Impingement: Analysis from the Embedded Prospective Cohort of the Femoroacetabular Impingement RandomiSed Controlled Trial (FIRST). *Arthroscopy.* 2022;38(3):818-830.

Marmura H, **Firth A**, Batty L et al. Meniscal Repair at the Time of Primary ACL Reconstruction Does Not Result in Clinically Significant Reductions in Short Term Patient Reported Outcome Measures, yet Addition of LET improves Activity Scores: The STABILITY Experience. *KSSTA. 2022. Doi: 10.1007/s00167-022-06962-z.*

Kay J, Simunovic N, Ayeni OR, **FIRST Investigators**. Effect of Osteochondroplasty on Time to Reoperation After Arthroscopic Management of Femoroacetabular Impingement: Analysis of a Randomized Controlled Trial. *Orthop J Sports Med*. 2022;10(4):23259671211041400.

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Ohlin A, Simunovic N, Heels-Ansdell D, Ayeni OR, **FIRST Investigators**. Low Rate of Adverse Events in a Randomized Controlled Trial Addressing the Surgical Treatment of Femoroacetabular Impingement (FAI) Syndrome. *Knee Surgery, Sports Traumatology, Arthroscopy.* 2021;29(6):2015-2020.

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Pollock M, Sommerville L, **Firth A**, Lanting B. Total hip arthroplasty, total knee arthroplasty, and unicompartmental knee arthroplasty: a systematic review of the literature. JBJS Rev. 2016; 4(12).
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In Development:

Rezansoff A, **Firth AD**, Getgood A, et al. No Difference in Rates of Return to Sport when ACL Reconstruction Lateral Extra-Articular Tenodesis – Results from the Stability 1 Study Randomized Clinical Trial.

Firth AD, Jesani S, Bryant DM, Milner JS, Pritchett S, Litchfield R, Willits K, Holdsworth D, Stability Study Group, Getgood AMJ. Mensical root repair healing at 2-years following anterior cruciate ligament reconstruction with or without a lateral extra-articular tenodesis.

Firth AD, Pritchett S, Milner JS, Bryant DM, Holdsworth D, Stability Study Group, Getgood AMJ. Quantitative evaluation of lateral articular cartilage quality on magnetic resonance imaging at 2-years following anterior cruciate ligament reconstruction with or without a lateral extra-articular tenodesis.

BOOK CHAPTERS:

Bryant D, **Firth A**, Guyatt G, Arnold R. (2019). Patient-Reported Outcome Measures. Arnold (ed.), Pharmacoeconomics: from Theory to Practice, 2nd ed. Available August 26, 2020. CRC Press.

Firth A, Bryant D, Menetrey J, Getgood A. (2019). Health Measurement Development and Interpretation. Musahl (ed.), *ISAKOS: Basic Methods Handbook for Clinical Orthopaedic Research: A Practical Guide and Case Based Research Approach*. Springer-Verlag Berlin Heidelberg.

PRESENTATIONS:

Firth A, Bryant D, Getgood A, et al. Young age, increased posterior tibial slope and early return to sport are associated with increased risk of ACL graft rupture while Lateral Extra-articular Tenodesis is Protective: The *Stability Experience.* London Health Research Day 2021.

A. Firth, D. Bryant, J. Milner, A. Martindale, J. Schultz, D. Holdsworth, *Stability Study Group*, A. Getgood. Quantitative evaluation of lateral articular cartilage morphology on magnetic resonance imaging at 2-years following anterior cruciate ligament reconstruction with or without a lateral extra-articular tenodesis. ESSKA Congress 2020 in Milan, Italy. Accepted for podium presentation.

A. Firth, D. Bryant, J. Milner, A. Martindale, J. Schultz, D. Holdsworth, *Stability Study Group*, A. Getgood. Quantitative evaluation of lateral articular cartilage morphology on magnetic resonance imaging at 2-years following anterior cruciate ligament reconstruction with or without a lateral extra-articular tenodesis. AOSSM Annual Symposium 2020 in Seattle, USA. Accepted for podium presentation.

A. Firth, S. Jesani, A. Getgood, D. Bryant, R. Litchfield, K. Willits, STABILITY Study Group. Outcomes of Lateral Meniscal Root Repair at 2-years Following Anterior Cruciate Ligament Reconstruction With or Without a Lateral Extra-Articular Tenodesis. (Poster presentation) ISAKOS Congress 2019 in Cancun, Mexico.

R. McCormack, D. Boyer, A. Getgood, C. Hewison, **A. Firth**, D. Bryant, R. Litchfield, M. Heard, P. MacDonald, STABILITY Study Group. Anterior Cruciate Ligament Reconstruction With or Without A Lateral Extra-Articular Tenodesis – Functional Outcomes from the Stability Study. (Poster Presentation) CASEM 2019, Vancouver BC.

D. Bryant, A. Getgood, R. Litchfield, R.McCormack, D. Boyer, M. Heard, and P. MacDonald, **STABILITY Study Group**. Predictors of Poor Outcome Following ACL Reconstruction With or Without Lateral Extraarticular Tenodesis: The STABILITY Trial. (Poster Presentation) CASEM 2019, Vancouver BC

A. Rezansoff, **A. Firth**, A. Getgood, D. Bryant, R. Litchfield, R. McCormack, M. Heard, P. MacDonald, T. Spalding, P. Verdonk, D. Peterson, D. Bardana, STABILITY Study Group. Return to Sport Following Anterior Cruciate Ligament Reconstruction With or Without A Lateral Extra-Articular tenodesis – Results from the ISAKOS Sponsored STABILITY Study. (Oral presentation) ISAKOS Congress 2019 in Cancun, Mexico.

R. McCormack, A. Getgood, C. Hewison, **A. Firth**, D. Bryant, R. Litchfield, M. Heard, P. MacDonald, T. Spalding, P. Verdonk, D. Peterson, D. Bardana, A. Rezansoff, STABILITY Study Group. Anterior Cruciate Ligament Reconstruction With or Without A Lateral Extra-Articular Tenodesis – Functional Outcomes From the ISAKOS Sponsored STABILITY Study. (Poster presentation) ISAKOS Congress 2019 in Cancun, Mexico.

A. Firth, D. Bryant, G. Alcock, J. Dickey, A. Getgood. Reliability and Validity of the Star Excursion Balance Test for Chronic Patellar Instability. (Oral presentation) 2017 Orthopaedic National Symposium for the Orthopaedic Division of the Canadian Physiotherapy Association in London, ON.

A. Firth, D. Bryant, G. Alcock, J. Dickey, A. Getgood. Reliability and Validity of the Star Excursion Balance Test for Chronic Patellar Instability. (Oral presentation) 2017 Fowler Kennedy Sport Medicine Day Symposium in London, ON.

A. Firth, D. Bryant, G. Alcock, J. Dickey, A. Getgood. Reliability and Validity of the Star Excursion Balance Test for Chronic Patellar Instability. (Poster presentation) Canadian Bone and Joint Conference 2016 in London, ON.

A. Firth, D. Bryant, G. Alcock, J. Dickey, A. Getgood. Reliability and Validity of the Star Excursion Balance Test for Chronic Patellar Instability. (Poster presentation) FHS Research Day 2016 in London, ON.

A. Firth, D. Bryant, G. Alcock, J. Dickey, A. Getgood. Reliability and Validity of the Star Excursion Balance Test for Chronic Patellar Instability. (Poster presentation) Bodies of Knowledge Conference 2015 in Toronto, ON.

A. Firth, D. Bryant, G. Alcock, J. Dickey, A. Getgood. Reliability and Validity of the Star Excursion Balance Test for Chronic Patellar Instability. (Poster presentation) FHS Research Day 2015 in London, ON.

AWARDS:

Arthroscopy – Best Clinical Research Paper 2020. Getgood et al. No Difference in Functional Outcomes When Lateral Extra-Articular Tenodesis is Added to Anterior Cruciate Ligament Reconstruction in Young Active Patients: The Stability Study.

Ontario Graduate Scholarship | 2019-20, 2020-21, 2021-22
Merit-based award for excellence in graduate studies

AOSSM O'Donoghue Award | Stability Study Team
Dec. 2018
Awarded to the best clinical research paper submitted to AOSSM in Boston, 2019

Jan Gillquist Scientific Research Award | Stability Study Team
May 2019
Awarded to the best scientific research presentation at ISAKOS Congress

Bobby Gaul Award Winner | UBC
April 2014
Graduating Male Athlete of the Year
Displaying leadership and sportsmanship qualities while excelling in athletics at UBC

Capital One First Team Academic All-American
May 2013
Awarded to one NAIA Baseball player at each position who excels academically

Academic All-Canadian | University of British Columbia
2009-2012
Recognized for academic excellence while participating in a varsity sport

RESEARCH EXPERIENCE:

Research Assistant | Fowler Kennedy Sport Medicine Clinic May 2016 - Present
• Manage the day-to-day recruitment and follow-up of research patients