The Effect of Gender-Related Differences in Knee Morphology on Peak ACL Strain During Repeated Simulated Pivot Landings: An *In Vitro* Investigation

by

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**A dissertation submitted in partial fulfillment
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"You can't connect the dots looking forward;

you can only connect them looking backwards."

Steve Jobs

To my parents and wife

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PREFACE

The chapters have been written as separate manuscripts for submission, and there may be some reputation between chapters, specifically in the materials and methods sections. Chapter Two has been published in the *American Journal of Sports Medicine*.

TABLE OF CONTENTS

LIST OF FIGURES

CHAPTER 2

Figure

CHAPTER 3

Figure

CHAPTER 4

Figure

CHAPTER 5

Figure

APPENDIX B

<u>Figure</u>

APPENDIX C

<u>Figure</u>

APPENDIX D

<u>Figure</u>

LIST OF TABLES

CHAPTER 6

Table

APPENDIX E

Table

LIST OF APPENDICES

APPENDIX

ABSTRACT

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Anterior cruciate ligament (ACL) injuries are associated with considerable morbidity, including the development of knee osteoarthritis. A smaller ACL cross-sectional volume and a steeper lateral tibial slope have been associated with increased ACL injury risk. A knowledge gap exists as to why adolescent females have a 2- to 8-fold greater ACL injury rate than males, and whether the human ACL is susceptible to a fatigue failure under repeated loading. This dissertation tests the research hypotheses that (1) the female ACL exhibits greater peak strain than the male ACL during a two-times body weight (2*BW) simulated pivot landing because of a smaller ACL cross-sectional area and steeper lateral tibial slope, and (2) the ACL is susceptible to fatigue failure under repeated 3 - 4*BW simulated pivot landings.

Ten male and 10 female knees from age- and size-matched donors were subjected to 3T MR imaging to measure ACL cross-sectional area and lateral tibial slope. Each knee was loaded into a custom testing apparatus which delivered a standardized 2*BW compound impulsive load (compression force, knee flexion moment, internal tibial torque and muscle forces). The quadriceps' resistance to rapid stretch was modeled using a novel non-linear spring. The 3-D tibiofemoral kinematics and kinetics, muscle forces, and anteromedial ACL relative strain were recorded for 100 ms. Females ACLs exhibited 95% greater peak strain than male ACLs during the pivot landing, and ACL cross-sectional area and lateral tibial slope explained 59% of the variance in peak ACL strain. These results suggest an individual's knee morphology can predispose them to an ACL injury.

Using similar methods and 10 pairs of knees, the human ACL exhibited fatigue failure under repetitive 3*BW and 4*BW pivot landings. The larger the applied cyclic loading, and the smaller the ACL cross-sectional area, the fewer cycles it took for the ACL to fail. Finally, in 12 female knees increasing quadriceps tensile stiffness by 33% reduced peak ACL strain by 16%, thereby reducing the risk for injury.

Future interventions should target the magnitude and frequency of pivot landing loading cycles and screen for high-risk knee morphologies in order to reduce ACL injury risk.

CHAPTER 1

INTRODUCTION

1.1 Overview

About 350,000 anterior cruciate ligament (ACL) injuries occur in the United States each year[23]. The highest risk of ACL injuries occurs during five sports: basketball, football, gymnastics, lacrosse, and soccer[29]. These sports involve frequent jumps, landings and turns, as well as abrupt cutting maneuvers, sudden stops and changes in direction[11], often to beat an opponent so that an important pass or shot can be taken without interference. ACL injuries are primarily non-contact[12], meaning they do not involve another player physically contacting the injured athlete. These sports are often played in footwear that is designed to offer high coefficients of friction between the shoe sole and playing surface in order to promote the success of such maneuvers. In turn, because these maneuvers engender large changes in body momentum caused by foot-ground forces and/or torques, they necessarily place large 3-D dynamic loads on the stance knee[61].

A current knowledge gap which will be addressed in Chapter 2 of this dissertation concerns why female athletes have a two- to eight-fold higher ACL injury rate compared to sport-matched males[1, 4, 29, 49, 50, 58]. Patients with an ACL tear commonly present with a concomitant impact injury to their knee articular cartilage[57, 71, 76], along with meniscal tears[32, 34, 71, 82] and tears to other knee ligamentous structures[39]. ACL ruptures are often treated with an ACL reconstruction to restore knee function and mechanical stability[72].

However, operative and non-operative treatments of ACL injuries have been unable to prevent early onset knee osteoarthritis. Over 50% of knees with ACL injuries show signs of osteoarthritis 10-20 years following injury[42, 55]. This increases to 80% in patients with an ACL rupture combined with a meniscal injury, chondral lesion and/or medial collateral ligament injury[55]. These long-term health consequences underline the need for a better understanding of ACL injury mechanisms in order to reduce the risk of short- and long-term sequelae in male and, especially, female athletes.

Biomechanical and hormonal differences between male and female athletes could contribute to the gender difference in ACL injury rates. For example, increases in knee valgus loading have been retrospectively linked with ACL injuries *in vivo*[27]. Differences in landing biomechanics have been noted with females typically showing greater knee abduction[21, 44], greater internal tibial rotation[14, 44, 52], and greater knee extension[14] than males. Females also exhibit greater knee joint laxity than males[31, 59], which has been retrospectively shown to lead to a greater ACL injury rate[75]. Hormonal differences have been invoked to explain the gender difference in injury rate. The phases of the menstrual cycle have been linked with variations in knee joint laxity[64, 65] and estrogen can affect hamstrings muscle stiffness and the rate of force production[5]. Estrogen receptors are known to be present on the ACL[41], and an association has been reported between the pre-ovulatory phase of the menstrual cycle and a greater risk of ACL injury[67, 80, 81].

Differences in neuromuscular control contribute to the gender difference in ACL injury risk. For example, females generally land with greater quadriceps activation than males[43, 78]. However, this could be a compensatory response in females due to their lower active muscle strength and tensile stiffness than males, as measured in the quadriceps[22], hamstrings[6, 8] and triceps surae[7, 9] muscles. Muscle stiffness is a function of the muscle size and muscle activation[10] and females have less lower extremity muscle mass than males[36]. Greater hamstring muscle forces can reduce peak anteromedial bundle (AM)-ACL relative strain[79], and thereby ACL injury risk. While an aggressive quadriceps force can rupture the ACL[17, 77], these laboratory-produced ruptures may be the result of non-physiologic levels of quadriceps force[19] and/or axial compression[84]. Contrary to those results, an increase in quadriceps pre-activation force can reduce ACL strain during the landing phase[24].

Since female active quadriceps tensile stiffness is upwards of 45% less than males [22], it seems plausible that targeting the quadriceps muscle in female athletes through muscle hypertrophy and/or increased muscle activation could reduce ACL injuries. Current ACL injury prevention programs have already included knee extensor strength training[26, 40, 51]. For example, progressive resistance training for 3 days/week can increase knee extensor strength by 38% and type II muscle fiber cross-sectional area by 28% in 16 weeks[38], as well as increasing overall quadriceps muscle volume by 6-8% in 9 weeks[35, 74]. These changes in muscle size should lead to an increase in the overall tensile stiffness of the striated muscle due to the additional number of cross-bridges in parallel, as well as adaptive changes in the connective tissues[37]. However, it remains unknown whether the risk of ACL injuries in females would be reduced if their quadriceps tensile stiffness were increased via training. We shall address this issue further in Chapter 3.

Current ACL research has also been focused on whether differences in knee morphology could help explain the gender difference in ACL injuries. For example, retrospective studies have shown that ACL injury rates are increased in individuals with a greater lateral tibial slope and smaller medial tibial depth[25]. Lateral tibial slope refers to the angulation of the anterior-posterior slope of the lateral tibial plateau, while medial tibial depth refers to the peak depth of the concavity of the medial tibial plateau. A greater lateral tibial slope will increase the tibiofemoral translation of the knee joint under a large joint compression force, as shown by the positive correlation between anterior tibial deceleration and posterior tibial slope[45]. A smaller notch-width index (the quotient of femoral intercondylar and bicondylar widths) has also been associated with increased ACL injury risk[33, 62, 70, 75]. There are also known gender differences in ACL size (both in volume[15] and cross-sectional area[3, 18]), along with the ACL's modulus of elasticity[13].

A knowledge gap remains regarding how peak AM-ACL relative strain, and ultimately the risk of ACL rupture, is modulated by knee morphologic differences under maneuvers that place the knee under high loading rates; few studies have reported the behavior of the knee under loading rates typical of an injury. Furthermore, multiple methods for measuring lateral tibial slope with a proximal tibia magnetic resonance imaging (MRI) scan have been proposed[25, 30], but inter-method validation has not been performed. We shall address these issues in Chapter 2, 5, and 6.

A characteristic of all athletic training and competition involves performing certain maneuvers hundreds if not thousands of times a season on the playing field or court. This includes jumps, jump landings, pivot landings, cuts or sudden changes in direction, all of which are known to place large dynamic loads on the knee[61]. Elite soccer players will perform 727 turning or swerving maneuvers, on average, during a single match[11]. It is possible that some ACL failures are caused not by a single awkward landing, but instead by repetitive loading that induces a fatigue failure in the ligament due to damage cumulated over those loading cycles. This hypothesis has been broached by some as a possibility[73, 83] but never been tested directly during a simulated landing maneuver.

The Goodman diagram suggests that for a passive material placed under tensile loading, the greater the cyclic stress applied to the material, the fewer the number of loading cycles required to fail it[63]. The failure occurs as a result of microscopic damage accumulated as a result of each of the larger loading cycles reducing the tensile modulus of the ligament[73]. There is evidence that this concept holds in collagenous tissues like ligament and tendon, because the number of cycles to failure is inversely proportional to the peak cyclic stress applied to the tensile structure[60, 68, 73, 83]. It seems plausible that systematic gender differences in the ACL's modulus of elasticity[13] as well as ACL cross-sectional area[18] and lateral tibial slope[25] could lead to systematically greater ACL strain, and ultimately a greater risk of ACL injury, in females if the ultimate tensile stress or strain are similar in both genders. However, it is not known if the human ACL is susceptible to ligament fatigue failure or whether the morphology of the knee joint can influence the number of cycles to ACL failure. We shall test this hypothesis directly in Chapter 4.

Over the past eight years our laboratory has worked to identify the combination of of 3-D forces and moments direction that, when impulsively applied to the human knee, induce the largest relative strain in the AM-ACL. With the knee initially maintained in 15 degrees of flexion by trans-knee muscle forces, the combination of compression, knee flexion moment and internal tibial torque induced the largest AM-ACL relative strain during a 2*BW simulated dynamic maneuver, regardless of whether a modest adduction or abduction knee moment was also applied[54]. This is the 'worst case' 3-D loading scenario for the ACL. It is therefore plausible that internal tibial torque combined with increased simulated compressive landing forces of 3*BW and 4*BW could eventually produce an ACL rupture. Internal tibial torque can produce ACL failures in a cadaveric model[47, 48]; however, these studies were performed without muscle forces, employed small quasi-statically applied compressive forces, and a slower rate of internal tibial torque development than measured *in vivo*. The two most common failure patterns under internal tibial torque within this prior cadaveric model were partial tears of the posterolateral bundle near the femoral insertion, as well as tibial avulsions[47].

The ACL has been described as having a 'two-bundle' morphology[16, 20, 56], with the anteromedial and posterolateral bundles reciprocally sharing the loads on the ACL. The anteromedial bundle primarily resists anterior tibial translation and the posterolateral bundle resists axial rotation[2]. Therefore, it stands to reason that the application of internal tibial torque may be responsible for straining the ACL's posterolateral bundle. Partial tears of the ACL are not thought to be as common as complete tears, accounting for 10-25% of ACL ruptures[66, 69]. While there are better long-term outcomes for partial tears than complete tears[46, 68], a partial ACL tear can cause functional instability and can progress to ACL failure[53]. Isolated tears of the posterolateral bundle account for upwards of 40% of partial ACL tears[69]. However, isolated posterolateral bundle tears could be unrecognized in the clinical literature because they do not increase anterior tibial translation[28] despite increases in internal tibial rotation[85]. The injury pattern of the ACL for simulated pivot landings of 3 - 5*BW in the presence of realistic muscles forces is unknown. We shall address this issue further in Chapter 4.

1.2 Objectives and Experimental and Imaging Approach

The objective of this dissertation is to understand why the female ACL is susceptible to a higher injury rate than the male ACL. The literature suggests that gender-related differences in the morphology of the tibia, femur, and ACL can affect the risk of ACL injury. When we combine the known gender differences in ACL mechanical properties with the possibility that the ligament's is prone to fatigue failure, the female ACL may fail in fewer cycles than the male ACL for a given repeated loading.

We adopted an experimental approach that utilizes an established *in vitro* testing apparatus capable of simulating the 3-D impulsive knee loading associated with pivot landings ranging from 2 - 5*BW compressive force, with a knee flexion moment, internal tibial torque, and realistic muscle forces. A novel non-linear quadriceps spring was developed to represent the rapid stretch behavior of the muscle during the first 100 ms of a pivot landing, along with the ability to modulate the quadriceps stiffness to model the gender difference in stiffness, along with the effects of quadriceps hypertrophy. Finally, we shall investigate whether ligament fatigue failure may explain why individuals who have performed the same maneuver hundreds, if not thousands of times, fail their ACL by tracking the cycles to ACL failure using matched-pair knees with varying simulated pivot landing forces.

This dissertation utilized MRI scans of each knee joint prior to testing to identify key morphological characteristics that can influence peak AM-ACL relative strain during pivot landings. Specifically, ACL cross-sectional area, lateral tibial slope, medial tibial depth, and notch width index were investigated. Since lateral tibial slope may be an important predictor of peak AM-ACL relative strain, MRI was further utilized to determine if lateral tibial slope differs between three different methods for making the measurement.

1.3 Hypotheses and Significance

We hypothesize the female ACL will undergo systematically greater peak AM-ACL relative strain than the male ACL from height- and weight-matched donors, and that a smaller ACL cross-sectional area and greater lateral tibial slope are partially responsible for this gender difference in peak AM-ACL relative strain. Since knee morphological parameters are important, these could be used to screen athletes at high-risk of suffering an ACL injury. Secondly, we hypothesize that increasing quadriceps muscle tensile stiffness, which can be achieved with greater muscle activation and strength training, can reduce peak AM-ACL relative strain in female knees. Muscle hypertrophy via knee extensor strength training in females could reduce ACL injury risk. Thirdly, we hypothesize that the human ACL is susceptible to fatigue failures during a simulated pivot landing, with the number of cycles to ACL failure influenced by the magnitude of the repetitive external impulsive force applied to the distal end of the tibia, as well as the morphology of the knee joint. If the ACL is prone to fatigue failure, then there is a need to monitor the intensity and duration of pivot landings during competition and practice to lower ACL injury risk. Finally, we will test hypotheses relating the strengths and weaknesses of various methods for clinically measuring lateral tibial slope with MRI.

1.4 Organization of Dissertation

This dissertation consists of nine chapters and five appendices. Chapters 2-6 represent full length manuscripts either submitted or prepared for publication in peerreviewed journals. Chapter 2 investigates the gender difference in peak AM-ACL relative strain, and relates this gender difference in AM-ACL relative strain to differences in knee morphology. Chapter 3 examines the effect of increasing quadriceps stiffness on peak AM-ACL relative strain in female knees, and identifies knee morphologies that will be benefited the most by strength training the knee extensor muscles. Chapter 4 tests the hypothesis that the human ACL is prone to fatigue failure and identifies the fatigue life of the ACL during simulated dynamic pivot landings of different magnitudes in matched-paired male and female knees. Chapter 5 compares three different methodologies for measuring lateral tibial slope using MRI. Chapter 6 expands the investigation of the effect of knee morphological parameters on peak AM-ACL relative strain by performing a secondary analysis on the knees tested in Chapters 2 and 3 to test the hypothesis that additional morphologic characteristics and 2-way interactions will explain additional variance in peak AM-ACL relative strain during a pivot landing beyond the findings of Chapter 2.

Chapters 7, 8 and 9 discuss the strengths and weaknesses of this dissertation, summarize the conclusions, and offer suggestions for future research, respectively. Appendix A describes the novel non-linear quadriceps spring that was developed to reflect the stretch behavior of quadriceps during sudden knee flexion induced in Chapter 2, 3, and 6 of this dissertation. Appendix B describes a simple model to explain how gender differences in ACL strain can be influenced by gender differences in ACL structural properties, as discussed in Chapter 2. Appendix C provides details on a three-dimensional biomechanical model used to interpret the results of Chapter 3. Appendix D documents the ACL fatigue failures that occurred during the Chapter 4 tests. Finally, Appendix E contains the comprehensive datasets from Chapters 2-6 of this dissertation.

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CHAPTER 2

MORPHOLOGIC CHARACTERISTICS HELP EXPLAIN THE GENDER DIFFERENCE IN PEAK ACL STRAIN DURING A SIMULATED PIVOT LANDING

The following chapter was published in the *American Journal of Sports Medicine*, and all images contained in this chapter are copyrighted by Sage Publications. Please refer to the following publication when referencing this work: Lipps DB, Oh YK, Ashton-Miller JA, Wojtys EM. Morphologic characteristics help explain the gender difference in peak anterior cruciate ligament strain during a simulated pivot landing. *Am J Sports Med.* 2012;40(1):32-40.

2.1 Abstract

Gender differences exist in anterior cruciate ligament (ACL) cross-sectional area and lateral tibial slope. Biomechanical principles suggest that the direction of these gender differences should induce larger peak ACL strains in females under dynamic loading. We tested the hypothesis that peak ACL relative strain during a simulated landing is significantly greater in female ACLs than male ACLs, and that the greater strain in female ACLs is related to females have a smaller ACL cross-sectional are and greater lateral tibial slope.

Twenty cadaveric knees from height- and weight-matched male and female cadavers were subjected to impulsive 3-D test loads of two-times body weight in

compression, flexion and internal tibial torque starting at 15 degrees flexion. Load cells measured the 3-D forces and moments applied to the knee, and forces in the pre-tensioned quadriceps, hamstring and gastrocnemius muscle-equivalents. A novel gender-specific non-linear spring simulated short- and longer-range quadriceps muscle tensile stiffness. Peak relative strain in the anteromedial bundle of the ACL ('AM-ACL') was measured using a DVRT, while ACL cross-sectional area, and lateral tibial slope were measured using magnetic resonance imaging. A repeated measures Mann-Whitney signed-rank test was used to test the hypothesis.

Female knees exhibited 95% greater peak AM-ACL relative strain than males (6.37% [2.53%] vs. 3.26% [1.89%], $p = 0.004$) during a simulated pivot landing. ACL cross-sectional area and lateral tibial slope were significant predictors of peak AM-ACL relative strain ($R^2 = 0.59$, $p = 0.001$).

Peak AM-ACL relative strain was significantly greater in females than males of the same height and weight. This gender difference is attributed to a smaller female ACL cross-sectional area and a greater lateral tibial slope. Since female ACLs were systematically exposed to greater strain than their male counterparts, training and injury prevention programs should take this fact into consideration.

2.2 Introduction

More than 350,000 anterior cruciate ligament ('ACL') injuries occur in the United States each year[19]. These injuries, which typically occur during jump and pivot landings[7, 40] in sports like basketball, volleyball, and soccer[1, 3, 34, 45], are of considerable public health concern because they significantly increase the risk for developing knee osteoarthritis later in life[31].

It is unclear why a disproportionate number of these injuries occur in females[1, 3, 25, 34, 36, 45]. Possible explanations include hormonal effects[48, 58], differences in knee alignment[16, 24], knee joint laxity[48, 51], as well as anatomic differences in intercondylar notch[2, 13, 51], posterior tibial slope[8, 22], and medial tibial depth ('MTD')[22]. The female ACL has a cross-sectional area ('CSA') that is 20-30% smaller than the male ACL[2, 11, 13, 37], along with fewer collagen fibrils per unit area[23] and a slightly smaller tensile elastic modulus[11]. Furthermore, smaller female muscles provide significantly less resistance to shear and torque at the knee[57, 59]. However, there is no evidence that any of the above factors result in greater ACL strain in the female during a pivot landing.

From basic biomechanical principles, the strain in a ligament is proportional to the tensile force on the ligament, and inversely proportional to its CSA and tensile modulus of elasticity. For a given tensile force, the smaller the CSA and/or modulus, the greater the strain on the ligament; this places a smaller ACL at a greater risk of rupture than a larger ACL for a given ultimate tensile stress or strain. The question addressed in this study is whether the smaller female ACL experiences greater strains than the larger male ACL in a pivot landing? If so, the clinical significance is that females would be at increased risk for an earlier ACL rupture because of the well-known inverse relationship between the permissible cyclic stress in the ligament and the number of cycles that it can survive before material fatigue failure[47, 50]. From biomechanical principles a greater tibial plateau slope would be expected to further increase the stress placed on the ligament by increasing tibiofemoral translation under the dynamic compressive load associated with landing. This effect would further reduce the number of loading cycles an ACL might sustain before rupture. Indeed, increased lateral tibial slope ('LTS') and decreased MTD have previously been shown to greatly increase the risk of ACL injury in females[22].

The objectives of this study, therefore, were to determine (a) whether a gender difference exists in ACL strain, and (b) whether this gender difference in ACL strain can be explained by differences in knee morphology as exemplified by ACL cross-sectional area and lateral tibial slope. An established cadaveric knee construct capable of delivering a two-times body weight ('2*BW') impulsive compound load (compression, flexion, and internal tibial torque) was utilized to measure the peak strain in the anteromedial ('AM-') bundle of the ACL[39, 54-56]. A new feature was the addition of a custom spring to represent the gender-specific non-linear quadriceps response to stretch to better model both the known gender difference in quadriceps stiffness[18] and the bi-linear stiffness of a whole muscle responding to rapid stretch *in vivo* [14, 15, 20, 30, 32]. Our primary null hypothesis was that there is no difference in peak AM-ACL relative strain between height- and weight-matched female and male knees equipped with their gender-specific quadriceps muscle. Our secondary hypothesis was that a smaller ACL CSA (at 30% length from the tibial insertion), a greater LTS, and a shallower MTD, determined from magnetic resonance imaging ('MRI') scans prior to impact testing, would correlate with increased peak AM-ACL relative strain.

2.3 Materials and Methods

Specimen Procurement and Preparation

Unembalmed cadaver limbs were acquired from the University of Michigan Anatomical Donations Program and were visually examined for indications of surgery and deformities prior to specimen harvesting. The age, height, and body mass of the ten male and ten female donors are shown in Table 2.1. The donors were height- and weight-matched to ensure each specimen was within 10% of our target weight of 73 kg and height of 175 cm. Following harvesting, the cadaver limbs were dissected, keeping the knee ligamentous structures intact, along with the tendons of the quadriceps (rectus femoris), medial hamstrings (gracilis, sartorius, semimembranosus, semitendinosus), lateral hamstrings (biceps femoris), and the medial and lateral gastrocnemius. The distal tibia and proximal femur were cut 20 cm from the knee joint line. The distal tibia and fibula and proximal femur was potted in a PVC cylinder (6 cm tall, 10 cm diameter) filled with polymethylmethacrylate (PMMA). The specimens were stored frozen at -20 degrees Celsius, and thawed at room temperature for 12 hours prior to impact testing.

Table 2.1 Mean (±SD) descriptive statistics describing the study donors.

Gender	N	Age (years)	Height (cm)	Body Mass (kg)
Female	10	65.7 ± 18.4	171.5 ± 3.4	68.8 ± 5.0
Male	10	60.8 ± 17.2	174.5 ± 9.7	71.8 ± 5.3

Testing Apparatus

A single-leg pivot landing was simulated with a modified Withrow-Oh testing apparatus[54-56] (Figure 2.1). To commence each trial, a crossbow hair-trigger release mechanism was tripped to abruptly release a mass (‘W’, Figure 2.1) to fall 7 cm and strike an impact shaft. The impact shaft was located in series with an axial rotational device[39] (‘T’, Figure 2.1), delivering an impulsive compression force and axial torque to a universal joint connected in series with a 6-axis load cell (MC3A-1000, AMTI, Watertown, MA) attached to the distal tibia (‘L’, Figure 2.1). The axial rotation device consisted of two circular aluminum plates spaced by three equi-inclined struts. By adjusting the strut angle, the desired gain between applied compressive force and internal tibial torque can be produced. If only a compressive force was desired (i.e., the baseline trials), an axial cylindrical rod was keyed between the two circular plates to prevent an internal tibial torque from being applied. The impulsive force delivered to the specimen was equivalent to 2*BW of each specimen and peaked at 60 ms. This system has been previously shown to be reproducible and a good representation of the knee loading during a jump or pivot landing[39, 54-56]. The initial knee flexion angle was 15 degrees, consistent with ACL injury video analysis[40], and the impulsive force was delivered 3 cm posterior to the knee joint. The three-dimensional (3-D) action forces and moments on the distal tibia were measured at 2 kHz with the 6-axis load cell. As a double check on the loads applied to the knee, a second 6-axis load cell identical to the first recorded the 3-D reaction forces and moments at the proximal femur.

Knee kinematics were recorded with an Optotrak Certus camera system (Northern Digital, Inc., Waterloo, Ontario, Canada) at 400 Hz with two sets of three infrared emitting diodes (IREDS) attached to a plate affixed to the 6-axis load cells, which were rigidly attached to the tibia and femur by securing the PMMA-potted bones in an aluminum cylinder in series with the load cell. Prior to impact testing, the IREDS triads affixed to the sagittal plane of the 6-axis load cell were aligned to be parallel with the sagittal plane of the specimen. The knee construct was digitized to relate IRED location to anatomic landmarks on the knee. This setup allows the absolute and relative 3-D translations and rotations of each condyle, relative to the tibial plateau, to be calculated throughout the entire impact trial.

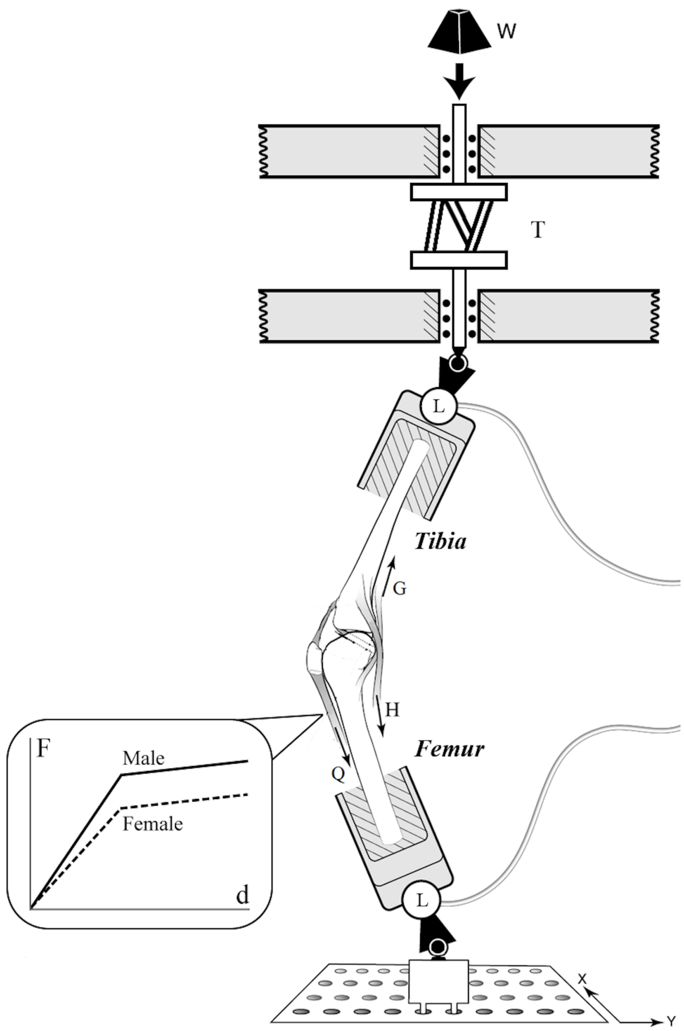

Figure 2.1 Diagram of the modified Withrow-Oh testing apparatus. Inset: A novel bi-linear stiffness quadriceps spring was developed for this experiment to model the *in vivo* female quadriceps muscle response to stretch. Additional springs were added in parallel to achieve the 20% greater quadriceps stiffness in males.

The relative strain was measured with a differential variable reluctance transducer (DVRT) placed at the distal third of the anteromedial region of the ACL (3-mm stroke length, MicroStrain, Inc., Burlington, VT). Absolute AM-ACL strain cannot be measured because the length of the ligament in a zero-strain state is unknown. Cryoclamps were used to grip the tendons of the rectus femoris, lateral and medial hamstrings, and lateral and medial gastrocnemius. Muscle tension was recorded with series load cells attached to the cryoclamps (TLL-1K and TLL-500, Transducer

Techniques, Inc., Temecula, CA). The quadriceps was attached to a 4.5 kN load cell, while the hamstrings and gastrocnemius muscles were attached to a 2.25 kN load cell (see Q, H, and G in Figure 2.1). Each muscle tendon and its corresponding load cell were attached in series with a spring acting as a muscle-equivalent in order to model each muscle's stretch response to the simulated pivot landing. These muscle-equivalents were monitored before each trial to ensure the muscle forces were balanced and the knee maintained an initial knee flexion angle of 15 degrees. The five muscle tendons were attached to winches on the distal tibia and proximal femur which could be ratcheted to increase or decrease muscle force prior to the impact trial.

The medial and lateral hamstrings and medial and lateral gastrocnemius were pre-tensioned to 70 N using woven nylon cord (stiffness: 200 N/mm). A new addition to the modified Withrow testing apparatus for this study was the use of a non-linear spring to represent the short- and longer-range quadriceps bi-linear elastic and viscous resistance to rapid stretch (Figure 2.1, inset) during the first 100 ms of the impulsive loading (Appendix A). This stretch response is similar to the response of *in vivo* muscle, as seen in muscle fibers[14, 15, 30, 32] and whole muscle[20] near optimal sarcomere and fiber length. The female spring (initial stiffness: 155 N/mm; final stiffness: 27 N/mm) was assigned systematically 20% less muscle stiffness than the male spring (initial stiffness: 193 N/mm; final stiffness: 46 N/mm), reflecting *in vivo* data on gender difference in muscle properties[18] due to muscle mass representing a smaller percentage of body mass in the female[29]. The non-linear quadriceps stiffness values were determined experimentally with a linear best fit to the spring's short-range and long-range force-length curve. The pre-impact quadriceps muscle tension was 180 N.

Testing Protocol

A cross-sectional repeated measures design (A-B-A, Figure 2.2) was used to measure peak AM-ACL relative strain in height- and weight-matched male and female cadaver limbs. The impact mass was dropped from the same 7 cm drop height to deliver the same energy input across all three testing blocks. The 'A' testing blocks represent the pre-baseline and post-baseline trials of a 2*BW compression force with a nominal 41 Nm flexion moment. The 'B' testing block simulated a pivot landing using a 2*BW compression force combined with a 17.5 Nm internal tibial torque and 37 Nm knee flexion moment. Since these are orthogonal moments, the same resultant moment (41 Nm) as testing blocks 'A' will occur, but the resultant moment will have a different direction. This loading combination has been shown to induce large dynamic ACL strains[39]. A comparison of the pre-baseline and post-baseline trials allows for a final check on the integrity of the ACL response to the standardized baseline loading following the simulated pivot landing trials. Each specimen was pre-conditioned with five trials at the beginning of the experiment to reduce data variability. The specimen underwent five impact trials for each testing block in the A-B-A design, with one pre-conditioning trial between each testing block to remove hysteresis effects. A total of 22 impact trials were applied to each specimen. This is less than the half the number of trials used in the original Withrow et al.[55] experiment in order to minimize the risk of injuring the ACL.

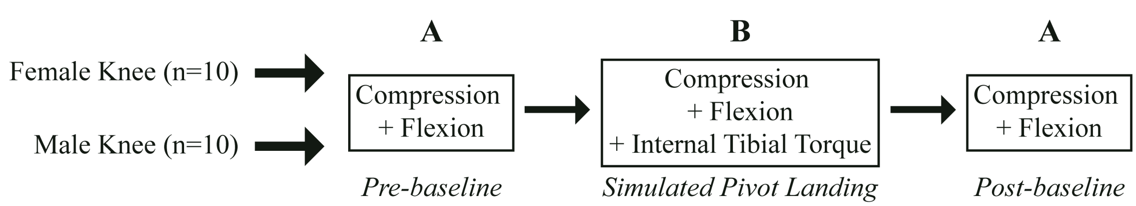

Figure 2.2 Flow chart for the repeated measures experimental design.

Magnetic Resonance Imaging Scans

T2-weighted 3-D sagittal magnetic resonance imaging (MRI) scans were acquired from nine male and nine female thawed cadaver limbs prior to impact testing (Phillips Healthcare 3T Scanner, 3D-PD sequence, TR/TE: 1000/35 ms, slice thickness: 0.7 mm, pixel spacing: 0.35 mm x 0.35 mm, field of view: 160 mm) and examined by a blinded observer using OSiriX (version 3.7.1, open source, www.osirix-viewer.com). The MRI scans were reconstructed to measure the ACL CSA from an oblique-axial view of the ligament[13] (Figure 2.3). The length of the ligament was measured using an oblique-coronal view, and the ACL CSA was measured at 30% of the ligament's length from the tibial insertion. The measurement location is consistent with the DVRT's placement on the distal third of the AM-ACL during impact testing and the known location of the minimum CSA of the ligament[21]. The ACL CSA was outlined with a pencil tool and OsiriX calculated the area within the pencil border.

Lateral tibial slope was measured *ad modam* Hudek et al.[27]. The longitudinal axis of the tibia was defined by a line connecting the centers of two circles fit within the proximal tibial head on the central sagittal image. The center of articulation of the lateral tibial compartment was selected from an axial view, and a line was connected between the most anterior and posterior points of the lateral tibial plateau using the sagittal view. The angle between this line and a line perpendicular to the longitudinal axis was defined as the LTS. To determine medial tibial slope (MTS) and MTD, the tibial center of articulation of the medial tibial plateau was defined. MTS was measured as the angle between the line perpendicular to the longitudinal axis and a line connecting the superior-anterior and posterior points on the medial tibial plateau. MTD was measured by drawing a line along the subchondral bone margin from the most anterior to the most posterior medial tibial plateau. Using a custom algorithm, MTD was calculated as the peak distance between the subchondryal bone line and a line connecting the most superior points on the anterior and posterior portions of the medial tibial plateau. The intraclass correlation coefficient (ICC) for these MRI measurements was 0.88 for ACL CSA, 0.93 for LTS and MTS, and 0.88 for MTD. Finally, femoral bicondylar width was measured at the level of the popliteal groove using a coronal view to determine the relative knee size of the age, height, and weight-matched donors, *ad modam* Vrooijink et al.[52].

Statistical Analyses

The raw kinematic and 6-axis load cell data were analyzed using a custom algorithm in MATLAB (2009b, The Mathworks, Natick, MA). For each specimen, the mean peak AM-ACL relative strain over five impact trials was recorded for the pre-baseline, simulated pivot landing, and post-baseline testing blocks. The primary and secondary hypotheses tested were: H1, there would be no significant gender difference in peak AM-ACL relative strain under pre-baseline, simulated pivot landing, or post-baseline testing (i.e., Blocks A-B-A, Figure 2.2) and H2, there would not be a significant linear correlation between peak AM-ACL relative strain during the simulated pivot landing and ACL CSA, LTS, MTS, and MTD. In addition, a tertiary hypothesis (H3) that there was no significant difference in peak AM-ACL relative strain between the pre-baseline and post-baseline testing blocks by gender was tested as a check of ACL integrity. All statistical analyses were performed with PASW Statistics 18 (SPSS Inc., Chicago, IL). H1 was tested with a non-parametric Mann-Whitney signed rank test with exact significance. H2 was tested with a stepwise multiple linear regression between peak AM-ACL relative strain and the independent variables (gender, ACL CSA, LTS, and MTD). H3 was tested with a Wilcoxon signed rank test with exact significance. Independent t-tests were used to test if gender differences existed in ACL CSA, LTS, MTS, MTD, and femoral bicondylar width, along with exploring the effect of gender on peak AM-ACL strain rate. A simulated pivot landing with an internal tibial torque was selected for our ACL strain measurement because it results in greater ACL strain within our knee construct than valgus loading[39, 54]. All statistical tests assumed significance at a p-value < 0.05. Assuming an alpha level of 0.05 and a power of 80%, the sample size was determined from a two-tailed, independent power analysis using pilot data on the peak AM-ACL relative strain under the simulated pivot landing for each gender. The effect size was found to be 1.38, requiring 10 male and 10 female knees to reach 80% power. A *post-hoc* power analysis showed 84% power was achieved. Finally, a hyperelastic representation of ACL response to uniaxial elongation[17] was used to calculate the theoretical effect on peak ACL strain of known gender differences in ACL CSAs and moduli of elasticity[11] (Appendix B).

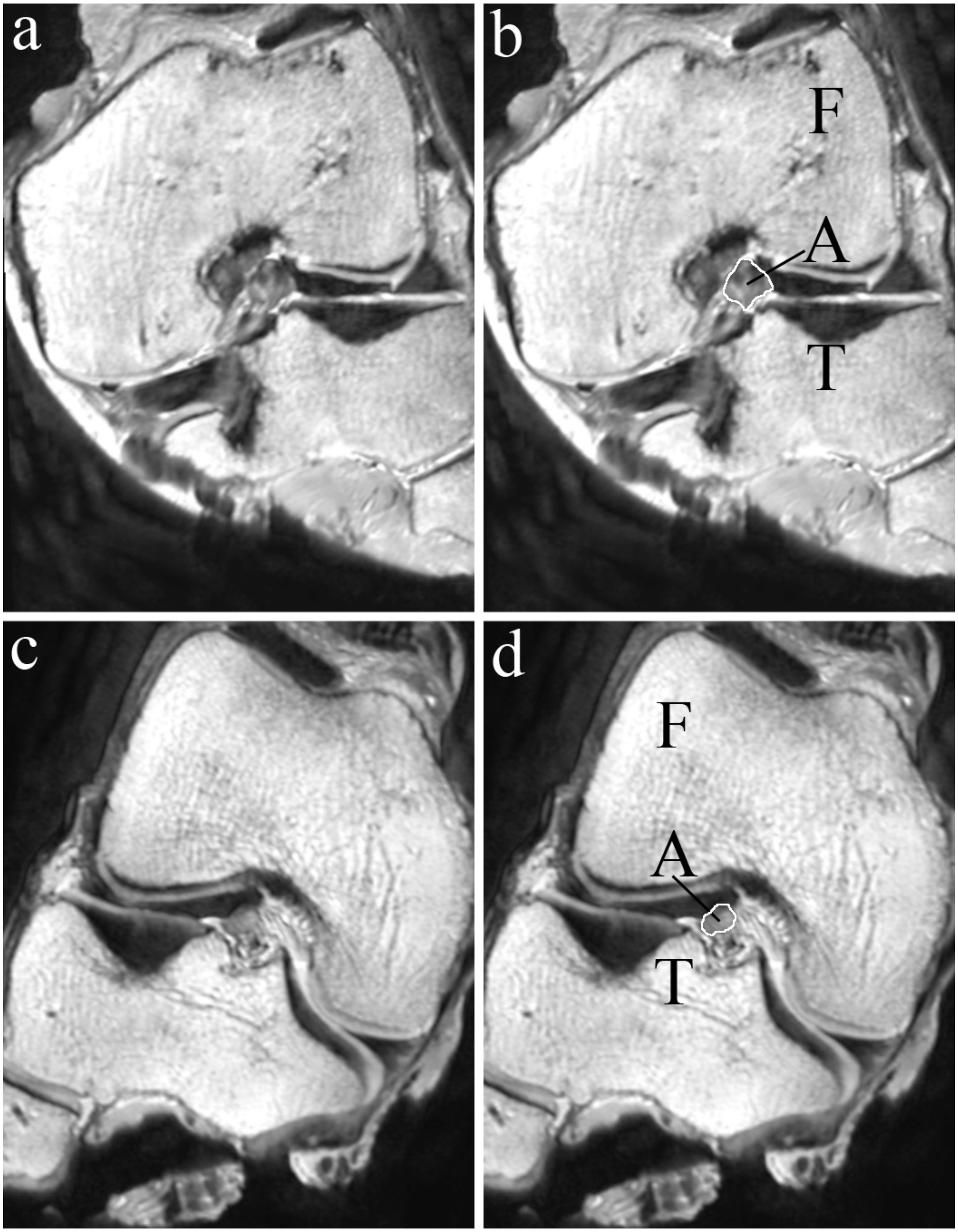

Figure 2.3 Oblique-view of the knee joint to measure ACL cross-sectional area. (a) Oblique-axial view of the left knee of male specimen #33400 at 30% of the ligament's length from the tibial insertion. (b) The femur (F), tibia (T), and ACL (A) are labeled on male specimen #33400. The cross-sectional area of the ACL is outlined in white. (c) Oblique-axial view of the right knee of female specimen #33272 at 30% of the ligament's length from the tibial insertion. (d) The femur (F), tibia (T), and ACL (A) are labeled on female specimen #33272. The cross-sectional area of the ACL is outlined in white.

2.4 Results

The simulated pivot landing test condition (i.e., Block 'B', Figure 2.2) resulted in significantly greater peak AM-ACL relative strain than the pre-baseline and post-baseline test conditions in male ($p = 0.005$ and $p = 0.005$, respectively) and female ($p = 0.005$ and $p = 0.005$, respectively) knees. The primary hypothesis, H1, was rejected in that the peak AM-ACL relative strain was significantly different between male and female cadaver knees under the simulated pivot landing test condition ($p = 0.004$, Figure 2.4), along with both the pre-baseline and post-baseline test conditions ($p = 0.023$ and $p = 0.011$, respectively). As a check on ACL integrity following the simulated pivot landing testing block, we failed to reject H3 in that no significant difference in peak AM-ACL relative strain was found between the pre-baseline and post-baseline conditions in male ($p = 0.508$) or female ($p = 0.139$) knees. There is a trend ($p=0.068$) towards a difference in peak AM-ACL strain rate between female knees (232.4 ± 90.6 %/s) and male knees (156.2 ± 84.5 %/s) under the simulated pivot landing testing block.

Gender differences in the loads applied to the knee and the resultant kinematics and muscle loads were examined in Table 2.2. There was a trend towards female knees being loaded under a lower peak impulsive compressive force across all three testing conditions, along with a smaller peak internal tibial torque during the simulated pivot landing. Since the knees were height- and weight-matched and received the same energy input, the trend toward lower peak compressive force and internal tibial torque was likely due to the female knees having lower input impedance due to their lower quadriceps stiffness, leading to their significantly greater knee flexion (as seen in Table 2.2). The resultant peak quadriceps force was 5% less in the female knees in spite of the larger change in knee flexion angle. Lastly, the female knees exhibited a significantly larger increase in internal tibial rotation than the male knees.

The secondary hypothesis H2 was rejected because ACL CSA (standardized β = -0.480, p = 0.015, Figure 2.5) and LTS (β = 0.459, p = 0.016) were significant coefficients within the linear regression with peak AM-ACL relative strain, ($R^2 = 0.59$, $p = 0.001$). Knees with increased peak AM-ACL relative strain had increased LTS and decreased ACL CSA, relative to the mean values of the entire subset of knees tested (Figure 2.6). The stepwise regression eliminated gender and MTD as significant coefficients. There were significant gender differences in ACL CSA, MTD and bicondylar width, while LTS and MTS did not reach the level of significance (Table 2.3).

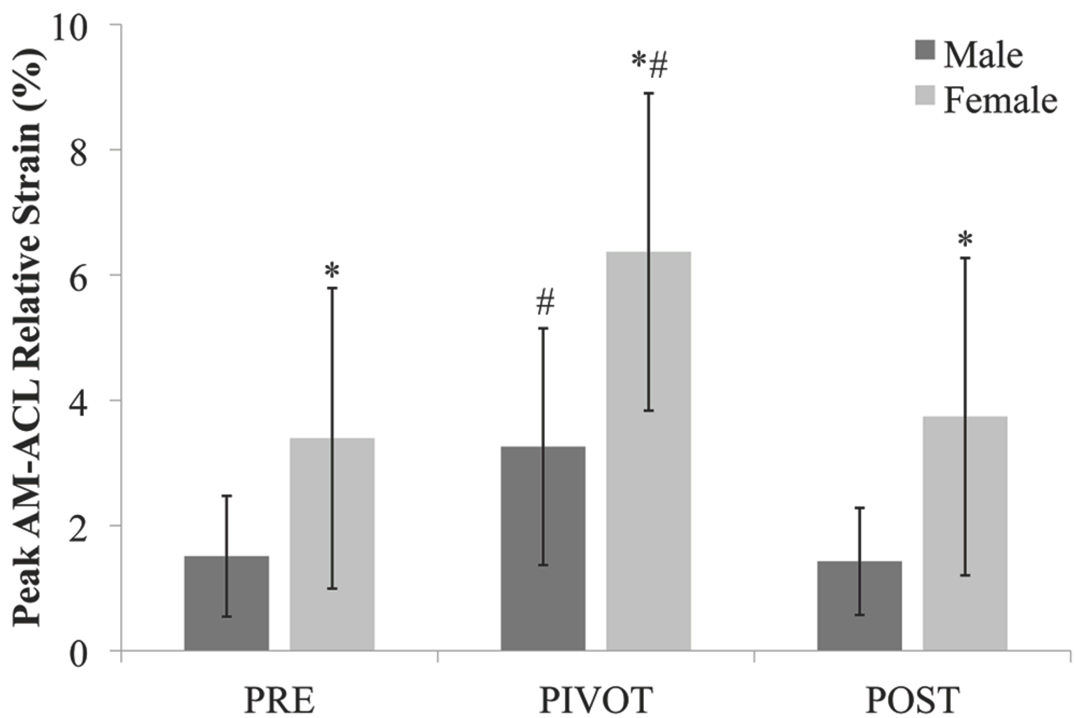

Figure 2.4 The mean peak AM-ACL relative strain (error bars = 1 standard deviation) for male (dark grey) and female (light grey) height- and weight-matched cadaver knees over the three loading trial blocks: pre-baseline (PRE), simulated pivot landing (PIVOT), and post-baseline (POST). * - denotes significant gender difference within testing block(p < 0.05); # - denotes significant difference between PIVOT testing block and the corresponding PRE and POST testing blocks by gender (p < 0.05).

Table 2.2 The mean ± SD input forces and torques, and outcome forces and kinematics, under the three loading conditions by gender.

	Pre-Baseline		Simulated Pivot Landing		Post-Baseline	
Inputs	Female	Male	Female	Male	Female	Male
Compressive Force (N)	1,196 ± 189	1,416 ± 84	688 ± 95	814 ± 119	1,183 ± 207	1,361 ± 139
Internal Tibial Torque (Nm)	1.0 ± 1.0	1.0 ± 0.5	17.6 ± 4.9	19.5 ± 4.9	0.9 ± 0.9	1.2 ± 0.9
Outcomes						
Quadriceps Force (N)	774 ± 106	806 ± 118	888 ± 128	928 ± 115	772 ± 91	783 ± 163
Knee Flexion Angle (deg)	7.1 ± 2.1†	4.6 ± 0.7	8.9 ± 2.3	6.5 ± 1.0	7.1 ± 2.2	4.7 ± 0.9
Anterior Tibial Translation (mm)	2.5 ± 0.9	1.7 ± 0.8	4.0 ± 1.1	3.4 ± 1.7	2.4 ± 1.1	1.7 ± 0.7
Internal Tibial Rotation (deg)	3.5 ± 1.7	2.9 ± 1.1	16.3 ± 3.2†	11.6 ± 2.3	3.6 ± 1.9	2.9 ± 0.9

† - Using the Bonferroni correction, only values with $p < 0.0028$ were considered significant for the 3 x 6 gender comparisons in this table.

Table 2.3 Descriptive statistics (mean ± SD) for the knee morphological parameters

	Female	Male
ACL cross-sectional area (cm^2)	24.2 ± 8.4#	39.6 ± 11.7
Lateral tibial slope (deg)	5.3 ± 2.5	4.3 ± 1.7
Medial tibial slope (deg)	4.8 ± 1.9	4.2 ± 2.8
Medial tibial depth (mm)	1.6 ± 0.6*	2.5 ± 0.8
Femoral bicondylar width (mm)	67.8 ± 4.3*	73.8 ± 3.9

*: $p < 0.05$; #: $p < 0.001$

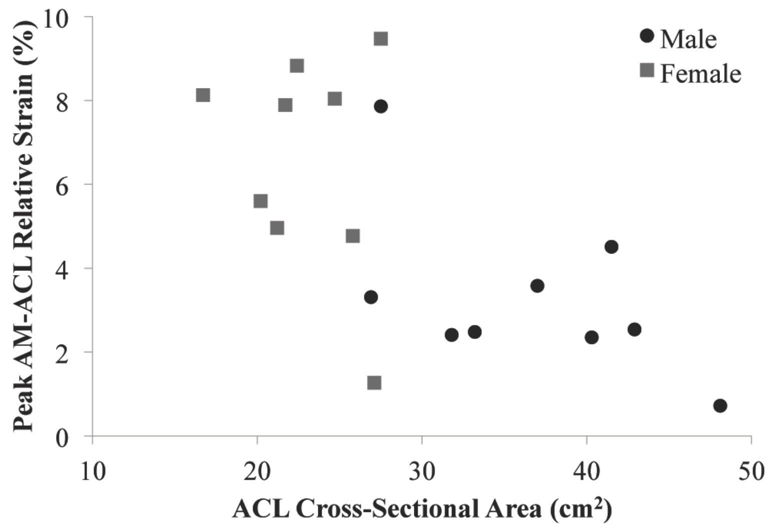

Figure 2.5 A scatter plot of peak AM-ACL relative strain vs. ACL cross-sectional area for 18 knees under the simulated pivot landing testing block 'B'. Male knees are represented by black circles and female knees are represented by gray squares.

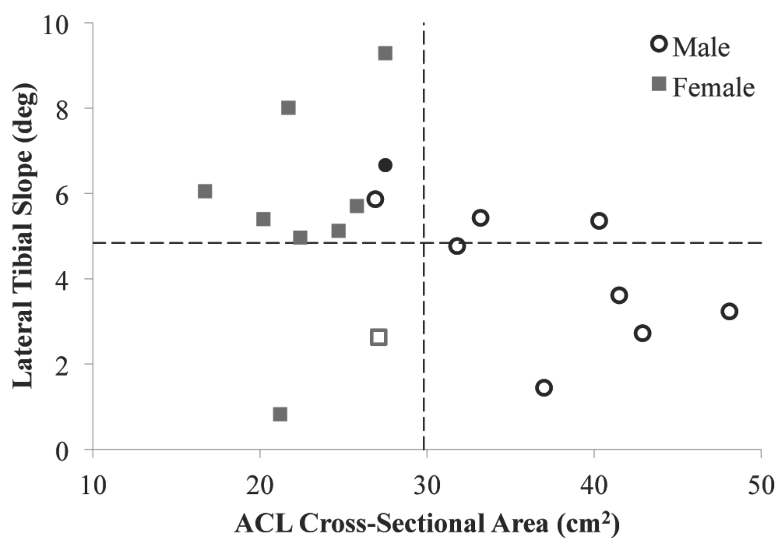

Figure 2.6 A scatter plot of lateral tibial slope vs. ACL cross-sectional area for 18 knees under the simulated pivot landing testing block 'B'. Dashed lines indicate the mean lateral tibial slope and ACL cross-sectional area for the entire group. Male knees are represented by circles and female knees are represented by squares. A filled marker indicates a peak AM-ACL relative strain greater than the median strain, and an unfilled marker indicates a peak AM-ACL relative strain less than the median strain.

2.5 Discussion

This study demonstrates a gender difference in peak AM-ACL relative strain in knees from age-, height- and weight-matched male and female cadavers placed under 3-D standardized impulsive loads simulating a unipedal pivot landing. Our results support the primary hypothesis that female knees equipped with realistic female muscle-equivalents will develop greater peak AM-ACL relative strain in the anteromedial bundle of the ACL than male knees equipped with male muscle-equivalents. It is noteworthy that the female knees demonstrated greater peak AM-ACL relative strain with and without the addition of a 17.5 Nm internal tibial torque to the testing protocol.

This study utilized a novel non-linear quadriceps spring *in vitro* (Appendix A) to model the known *in vivo* force-length behavior of a whole muscle placed under rapid stretch[20] since the quadriceps muscle will rapidly stretch during the first 100 ms of a jump landing[28]. Whole muscle exhibits both elastic and viscous (time-dependent) behavior under sudden stretch[49]: its short-range stiffness is dominated by its strongly bound sarcomeres and its longer-range behavior is determined by reflex, elastic and viscous behaviors. These properties combine to yield the non-linear behavior that has been shown in frog muscle fibrils[14, 15, 30, 49], feline muscle fibers[32], and rabbit whole muscle[20] under rapid stretch. Because the quadriceps stretch phase only lasts 80 ms, this interval is too short for any reflex[38] or volitional changes in muscle activation to substantially affect quadriceps force, so the non-linear spring representation of muscle stretch behavior is reasonable.

Muscles are the primary active joint stabilizers helping to protect knee ligaments from injury. A third novel feature of this study is the experimental design: male knees were equipped with male muscle-equivalents and female knees with female muscle-equivalents. This design was based on the knowledge that females have lower whole body muscle mass than males[29], leading to female knee muscles developing less shear[57] and torsional[26, 41, 46, 59] resistance at the knee. Because of lower muscle mass, females develop less active muscle stiffness in their quadriceps[18] and hamstrings[4, 5, 18] than males. Hence, the female quadriceps spring device was designed to have 20% less quadriceps stiffness[18] because females have approximately 20% less knee muscle extensor strength[42-44, 57] (the maximal tensile stiffness of a muscle being proportional to its muscle strength[6]).

The effect of gender on peak ACL strain has only been examined in two prior studies. Mizuno et al.[35] compared gender-specific models of ACL strain using both a computer simulation and modest quasi-static loading of cadaver knees in the absence of muscle forces. Their models exhibited a 65% greater strain in females under a 10 Nm internal tibial torque combined with a 10 Nm valgus moment when the knee was in 15 degrees flexion. Our study corroborates and extends Mizuno et al. by representing a pivot landing under realistic athletic ground reactions (2*BW impulsive compressive load with knee flexion moment and 17.5 Nm internal tibial torque, along with realistic muscle forces). Weinhold et al.[53] also demonstrated greater AM-ACL relative strain in knees of unspecified gender with quasi-static female muscle loads. Our study also extends Weinhold et al. by dynamically modeling the muscle response to a pivot landing, rather than using a quasi-static approach.

The gender difference in ACL strain appears to be partially due to gender differences in ACL CSA and the modulus of elasticity. A hyperelastic model predicts a 1.67-fold difference in ACL strain between males and females based on the gender difference in ACL CSAs reported in this study and in the published moduli of elasticity[11] (Appendix B). Hence, the gender difference in ACL CSA and modulus of elasticity theoretically explains about two-thirds of the observed 95% gender difference in peak ACL strain. LTS, as demonstrated in our regression model, explains some of the remaining gender difference in ACL strain. Our theoretical analysis in Appendix B assumed that the ACL primarily exhibits hyperelastic behavior[9, 10, 60]; we assume that viscous effects are small because hysteresis was minimal after several loading cycles. Although there was a trend towards a gender difference in peak AM-ACL strain rate, the 30% difference in strain rate would have little effect on ACL behavior[61].

The ACL CSAs in the present study are smaller than those reported, for example, by Chandrashekar et al.[11] and Dienst et al.[13]. Our measurements differ from the Chandrashekar et al. study because a different imaging modality (3D scanner) was used, and their study did not control for the height and weight of the specimens; these studies used larger specimens than in the present study. We utilized a similar method for measuring ACL CSA as Dienst et al.; they measured ACL CSA at mid-substance. We measured the ACL CSA at 30% ligament length from the tibial insertion because it corresponds with the location of the DVRT during testing and is the minimum ACL CSA[21].

The present study finds a significant inverse linear relationship between peak AM-ACL relative strain and ACL CSA (Figure 2.5). Although Chandrashekar et al.[11] examined the relationship between ACL size and strain using tensile testing of the femur-ACL-tibia complex, they failed to demonstrate any relationship between the ACL strain at failure and the minimum area of the ligament. Our results agree with recent work showing that ACL-injured subjects have a smaller ACL volume in the contralateral knee when compared to matched controls, with gender being an insignificant regression covariate[12]. LTS has been identified as an important risk factor in ACL injuries[8, 22], but we are unaware of a previous study that has demonstrated a strong linear relationship between LTS and ACL strain. It is plausible that a greater LTS will increase the anterior tibial translation and internal rotation of the tibia during a pivot landing, thus leading to an increase in ACL strain.

The strengths of this study include the repeated measures design, the use of age, height and weight-matched cadavers, the inclusion of muscle forces including a non-linear representation of quadriceps behavior, and a blinded observer to measure the morphological parameters on the MR scans. The study has limitations unlikely to affect the overall findings. First, the strain was only measured within the anteromedial region of the ACL and may not represent the overall strain on the ligament. However, Markolf et al.[33] found a strong relationship between AM-ACL strain and overall ACL force. In addition, we were only able to record relative strain, rather than absolute strain. The absolute strain on the ACL is likely larger than the relative strain because the pre-tensioned muscle forces place a preload on the ligament prior to impact. Although the cadaver donors were age-, height-, and weight-matched, the female knee was smaller than the male knee, indicated by a gender difference in bicondylar width. While ACL CSA and LTS are important determinant of ACL strain in a pivot landing, it explains only 60% of the variance in the strain data. Other potential sources of variance include the ligament's modulus of elasticity, indicated by the hyperelastic model, and other morphological parameters including MTD, MTS, and femoral notch size. Increasing the sample size would likely increase the number of significant morphological parameters within our regression model, including MTD. Although currently insignificant within our regression model, MTD was significantly smaller in the female knees in our study and previous work has indicated that a 1 mm reduction in MTD will triple the odds of an ACL injury occurring[22].

2.6 Conclusions

1) During a 2*BW simulated pivot landing, the female ACL will experience systemically greater peak AM-ACL relative strain than the male ACL from age, height, and weight matched donors.

2) ACL cross-sectional area was negatively associated and lateral tibial slope was positively associated with peak AM-ACL relative strain during a 2*BW simulated pivot landing. Together, these two morphologic characteristics explained 59% of the variance in peak AM-ACL relative strain.

3) Future ACL prevention programs might benefit from considering these morphological factors for ACL injury risk screening.

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CHAPTER 3

EFFECT OF INCREASED QUADRICEPS TENSILE STIFFNESS ON PEAK ACL STRAIN DURING A SIMULATED PIVOT LANDING

3.1 Abstract

Current ACL injury prevention programs involve training the muscles crossing the knee. It is widely accepted that muscle tensile stiffness can be increased by muscle hypertrophy and./or increased muscle activation. We tested the hypothesis that an increased quadriceps tensile stiffness would reduce peak anteromedial bundle (AM-ACL) relative strain in female knees.

Twelve female cadaver knees were subjected to compound impulsive two-times body weight loads in compression, flexion, and internal tibial torque beginning at 15° flexion. Knees were equipped with a modifiable custom springs to represent the non-linear rapid stretch behavior of a normal and increased stiffness female quadriceps (i.e., 33% greater stiffness). Peak AM-ACL relative strain was measured using an in situ transducer while muscle forces and tibiofemoral kinematics and kinetics were recorded. A 3D ADAMS™ dynamic biomechanical knee model was used *in silico* to interpret the experimental results which were analyzed using a repeated-measures Wilcoxon signed-rank test.

Female knees exhibited a 16% reduction in peak AM-ACL relative strain and 21% reduction in change in flexion when quadriceps tensile stiffness was increased by

33% (mean (SD) difference: 0.97% (0.65%), P = 0.003). We conclude that increased quadriceps tensile stiffness reduces peak ACL strain during a pivot landing.

3.2 Introduction

There are 350,000 anterior cruciate ligament (ACL) injuries in the United States each year[13], with a disproportionate number of these injuries occurring in female athletes[1, 3]. ACL injuries are a major public health concern due to the associated treatment costs, lost time, and the increased risk of developing early onset knee osteoarthritis[27]. ACL injury prevention programs aimed at reducing the number of injuries in female athletes often prescribe exercises to strengthen the knee extensor muscles[14, 25, 30]. However, the benefits of such exercises remain uncertain given limited success[31].

The muscles of female athletes provide less resistance to knee joint shear and torsional loads than for male athletes[43, 44]. Since females have 45% less active quadriceps stiffness than males[12], one might expect peak ACL strain to be higher in females. Indeed, Lipps et al. used a Withrow-Oh *in vitro* testing apparatus to show that female knees equipped with a female quadriceps tensile stiffness value had 95% greater peak ACL strain than height- and weight-matched male knees equipped with 25% greater quadriceps tensile stiffness in simulated pivot landings[26].

It is widely accepted that muscle tensile stiffness can be increased by either muscle hypertrophy and/or increased muscle activation[5]. For example, an increase in vastus lateralis musculotendon stiffness, ranging from 16% to 58% after 12 weeks of training, was more strongly associated with gains in strength than in muscle activation[21-23]. However, a knowledge gap exists regarding whether an increase in quadriceps tensile stiffness in females can reduce their peak ACL strain during a stressful activity such as a given pivot landing[34]. We therefore tested the primary hypothesis *in vitro* that increasing quadriceps tensile stiffness would reduce peak AM-ACL relative strain in female knees during a simulated pivot landing, and interpreted our results using an *in silico* model.

3.3 Materials and Methods

Twelve female unembalmed cadaver limbs with no visual signs of surgery and deformities were acquired from the University of Michigan Anatomical Donations Program and the Anatomy Gifts Registry (Hanover, MD). The specimens were of height and weight (mean (SD) age: 58 (14) yrs; height: 164.5 (6.8) cm; body mass: 70.2 (5.3) kg). As previously described[26], the limbs were dissected, leaving the ligamentous structures of the knee joint intact along with the tendons of the quadriceps, medial and lateral hamstrings, and medial and lateral gastrocnemius. The proximal femur and distal tibia and fibula were cut 20 cm from the knee joint line and potted in a PVC cylinder filled with polymethylmethacrylate **(**PMMA). The specimens were stored at -20° C until being thawed at room temperature 12 hours prior to testing.

The cadaver limbs were placed in a modified Withrow testing apparatus[42] capable of simulating a single-leg 2*BW pivot landing[26, 35] (Figure 3.1). The methods for this testing apparatus have been previously outlined[26]. Briefly, each trial begins by dropping an impact mass from 7 cm onto an impact rod in series with a torsional device, delivering an impulsive compound load to the knee joint (Figure 3.1). The strut angle within the axial torsional device controls the gain between internal tibial torque and the compression force, and a cylinder can be keyed into the center of the torsional device to only allow a compressive load. The applied impulsive load was standardized to 2*BW of the specimen and consisted of a compression force, knee flexion moment, and internal tibial torque, peaking at 60 ms. The initial knee flexion angle was 15°, consistent with the knee flexion angle at the time of ACL injury[36], delivering the impulsive force 3 cm posterior to the knee joint.

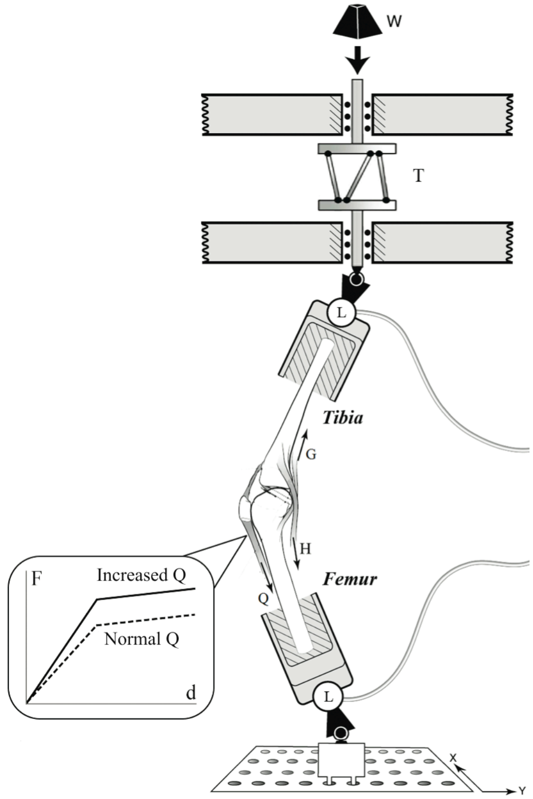

Figure 3.1 Diagram of the modified Withrow-Oh testing apparatus. Inset: Force-displacement relationship for a non-linear quadriceps spring representing the normal and increased stiffness female quadriceps values. Figure Abbreviations: W – drop weight; T – torsional device; L – 6-axis load cell; Q: quadriceps tendon; H: hamstrings tendon; G: gastrocnemius tendon.

Tibiofemoral kinematics were recorded at 400 Hz with 2 sets of 3 infrared emitting diodes (IREDs) using an Optotrak Certus camera system (Northern Digital, Inc., Waterloo, Ontario, Canada). A digitizer related anatomic landmarks to the IRED location in order to follow the absolute and relative 3D translations and rotations of the femoral condyles, relative to the tibial plateau, throughout each trial. The input and reaction three-dimensional forces and torques applied to the distal tibia and fibula were measured at 2 kHz with 6-axis load cells (MC3A-1000, AMTI, Watertown, MA). Relative strain was measured on the distal 3rd of the anteromedial bundle of the ACL using a differential variable reluctance transducer (DVRT) (3-mm stroke length, MicroStrain, Inc., Burlington, VT).

Cryoclamps were attached to the quadriceps, hamstrings, and gastrocnemius muscle tendons. Muscle tension was recorded at 2 kHz with in-series uniaxial load cells (TLL-1K and TLL-500, Transducer Techniques, Inc., Temecula, CA). Each muscle tendon and its corresponding load cell were in series with a spring acting as a muscle equivalent. Woven nylon cord (stiffness: 200 N/mm) pretensioned to 70 N served as the muscle equivalent for the medial and lateral hamstrings and medial and lateral gastrocnemius muscles. The quadriceps tendon was pre-tensioned to 180 N and utilized a non-linear spring to model the muscle's bi-linear stiffness response to rapid stretch[26] (Appendix A). This study utilized two quadriceps tensile stiffness values: a stiffness values similar to those seen in a typical females (initial stiffness: 156 N/mm; final stiffness: 35 N/mm) as well as a 33% increase in quadriceps tensile stiffness to simulate training increases in musculo-tendon unit stiffness (initial stiffness: 208 N/mm; final stiffness: 47 N/mm). The freezing of the rectus femoris tendon made the tendon very stiff; therefore, any changes in the stiffness within our *in vitro* quadriceps musculo-tendon unit would be caused by changes in stiffness within our non-linear quadriceps spring.

A repeated measures design (A-B-C-A) was used to measure peak AM-ACL relative strain in female knees undergoing a simulated pivot landing with a normal and increased stiffness female quadriceps spring. Since the impact mass and drop height remained constant between trial blocks, the knee received the same energy input in each trial block. The A trial blocks represented prebaseline and postbaseline non-pivot landings consisting of 2*BW compressive force with a resultant knee flexion moment. No significant difference in peak AM-ACL relative strain between the baseline blocks indicated that ACL integrity was maintained. The torsional device was activated for the B and C trial blocks to load the knee joint with 2*BW simulated pivot landing consisting of compression force, knee flexion moment, and a 20 Nm internal tibial torque, which represents the worst-case scenario loading for the ACL in regard to straining the ligament[35]. The B trial block tested female knees with female quadriceps tensile stiffness under a simulated pivot landing, while the C trial block increased the short range stiffness of the quadriceps spring by 33% to represent a female muscle with increased stiffness. The order of the B and C trial blocks was randomized. Five preconditioning trials were performed prior to data collection to remove hysteresis effects. Following the preconditioning trials, 5 impact trials was performed for each trial block, with 1 preconditioning trial between testing blocks, resulting in 28 total trials.

Biomechanical Model

A published three-dimensional lower-limb dynamic biomechanical model was used to replicate the knee loading within the Withrow-Oh *in vitro* testing apparatus in order to interpret the experiment results[35]. The model was updated (Appendix C) to use bone morphology obtained by segmenting the distal femur, proximal tibia and fibula, and patella from magnetic resonance imaging scans of a human knee (SolidWorks 2010, Dassault Systems SolidWorks Corp., Concord, MA; Rhinoceros, McNeel North America, Seattle, WA). The model was then imported into a dynamic motion simulation software package (MD Adams R3, MSC.Software, Inc., Santa Ana, CA), where the visco-elastic muscles, ligaments and capsule structures were modeled using Kelvin-Voigt elements. For the dynamic analysis, the forces and moments from experimental data were applied to the distal tibia. The quadriceps tensile stiffness was varied in 5% increments from 70-130%, with 70% and 100% quadriceps tensile stiffness representing the normal and increased stiffness female experimental values. Peak AM-ACL relative strain and change in knee flexion angle were monitored.

Statistical Analysis

Statistical analyses were performed in SPSS 19 (IBM Inc., Armonk, NY). The primary hypothesis was tested with Wilcoxon signed-rank tests to analyze the differences in peak AM-ACL relative strain between the A-B-C-A testing blocks. Two-sided paired t-tests were used to analyze dynamic inputs and kinematic outputs between the B and C testing blocks. Pearson correlations were utilized for secondary analyses to compare knee flexion angle and knee abduction angle, along with anterior tibial translation and quadriceps force. A p-value < 0.05 and a correlation coefficient, ρ, $< |0.575|$ (which is equivalent to $p < 0.05$ for $n = 12$) was considered statistically significant. The sample size ($n=12$) was based on a two-tailed dependent means power analysis of peak AM-ACL relative strain with varying quadriceps tensile stiffness for six female knees with alpha = 0.05 and power = 0.8. The *a priori* effect size was 1.29, requiring a sample size of 7 female knees. Additional knees were included in the study to improve power, resulting in a post-hoc power of 0.997 and a post-hoc effect size of 1.49.

3.4 Results

The primary hypothesis was supported in that peak AM-ACL relative strain was reduced in female knees with increased quadriceps tensile stiffness during under a 2*BW simulated pivot landing (mean (SD) difference: 0.97 (0.65) %, $p = 0.003$, Figure 3.2). On average, this resulted in a 16% decrease in peak AM-ACL relative strain with a 33% increase in the short-range quadriceps tensile stiffness. When compared to pre-baseline and post-baseline trials, peak AM-ACL relative strain was greater for simulated pivot landings with the both the normal ($p = 0.002$ and $p = 0.002$, respectively) and increased female quadriceps tensile stiffness ($p = 0.002$ and $p = 0.002$, respectively). There was no difference between pre-baseline and post-baseline testing ($p = 0.875$), indicating ACL integrity was maintained throughout testing.

The loads applied to the knee and the resultant kinematics and muscles loads for the four trial blocks are shown in Table 3.1. The change in knee flexion angle and the knee abduction angle were correlated ($\rho = 0.67$) with the lesser quadriceps tensile stiffness spring, while both the change in knee flexion angle and knee abduction angle were reduced using the greater quadriceps tensile stiffness ($p < 0.001$ and $p < 0.001$, respectively). The greater quadriceps tensile stiffness did produce a small increase in anterior tibial translation over the lesser quadriceps spring ($p = 0.009$). However, this likely occurs due to the significantly greater dynamic quadriceps force with the greater quadriceps tensile stiffness ($p < 0.001$). Quadriceps force and anterior tibial translation were highly correlated ($\rho = 0.595$).

Experimentally, the increase in quadriceps tensile stiffness from the normal to the greater quadriceps stiffness resulted in a large reduction in knee flexion in each knee, and a corresponding reduction in peak AM-ACL relative strain (Figure 3.3). The effect of quadriceps tensile stiffness on peak AM-ACL relative strain was further investigated with a dynamic biomechanical model, which confirmed the experimental results (Figure 3.4). The *in silico* model demonstrated that an increase in quadriceps tensile stiffness reduced the peak change in knee flexion angle, as seen experimentally, thereby reducing the amount the femur rolled posteriorly on the tibial plateau.

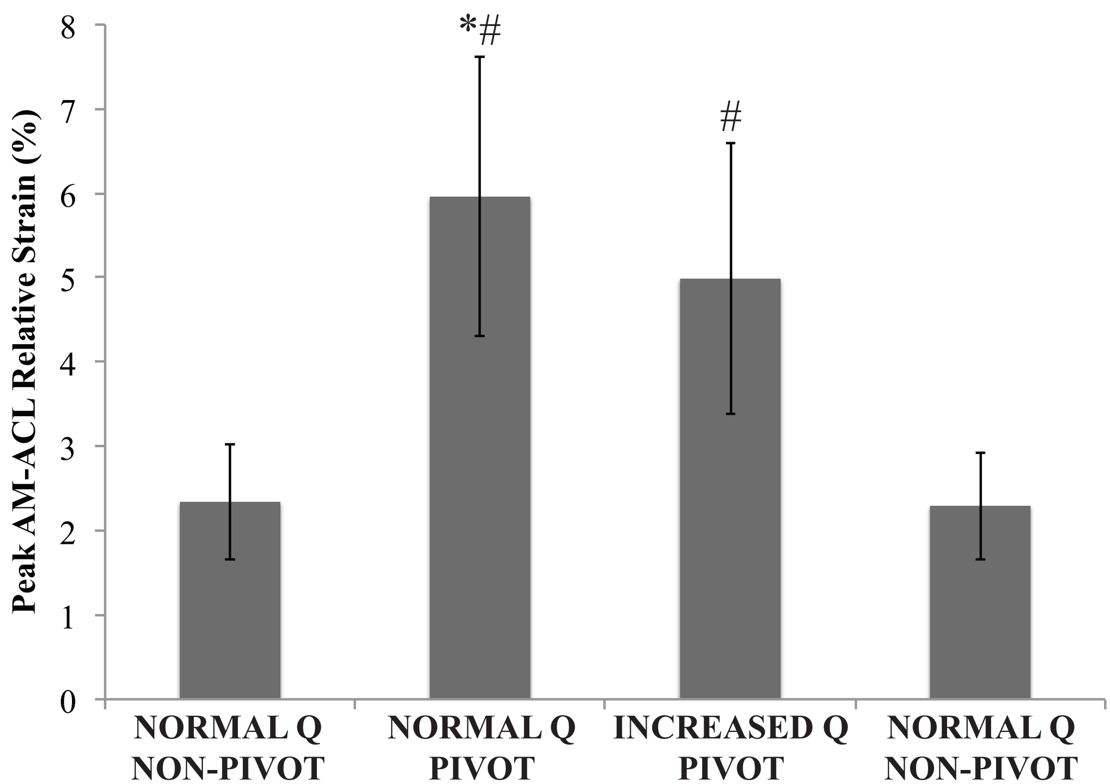

Figure 3.2 Peak AM-ACL relative strain for 12 female knees tested under the four repeated measures testing conditions. Pre-baseline and post-baseline 2*BW non-pivoting landings (NON-PIVOT) are simulated with compression + flexion knee loads are compared to 2*BW pivot landings (PIVOT) under compression, flexion, and internal tibial torque knee loads. The pivot landings were tested with the knee protected by normal and increased stiffness female quadriceps (Q) muscle springs. Error bars indicate 95% confidence intervals.* - significant stiffness difference ($p = 0.003$); # - significant greater than baseline testing ($p < 0.01$)

Table 3.1 Input forces and torques and outcome strains, forces, and kinematics under four loading conditions for 12 female knees. Q denotes quadriceps.

	Non-Pivot Landing	Pivot Landing		Non-Pivot Landing
	Prebaseline	Normal Q Stiffness	Increased Q Stiffness	Postbaseline
Loading Inputs				
Peak Impact Force (N)	1158 (117)	622 (102)	652 (90)	1143 (126)
Peak Internal Tibial Torque (Nm)	1.8 (0.5)	20.0 (2.1)*	21.2 (2.2)	1.8 (0.4)
Primary Outcomes				
Peak AM-ACL Strain (%)	2.34 (1.22)	5.96 (2.92)*	4.99 (2.85)	2.29 (1.12)
Normalized Peak AM-ACL Strain	0.99 (0.12)	2.66 (0.93)*	2.13 (0.75)	0.99 (0.10)
Secondary Outcomes				
Quadriceps Force (N)	766 (61)	924 (61)**	1023 (88)	759 (75)
Change in Knee Flexion (deg)	7.0 (1.1)	10.1 (1.7)**	8.0 (1.6)	6.8 (1.0)
Change in Knee Abduction (deg)	1.8 (1.0)	4.8 (1.7)**	3.4 (1.1)	1.7 (1.0)
Anterior Tibial Translation (mm)	2.5 (0.9)	4.9 (1.3)*	5.4 (1.3)	2.4 (0.9)
Internal Tibial Rotation (deg)	4.5 (1.0)	17.3 (2.3)	17.7 (2.2)	4.6 (1.2)

* - Significant stiffness effect $p < 0.01$; ** - Significant stiffness effect $p < 0.001$

Note: Non-pivot landings were only performed with the normal female quadriceps tensile stiffness

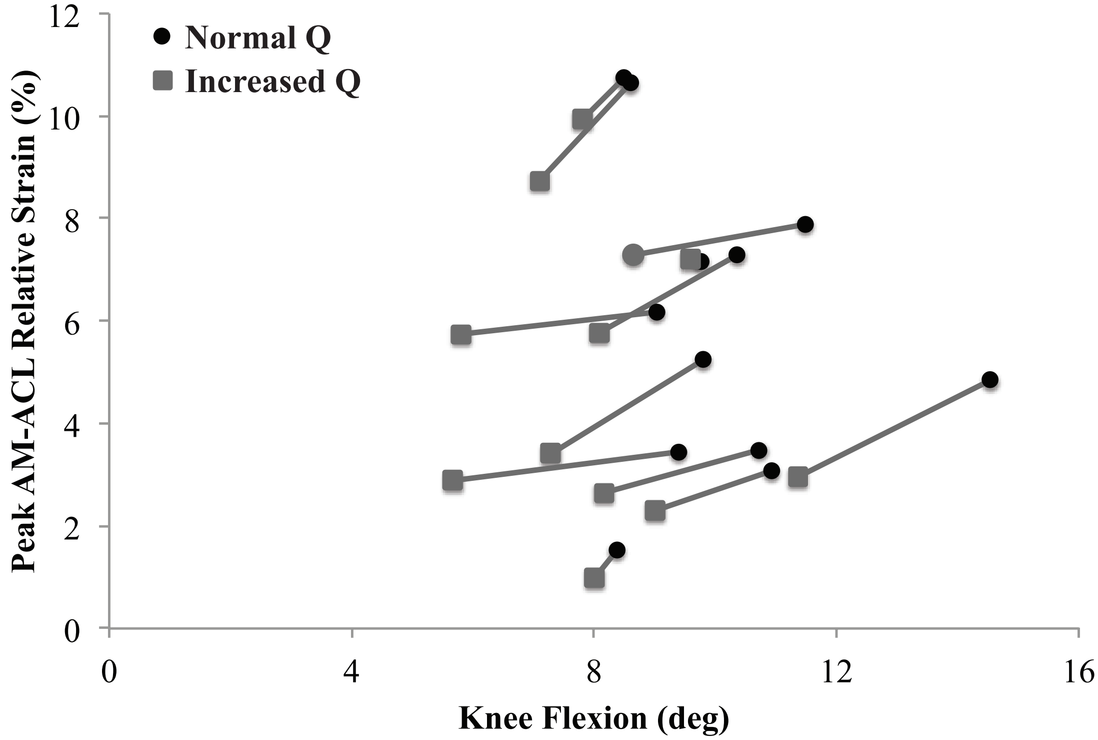

Figure 3.3 Scatterplot of peak AM-ACL relative vs. peak change in knee flexion angle during the experimental studies of a simulated pivot landing. For each female knee, the effect of the normal and increased female quadriceps tensile stiffness is shown by the square and circle symbols, respectively, which are connected by a straight line for ease of identification.

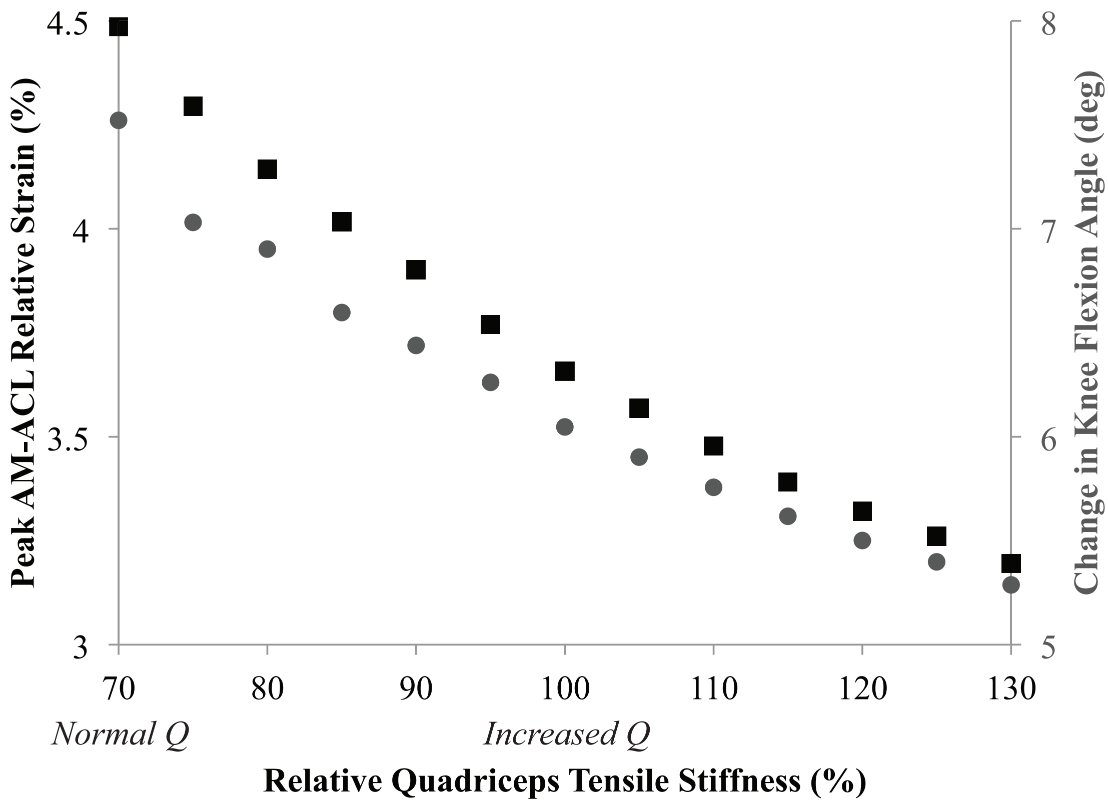

Figure 3.4 *In silico* results showing the predicted effect of varying quadriceps tensile stiffness on peak AM-ACL relative strain (black squares) and the peak change in knee flexion angle (gray circles) during a pivot landing. The normal and increased female quadriceps tensile stiffness values used during the experimental model are labeled as *Normal Q* and *Increased Q*, respectively.

3.5 Discussion

This study demonstrates for the first time that an increased quadriceps muscle resistance to rapid stretch significantly reduces peak AM-ACL strain during a 2*BW pivot landing in female knees. The *in vitro* experimental results showed a 33% increase in quadriceps tensile stiffness led to a 16% reduction in peak AM-ACL relative strain during a pivot landing; the *in silico* model predicted a 19% reduction in peak AM-ACL relative strain with a 30% increase in quadriceps tensile stiffness. These reductions in peak AM-ACL relative strain were associated with a smaller increase in knee flexion and knee abduction during the pivot landing. Hence one would predict that increasing the tensile stiffness of the quadriceps, either via muscle hypertrophy or by increased neural drive, could reduce peak ACL strains.

ACL injury prevention programs have had limited success[31], and there is little evidence as to how exactly these prevention programs reduce ACL injury risk. A common component of ACL injury prevention programs involves knee extensor strength training[14, 25, 30]. Progressive resistance training will produce gains in muscle strength and muscle hypertrophy[27,28], and should increase muscle tensile stiffness[8, 19]. For example, young females enrolled in a 16-week, 3 days/week progressive resistance training program developed a 38% increase in knee extensor strength[19]. The corresponding increase in muscle size was 6-8% in quadriceps femoris muscle volume during a 9-week, 3 days/week strength training program[16, 39]. Similar gains in knee extensor strength (32-34%), muscle volume (6-8%) and 30-58% increase in vastus lateralis musculotendon stiffness were found in young males after a 12-week knee extensor strength training program[21, 22]. It is also possible to achieve a 34% gain in musculotendon stiffness in 4 weeks by increasing muscle activation, rather than muscle strength[38]. We conclude that the 33% increase in female quadriceps tensile stiffness used in this study is achievable by *in vivo* resistance training, but it nears the maximum that can be expected with a 3-month training program.

The quadriceps is the primary knee muscle resisting lengthening during the first 100 ms of a jump landing. Since females have less quadriceps tensile stiffness[12] and greater ACL strain[26] than males, it seemed important to investigate the effect of increasing female quadriceps tensile stiffness on peak ACL strain. The gender difference in muscle stiffness is mainly due to a larger male muscle volume[33] and mass[11], therefore it is not surprising that passive muscle stiffness is highly associated with muscle cross-sectional area[37] and volume[7]. Females adopt a landing strategy with greater quadriceps activation than males[28, 41], which may allow them to compensate for their reduced lower extremity muscle mass[18]. Since active muscle stiffness is proportional to muscle strength[5], strengthening the quadriceps should increase its tensile stiffness thereby reducing ACL strain.

The finding that peak AM-ACL relative strain should increase with knee flexion excursion may seem counterintuitive, since ACL strain under passive[2] and active flexion-extension[4] decreases as the knee is flexed from 15 degrees. However, a knowledge gap concerns the effect of dynamic knee flexion on *in vivo* ACL strain during a jump or pivot landing: only one study has examined ACL strain during a jump landing and that was in a single individual[6]. The rolling-sliding that occurs with knee flexion may explain why increases in dynamic knee flexion can lead to greater ACL strain (Figure 3.5); there was greater *in vitro* quadriceps force and anterior tibial translation with the stiffer quadriceps spring despite lower AM-ACL relative strain. Dynamic knee flexion under a given load will cause the femoral condyles to roll posteriorly relative to the tibial plateau[17, 24, 32], thereby loading the ACL. As the femur rolls, the initial femoral contact point will eventually slide anteriorly relative to the initial tibial contact point, thereby unloading the ACL. Femoral rolling will dominate sliding in extended weight-bearing knees, near full extension, with reduced quadriceps activation[15] (i.e., less quadriceps tensile stiffness). The sliding likely occurs because the condyle has a smaller radius of curvature as the knee flexes[20]. The *in vitro* (Figure 3.3) and *in silico* (Figure 3.4) results are similar: the less-stiff female quadriceps will allow for a greater increase in dynamic knee flexion, leading to greater peak AM-ACL relative strain than with the female quadriceps with greater stiffness.

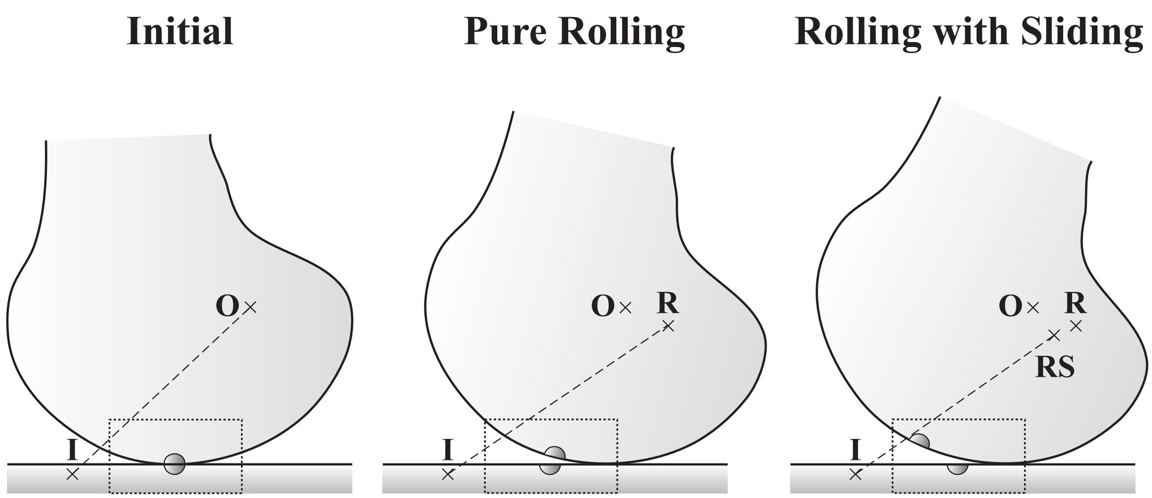

Figure 3.5 Schematic drawing (lateral view) showing the effect of femoral condyle rolling (top) on the tibial plateau (bottom). The ACL tibial insertion (I) and femoral origin (O) are marked with x symbols. (a) Initial tibiofemoral contact prior to the application of knee flexion. (b) To show pure rolling, the femur rolls 15 degrees posteriorly down the tibial plateau, increasing ACL strain as indicated by the new ACL femoral origin location (R). (c) As the femur continues to roll, simultaneous sliding will develop, as shown by the initial femur contact point being located more anterior than the initial tibial contact point in the dotted box. This sliding mechanism will begin to unload the ACL, as shown by the new location of the ACL femoral origin (R+S).

Strengths of this study include the use of a novel non-linear quadriceps spring to investigate *in vivo* differences in muscle stiffness with an *in vitro* testing apparatus, a repeated measures design with randomized testing blocks, and the use of a dynamic biomechanical model to interpret *in silico* the *in vitro* testing results. Limitations include this study being only performed at 15° initial knee flexion. Previous studies show that large quadriceps forces can rupture the ACL near extension[9, 40]; however, those studies utilized non-physiological levels of quadriceps force[10] and/or axial compression[45]. Second, we utilized the rectus femoris tendon for the quadriceps muscle equivalent; altering the stiffness of the other quadriceps muscles could affect frontal and axial plane movements. Third, we only measured ACL strain in the anteromedial bundle, which is highly correlated with overall ACL force[29]. The DVRT only measures relative strain, which likely underestimates the absolute strain on the ligament due to the pretensioned muscle forces. Finally, the specimens utilized in this experiment were older than the adolescents and young adult populations at the highest risk for ACL injuries. Limitations of the dynamic biomechanical model are explained in Appendix C.

3.6 Conclusions

1) An increase in quadriceps tensile stiffness by 33% can reduce peak AM-ACL relative strain by 16% in female knees during a 2*BW simulated pivot landing.
2) An *in silico* model confirmed the main experimental findings: the increase in quadriceps tensile stiffness produced a reduction of dynamic knee flexion and a corresponding reduction in peak ACL strain.
3) Muscle hypertrophy and/or increased muscle activation via knee extensor strength training may reduce the risk of ACL injuries.

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CHAPTER 4

ON THE FATIGUE LIFE OF THE HUMAN ANTERIOR CRUCIATE LIGAMENT DURING SIMULATED PIVOT LANDINGS

4.1 Abstract

It is not known whether the human anterior cruciate ligament (ACL) fails due fatigue or whether knee morphology affects this behavior. We hypothesize that the number of cycles to ACL failure is unaffected by the magnitude of the external load, gender, ACL cross-sectional area, or lateral tibial slope.

Matched-paired knees from 10 cadaveric donors (5 female) of similar age, height, and weight were imaged with 3-Tesla magnetic resonance imaging to measure lateral tibial slope and ACL cross-sectional area. Then, a knee from each pair was subjected to repeated three-times body weight (3*BW) or 4*BW loading under combined impulsive compression, knee flexion moment and internal tibial torque with realistic muscle forces. The resulting 3-D tibiofemoral kinematics and kinetics were recorded, along with ACL relative strain and quadriceps, hamstrings, and gastrocnemius muscle forces. The loading cycle was repeated until the ACL ruptured, a 3-mm increase in cumulative anterior tibial translation occurred, or a minimum of 50 trials was reached.

Thirteen of 20 knees failed during testing: 4 knees with a 3-mm increase in anterior tibial translation, 7 partial or complete visible tears, and 2 tibial avulsions. A Cox regression showed that the number of cycles to ACL failure was influenced by the

simulated landing force ($p = 0.04$) and ACL cross-sectional area ($p = 0.03$). Peak anterior tibial translation during impact differed between knees with failed and intact ACLs ($p = 0.021$). We conclude the human ACL is susceptible to fatigue failure and ACLs with smaller cross-sectional areas are at particular risk for this mode of failure. Limiting the number of times the knee is subjected to large compression, flexion and internal tibial torque knee loads within a given time interval may reduce an athlete's risk for ACL injury.

4.2 Introduction

There are over 350,000 anterior cruciate ligament (ACL) injuries in the United States each year[20], with the onset of these injuries often occurring by the age of 12 years[55]. Females seem to be predisposed to ACL injuries, with a two-to-eight times greater risk than sports-matched males[3, 25, 37, 38, 52]. ACL injuries can lead to considerable morbidity with 50% of ACL-injured subjects developing knee osteoarthritis within a 10-20 year span following injury[30]. This risk for osteoarthritis increases to 80% in individuals when ACL injury is combined with a meniscal tear and/or chondral lesion and/or medial collateral ligament injury[46]. A better understanding of ACL injury mechanisms is needed to prevent both the initial injury and its long-term consequences.

It is widely acknowledged that an ACL failure can and does occur during an awkward single leg landing or cutting maneuver that imposes large external loads on the knee [5, 47]. It is not known whether the ACL can also fail due to repetitive loading[57], in other words due to a fatigue failure. While video analyses have traditionally focused on the body movements at the time of the ACL injury[6, 47], athletes often perform similar movements hundreds, if not thousands, of times before that season. For example, females participating in recreational soccer perform 1.6 stopping or turning maneuvers per minute[50] while professional soccer players in the FA Premier League spend 7.2% of their playing time moving in the lateral or forward diagonal direction[4]; on average, this equated to 727 turning or swerving maneuvers per match. Similar movements can result in a wide variation of joint loading because of the many different combinations of muscle forces that counteract the external loads[22]. When the same landing (or cutting) maneuver is repeated, the ACL is likely subjected to a normal distribution of loading intensities, including a few low or high loads combined with many more moderate loads. Our working hypothesis is when a certain number of high ACL loading cycles is achieved, the ACL will fail, likely as a result of the aggregated damage over a given time frame.

Animal and cadaveric tensile testing has shown that passive collagenous structures like ligament are susceptible to fatigue failures, taking fewer higher stress cycles to fail when cyclically loaded[54, 61, 63, 68]. Collagenous structures behave according to the well known 'S-N' curve relating the tensile stress in the material, S, to the number of cycles before failure, N, as described by the Goodman diagram[56]. The damage accumulation over the course of a fatigue failure will reduce the ligament's modulus of elasticity[62], placing the ligament in a susceptible state. This may be especially true for females, given their smaller ACL diameter[9, 15] and volume[10], and smaller modulus of elasticity[9]. Since a greater lateral tibial slope and a smaller ACL cross-sectional area are associated with increased peak ACL strain during a simulated pivot landing[29], we hypothesize that these factors will reduce the number of cycles to ACL failure during a dynamic maneuver.

The objective of this study was to determine whether the ACL exhibits fatigue behavior under repetitive simulated pivot landings. This represents a major paradigm shift in ACL injury mechanism research because it would explain why athletes that perform the same maneuver time after time suddenly rupture their ACL. To reduce the effect of inter-subject variability, matched-paired knees were used. Donors of similar age, height, and weight were utilized to reduce the effect of size differences between males and females. The number of cycles to ACL failure (defined as a macroscopic tear or a 3-mm increase in cumulative anterior tibial translation) was recorded as each knee in the matched pair underwent a three-times body weight (3*BW) or 4*BW simulated pivot landing. The primary null hypothesis was that the simulated landing force, gender, ACL cross-sectional area, and lateral tibial slope would not affect the number of cycles to ACL failure. A secondary analysis on cumulative anterior tibial translation and internal tibial rotation was performed in order to determine if these variables differ between the knees with intact and failed ACLs.

4.3 Materials and Methods

Ten pairs of human lower extremities (5 females) from donors of similar age, height and weight (5 female pairs, 5 male pairs; mean (SD) age: 53(7) years, height: 174(9) cm, body mass: 69(9) kg) were acquired from the University of Michigan Anatomical Donation unit and the Anatomy Gift Registry (Hanover, MD). The specimens were screened to eliminate a history of lower extremity surgery, trauma or degenerative changes, as evidenced by visual scars or deformities of the knee joint. The specimens were harvested and dissected, keeping the muscle tendons of the quadriceps, medial and lateral hamstrings, and medial and lateral gastrocnemius intact, as well as the ligamentous capsular structures. The distal femur and proximal tibia and fibula were cut 20 cm from the knee joint line. Specimens were stored frozen at -20° C and were thawed at room temperature prior to imaging and testing.

Prior to testing, all twenty knees were imaged with a 3-Tesla T2-weighted MR scan (Philips Healthcare 3T scanner [Best, the Netherlands], 3D proton-density sequence; repetition time/echo time, 1000/35 milliseconds; slice thickness, 0.7 mm; pixel spacing, 0.35 mm x 0.35 mm; field of view, 330 mm). The scans were viewed and measured in OsiriX (v3.9, open source, www.osirix-viewer.com). ACL cross-sectional area was measured by outlining the circumference at 30% ligament length from the tibial origin with an oblique-axial view perpendicular to the ligament[29]. Lateral tibial slope was measured *ad modam* Hashemi et al.[23]: two anteroposterior lines were drawn 10 cm and 15 cm from the most proximal point on the central axis image, defined as the slice were the tibial attachment of the posterior cruciate ligament and the intercondylar eminence were visible. The midpoints of the anteroposterior lines were connected to define the tibial proximal anatomic axis. Lateral tibial slope was measured at the tibial center of articulation on the lateral tibial plateau, and was defined as the angle between a line perpendicular to the tibial proximal anatomic axis and a line fit to the posterior-inferior subchondral bone surface.

Following imaging, the distal femur and proximal tibia and fibula were potted in a 7.8-cm diameter PVC cylinder filled with PMMA. The ends of the potted bones were placed into aluminum housings within the Withrow-Oh testing apparatus[29, 44, 45, 64-66], which is capable of impulsively simulating a pivot landing with loads up to five-times body weight (5*BW) compression force with an added flexion moment (up to 120 Nm) and internal tibial torque (up to 45 Nm). This combination of loading vectors induces larger ACL strains than other combinations[45]. To minimize inter-subject variability, the experimental design randomly assigned one knee to a 3*BW simulated pivot landing and the paired knee to a 4*BW pivot landing. The drop height and drop weight were adjusted to apply the desired magnitude of compressive force to the specimen. Each trial was initiated by dropping a weight ('W') onto an impact rod in series with a torsional device ('T') as the loads applied to the knee are monitored with load cells ('L') on the distal femur and proximal tibia (Figure 4.1). The angle of the struts within the torsional device controls the gain between the compressive force and applied internal tibial torque.

Tibiofemoral kinematics were measured at 400 Hz using optoelectronic marker triads on the proximal tibia and distal femur (Optotrak Certus, Northern Digital, Inc., Waterloo, Ontario, Canada). A 3-D digitizing wand was used to define standard anatomical landmarks on the knee joint in order measure relative and absolute changes in tibiofemoral 3-D translations and rotations. Specifically, anterior tibial translation and internal tibial rotation were measured relative to each trial (referred to as a relative measurement) as well as the first pivot trial (referred to as a cumulative measurement). Two six-axis load cells (MC3A-1000, AMTI, Watertown, MA) were used to monitor the input and the reaction forces and moments applied to the proximal tibia and distal femur. Nylon string (stiffness: 250 N/mm for male knees and 200 N/mm for female knees, to account for gender difference in quadriceps tensile stiffness[18]) served as a muscle-equivalent for the pre-tensioned the quadriceps ('Q': 180 N), hamstrings ('H': 70 N each), and gastrocnemius ('G': 70 N each) muscles.

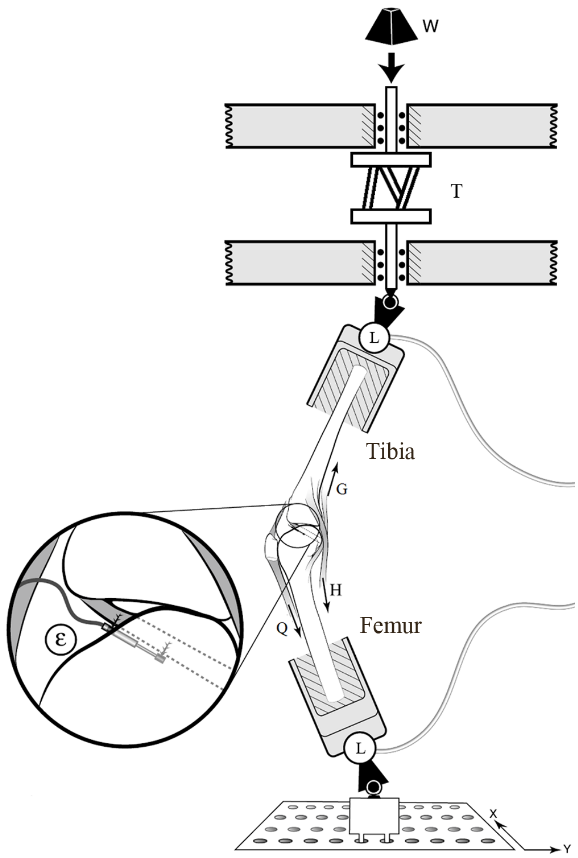

Figure 4.1 The modified Withrow-Oh testing apparatus. A drop weight ('W') results in an impulsive compressive force posterior to the knee joint that also induces a knee flexion moment. A torsional device ('T') added an internal tibial torque component to the compound loading. Load cells ('L') monitor the 3-D input and reaction forces and moments at the proximal tibial and distal femur. The quadriceps ('Q'), hamstrings ('H'), and gastrocnemius ('G') muscles were pre-tensioned prior to each trial, placing the knee initially at 20° knee flexion. A DVRT (inset) measured relative strain on the anteromedial bundle of the ACL during the impact.

The knee was placed at an initial 20° knee flexion angle prior to each trial. The muscle equivalents were located in series with a cryo-clamp frozen with liquid nitrogen, as well as a uniaxial load cell (TLL-1K and TLL-500, Transducer Techniques, Inc., Temecula, CA). Peak relative strain on the anteromedial (AM-) bundle of the ACL was monitored with a differential variable reluctance transducer (DVRT) (3-mm stroke length, MicroStrain, Inc., Burlington, VT) installed at a location one-third of the length of the ligament from its tibial insertion. The initial DVRT length used to calculate strain was relative to the DVRT's inter-barb length at the beginning of each trial (peak AM-ACL relative strain) and the first pivot trial (peak AM-ACL cumulative strain). The tibiofemoral kinetics, muscle forces, and strain data were measured at 2 kHz.

The testing protocol began with five preconditioning non-pivot trials of compression + flexion moment. During the preconditioning trials, the drop height and drop weight were adjusted to the target compressive force of 3*BW or 4*BW by the final non-pivot trial. These trials also minimized hysteresis effects prior to the pivot trials. After five non-pivot trials, the drop height and drop weight remained constant in order to insure the same energy was applied to the knee. The torsional device was activated to apply, on average, 30 Nm internal tibial torque for the 3*BW and 35 Nm internal tibial torque for the 4*BW test loads, in addition to compressive force and a knee flexion moment (78 and 97 Nm, respectively), simulating a pivot landing. The pivot landings were repeated until either (a) the ligament had failed, (b) a 3-mm increase in the cumulative anterior tibial translation occurred, or (c) a minimum of 50 trials were performed. Following testing, the ACL was visually inspected for macroscopic failure of the AM as well as posterolateral (PL) bundles.

An ACL failure was confirmed if there was visual evidence of a complete or partial ACL tear, an ACL avulsion occurred, or cumulative anterior tibial translation increased by 3 mm. The primary hypothesis was statistically tested using a Cox regression model with shared frailty in Stata 12 (StataCorp LP, College Station, TX) to predict the number of cycles to ACL failure, with gender, simulated landing force, ACL cross-sectional area, and lateral tibial slope as covariates. A secondary analysis was performed in SPSS 19 (IBM Inc., Armonk, NY) to determine if anterior tibial translation or internal tibial rotation were most influenced by the repetitive loading. Anterior tibial translation and internal tibial rotation were compared longitudinally through the experiment using a repeated-measures factorial linear mixed model. Ligament status (coded as 0 = intact and 1 = failed) and measurement condition (coded as 1 = last non-pivot trial, 2 = first pivot trial, 3 = final pivot trial, relative to start of final trial, and 4 = final pivot trial, relative to start of first pivot trial (i.e. cumulative change)) were treated as fixed factors. Since there were four measurement conditions, this was treated as a repeated measurement. A random intercept was utilized for each subject (coded by their donor ID) to account for differences in anterior tibial translation between donors. A p-value < 0.05 was considered significant for the primary and secondary analysis.

4.4 Results

Of the 20 knees tested, 13 met the criteria for ACL failure: one complete tear, six partial tears, two avulsions, and four permanent elongations of the ACL (i.e. 3 mm increase in cumulative anterior tibial translation) (Table 4.1). No macroscopic medial collateral ligament tears were observed. A set of matched-pair knees which displayed no damage and permanent elongation, and a second set of matched-pair knees which displayed permanent elongation and a complete mid-substance tear (>75% damage) are illustrated in Figure 4.2 and Figure 4.3. Appendix D contains images from all 10 matched-pair knees. The mean (SD) landing force and internal tibial torque were 4.3 (0.4) BWs and 34.5 (7.3) Nm for the higher impact landing and 3.5 (0.3) BWs and 29.8 (5.4) Nm for the lower impact landing. The female knees showed less rotational resistance to internal tibial torque than the male knees (0.65 (0.11) °/Nm vs. 0.47 (0.11) °/Nm, respectively), but exhibited smaller anterior tibial decelerations during the pivot landing (-14.5 (4.1) m/s^2 vs. -18.0 (4.5) m/s^2, respectively).

Table 4.1 Injury description and descriptive information for the 20 study donors

ID	Gender	Age (yrs)	Height (m)	Mass (kg)	Leg	Landing Force (BW)	Internal Tibial Torque (Nm)	Injury Description
32381	M	54	1.83	72.6	L	3.6	32.3	Permanent elongation*
					R	4.5	43.2	Partial tear PL bundle near (F)
61535	M	59	1.73	74.9	L	4.8	39.2	Did not fail
					R	3.9	33.2	Did not fail
33449	M	40	1.88	74.9	L	3.8	38.8	Did not fail
					R	4.7	42.7	Permanent elongation*
33812	M	58	1.79	63.6	L	4.1	34.0	Tibial avulsion
					R	3.6	30.6	Partial tears of PL bundle near (F) and AM bundle near (T)
72780	M	52	1.83	84.0	L	3.9	43.1	Did not fail
					R	3.1	36.5	Did not fail
42263	F	46	1.60	59.0	L	3.5	25.9	Permanent elongation*
					R	4.6	28.1	Partial tear PL bundle (M)
33913	F	59	1.68	59.0	L	4.2	23.0	Partial tear PL bundle (M)
					R	3.4	22.6	Partial tear PL bundle near (F)
34015	F	48	1.65	59.0	L	3.3	24.3	Did not fail
					R	4.1	27.6	Partial tear PL bundle near (M)
11442	F	55	1.73	77.2	L	3.8	34.0	Complete tear (M)
					R	3.1	28.3	Permanent elongation*
34090	F	63	1.70	68.1	L	4.0	29.8	Tibial avulsion
					R	3.2	25.9	Did not fail

* Permanent ACL elongation was defined as a 3-mm increase in absolute anterior tibial translation from the first pivot trial.

Abbreviations: BW – normalized to body weight; (F) – Femur; (T) – Tibia; (M) – Mid-substance.

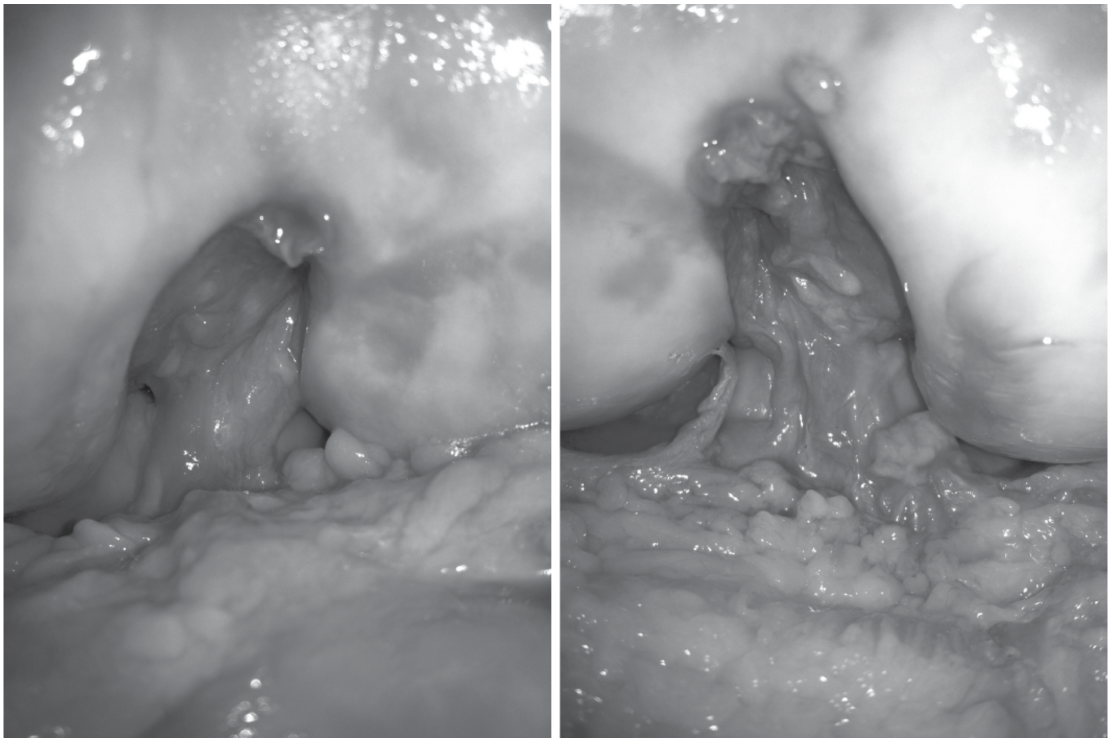

Figure 4.2 Post-testing images of male specimen #33449. The left ACL remained intact after 100 cycles of a 3.8-times body-weight (3.8*BW) simulated pivot landing. In contrast, the right ACL shows the ligament became elongated, especially on the posterolateral bundle, with a 3-mm increase in cumulative anterior tibial translation occurring after 58 trials at 4.7*BW. No macroscopic signs of tearing were visually seen from distal view of the femur with the knee joint flexed at 120 degrees.

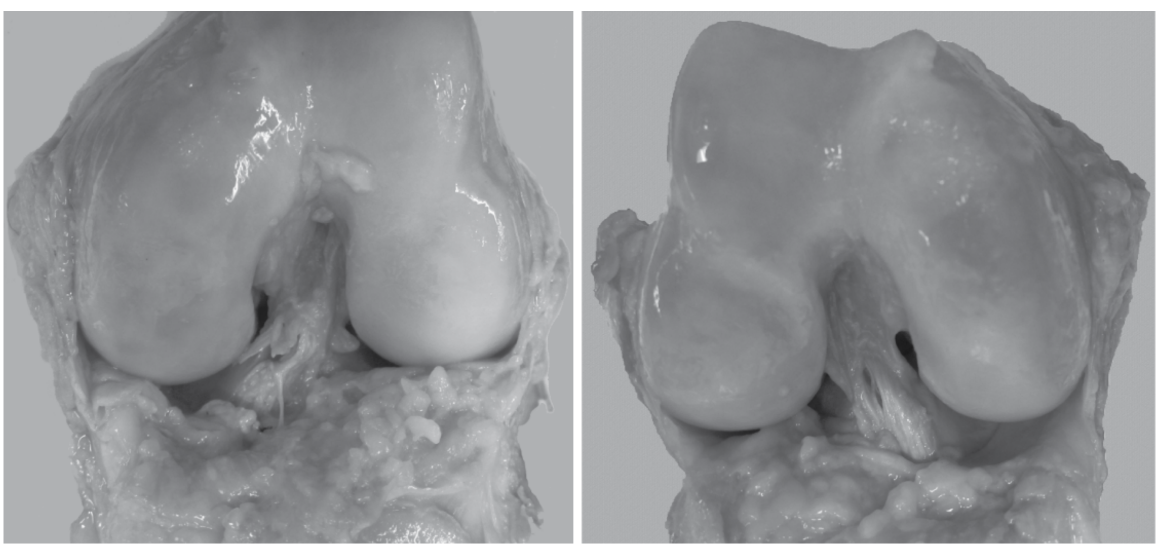

Figure 4.3 Post-testing images of female specimen #11442. The left ACL shows a complete ACL mid-substance rupture under 3.8*BW simulated landing forces. The posterolateral bundle damage is not visible from the distal view of the femur as clearly as the anteromedial bundle damage. The right ACL was permanently elongated under 3.1*BW simulated landing forces.

The primary hypothesis was rejected: a greater simulated landing force (Figure 4.4) and a smaller ACL cross-sectional area were significantly associated with fewer loading cycles to ACL failure (Wald $\chi^2 = 11.13$; $p = 0.025$, Table 4.2). Neither lateral tibial slope nor gender were significant predictors of the number of cycles to ACL failure. The mean (SD) ACL cross-sectional area and lateral tibial slope were 38.3 (8.9) mm^2 and 8.7 (3.3)°, respectively, for male knees and 31.8 (4.8) mm^2 and 9.9 (2.8)°, respectively, for female knees.

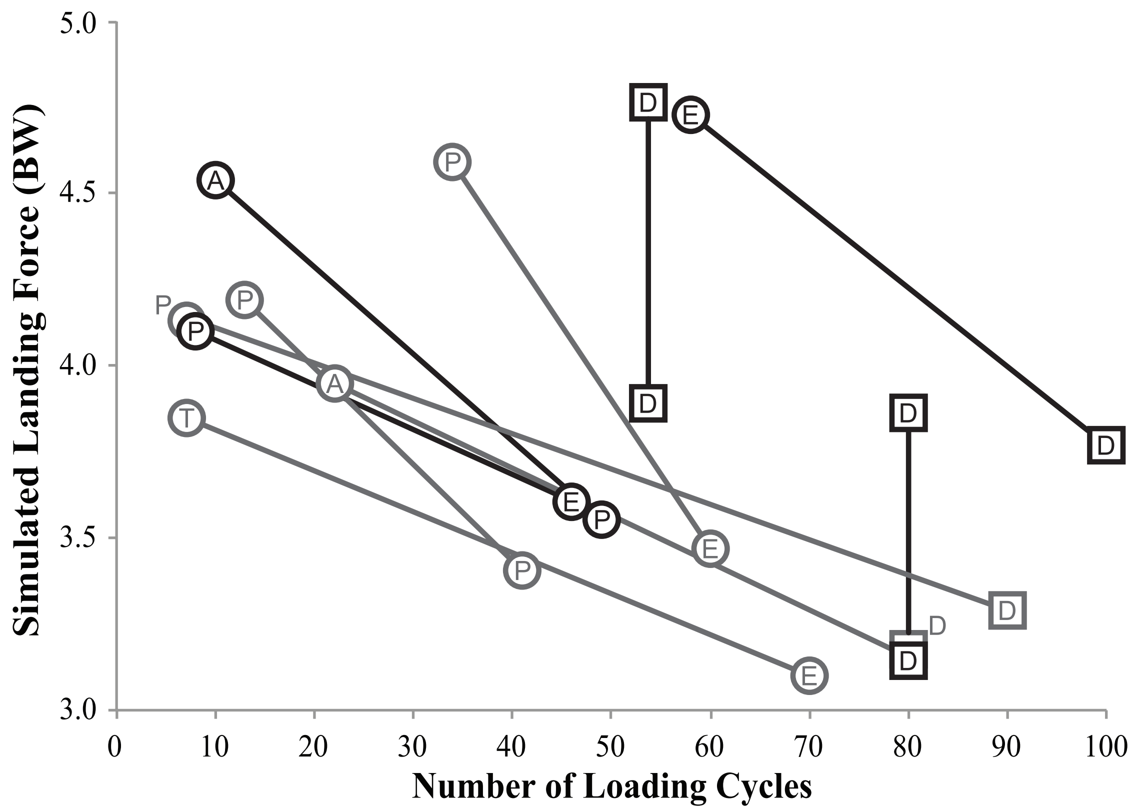

Figure 4.4 A scatterplot of the simulated landing force (as recorded as the compressive force on the femoral load cell) vs. the number of loading cycles for the ACL. A circle represents an ACL failure. A square represents a knee with an intact ACL at the conclusion of testing. The black markers are male knees, the gray markers are female knees, and the matched pair of each donor is connected with a line. Abbreviations within the marker denote the type of ACL failure: A – tibial avulsion; P – partial ACL tear; T – complete ACL tear; E – permanent elongation of the ACL determined by a 3-mm increase in cumulative anterior tibial translation. D denotes a knee which did not fail.

Table 4.2 Cox regression results for twenty knees with shared frailty term (theta) to control for matched-pairs.

Regressor	Hazard Ratio	95% confidence interval	p-value
Landing Force	46.42	(2.79, 771.65)	0.007*
Gender	1.31	(0.06, 27.4)	0.86
ACL CSA	0.65	(0.44, 0.96)	0.03*
LTS	0.90	(0.54, 1.52)	0.70
Theta	3.07		0.002*

Abbreviations: CSA – cross-sectional area; LTS: lateral tibial slope. Asterisk indicates significant p-value

For the secondary analyses, anterior tibial translation (Figure 4.5) and internal tibial rotation (Figure 4.6) were compared longitudinally throughout the experiment by examining the final non-pivot trial, the first pivot trial, and the cumulative and relative measurements at the final pivot trial. Anterior tibial translation increased in the knees with failed ACLs when compared to the intact ACLs: there was a significant interaction between the failure status of the ligament and the measurement condition for anterior tibial translation ($F(3,54) = 3.903$, $p = 0.014$), as well as significant main effects for failure status ($F(1,16) = 6.597$, $p = 0.021$) and measurement condition ($F(3,54) = 50.597$, $p < 0.001$). There was no significant difference in internal tibial rotation between knees with intact and failed ACLs: the interaction of the ligament's failure status and measurement condition for internal tibial rotation was not significant ($F(3,54) = 0.372$, $p = 0.774$), nor was the main effect for failure status ($F(1,16) = 0.011$, $p = 0.920$). There was a significant main effect for the measurement condition ($F(3,54) = 421.5$, $p < 0.001$) due to the absence of internal tibial torque during non-pivot trials. The cumulative increases in anterior tibial translation and internal tibial rotation relative to the first pivot trial were monitored for the male (Figure 4.7) and female knees (Figure 4.8). In general, these plots show that a knee under a higher impact loading showed a greater increase in cumulative anterior tibial translation and cumulative internal tibial rotation than the matched-paired knee with smaller impact loads.

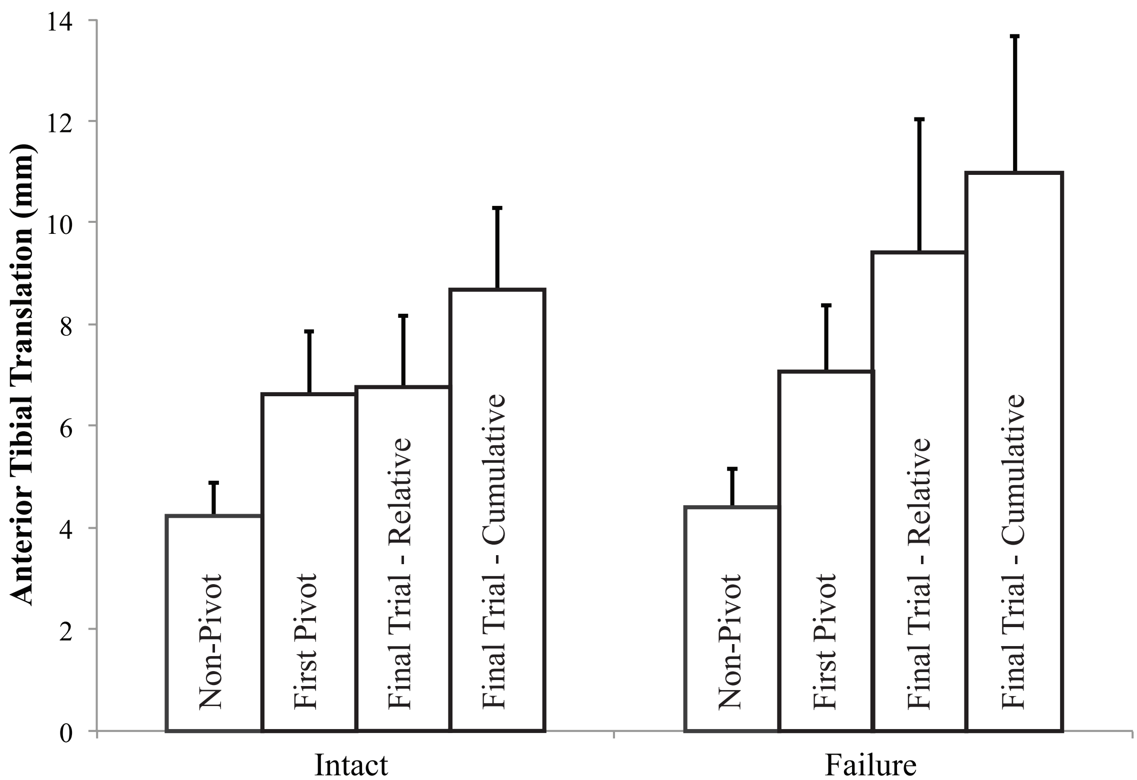

Figure 4.5 Anterior tibial translation for knees with an intact or failed ACL for the last non-pivot trial, the first pivot trial, and the final trial tested. For the final trial, anterior tibial translation is the change in anterior tibial translation relative to the tibial origin at the beginning of the final trial (relative) as well as the beginning of the first pivot trial (cumulative).

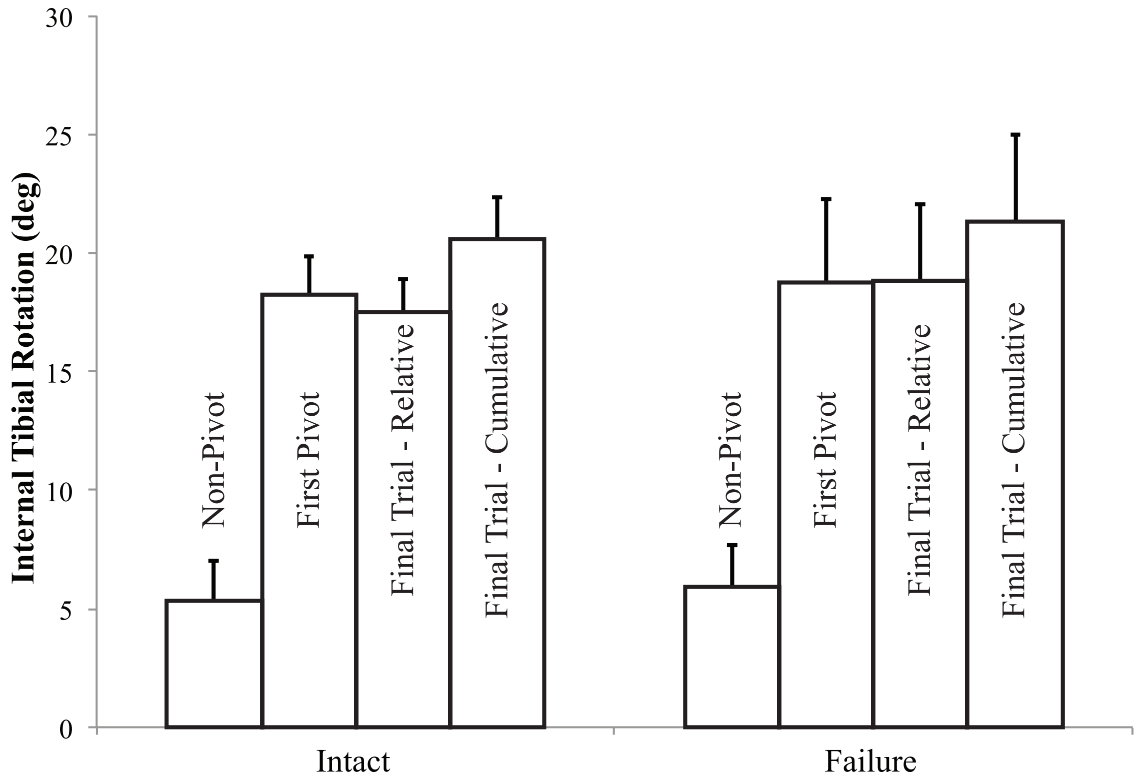

Figure 4.6 Internal tibial rotation for knees with an intact or failed ACL for the last non-pivot trial, the first pivot trial, and the final trial tested. For the final trial, internal tibial rotation is relative to the knee's position at the beginning of the final trial (relative), as well as the beginning of the first pivot trial (cumulative).

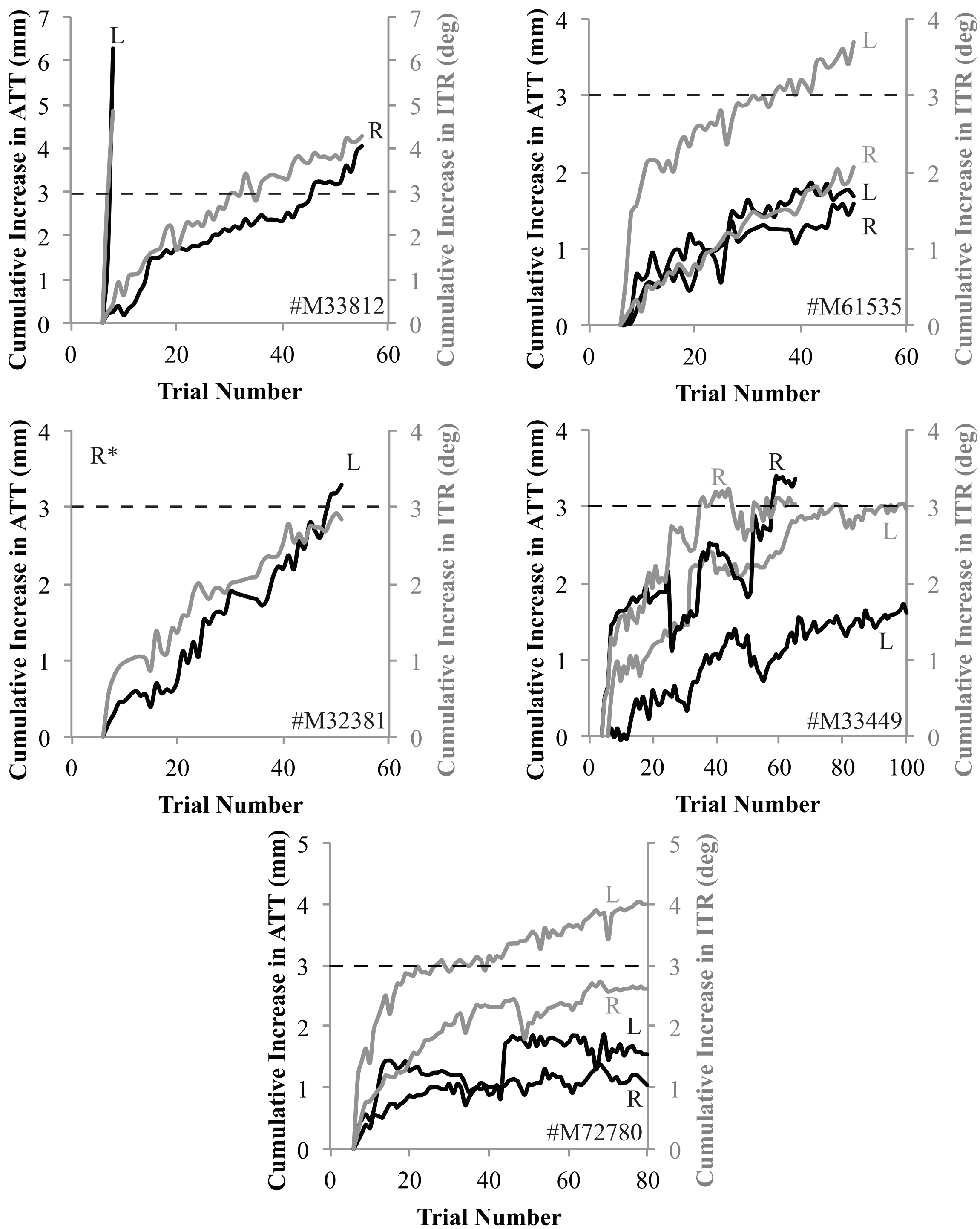

Figure 4.7 The cumulative increase in anterior tibial translation (ATT – black lines) and internal tibial rotation (ITR – gray lines) relative to the first simulated pivot landing trial for five pairs of male knees. There are no plots for the right knee of #M32381 because the knee failed on the first pivot trial.

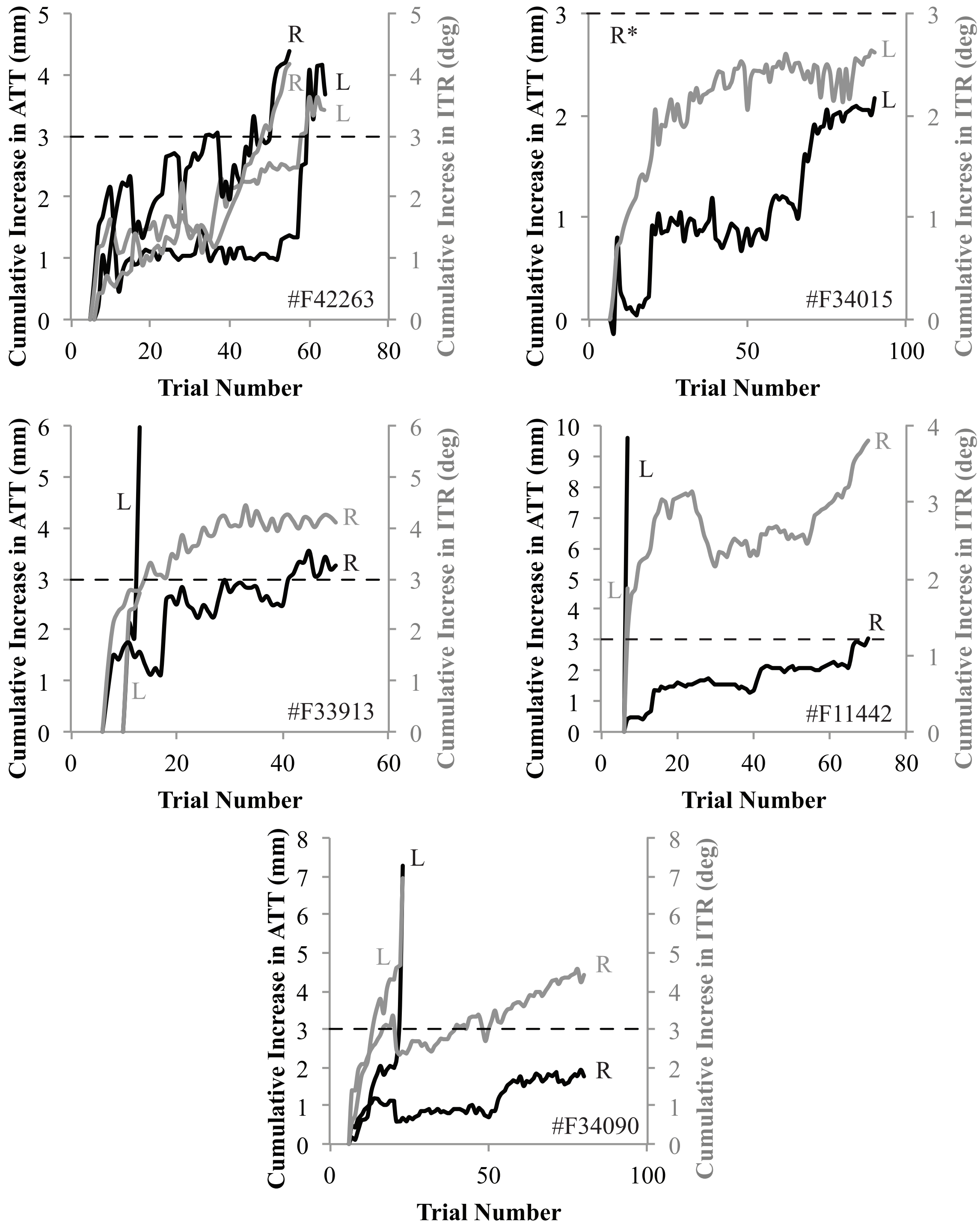

Figure 4.8 The cumulative increase in anterior tibial translation (ATT – black lines) and internal tibial rotation (ITR – gray lines) relative to the first simulated pivot landing trial for five pairs of female knees. There are no plots for the right knee of #F34015 because the knee failed on the second pivot trial and there was no substantial increase in translation or rotation from the first pivot trial.

Peak cumulative and relative AM-ACL strain was not as reliable in predicting failure status as anterior tibial translation. The mean (SD) non-pivot peak AM-ACL relative strain was 3.2 (1.6) % for intact ACLs and 4.5 (2.5) % for failed ACLs. After the first pivot trial, peak AM-ACL relative strain increased to 6.7 (3.4) % and 7.1 (3.8) % for intact and failed knees, respectively. By the final testing trial, peak AM-ACL relative and cumulative strain for intact knees were 4.7 (2.9) % and 7.1 (4.0) %, respectively. For knees with failed ACLs, peak AM-ACL relative and cumulative strain were 11.8 (12.0) % and 17.2 (14.5) %, respectively. There was a trend towards a negative relationship between peak AM-ACL cumulative strain and the number of cycles to ACL failure in the 13 failed knees ($\rho = -0.549$, $p = 0.054$) (Figure 4.9).

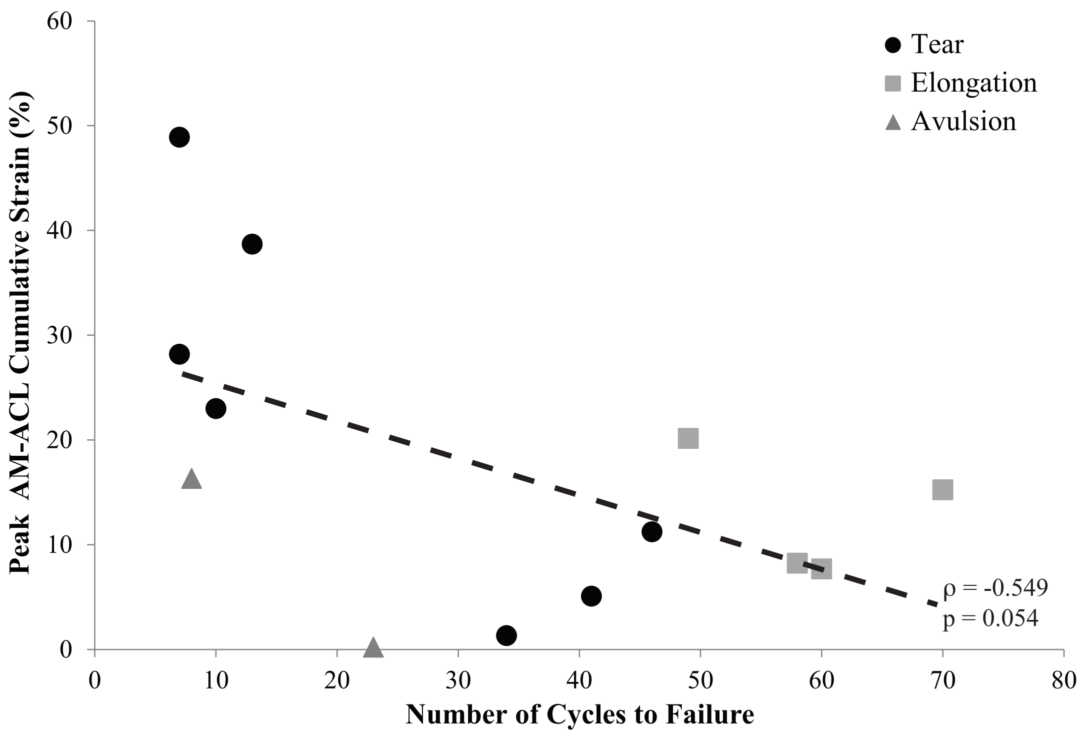

Figure 4.9 A scatterplot of peak AM-ACL cumulative strain vs. the number of cycles to ACL failure for the 13 knees, which underwent a complete tear, partial, tear, tibial avulsion, or permanent elongation. A linear fit to the scatterplot, with its associated Pearson correlation and p-value, is indicated with a dashed line.

4.5 Discussion

Since athletes perform the same cutting or pivoting maneuver hundreds, if not thousands, of times a season without rupturing an ACL, the loading history of the ACL might be just as important in determining whether an injury occurs as the particular body segment movements at the time of the ACL injury or the intensity of that final load. The present study tested the hypothesis that a fatigue failure can occur in the human ACL. The results support this hypothesis: a larger landing force, as well as a smaller ACL cross-sectional area, was predictive of fewer cycles to ACL failure. The finding that ACL cross-sectional area is predictive of the number of cycles to failure is not surprising. For a given load, a higher ligament stress would result for an ACL of smaller cross-sectional area, and the Goodman diagram shows that the number of cycles to a material failure is inversely proportional to the repetitive stress placed on that material[56],

Collagenous structures such as ligament and tendon are susceptible to fatigue behavior under repetitive loading. For example, rabbit medial collateral ligament[61], human Achilles tendon[68], wallaby tail tendons[63], and human extensor digitorium longus tendons[54] have a negative relationship between tensile stress and the number of cycles to failure. The damage accumulation associated with cyclic loading can cause ligaments to fail faster due to fatigue rather than creep[61]. A positive feedback cycle has been noted: the higher the tensile cyclic stress in the ligament, the more rapidly microdamage accumulates, due to a reduction in the modulus of elasticity[62].

Sex-based differences in structural and mechanical properties of the ACL could influence fatigue behavior because the human female ACL is 21-34% smaller in cross-sectional area[9, 15], 17-27% smaller in ACL volume[9, 10] and has a 22% lower tensile modulus of elasticity than the male ACL[9]. Therefore, for a given load in size-matched individuals, the female ACL will systematically experience greater stress than the male ACL. With a lower ultimate tensile stress[9], it is plausible that the female ACL experiences a fatigue failure in fewer loading cycles than the male ACL. While gender was not significant in the present study, ACL cross-sectional area was a significant predictor of the cycles to ACL failure. The lack of a sex effect is may be due to a small sample size.

This is the first study to dynamically fail the ACL under combined compression, flexion moment and internal tibial torque with realistic muscle loads. Only one previous study has failed the ACL under internal tibial torque[35, 36]: a robotic simulator quasi-statically preloaded seven knees with a 50 N or 1,000 N compressive force with the knee in 30 degrees flexion. Dynamically applied internal tibial torque was incrementally increased by 10 Nm after each trial until failure. The ACL failed under internal tibial torques ranging from 10 – 50 Nm[36], with four partial tears of the posterolateral bundle near the femur and three tibial avulsions[35]. However, the results of that study are limited because of compressive forces less than two body weights, the lack of simulating protective muscle forces, and the non-physiologic times used to reach peak torque (150 ms to 1.1 s). The present study utilized dynamic 3 – 5* BW compressive loads with realistic muscle forces, and 23 – 43 Nm internal tibial torques peaking within more physiologic 50 to 75 ms. Furthermore, the current study focused on repetitive ACL loading, while the Meyer et al.[36] study failed the ACL as quickly as possible. Similar injury patterns were seen in both studies[35], strongly suggesting the posterolateral bundle may be compromised during a pivot landing with internal tibial torque.

Greater damage to the posterolateral bundle during pivot landings near extension is understandable given the functional anatomy of the ACL. The ACL is the knee joint's primary restraint to anterior tibial translation[8, 43] and a secondary restraint to tibial rotation[39, 43]. The ACL is often described functionally as two-bundle ligament; the anteromedial and posterolateral bundles display independent tension patterns[11, 16, 51]. Other studies suggest the ACL has a three-bundle anatomy[2, 27, 39]. In reality, the ACL is a continuum. The posterolateral and anteromedial bundles reciprocally share anterior drawer forces[2]. Greater anterior drawer forces are detected in the posterolateral bundle towards extension and the anteromedial bundle as the knee is flexed[2, 17]. An isolated tear of the posterolateral bundle will not produce a detectable increase in anterior tibial translation from an intact ACL using a KT-1000[24] or Lachman test[11]. These studies could not distinguish between isolated anteromedial bundle tears and full ACL tears.

The posterolateral bundle likely contributes more resistance to a axial tibial rotation than anterior tibial translation[11], possibly due to its anatomical location and orientation[1]. Increasing internal tibial rotation produces a coupled increase in anterior tibial translation. Under the application of internal tibial torque and knee abduction moment near full extension, an isolated posterolateral bundle transection will significantly increase the coupled anterior tibial translation, while an isolated anteromedial bundle transection will not affect the coupled anterior tibial translation[71]. Since the posterolateral bundle resists rotational loads near full knee extension, it may be more vulnerable during a simulated pivot landing. The results of the current study support this view.

Partial ACL tears are of clinical importance due to functional instability and the risk of progressing to complete ACL deficiency[41], although the long-term outcomes of partial tears may be more favorable than complete tears[7, 34, 59]. A partial tear of the posterolateral bundle will result in rotational laxity, while a partial tear of the anteromedial bundle will cause anteriorly-directed laxity[51]. Partial ACL tears account for 10-25% of all ACL ruptures[42, 58, 60, 70] with isolated anteromedial bundles tears accounting for 60-93% of all partial ACL tears[41, 42, 60]. Nineteen partial tears of the posterolateral bundle were reported in a sample of 106 patients with knee locking[12]. Isolated posterolateral bundle tears appear to be most prevalent near the femoral insertion[12, 60], which supports the findings of our study as well as other cadaver studies[35]. It is plausible that isolated posterolateral bundle tears are more prevalent but may go undetected because of a negative Lachman test.

Permanently elongated ACLs were included in the failure subset. Clinically, a 3-mm increase in anterior tibial translation is an accepted sign of ACL failure regardless of whether the ACL appears partially or completely torn[13, 14]. The present knees had to exhibit a minimum 3-mm increase in cumulative anterior tibial translation during testing to be considered an ACL failure. The ligament's failure status was determined from measurements of anterior tibial translation or AM-ACL strain during testing. Unloading the knee joint following each trial to inspect the ligament would have yielded hysteresis effects and therefore complicated the tracking of cumulative anterior tibial translation.

The lack of macroscopic ACL damage does not preclude these ACLs from having undergone microstructural damage. There can be considerable disruption and disorganization of collagen fibrils in human ACL at ultimate failure without macroscopic signs of ligament tearing[28]. In rabbit medial collateral ligament, a 10% strain will cause disruption of thin collagen fibers without macroscopic tearing[69]. The disruption of the thick collagen fibers will occur by 20% strain. Therefore, macroscopic determination of an ACL injury does not truly reflect the functional capacity or the extent of residual elongation in the ligament[40]. Submaximal failures of ligament will affect viscoelastic properties, including a reduction in initial stiffness as well as viscosity[48]. Furthermore, the load-displacement behavior of the ligament's toe region will be elongated[49, 53], which may yield greater laxity during daily activities. There will be an overall reduction in the modulus of elasticity and ultimate stress[53], placing the ligament at risk for macroscopic damage. Since many submaximal elongation failures occurred at the lower simulated landing forces, partial or complete tears of these ligaments may occure with increased simulated landing forces and/or more cycles.

This study represents a paradigm shift in how ACL ruptures occur, addressing a major clinical problem that costs billions annually. The ACL is susceptible to fatigue failures: the intensity and frequency of pivot landings as well as ACL size may dictate how much sub-failure damage the ACL can accumulate before an ACL failure occurs. The strengths of this study design are the use of matched-paired knees from donors of similar age, height, and weight to investigate the potential of ligament fatigue failure, the inclusion of realistic muscle forces during the dynamic pivot landing, and the use a blinded observer for measuring ACL cross-sectional area and lateral tibial slope from MRI scans. The matched pair design eliminated inter-subject variability.

The limitations do not affect the overall findings of the study. First, a DVRT was inserted into the distal third of the ACL's anteromedial bundle in order to record strain during testing. The insertion of one or both of the DVRT barbs could potentially have initiated failure in the AM bundle. This concern is mitigated by the fact that the majority of the macroscopic ACL damage occurred sites remote to either DVRT barb. Second, the macroscopic tearing and/or microstructural damage of the PL bundle combined with sub-failure AM-ACL relative strain occurred suggests the PL bundle is loaded more than the AM bundle during pivot landings at 20° knee flexion. This is contrary to the finding that AM bundle strain is indicative of ACL force[33]. Clinically, anterior tibial translation is the most reliable measurement of the ACL's status. Some knees with a failed PL bundle showed no increase in peak AM-ACL strain while other knees showed a large reduction in peak AM-ACL strain. We speculate that this may be the result of either a malaligned DVRT with the AM bundle's fiber orientation or, more likely, that the fibers on the AM bundle were not being tensioned to the same extent as the PL bundles.

The classic method for investigating material fatigue behavior is to vary the cyclic stress applied to the structure and count the number of cycles to failure in tests conducted in multiple identical samples of the material, resulting in the classic S-N curve. ACL cross-sectional area is inversely proportional to ACL stress. We measured the initial ACL CSA via MRI, but real-time monitoring of ACL CSA during was not feasible due to the prohibitively expensive MR scanner. We also had no means for measuring the stress in the ACL without instrumenting it with a series force transducer *ad modam* Markolf et al.[32]. However, this would alter the ACL's physiological length and tension state unnecessarily. We used the external load as an estimate of ACL stress while we recorded the number of cycles to failure. We could use AM-ACL cumulative strain as a proxy for ACL stress, especially if the modulus of elasticity remained unchanged. This was examined in Figure 4.9, which shows a trend towards a negative correlation between ACL strain and the number of cycles to failure. This backs up the primary finding in this study (Figure 4.4).

This study used donors older than the adolescent and young adult populations who are most at risk for ACL injury[55]. Therefore, we cannot eliminate the possibility that the injury patterns observed in our *in vitro* testing apparatus may differ from those in young donors. While the tibial avulsions could be the result of poor bone quality in older donors, tibial ACL avulsions are also seen in adolescents and young adults[21]. We would expect younger donors to endure more cycles to reach their fatigue limit because their ultimate tensile load should be 40% higher than older donors[67].

Finally, the time interval between loading trials was typically one minute in order to reset the muscle forces and initial knee flexion angle, but the interval was not controlled which is a weakness of the experiment. Three to five minute breaks were taken every 20-30 trials to refreeze the rectus femoris tendon with liquid nitrogen, making a uniform inter-loading cycle of one minute difficult. In a few knees, we did witness some ligament recovery in the measurements of anterior tibial translation following freezing periods which does suggest viscoelastic behavior. However, these same knees quickly reached and exceeded the pre-freezing level of anterior tibial translation. Similar recovery behavior of cyclically strained tendon has been reported with a rest time of 30 minutes[26]. While we do not believe the variation in inter-trial interval could have introduced a systematic bias in the results (i.e., 4*BW trials having shorter inter-trial intervals than 3*BW trials), it would be worthwhile to formally study the effect of inter-trial interval on the number of cycles to failure at a given loading level.

The longer the inter-trial interval, the more cycles it may take to fail the ACL because a more complete recovery of initial ACL length can take place before the next loading cycle; similarly, the shorter the inter-trial interval, the fewer the number of cycles needed to fail the ACL.

The clinical implications of this study suggest that ACL injuries can be the result of repeated high-intensity loading events: in other words, the ACL loading history. Since fatigue failure has already been identified as the cause of tibial stress fractures in recruits[19] and elbow ligament failures in Little League pitchers[31], it make sense to limit the number of high intensity ACL loading cycles within a given time interval. Therefore, closer monitoring of the number of high-impact pivot landings during practice and games should reduce the risk for ACL injury. This does not eliminate the possibility for "single event" ACL injury, since fatigue failure theory predicts that the ACL will fail in one loading cycle if the landing force during a pivot landing is high enough. Future studies might usefully identify how fatigue life varies with loading intensity for each sex, age group and activity level.

4.6 Conclusions

1) The human ACL is susceptible to a fatigue failure under cyclic loading replicating repeated pivot landings.
2) In human knees from age-, height- and weight-matched donors, a smaller ACL CSA in its distal third significantly increased the risk for a fatigue failure of the ACL.
3) The fatigue limit for the older human ACL is 10-20 loading cycles at a 4*BW loading, and 41 – 70 loading cycles at 3*BW pivot landings.

4) The posterolateral bundle is more susceptible to fatigue failure and injury than the anteromedial bundle during 3-4*BW pivot landings.
5) A sex difference in the human ACL fatigue limit was not observed in this study, perhaps due to the modest sample size.
6) The clinical implications of this study are that human ACL injuries may result from multiple high-intensity loading events. Therefore, within a given time frame, limiting the number of pivot landings that place the knee under large impulsive compression, flexion, internal tibial torque (and possibly valgus or varus moment[45]) loadings that an athlete undergoes during practice and games could reduce their risk of ACL injury.
7) "Single event" ACL injuries are possible in one loading cycle if the loading intensity is high enough.

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CHAPTER 5

AN EXAMINATION OF DIFFERENT METHODS FOR MEASURING LATERAL TIBIAL SLOPE USING MAGNETIC RESONANCE IMAGING

5.1 Abstract

Since lateral tibial slope (LTS) affects the amount of anterior tibial translation and anterior cruciate ligament (ACL) strain during a dynamic maneuver, accurate measurements of lateral tibial slope may be beneficial in screening individuals for a higher risk for ACL injury. Methods for measuring LTS on magnetic resonance imaging scans of the proximal tibia include the midpoint and circle methods. There are no current studies that have validated different LTS measurements methods using a proximal tibia magnetic resonance imaging scan. We tested the null hypotheses that (1) LTS measurements were independent of the length of tibia imaged using the midpoint method, and (2) LTS measurements calculated from different methods ('midpoint', 'circle', and 'full tibia') would not differ significantly.

Blinded observers measured LTS from 3-Tesla 3D magnetic resonance images from 40 size-matched donors with the tibial proximal anatomical axis defined according to the midpoint and circle methods. Outcomes were then compared to the full tibial anatomical axis (line connecting the center of two circles fit within the proximal and distal tibia) in 12 donors. Bonferroni-correct paired t-tests ($p < 0.005$ significant) were used to compare the three methods.

LTS measured using the midpoint method was dependent on the length of tibia imaged (20 cm vs 15 cm: mean (SD) $1.6(1.4)^{o}$; $p < 0.001$). The midpoint method using 15 cm of proximal tibia gives significantly different lateral tibial slope measurements than the circle method ($3.1(3.2)^{o}$; $p < 0.001$), but not the full tibia anatomical axis ($0.45(2.0)^{o}$; $p = 0.474$).

LTS measurements utilizing the midpoint method are dependent on tibial length. The midpoint method is the better representation of LTS measurements with the full tibia than the circle method. The most repeatable LTS measurements were from the circle and full tibia methods; the least repeatable measurement method was the midpoint method using 10 cm of proximal tibia. We conclude that LTS measurements vary depending on the method utilized.

5.2 Introduction

Clinical measurements of posterior tibial slope are important for understanding anterior cruciate ligament (ACL) injury mechanisms. ACL-injured individuals have a greater posterior tibial slope than healthy controls[2, 3, 8, 9, 12, 19-23]. Posterior tibial slope is commonly measured in both the lateral and medial compartments of the tibial plateau. ACL-injured individuals have a greater lateral tibial slope than medial tibial slope[8, 21] and the difference between these two slopes may influence dynamic landing knee biomechanics[14, 19]. Previous studies have validated different radiographic methods for measuring posterior tibial slope[4]. No significant difference exists between radiographs, computed tomography, and magnetic resonance imaging (MRI)[24]. Recent work has focused on MRI[2, 8, 10, 11, 13, 19, 21, 22]. We are unaware of any studies that compare the different MRI methods for measuring lateral tibial slope. A recent review article has highlighted the need to validate lateral tibial slope measurements with magnetic resonance imaging, especially against a gold standard, because tibial slope measurements are becoming more important in understanding ACL injury mechanisms[25].

Tibial slope is commonly defined as the angle between a line fit to the posterior-inferior surface of the tibial plateau and a tibial anatomic reference line[3]. The proposed MRI methods for measuring lateral tibial slope the reference line by measuring the tibial proximal anatomical axis (TPAA) using either the "midpoint method"[2, 7, 8], which connects the midpoints of two anteroposterior tibial lines within the proximal end of the tibia, or the "circle method"[10, 11, 13], which connects the center of two circles within the proximal tibia (Figure 1). This study validates those different methods for measuring lateral tibial slope. Due to the concavity of the posterior tibial cortex and the presence of the tibial tuberosity, the midpoint method may be sensitive to proximal tibial bone length within the scan. Furthermore, the relationship between lateral tibial slope measurements using the midpoint method, circle method, and a control method utilizing the full tibia is unknown.

The objective of this study was to compare MRI methods of measuring lateral tibial slope with the midpoint method and the circle method, validating these measurements against an MR scan of the full tibia. Our null hypotheses were (1) lateral tibial slope measurements using the midpoint method will not be affected by the length of tibia in the image; (2) lateral tibial slope measurements will not differ between the midpoint method and the circle method; and (3) a new method using the full tibial longitudinal axis will not result in different lateral tibial slope measurements than methods which only utilize the proximal end of the tibia.

5.3 Materials and Methods

Forty cadaveric lower extremities from 22 female and 7 male height- and weight-matched donors (mean (SD) age: 59(14) yrs; height: 169(11) cm; weight: 70(7) kg) were acquired from the University of Michigan Anatomical Donations unit and the Anatomy Gift Registry (Hanover, MD). The limbs were MR scanned prior to their use in an *in vitro* experiment (not reported here All forty lower extremities underwent 3-Tesla MRI scans where a minimum of 20 cm of proximal tibia captured within the image set (3T Phillips Scanner, T2-weighted 3D-PE sequence; field of view: 290 mm; slice thickness: 0.7 mm). In addition, 11 of the 40 lower extremities underwent an additional scan that acquired the entire length of the tibia within the scan (same image sequence except field of view: 400 mm). The lateral tibial slope measurements were performed using the OsiriX software package (v3.9, open source, www.osirix-viewer.com). The 3D multi-planar reconstruction mode was utilized to ensure that the three imaging planes lay on the proper sagittal, axial, and coronal planes of the tibia. Two blinded observers measured lateral tibial slope with three different techniques.

To standardize the scan slices within each observation, the slices corresponding to the central axis and lateral tibial plateau were the same for all three methods for determining the tibial longitudinal axis. The central axis was defined according to the methods of Hudek et al.[10, 11]: the slice where the tibial attachment of the posterior cruciate ligament was present, the intercondylar eminence was visible, and the anterior and posterior tibial cortices were concave. Lateral tibial plateau measurements were performed at the center of articulation[7, 8], where a line was fit to the plateau's subchondral bone line from the most anterior-proximal point to the most posterior point.

All lateral tibial slope measurements were defined as the angle between this lateral tibial plateau line and a line perpendicular to the tibial longitudinal axis.

Three methods were used to measure the tibial anatomical axis on the central axis image. The midpoint method, developed by Hashemi et al.[7, 8], involved drawing two lines (4-5 cm apart) that connected the anterior and posterior cortices of the tibia (Figure 1(a)). The midpoints of these two lines were connected, defining the TPAA. The measurement was performed at three locations on the proximal tibia, with the most distal anteroposterior line located 20 cm, 15 cm, and 10 cm from the knee joint line. Secondly, the circle method, introduced by Hudek et al.[10, 11], involved drawing two circles within the proximal tibial (Figure 1(b)). The proximal circle was fit within the proximal, anterior, and posterior cortical borders. The center of the distal circle was positioned on the perimeter of the proximal circle, and was fit within the anterior and posterior cortices. A line connecting the center of these two circles defined the TPAA. Finally, a second scan that captured the entire tibia was collected for 11 specimens within the subset. Using the same central axis image, a method similar to the circle method was utilized to fit a circle within the proximal tibia (connecting the anterior, proximal, and distal cortical borders) and the distal tibia (connecting the anterior, distal, and posterior cortical borders) (Figure 1(c)). The center of these two circles was connected to define the full tibial anatomical axis.

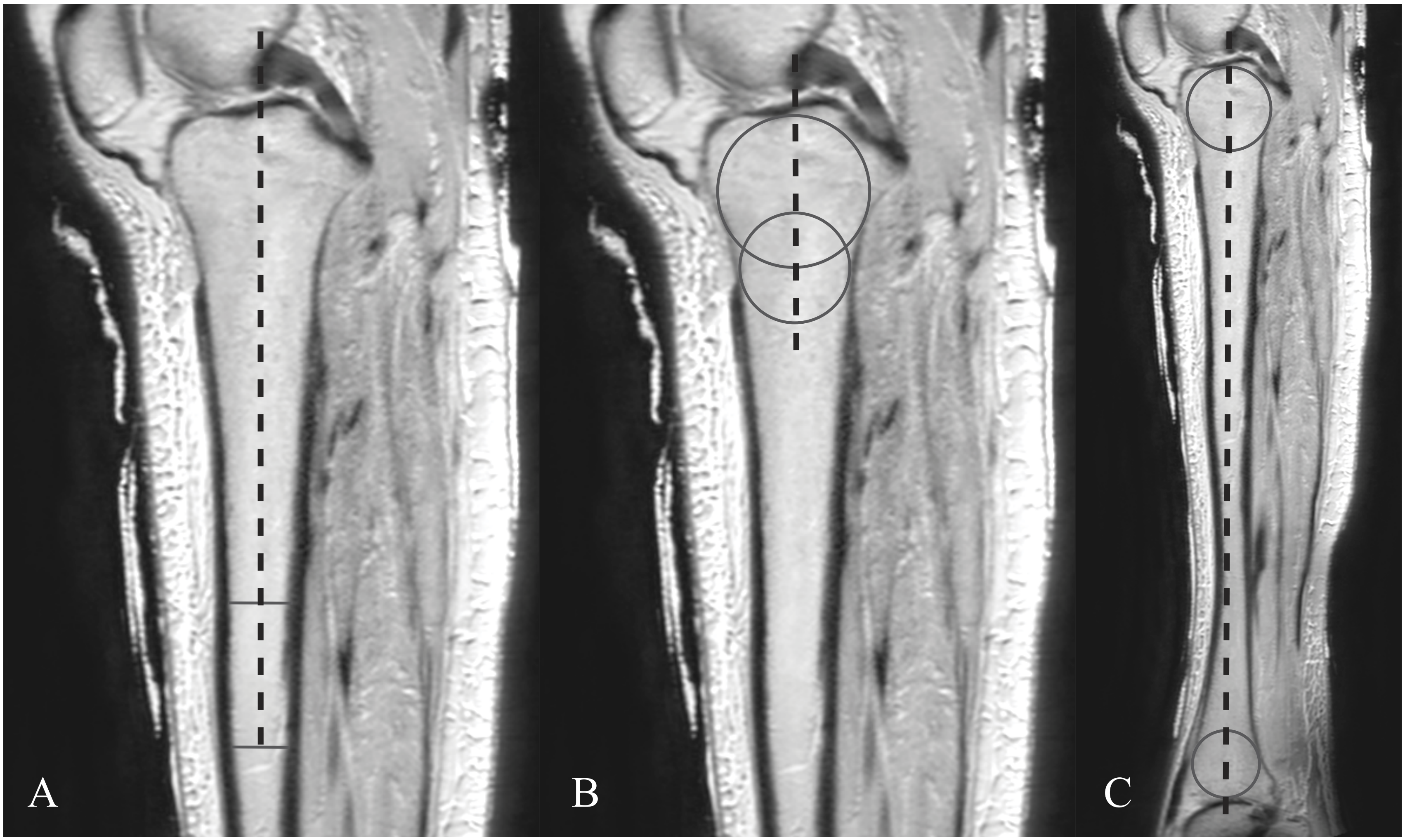

Figure 5.1 The tibial longitudinal axis (dashed lines) was defined using (a) the midpoint method, (b) the circle method, and (c) the full tibia method. The specifics for each method are outlined in the Materials and Methods section.

Paired two-sided t-tests, with a Bonferroni corrected significance level of $p = 0.005$ (calculated as alpha level/number of observations = 0.05 / 10), were used to compare lateral tibial slope using (a) the midpoint method using three different lengths of tibia, (b) the circle method, and (c) the full tibial longitudinal axis. Inter- and intra-observer reliability was examined using intra-class coefficients (ICC), where ICC values greater than 0.9 were considered excellent and values between 0.8 and 0.9 were considered good, as well as typical error calculations with associated 95% confidence intervals. The first blinded observer performed two sets of measurements on all 40 lower extremities with a minimum of one week between observations with a random specimen order. The second observer was blinded to the results of the first observer, and performed measurements on a random subset of 15 knees. All analyses were performed in SPSS 19 (IBM Corp., Armonk, NY).

5.4 Results

Lateral tibial slope measurements using the midpoint method were significantly different when 20 cm (mean ± SD: 10.0 ± 3.3 deg) and 15 cm (8.4 ± 3.4 deg) of proximal tibia were used ($p < 0.001$), as well as 20 cm and 10 cm (8.3 ± 3.7 deg) (Figure 5.2; $p < 0.001$). However, there was no significant difference in lateral tibial slope with the midpoint method when 15 cm and 10 cm of proximal tibia were used ($p = 0.687$). The circle method (5.3 ± 3.1 deg) resulted in significantly smaller lateral tibial slope measurements than the midpoint method, regardless of the amount of proximal tibial used (Figure 5.2; $p < 0.001$ for 20 cm, 15 cm, and 10 cm).

Using the full tibia method in a subset of 11 knees in this study, the full tibia method (6.9 ± 2.2 deg) was significantly different from the circle method ($p < 0.001$) and the midpoint method when 20 cm of proximal tibia was used ($p = 0.003$) (Figure 5.3). However, there was no significant difference between the full tibia method and the midpoint method using 15 cm ($p = 0.474$) and 10 cm ($p = 0.225$).

The results of this study showed excellent intra-observer reliability and good-to-excellent inter-observer reliability (Table 5.1). Based on the typical errors of each measurement, the most repeatable measurement techniques appeared to be the circle method and the full tibia method, while the least repeatable measurement method was the midpoint method using 10 cm of proximal tibia.

Table 5.1 Intra-observer and inter-observer reliability for all five lateral tibial slope measurement methods.

	Intra-observer		Inter-observer	
	Typical Error	ICC	Typical Error	ICC
Midpoint method, 20 cm	± 0.92° (CI 0.75° - 1.18°)	0.92	± 0.86° (CI 0.44° - 0.99°)	0.85
Midpoint method, 15 cm	± 1.08° (CI 0.89° - 1.39°)	0.9	± 0.85° (CI 0.43° - 0.97°)	0.87
Midpoint method, 10 cm	± 1.18° (CI 0.97° - 1.52°)	0.89	± 1.08° (CI 0.55° - 1.23°)	0.79
Circle method	± 0.84° (CI 0.69° - 1.08°)	0.92	± 0.75° (CI 0.38° - 0.86°)	0.93
Full tibia method	± 0.64° (CI 0.53° - 0.83°)	0.91	± 0.89° (CI 0.45° - 1.01°)	0.85

ICC: Intraclass coefficients; CI: 95% confidence intervals

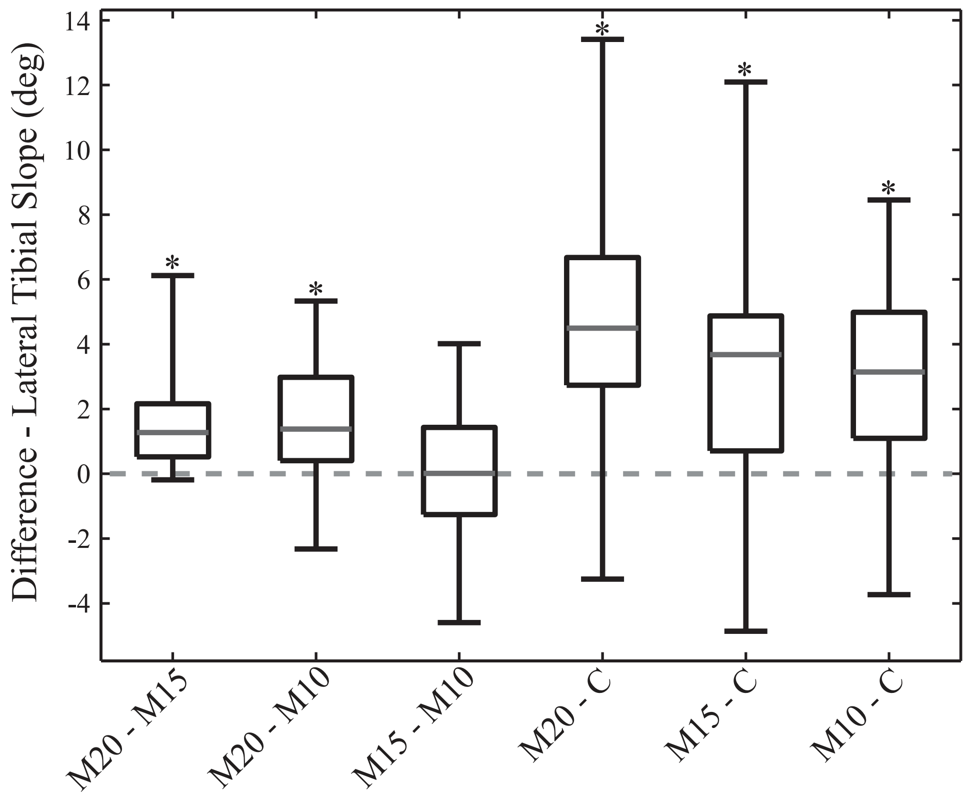

Figure 5.2 The box plots compare the difference in lateral tibial slope measurements for 40 knees using the circle method (C) and the midpoint method with 20 cm (M20), 15 cm (M15), and 10 cm (M10) of proximal tibia. Central mark indicates the median value, edges of box indicate 25% and 75% quartiles, and the whiskers indicate the maximum and minimum values. In this figure, the asterisk denotes a significant difference at $p < 0.005$.

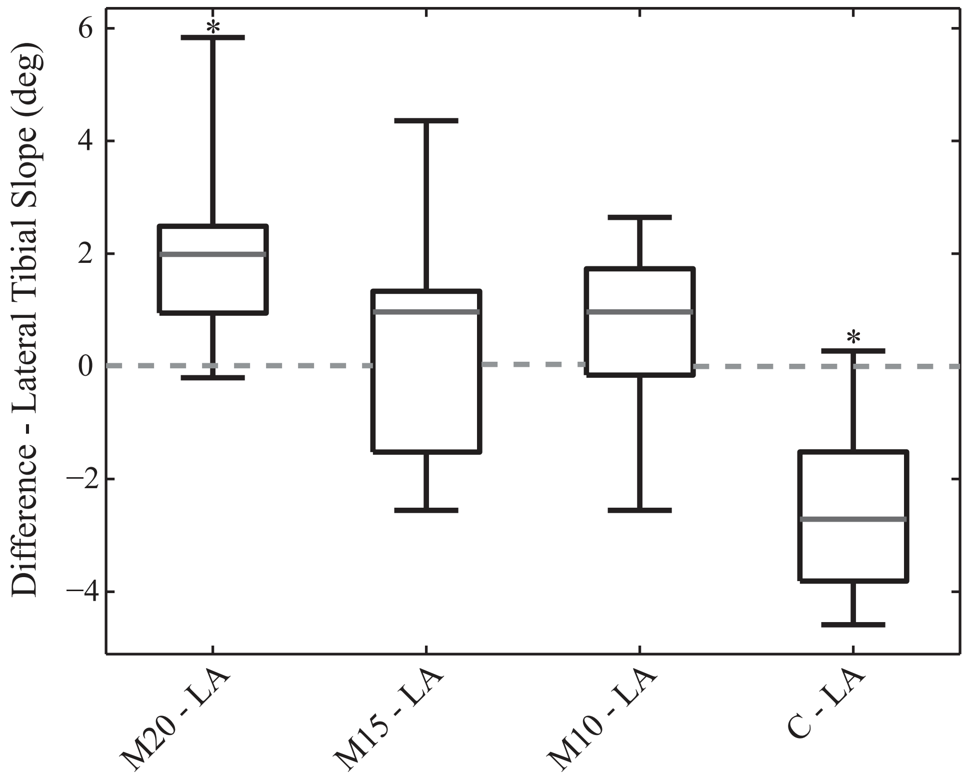

Figure 5.3 The box plots compare the difference in lateral tibial slope measurements for 12 knees using the full tibial longitudinal axis (LA) method with methods utilizing only the proximal tibia: the circle method (C) and the midpoint method (M20, M15, and M10). Central mark indicates the median value, edges of box indicate 25% and 75% quartiles, and the whiskers indicate the maximum and minimum values. In this figure, the asterisk denotes a significant difference at $p < 0.005$.

5.5 Discussion

Differences in lateral tibial slope measurements in clinical research studies may be due to the lack of agreement between measurement methods[25]. The proximal tibia shows a small range of variation in lateral tibial slope (0° – 14° with the midpoint method[8]), making accurate measurements most important for clinical assessments. The results show that lateral tibial slope measurements using the midpoint method are sensitive to the proximal tibial bone length used in the measurement. Secondly, different methods for defining the TPAA with MRI will produce different lateral tibial slope measurements. Finally, this study found in a subset of 11 knees that the TPAA defined by the midpoint method is a better representation of the full tibial anatomical axis than the circle method. Overall, this study found the circle method to be more repeatable than the midpoint method.

Reliable clinical measurements of posterior tibial slope are important for understanding ACL injury. An increased posterior tibial slope has been retrospectively linked with a greater ACL injury risk[2, 3, 8, 9, 12, 19-23]. Furthermore, an increased posterior tibial slope has been linked to greater peak ACL strain during a dynamic landing[13, 15], as well as greater anterior tibial translation[6, 17, 18] and acceleration[15]. An increased lateral tibial slope relative to the medial tibial slope can influence dynamic landing biomechanics by coupling knee abduction with internal tibial rotation[14, 16, 19]. These studies emphasize the importance of accurate, repeatable measurements of posterior tibial slope for clinical interventions.

Due to the concave shape of the posterior tibial cortex, the midpoint method is sensitive to the length of tibia in the MR image, as well as the spacing between the proximal and distal anteroposterior lines. The spacing between the proximal and distal lines was constant in this study, while the amount of tibia used for the measurement was varied, with the distal line positioned 20 cm, 15 cm, and 10 cm from the knee joint line. This controlled approach allowed more consistent measurements than previous work that did not control for tibial length[7, 8]. While there was no significant difference between 10 cm and 15 cm of proximal tibia using the midpoint method, the data shows that there was as much or more variability between these measurements and 20 cm of proximal tibia (Figure 5.2). The presence of both positive and negative values with the midpoint method when comparing 10 cm and 15 cm of proximal tibia may be due to the tibial tuberosity shifting the TPAA more anteriorly with the 10 cm midpoint method in some knees (Figure 5.4).

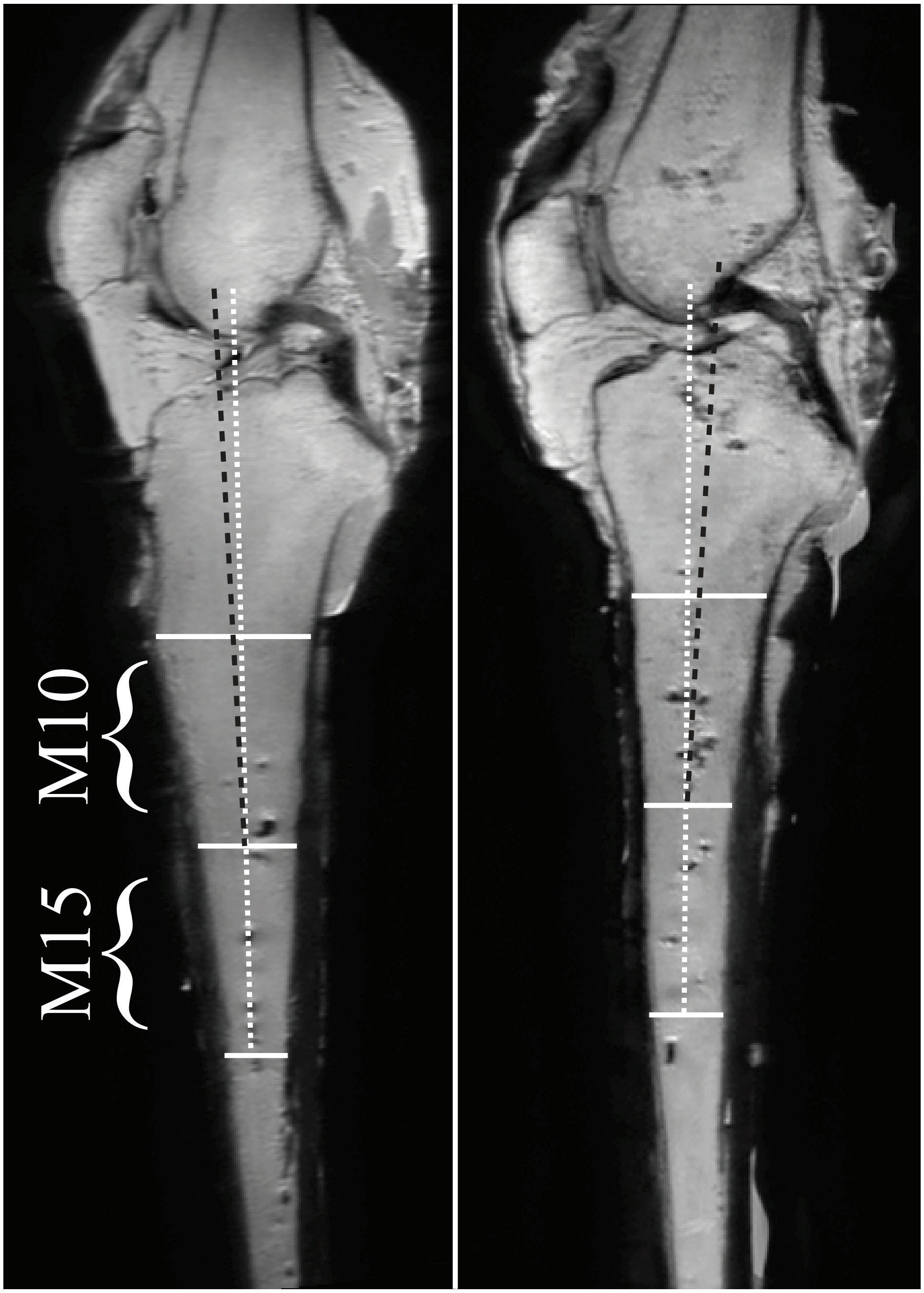

Figure 5.4 The tibial tuberosity can affect tibial slope measurements with the midpoint method, especially with the M10 measurement. The left image shows the tibial tuberosity better than the image on the right (at the level of the proximal anteroposterior line for the M10 measurement). This anatomical detail will affect the ability to perform the M10 measurement, as the tibial tuberosity will shift the tibial proximal anatomic axis (white dashed line) more anteriorly.

If future ACL injury prevention interventions involve morphological screening, it is important to recognize that lateral tibial slope measurements are method-dependent. The circle method will result in a lateral tibial slope measurement that is significantly smaller than that with the midpoint method. This finding is consistent with the results of studies that found the average lateral tibial slope in healthy females was 5.4 deg with the circle method[11] but 7.0 deg with the midpoint method[8]. An average lateral tibial slope of 8.4 degrees measured with the midpoint method has been implicated in females sustaining an ACL injury[8]. Based on these results, a lateral tibial slope closer to 5.3 degrees using the circle method would have a greater ACL injury risk, based on the mean difference (3.1 degrees) between the midpoint method using 15 cm of proximal tibia and the circle method.

This is the first study to consider the full tibial anatomical axis when utilizing MRI for measuring lateral tibial slope. The tibial shaft axis has been evaluated with radiographs[1, 4, 5] or manual measurements[26]. This study differs slightly by defining full tibial anatomic axis from the proximal and distal tibia, rather than the tibial shaft. It appears that the midpoint method, specifically with 15 cm or 10 cm of proximal tibia, is a better representation of the full tibial anatomical axis than the circle method (Figure 5.3). Despite this finding, the circle method is still an excellent choice for measuring lateral tibial slope when comparing knee-coil MR images with varying visibility of the proximal tibia. The circle method also had the best inter- and intra-observer reliability statistics (Table 5.1).

The strengths of this study are the use of two blinded observers for making multiple measurements of lateral tibial slope, the good to excellent ICC values for interand intra-observations of each method, and the introduction of a full tibial anatomical axis method for measuring posterior tibial slope. The limitations of this study are unlikely to affect the overall findings. Since these measurements are subjective to the individual observer, we accounted for these differences by reporting the inter-observer and intra-observer reliability. The inter-observer reliability was only performed on a random sample of 15 knees, but we are encouraged by the strong inter-observer reliability reported. Only 11 of the 40 donors had the additional full tibia scan performed. The donors were acquired for a separate *in vitro* study that focused on the knee joint, so the ankle joint was not always harvested. Due to the numerous observations, we used a Bonferroni correction to limit the potential for type II error.

The method we utilized for measuring the full tibial longitudinal axis was similar to the circle method proposed for the proximal tibia. While a method similar to the midpoint method could have been utilized, we felt that adjusting the circle method to measure the full tibial LA gave the best representation of the bone's anatomical axis in the sagittal plane. The selection of the central axis image for the longitudinal axis method differed slightly from the method described by Hashemi et al.[7, 8] in order to have consistency between the different methods of determining the tibial longitudinal axis. While this study has focused on measuring lateral tibial slope using the subchondral bone line, the slopes of the meniscus[10] and articular cartilage may not resemble the subchondral bone line and could influence dynamic knee mechanics. All of these images were acquired from cadaver lower extremities, and some of the knees imaged had the soft tissue distal of the knee joint removed in preparation for a separate *in vitro* testing protocol.

We conclude that MRI measurements of lateral tibial slope are method-dependent, and there are advantages and disadvantages of each method. The midpoint method allows for the best representation of the full tibia anatomical axis, but can be sensitive to the tibial bone length within the image. The circle method is independent of tibial bone length, but does not truly represent the full tibial anatomical axis. While both of these methods provide reliable and repeatable lateral tibial slope measurements, the absolute lateral tibial slope measurements between the circle and midpoint methods are not equivalent.

5.6 Conclusions

1) We conclude that MRI measurements of lateral tibial slope are method-dependent, and there are advantages and disadvantages of each method.
2) We recommend the circle method for measuring lateral tibial slope from a proximal tibia MR image. The circle method is independent of tibial bone length and was the most repeatable method. However, it is not a good representation of the full tibial anatomical axis.
3) The midpoint method allows for the best representation of the full tibia anatomical axis, but can be sensitive to the tibial bone length within the image.
4) While both of these methods provide reliable and repeatable lateral tibial slope measurements, it is important to notice that the absolute lateral tibial slope measurements between the circle and midpoint methods are not equivalent.

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CHAPTER 6

A SECONDARY ANALYSIS ON THE EFFECT OF MORPHOLOGIC CHARACTERISTICS ON PEAK ACL STRAIN DURING A SIMULATED PIVOT LANDING

6.1 Abstract

The morphology of the knee joint may affect the dynamic loads placed on the anterior cruciate ligament (ACL) during a pivot landing. We have previously shown in a subset of 18 cadaver lower extremities that ACL cross-sectional area and lateral tibial slope explain 59% of the variance in peak anteromedial bundle ('AM'-) ACL relative strain during a two-times body weight (2*BW) simulated pivot landing. Since a common limitation of cadaveric research is small sample sizes, an expanded sample may introduce new variables within our regression model.

We expanded the sample size to 29 age-, height-, and weight-matched knees (9 male, 20 female) using similar testing methods: a 2*BW compound impulse pivot landing with compression, flexion, and internal tibial torque with a gender-specific non-linear quadriceps spring. Tibiofemoral kinematics and kinetics were monitored at 400 Hz and 2 kHz, respectively, while peak AM-ACL relative strain was monitored using a differential variable reluctance transducer. Prior to testing, 3-Tesla magnetic resonance imaging scans were acquired, and ACL cross-sectional area, lateral tibial slope, notch width index, and medial tibial concavity depth were measured. A stepwise linear

regression compared peak AM-ACL relative strain with the morphologic characteristics and 2-way interactions ($p < 0.05$ significant).

The results show that ACL cross-sectional area (standardized $\beta = -0.725$, $p < 0.001$), ACL cross-sectional area x lateral tibial slope ($\beta = -0.425$, $p = 0.004$), and medial tibial concavity depth ($\beta = -0.274$, $p = 0.042$) were significant predictors of peak ACL strain, and notch width index x lateral tibial slope ($\beta = -0.251$, $p = 0.056$) trended towards significance. Together, these four morphologic factors and interactions explained 66% of the variance in peak AM-ACL relative strain during a 2*BW simulated pivot landing. We conclude that certain knee morphologies predispose the ACL to greater levels of strain during a dynamic pivot landing.

6.2 Introduction

Female athletes are at a greater risk of anterior cruciate ligament (ACL) ruptures than male athletes[1, 3, 17, 30, 31, 33]. There is considerably morbidity following an ACL rupture, with individuals who suffer a knee ligament injury being 7.4 times more likely to develop knee osteoarthritis[45], as evidenced by the presence of symptomatic osteoarthritis in 50% of individuals who suffer an ACL injury within 10-20 years[26]. With over 350,000 ACLs reconstructed in the United States alone each year, there is a need to understand the mechanisms of ACL injuries in order to better prevent them.

Over the past decade, increasing attention has been paid to the role of knee morphologic characteristics in ACL rupture. If there is a direct link between the two, it provides an opportunity to screen athletes for high-risk morphologies prior to injury in order to develop the proper training and medical attention needed to reduce the chances of ACL rupture. A greater lateral tibial slope[4, 15, 22, 35, 36, 42], a shallower medial tibial depth[15, 22], a narrower notch width index[11, 18, 21, 23, 37-39, 41, 43], and a smaller ACL[7] have all been linked with increasing the risk of ACL injuries in retrospective studies. The morphometry of the tibial plateau, specifically the lateral tibial slope and medial tibial concavity, can also influence the tibia's resistance to anterior translation[16, 25]. For a given load, a smaller ACL (which may be contained in a smaller femoral intercondylar notch[6]) will rupture at a lower ultimate load[5]. We have recently investigated the effects of morphologic characteristics on peak AM-ACL relative strain during a simulated pivot landing in 9 male and 9 female cadaver lower extremities matched for donor height and weight[24]. This study found that females undergo 95% greater peak AM-ACL relative strain than height- and weight-matched, with ACL cross-sectional area and lateral tibial slope explaining 59% of the variance.

While cadaveric testing has been beneficial to our understanding of ACL injury mechanisms, these same studies are often hampered by small sample sizes, primarily due to the difficulty and expense of acquiring healthy knee specimens. The smaller sample sizes prohibit examining many variables within the statistical analyses, and concentrate on only one or two factors. Chapters 2 and 3 of this dissertation measured peak ACL strain using the same dynamic two-times body weight ('2*BW') pivot landing: Chapter 2 focused on gender differences in peak AM-ACL relative strain, while Chapter 3 investigated the effect of quadriceps tensile stiffness on peak AM-ACL relative strain. Magnetic resonance imaging scans were acquired of each knee joint prior to impact testing in both studies to investigate the effect of morphologic characteristics on peak AM-ACL relative strain during a simulated pivot landing.

Using an expanded sample size of 29 knees from donors of similar age, height, and weight (17 knees from Chapter 2 and 12 knees from Chapter 3), a secondary analysis was performed using a stepwise linear regression with ACL cross-sectional area, lateral tibial slope, medial tibial depth, notch width index, and six 2-way interactions between the four morphological parameters as potential predictors. The hypothesis was that peak AM-ACL relative strain could be significantly predicted by these four morphologic characteristics.

6.3 Materials and Methods

Specimen Procurement and Preparation

Twenty-nine height-, weight-, and age-matched male and female lower extremities (20 female, 9 male; mean (SD) age: 60 (16) years; height: 169.6 (8.5) cm; weight: 70.3 (5.2) kg) were acquired from the University of Michigan Anatomical Donations Program and the Anatomic Gift Registry (Hanover, MD). The specimens were screened prior to harvesting and excluded from the study if there were signs of previous lower extremity injuries or limb deformities. The limbs were immediately stored frozen at -20 deg C and defrosted prior to dissection, imaging, and testing. Prior to imaging, the soft tissue surrounding the knee joint was dissected, leaving the ligamentous structures intact, as well as the tendons of the quadriceps (rectus femoris), medial and lateral hamstrings, and medial and lateral gastrocnemius muscles. Prior to testing, the distal femur and proximal tibia and fibula were cut 20 cm from the knee joint line and potted in a 7.6 cm PVC cylinder filled with para-methoxymethamphetamine (PMMA).

Magnetic Resonance Imaging Scans

Following dissection, each limb underwent a 3T T2-weighted magnetic resonance imaging scan (Philips Healthcare 3T scanner [Best, the Netherlands], 3D proton-density sequence; repetition time/echo time, 1000/35 milliseconds; slice thickness, 0.7 mm; pixel spacing, 0.35 mm x 0.35 mm; field of view, 160 mm). The scans were then analyzed in OsiriX (v3.9.4, open source, www.osirix-viewer.com) in order to measure ACL cross-sectional area, lateral tibial slope, medial tibial depth, and notch width index.

Using 3D multi-planar reconstruction, ACL cross-sectional area was measured using an oblique axial view perpendicular to the ligament's fibers[10]. This measurement was standardized using the oblique coronal view to insure the ligament was measured at 30% ligament length from the ACL tibial origin (relative to the length of the ligament from mid-insertion of the tibia to mid-insertion of the femur) (Figure 6.1). This location is consistent with DVRT placement during cadaveric testing, as well as the minimum cross-sectional area of the ligament[13].

Lateral tibial slope was measured *ad modam* Hudek et al.[20] (Figure 6.2). Using the central axis image (defined as the image where the posterior collateral ligament is visibly attached to the tibia and the intercondylar eminence is present), two circles are proximal tibia. The proximal circle was fit to the boundaries of the anterior, proximal, and posterior cortices, while the center of the distal circle was placed on the circumference of the proximal circle and was fit to the anterior and posterior cortical boundaries. A line connecting the center of these two circles defined the tibial proximal anatomical axis. The angle between a line perpendicular to the TPAA and a line fit from the most anterior-proximal to most posterior point on the lateral tibial plateau at the center of articulation was defined as lateral tibial slope.

Medial tibial depth was calculated using a custom MATLAB (Mathworks, Inc, Natick, MA) algorithm where a 9th-degree polynomial was fit to a curve drawn along the subchondral bone line of the medial tibial plateau at the center of articulation (Figure 6.3). An automated process determined the most proximal points on the anterior and posterior regions of the medial tibial plateau, measuring peak depth of the subchondral bone line relative to a line fit to the anterior-proximal and posterior-proximal points.

Finally, notch width index was measured using an oblique-coronal view taken parallel to the ligament's fibers[40]. Notch width index was defined as the ratio of the femoral intercondylar notch width to the bicondylar notch width (Figure 6.4). Intercondylar and bicondylar width were measured at the level of the inferior femoral ACL insertion with a line parallel to the most inferior points on the medial and lateral femoral condyle.

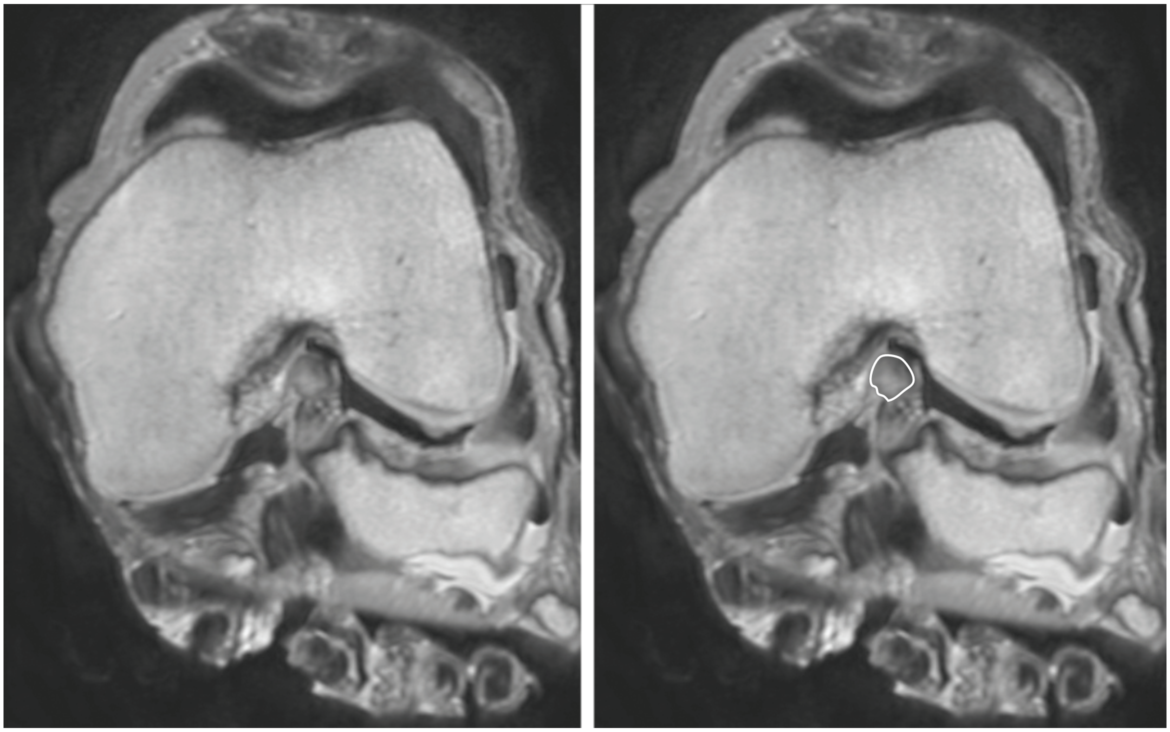

Figure 6.1 Method for measuring ACL cross-sectional area. (left) ACL cross-sectional area was measured from an oblique-axial view of the knee perpendicular to the ligament at 30% ligament length from the tibial insertion. (right) The cross-sectional area was determined from a trace around the circumference of the ligament (white line).

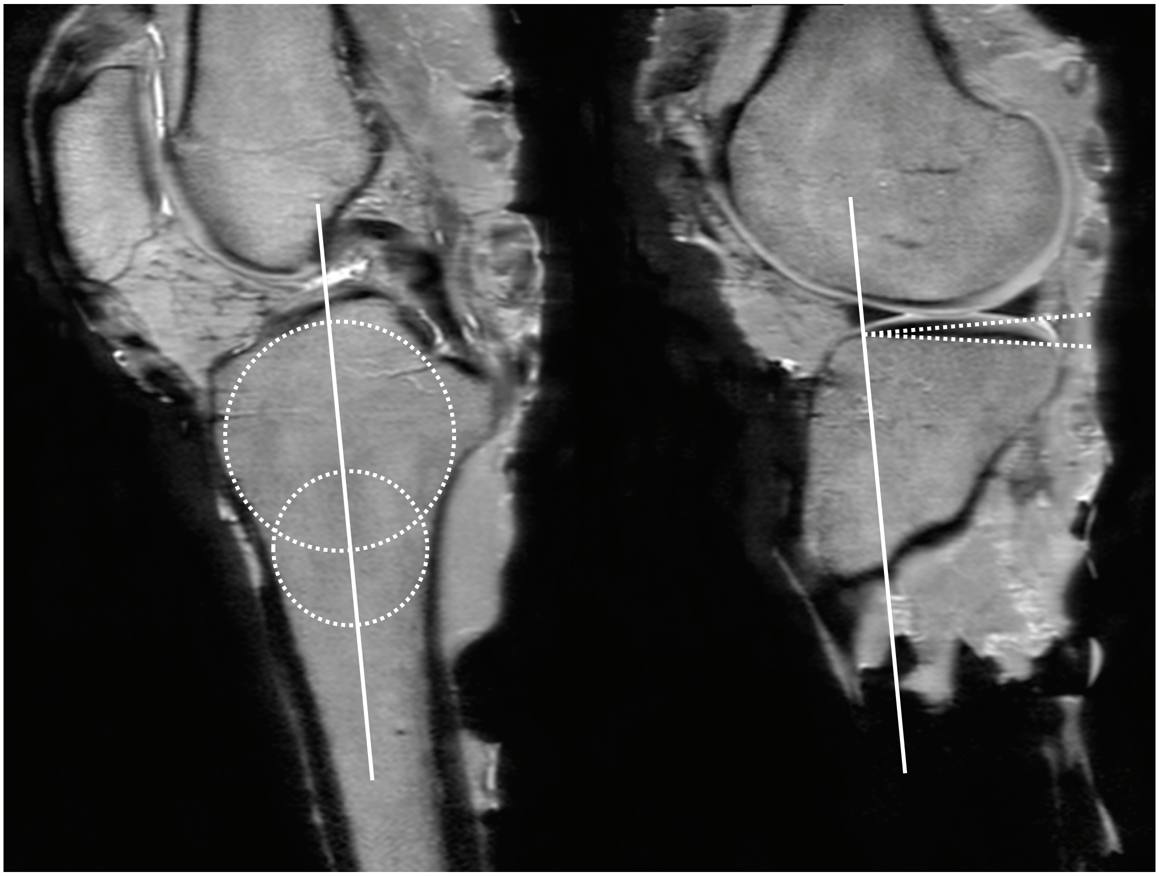

Figure 6.2 Method for measuring lateral tibial slope. (left) The tibial proximal anatomical axis was defined by fitting two circles within the the proximal tibia and connecting a line to the centers of each circle. (right) Lateral tibial slope was defined as the angle between a line fit to the subchondral bone line and a line perpindicular to the tibial proximal anatomical axis (dashed lines).

Figure 6.3 Method for measuring medial tibial depth. The subchondral bone line was traced (white) at the center of articulation on the medial tibial plateau. A 9^{th}-degree polynomial was fit to this trace in order to determine peak medial tibial depth.

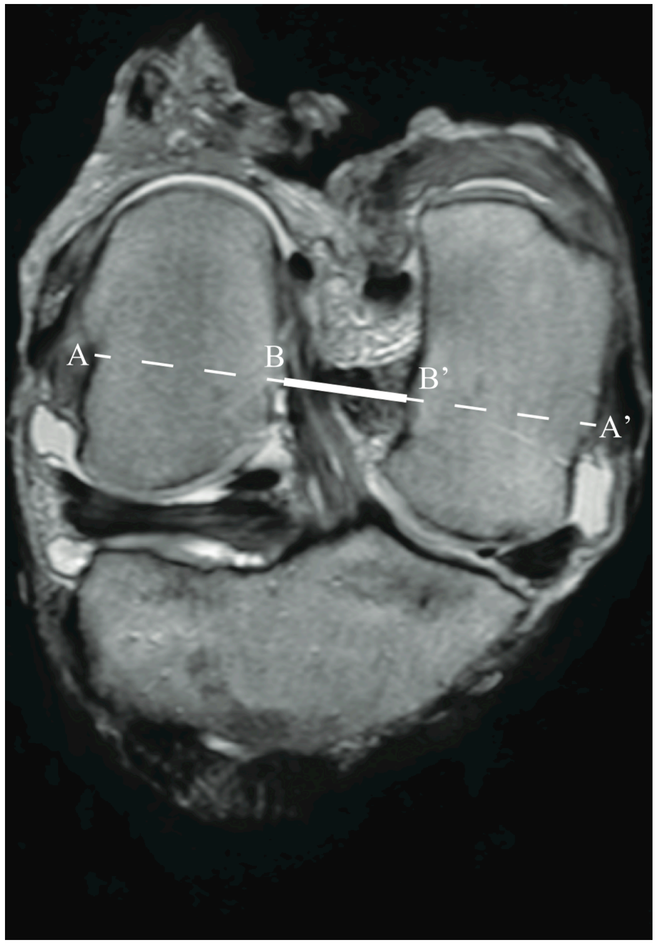

Figure 6.4 Method for measuring notch width index. Notch width index was measured from an oblique-coronal plane parallel to the ligament. Notch width index was defined as the ratio of intercondylar notch width (line BB') to bicondylar width (AA').

Cadaveric Testing

The modified Withrow-Oh testing apparatus[24] was utilized to deliver a dynamic, impulsive compound load (2*BW compressive force and knee flexion moment with/without internal tibial torque) to the proximal tibia, peaking at 60 ms. A differential variable reluctance transducer (DVRT, Microstrain Inc, Burlington, VT) installed on the distal 3rd of the anteromedial bundle ('AM') of the ACL measured peak AM-ACL relative strain during the first 100 ms of the simulated landing. Tibiofemoral kinematics were recorded at 400 Hz with an Optotrak Certus camera (Northern Digital Inc, Waterloo, ON, Canada) with a set of three infrared diodes on each bone. Anatomical landmarks were digitized to measure absolute and relative 3D translations and rotations. The input and resultant 3-D forces and moments applied to the proximal tibia and distal femur were recorded at 2 kHz with six-axis load cells (MC3A-1000, AMTI, Watertown, Massachusetts). Cryo-clamps were attached to each muscle tendon and placed in series with a uniaxial load cell (TLL-1K and TLL-500, Transducer Techniques, Inc, Temecula, California) and a muscle equivalent. The quadriceps muscle equivalent was a non-linear gender-specific quadriceps spring (female spring- initial stiffness: 155 N/mm, final stiffness: 27 N/mm; male spring- initial stiffness: 193 N/mm, final stiffness: 46 N/mm), while the knee flexor muscle equivalents were wraps of nylon string (stiffness: 200 N/mm). Prior to each trial, the knee was placed at an initial knee flexion angle of 15 degrees by ratcheting the pre-tension muscle forces to 200 N for the quadriceps and 70 N for the medial and lateral hamstrings and medial and lateral gastrocnemius. The specifics of the cadaveric testing are described in greater detail in Chapter 2 and Chapter 3.

The specimens were enrolled in one of two similar testing protocols. The first protocol investigated gender differences in peak ACL strain in 8 female and 9 male knees. (Note: One female knee was excluded from the original study in this secondary analysis because the most medial portion of the medial tibial compartment was not visible, preventing the measurement of bicondylar width and notch width index). The second protocol investigated the effect of increasing quadriceps tensile stiffness on peak ACL strain in 12 female knees. A repeated measures design with five trials per testing block was utilized. The first protocol followed an 'A-B-A' design and the second protocol followed an 'A-B-C-A' protocol. Using the modified Withrow testing apparatus, a standardized two-times body weight (2*BW) simulated non-pivot ('A' blocks) and pivot ('B' and 'C' blocks) landing was performed. Male and female knees in the first protocol utilized their gender-specific non-linear quadriceps stiffness spring, with initial stiffness being 25% higher in the male spring. Female knees in the second protocol underwent two pivot landing blocks. The 'B' block tested the female knees with the same non-linear female quadriceps stiffness as the first protocol. In addition, the 'C' block simulated a pivot landing with 33% greater quadriceps tensile stiffness. The pre- and post-baseline 'A' blocks served as a check of ACL integrity throughout testing. Since there were no loading differences between the pivot landings in the 'B' block between protocols, mean peak AM-ACL relative strain from these five trials were the primary outcome of the study.

Statistical Analysis

A stepwise linear regression was performed in SPSS 19 (IBM Corp., Armonk, NY) using an F probability less than 0.05 for entry and greater than 0.1 for removal. Mean peak AM-ACL relative strain during the simulated pivot landing trials utilizing the gender-specific quadriceps tensile stiffness was the dependent variable for the regression analysis. The independent variables were gender, ACL cross-sectional area, lateral tibial slope, medial tibial plateau concavity depth, and notch width index (i.e. intercondylar width/bicondylar width), as well as six interaction terms representing the interaction between the four morphologic characteristics. Morphologic variables were centered (subtracted by their mean value) for computing the interaction terms in order to prevent multicolinearity. Unstandardized coefficients with 95% confidence intervals were computed, as well as the standardized coefficients. Regression terms with a p-value <

0.05 were considered significant. In addition, two-sided independent t-tests were utilized to compare the effect of gender on peak AM-ACL relative strain as well as the four morphological characteristics. Finally, Pearson correlations (rho) were utilized to compare peak AM-ACL relative strain individually with the four morphological characteristics. For graphical purposes, the knees were grouped into three subsets: low strain (peak AM-ACL relative strain below the 33% quartile), medium strain (peak AM-ACL relative strain between the 33% and 67% quartiles), and high strain (peak AM-ACL relative strain above the 67% quartile).

6.4 Results

The individual effects of ACL cross-sectional area, lateral tibial slope, notch width index, and medial tibial plateau concavity depth on peak AM-ACL relative strain during a simulated pivot landing are shown in Figure 6.5. Peak AM-ACL relative strain was significantly positively correlated lateral tibial slope (rho = 0.577; $p = 0.001$) and negatively correlated with ACL cross-sectional area (rho = -0.655; $p < 0.001$). Notch width index trended towards a negative correlation with peak AM-ACL relative strain (rho = -0.352; $p = 0.061$), while medial tibial plateau concavity depth was not significantly correlated (rho = -0.256; $p = 0.181$).

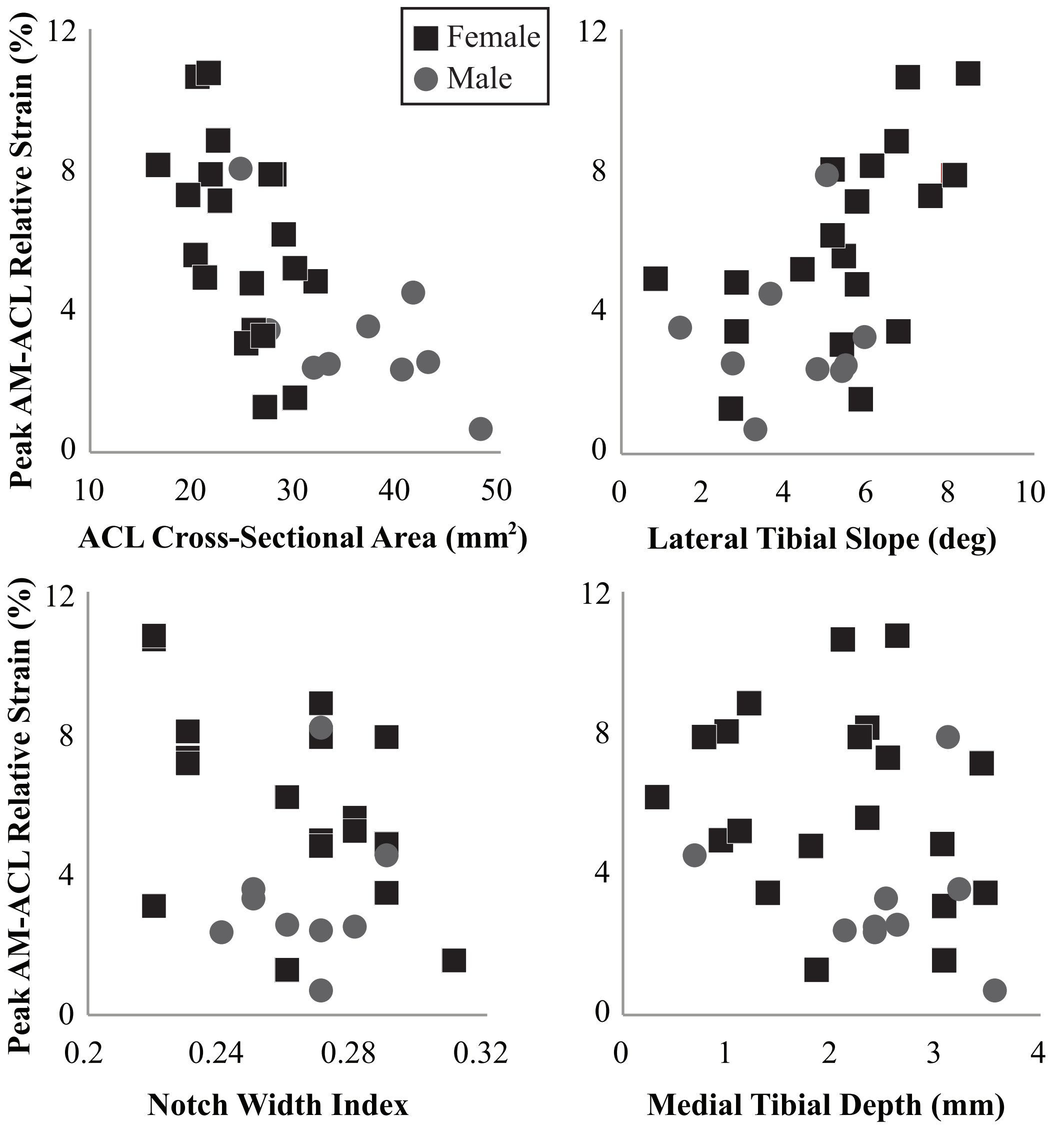

Figure 6.5 Scatterplots of peak AM-ACL relative strain during a simulated pivot landings vs. (top left) ACL cross-sectional area, (top right) lateral tibial slope, (bottom left) notch width index, and (bottom right) medial tibial depth. Female data is shown as black squares and male data is shown as grey circles.

The four morphologic characteristics, the six interaction terms between each morphology variable, and gender were examined using a stepwise linear regression model (Table 6.1). ACL cross-sectional area ($p < 0.001$) and medial tibial depth ($p = 0.042$) were significant negative predictors of peak AM-ACL relative strain, as well as the negative interaction between ACL cross-sectional area and lateral tibial slope (Figure

6.6; $p < 0.001$). A predictor of peak AM-ACL relative strain that trended towards significance was the negative interaction of notch width index and lateral tibial slope (Figure 6.7; $p = 0.056$). This stepwise regression model had an R^2 value of 0.658 ($p < 0.001$). While lateral tibial slope had a strong positive correlation with peak AM-ACL relative strain, it was excluded from the regression model ($p = 0.126$). All remaining coefficients within the stepwise regression model were excluded with p-values greater than 0.5: notch width index, gender, the interactions of medial tibial depth with notch width index, lateral tibial slope, and ACL cross-sectional area, as well as the interaction between notch width index and ACL cross-sectional area.

Table 6.1 Stepwise multivariable linear regression results for peak AM-ACL relative strain in 29 knees during a simulated pivot landing with gender-specific quadriceps tensile stiffness

	Unstandardized	Standardized	t-statistic	p-value
Significant Regressors	B (95% CI)	Beta		
Constant	13.717 (10.668,16.766)		9.286	<0.001
ACL CSA	-0.265 (-0.365,-0.164)	-0.725	-5.426	<0.001
MTD	-0.828 (-1.623,-0.032)	-0.274	-2.148	0.042
ACL CSA x LTS	-0.086 (-0.142,-0.031)	-0.425	-3.208	0.004
Non-significant Regressors				
NWI x LTS	-15.614 (-31.67,0.442)	-0.251	-2.007	0.056
Excluded Variables				
LTS		0.229	1.587	0.126
NWI		-0.095	-0.688	0.498
Gender		0.111	0.608	0.549
MTD x LTS		-0.042	-0.24	0.812
MTD x NWI		0.024	0.186	0.854
MTD x ACL CSA		-0.023	-0.174	0.864
ACL CSA x NWI		0.005	0.032	0.975

Abbreviations- CSA: cross-sectional area; MTD: medial tibial depth; LTS: lateral tibial slope; NWI: notch width index; CI: confidence interval

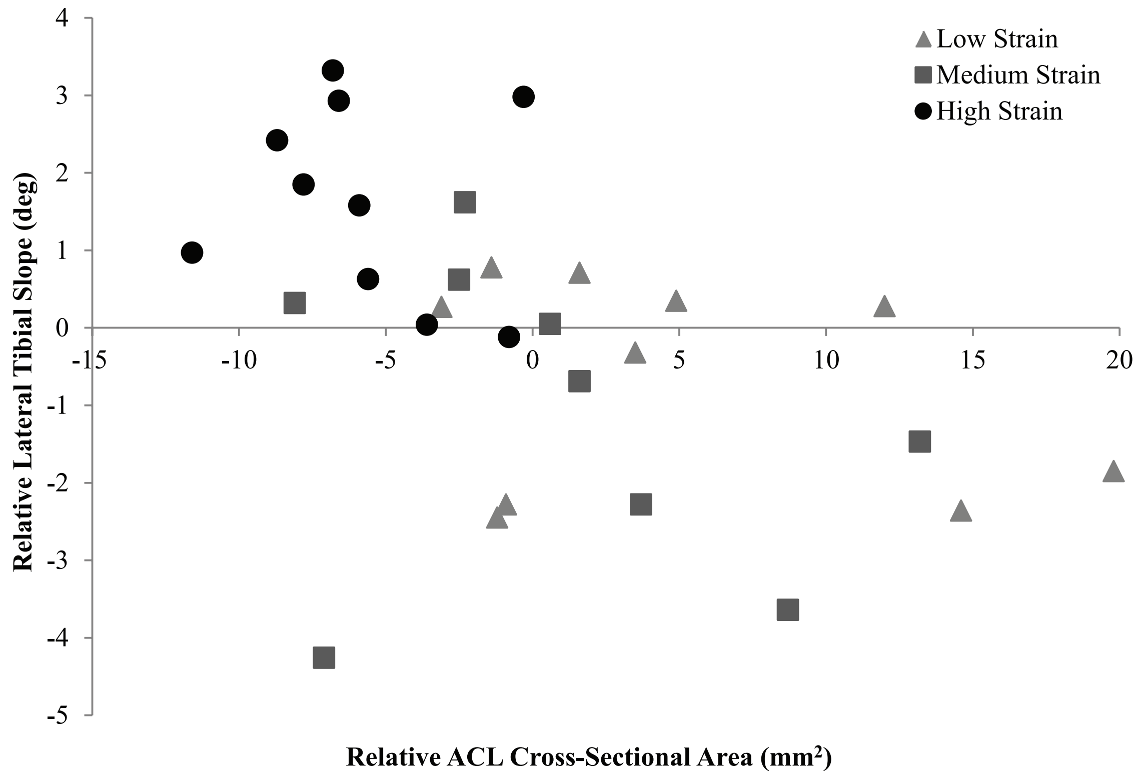

Figure 6.6 Scatterplot of relative lateral tibial slope vs. relative ACL cross-sectional area, with measurements taken relative to their mean values. Data points are grouped into low, medium, and high peak ACL strain.

There was a significant gender difference in peak AM-ACL relative strain during a simulated pivot landing with gender specific quadriceps stiffness ($p = 0.011$) (Table 6.2). The only significant gender difference in a morphology variable was ACL cross-sectional area, as well as a trend towards significance for lateral tibial slope ($p = 0.084$). There was no significant gender difference in medial tibial depth ($p = 0.198$) or notch width index ($p = 0.945$)

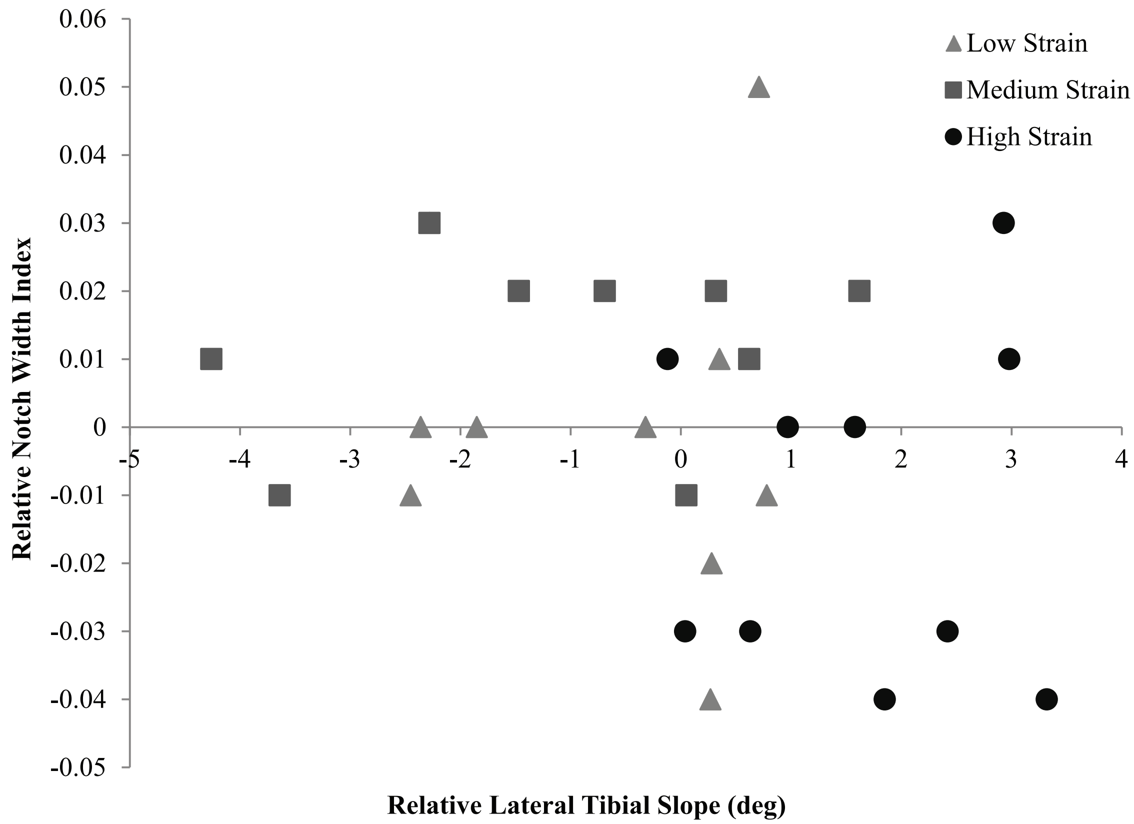

Figure 6.7 Scatterplot of relative notch width index vs. relative lateral tibial slope, with measurements taken relative to their mean values. Data points are grouped into low, medium, and high peak ACL strain.

Table 6.2 Gender comparisons of peak AM-ACL relative strain and morphologic characteristics in 29 knees

	Male	Female	t-statistic	p-value
Sample Size	9	20		
Peak AM-ACL Relative Strain (%)	3.31 (2.00)	6.05 (2.71)	-2.716	0.011
ACL Cross-Sectional Area (mm^2)	36.58 (7.26)	24.57 (4.11)	5.708	<0.001
Lateral Tibial Slope (deg)	4.2 (1.5)	5.5 (2.0)	-1.792	0.084
Notch Width Index (mm/mm)	0.263 (0.014)	0.262 (0.028)	0.069	0.945
Medial Tibial Depth (mm)	2.52 (0.83)	2.03 (0.95)	1.32	0.198

6.5 Discussion

This secondary analysis enhances our understanding of the interaction between the morphology of the knee joint and the dynamic ACL loading during a pivot landing. We found that a smaller ACL cross-sectional area, a shallower medial tibial plateau depth, and a smaller ACL cross-sectional area combined with a larger lateral tibial slope were the most significant predictors of peak AM-ACL relative strain during a 2*BW simulated pivot landing. In addition, a smaller notch width index combined with a larger lateral tibial slope trended towards being a significant predictor of peak AM-ACL relative strain. These four factors explained 65% of the variance in peak AM-ACL relative strain. While female knees were prone to the high-risk morphologic characteristics, they were not exclusive to females, which may help explain why females have a greater ACL injury risk than males[1, 3, 17, 30, 31, 33].

Females have a smaller ACL than males, as seen in measurements of ACL cross-sectional area[2, 6, 24, 32] and ACL volume[6, 7]. The female ACL also has a lower modulus of elasticity[5] and lower collagen fibril concentration[16]. A smaller ACL volume is associated with an increased risk of ACL injury, especially in females[7]. This secondary analysis confirms our previous finding[24] in a subset of 9 male and 9 female knees that ACL cross-sectional area is negatively associated with an increased peak AM-ACL relative strain during a pivot landing. For a given load and elastic modulus, a smaller ACL will undergo a greater stress and strain during dynamic loading, which ultimately increases the risk of ligament rupture.

Notch width index, assessed with either radiographs or MRI, is associated with an increased risk of ACL injury[11, 18, 21, 23, 37-39, 41, 43]. However, other studies have been inconclusive about the link between ACL injuries and notch width index in U.S. naval cadets[12] or NBA basketball players[27]. The smaller notch width index may be representative of a smaller ACL within the femoral notch: notch width has been correlated with ACL width[9], ACL cross-sectional area has been correlated with notch width index in male knees but not female knees[6], and ACL cross-sectional area at midsubstance has been correlated with notch width at 2/3rds notch height in females[2]. Notch width index alone was not a significant regressor in this larger secondary analysis of 29 knees.

Increased lateral tibial slope has been retrospectively linked with an increased ACL injury risk[4, 15, 22, 35, 36, 42], with females having greater lateral tibial slopes than males[15]. Other studies have not shown any link between lateral tibial slope and ACL injury risk[19]. An elevated posterior tibial slope, specifically in the lateral tibial compartment, will produce increased anterior tibial translation under weightbearing conditions[25], leading to an increase in peak ACL force[34, 35]. Posterior tibial slope has been positively correlated with anterior tibial deceleration during a *in vitro* drop landing[29]; lateral tibial slope was a significant predictor of increased peak ACL strain during an *in vitro* pivot landing[24]. The concavity of the medial tibial compartment may influence the knee's resistance to anterior tibial translation[14]. Previous studies have linked a shallower medial tibial depth with increased ACL injury risk[15, 22]. Our previous work did not find medial tibial depth to be a significant regressor of peak AM-ACL realtive strain in 18 knees; however, it was a significant predictor of peak AM-ACL relative strain when the sample size was expanded to 29 knees in our secondary analysis.

The examination of morphologic characteristics in combination, rather that isolation, was suggested by Sonnery-Cottet et al.[37]. In their study, posterior tibial slope and notch width index were highly negatively correlated in individuals with ruptured ACLs; 24% of patients with ruptured ACLs had a combination of posterior tibial slopes greater than 10 degrees and notch width indices lower than 0.21. The present study did find that a greater lateral tibial slope in combination with a decreased notch width index trended towards significance when predicting peak AM-ACL relative strain.

One morphologic combination achieved significance within the regression model: the negative interaction between ACL cross-sectional area and lateral tibial slope. Dargel et al.[8] hypothesized that a larger lateral tibial slope would result in a larger ACL cross-sectional area in order to compensate for the increased anterior tibial translation caused by the greater slope. To the contrary, we show that knees with both a smaller ACL cross-sectional and greater lateral tibial slope produce greater amounts of peak ACL strain during a pivot landing, ultimately increasing the risk of ACL rupture. We hypothesize that, for a given load, the ACL will undergo greater stress due to the smaller ACL cross-sectional area as well as the greater anterior drawer force resulting from the increased lateral tibial slope. When the ACL reaches its ultimate stress and/or strain, the ligament will rupture. Finally, Hashemi et al.[15] has shown that individuals with a shallower concavity of the medial tibial plateau in combination with a steeper lateral tibial slope have a greater risk of ACL injury. An increased lateral tibial slope with a shallower medial tibial depth will increase anterior tibial subluxation, imparting greater stress on the ACL[8]. However, the combination of medial tibial depth and lateral tibial slope was not significance in our study.

The strengths of this study include the use of size-matched male and female knees, a large sample size of 29 cadaveric knees, and our investigation of morphologic combinations within the statistical model. This study has its limitations, but they are unlikely to affect the overall findings of the study. First, peak ACL strain is only monitored on the anteromedial bundle; however, this has been shown to be indicative of overall ACL force[28]. This study has focused on morphologic parameters that can be measured from a single MR slice. ACL volume as well as measurements of tibial slope and depth across the entire tibial plateau (rather than the center of articulation) could give us more information regarding the effect of morphology on knee and ACL mechanics. However, these are more computationally intensive measurements to perform. This study does not consider the shape of the femoral notch, which may be an important parameter to consider in addition to notch width index[44]. Finally, a full factorial statistical model with three-way and four-way interactions was not utilized in order to conserve degrees of freedom for the present analysis.

6.6 Conclusions

1) In an expanded sample size of 29 knees, ACL cross-sectional area, the interaction of ACL cross-sectional area and lateral tibial slope, medial tibial depth, and the interaction of lateral tibial slope and notch width index were negatively associated with peak AM-ACL relative strain during a simulated pivot landing, explaining 66% of the variance in peak AM-ACL relative strain. ACL cross-sectional area and lateral tibial slope previously explained 59% of the variance in peak AM-ACL relative strain in Chapter 2.

2) This study highlights that interactions of morphologic characteristics (ACL cross-sectional area x lateral tibial slope; lateral tibial slope x notch width index) can predict ACLs with greater AM-ACL relative strain, and ultimately a greater ACL injury risk.

6.7 References

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CHAPTER 7

GENERAL DISCUSSION

This dissertation addresses three important knowledge gaps pertaining to ACL injury mechanisms: (1) why do females have a greater ACL injury rate than males, (2) how does knee morphology affect ACL strain during dynamic maneuvers, and (3) are ACL injuries the result of a single event or multiple events? Furthermore, this dissertation addresses a knowledge gap in ACL injury prevention: does the increase in knee extensor tensile stiffness, that should accompany an increase in strength caused by training, affect peak ACL strain during a pivot landing maneuver? Finally, this dissertation addresses the need to develop an accurate, repeatable measurement of lateral tibial slope in order to clinical diagnosis it for ACL injury screening as well as introduces a novel method for modeling *in vivo* tensile muscle behavior under rapid stretch loading in an *in vitro* testing apparatus.

7.1 Implications for ACL Injury Mechanisms

The Effect of Gender-Related Differences in Knee Morphology on ACL Strain

The current dogma suggests that females are predisposed to ACL injuries because they land with greater knee abduction than males, which has been observed both in video analyses[6, 7, 65] and landing mechanics[20, 52]. However, it is unlikely that landing with a knee valgus posture alone can account for the gender difference in ACL injury rates because bone bruising of ACL-injured subjects suggests ACL injuries are caused by the coupling of anterior tibial translation and internal tibial rotation, not knee valgus loading[83]. Furthermore, in *in vitro* studies, internal tibial torque results in the greatest ACL strains during a simulated pivot landing, regardless of whether knee valgus or varus frontal plane moments act[64].

One might posit from the epidemiology studies showing females to be at greater risk for ACL injuries than males (see Introduction) that the female ACL is systematically undergoing greater stresses and strains than the male ACL. The first evidence to support this hypothesis comes from this dissertation, which shows that the female knees will undergo 95% greater peak AM-ACL relative strain than knees from age-, height-, and weight-matched males during a 2*BW simulated pivot landing with internal tibial torque (Chapter 2). ACL cross-sectional area and lateral tibial slope explained 59% of the variance in peak AM-ACL relative strain. Overall, these findings suggest that intrinsic ACL mechanical properties and structural knee joint properties may matter more than how the knee joint is externally loaded, and could ultimately be responsible for the greater ACL injury rate in females. They would be confirmatory if the modulus of elasticity and ultimate tensile strain of the female ACL was found to be similar or less than a male control.

Previous studies have indeed shown the female ACL has inferior mechanical properties than the male ACL, including a lower tensile modulus of elasticity and ultimate failure load than the male ACL[9]. Since the female ACL is smaller in both cross-sectional area[3, 9, 10, 15] and volume[9-11], it is not surprising that the female ACL exhibits greater strain in our tests. For a given load, ACL strain will be inversely proportional to the cross-sectional area and modulus of elasticity of the ligament. Since both these properties are lower in the female ACL, it undergoes greater strain than the male ACL (Chapter 2). A more slender ACL does not necessarily place that ligament at a higher risk for injury if it has superior mechanical proprieties due, for example, to having a denser concentration of collagen fibrils. However, we are aware of only one study which has investigated the ultrastructure of the male and female ACL: the female ACL had fewer collagen fibrils per unit area than the male ACL[29]. While this suggests the female ACL may have had a lower collagen density in this subset of 12 cadaver knees, it does not rule the possibility that some females could have a slender ACL with a denser collagen concentration.

This is the first time that the ACL strain during a dynamic maneuver has been demonstrated to be influenced by the morphology of the knee joint: ACL cross-sectional area was negatively associated and lateral tibial slope was positively associated with increased AM-ACL relative strain during a simulated pivot landing, and together explained 59% of the variance in peak AM-ACL relative strain (Chapter 2). Although gender was insignificant within our regression model, the female knees in our study had a significantly smaller ACL cross-sectional area and trended towards a greater lateral tibial slope than height and weight matched male knees. As outlined above, a smaller ACL cross-sectional area is inversely proportional to ACL strain for a given load. Lateral tibial slope has been previously associated with a greater ACL injury risk[28], and increasing the slope will produce greater ACL force[68, 72], anterior tibial translation[13, 68, 72], and anterior tibial deceleration[53].

A secondary analysis was performed in Chapter 6 with an expanded sample size of 29 knees from age-, height-, and weight-matched donors. Since multiple morphologic factors may contribute to how the ACL is strained during a dynamic maneuver, we introduced 2-way interactions to the regression models. An increased ACL injury risk has been associated with a smaller notch width index[34, 71, 79] and a shallower concavity of the medial tibial plateau[28], so the expanded sample size included these factors in the regression model. The results showed, in order of importance, that ACL cross-sectional area, the interaction of ACL cross-sectional area and lateral tibial slope, medial tibial depth, and the interaction of notch width index and lateral tibial slope accounted for 66% of the variance in peak AM-ACL relative strain during a simulated pivot landing. This extends the results of Chapter 2, and suggests that combinations of morphologic characteristics (i.e. a large lateral tibial slope combined with either a small ACL cross-sectional area or a small notch width index) could be used to predict knees that will have higher ACL strain, and ultimately a higher ACL injury risk.

Finally, the effect of ACL cross-sectional area and lateral tibial slope on the number of cycles to ACL failure was analyzed in Chapter 6. A smaller ACL cross-sectional area was associated with a reduction in the number of cycles to ACL failure. However, lateral tibial slope was not significant, which can be attributed to the small sample size of the study (10 matched-pair specimens). Nonetheless, this dissertation demonstrates a clear link between the morphology of the knee joint and the fatigue life of the ACL during repeated simulated pivot landings.

Overall, this dissertation shows why females may be more susceptible to ACL injuries than male. Females are more likely than males to have the high-risk knee morphologies (smaller ACL, greater lateral tibial slope, shallower medial tibial depth, smaller notch-width index) associated with greater peak AM-ACL relative strain, that ultimately increase their risk for ACL failure. Therefore, future ACL injury mechanism research should continue to focus on why individuals with high-risk knee morphologies are more susceptible to ACL injury, independent of gender.

The Effect of Repetitive Pivot Landings on Human ACL Fatigue Failures

It is currently unknown if ACL injuries are the result of a single event or multiple events[75]. For the first time we demonstrate in this dissertation that the human ACL can undergo a fatigue failure from repeated simulated pivot landings. If this finding is confirmed by others, then this extends the findings that fatigue failures can occur in other collagenous structures including human Achilles tendon[91], wallaby tail tendon[85], and rabbit medial collateral ligament[80, 81]. There will be a fewer number of cycles to ACL failure if the pivot landing force is increased and/or the ACL cross-sectional area is smaller. Using the S-N curve for materials[73], our proposed mechanism of ACL fatigue failure is illustrated in Figure 7.1. As the landing force increases, we would expect the damage accumulation in the ligament to cause the ACL to fail in fewer loading cycles. The damage accumulation under high cyclic loads will cause the ligament to reduce its modulus of elasticity over time[81], making the ligament more susceptible to failure. We speculate that the ACL's fatigue life in both males and females can be extended with training (i.e. the dashed line in Figure 7.1).

A gender difference may also exist in the ACL fatigue life, as illustrated in Figure 7.1. We speculate that this may occur due to the known gender differences in the mechanical and structural properties of the ACL. Females have a smaller ACL (both in volume[9-11] and cross-sectional area[3, 9, 10, 15]) as well as a lower modulus of elasticity and lower ultimate stress[9]. For a given landing force, we would suspect the male ACL to take a greater number of cycles to reach ACL failure than the female ACL. While gender did not reach significance, ACL cross-sectional area was a significant predictor of the number of cycles to ACL failure. We cannot rule out that gender did not reach significance due to a small sample size; however, other chapters in this dissertation have not found a significant gender effect while finding a significant ACL cross-sectional area effect. Therefore, these findings suggest future work should concentrate less on gender and more on ACL size as a risk factor for ACL injury (in either gender). Future work should investigate whether enhancing quadriceps tensile stiffness reduces the risk for fatigue failure since it reduced peak AM-ACL relative strain in Chapter 3.

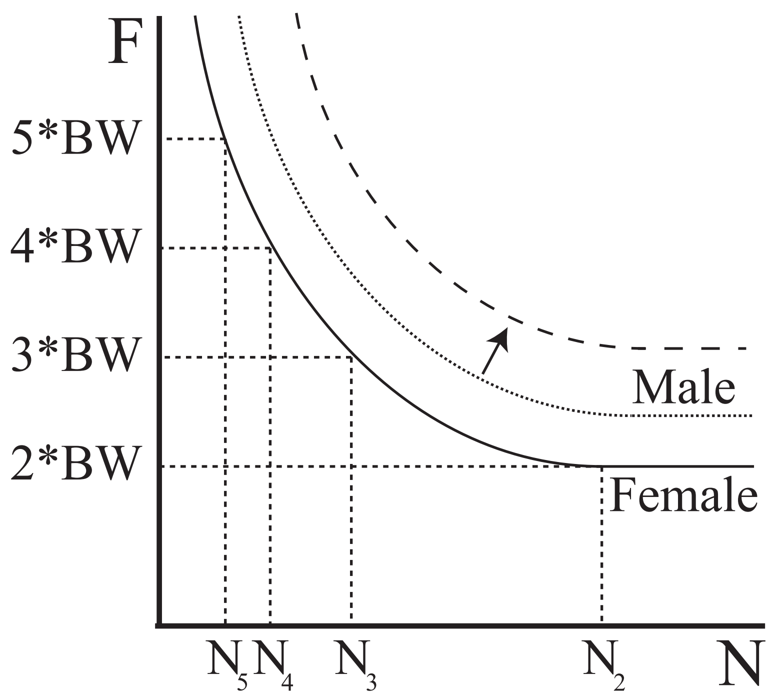

Figure 7.1 The proposed relationship between the pivot landing force (F) vs. the number of loading cycles to ACL failure (N). The number of cycles to ACL failure increases as the repetitive landing force is decreased. We propose that a gender difference in this fatigue failure behavior may explain the greater ACL injury risk in females. For the same level of loading force standardized to body weight, the female ACL should fail in fewer cycles than the male ACL. The inverse relationship may exponential as shown here, but it could also have another form. Further research is needed to determine the relationships. One might speculate that the punitive effect of training would move the male curve to the dashed line, thereby increasing the ACL's fatigue life.

This dissertation also provides new insights into the types of ACL failures that occur during a simulated pivot landing. The primary failure type and location in this study was a partial tear of the posterolateral bundle between the femoral insertion and mid-substance. This agrees with the work of Meyer et al., who found posterolateral bundle tears near the femoral insertion occurred in four of seven failed cadaver knees with internal tibial torques ranging from 10 – 50 Nm[54, 55]. Partial tears are a common form of ACL injury, ranging from 10-25% of all ACL injuries[60, 76, 78, 94]. While partial tears of the anteromedial bundle are more often reported in the literature[60, 78], it is plausible that partial tears of the posterolateral bundle are underreported because they do not exhibit the increase of anteriorly-directed laxity seen in partial tears of anteromedial bundle[31]. A partial tear of the posterolateral bundle will lead to rotational instability and a coupled increase in anterior tibial translation during a simulated pivot shift test[95]. While the long-term prognosis of partial ACL tears is better than complete tears[77], it can also lead to future ACL deficiency[59].

Previous studies have suggested the ACL can be functionally compromised without macroscopic tearing[41, 58, 92]. We replicated this type of permanent elongation ACL failure during our simulated pivot landings; four knees that had no visual signs of ACL tearing to the human eye, but increased anterior tibial translation by at least 3 mm relative to the start of the experiment. Previous studies have shown an increase in 3 mm of anterior tibial translation, relative to the uninjured limb, during an anterior drawer test is associated with 85% of complete tears under anesthesia[12]. While we were able to track anterior tibial translation, this study is limited by the lack of histology to confirm microscopic damage has occurred, especially near the bone-ligament interface at the femoral attachment.

Based on the ligament fatigue failure theory proposed in Figure 7.1, we believe that partial tears and permanent elongation failures can progress to complete ACL tears if the loading intensity was increased and/or the number of loading cycles was increased. The clinical implications of this study are the need to study the frequency and magnitude of high-intensity impacts during practices and competitions by age, gender and skill level. This can be accomplished by instrumenting the lower extremity. This would help limit an athlete's exposure to high-risk maneuvers for the ACL, similar to the Little League pitch count which was adopted to limit elbow ligament failures in young athletes[47]. We note that Figure 7.1 reminds one that a single event ACL failure can still occur within the framework of ligament fatigue failures, if the dynamic loading is high enough and the individual has a small enough ACL. This could lead to a high enough strain to exceed the ultimate tensile strain for the ACL.

The Role of the Quadriceps During a Dynamic Landing

In Chapter 3, we used a novel non-linear quadriceps spring to model the behavior of the female quadriceps with normal and increased (i.e. 33% greater) stiffness values. We found that a 33% increase in quadriceps tensile stiffness produced a 16% reduction in peak AM-ACL relative strain during a 2*BW pivot landing in 12 female knees. This increase in quadriceps tensile stiffness significantly reduced the change in knee flexion and knee abduction angles during the *in vitro* experiment. Using a 3-D biomechanical model, the experimental results were confirmed: increasing quadriceps tensile stiffness caused peak AM-ACL relative strain and change in knee flexion angle to decrease. The current dogma suggests greater knee flexion will reduce ACL strain during passive and active flexion-extension tasks[4]. However, those studies did not investigate the effect of knee flexion on ACL strain during dynamic landing maneuvers. Previous work has indicated a rolling-sliding mechanism within the knee joint[32, 45, 57]. If the knee were to purely roll during knee flexion, as illustrated in Figure 3.5, we would expect an increase in ACL strain will occur. However, as the knee flexes more, we would eventually expect some anterior sliding of the femur, thereby reducing ACL strain. We feel Chapter 3 corroborates a previous study that found an increase in rolling relative to sliding in knees with reduced quadriceps muscle activity (i.e., less quadriceps tensile stiffness) in knees near extension performing weight-bearing active flexion-extension[32]. Therefore, during a dynamic landing task, the increase in quadriceps tensile stiffness results in less pure rolling of the femur on the tibia, resulting in a reduction in peak AM-ACL relative strain.

One might expect, however, an increase in quadriceps force with increasing quadriceps tensile stiffness. A maximal contraction of the quadriceps may be detrimental to the ACL, as shown by a large quadriceps load of 4,500 N resulting in ACL failures in older cadaveric knees[14]. However, it is unlikely that quadriceps force would exceed 3,000 N during a maximum voluntary contraction during the first 50 ms of a jump landing[16]. While more recent studies have failed the ACL with 2,000 – 3,000 N of quadriceps force[84], this was performed in combination with axial compressive forces much greater than ground reaction forces seen during a typical single leg *in vivo* drop landing[93]. Therefore, the DeMorat et al.[14] and Wall et al.[84] studies may over-exaggerate *in vivo* conditions which allow a large quadriceps force to rupture the ACL.

A sub-maximal level of quadriceps force may not be as detrimental to the ACL as discussed in the above paragraph. Despite an increase of quadriceps force of ~100 N with the increased quadriceps tensile stiffness, we still had a reduction in peak AM-ACL relative strain during a 2*BW simulated pivot landing. Other researchers have found ACL strain during the landing phase of a jump was reduced as quadriceps pre-activation force was increased[27]. As knee flexion is initiated during a jump landing, the increased quadriceps pre-activation force will increase the posteriorly directed joint compressive force to the tibia, thereby protecting the ACL against the quadriceps force via the patellar tendon pulling the tibia anteriorly[27]. However, our current study does show a small increase in anterior tibial translation (on average, 0.5 mm) with the increased quadriceps tensile stiffness. We feel this is an artifact in the data set from the significantly greater quadriceps force with the increased muscle stiffness, especially since quadriceps force and anterior tibial translation were highly correlated. We believe that dynamic knee flexion, as presented above, was just as important as anterior tibial translation when straining the ACL. Overall, the results of Chapter 3 show that sub-failure levels of quadriceps stiffness and quadriceps force are beneficial for the ACL in terms of lowering peak AM-ACL relative strain. Future work is needed to determine if there is a certain level of quadriceps stiffness and quadriceps force where the muscle transitions from being beneficial for the ACL to being detrimental.

7.2 Implications for ACL Injury Prevention and Screening

Prevention and Screening of Knee Morphology

With a better understanding of how morphologic risk factors affect ACL strain and ACL failures during a pivot landing (Chapters 2, 4, and 6), these results will hopefully influence future ACL injury prevention programs. It is plausible, but as yet unproven, that the ACL can be hypertrophied with training over many years, which should lower an individual's risk for ACL injury. For example, high-performance weightlifters that began their training between the ages of nine and twelve had an ACL that was nearly 80% larger than controls of similar age, height, and weight[25]. Furthermore, a stronger quadriceps muscle has been linked with a larger ACL[3], suggesting that ligament hypertrophy could accompany quadriceps hypertrophy, and perhaps the mechanism by which the weightlifter ACLs were larger. However, a prospective study is needed to fully understand if human ligament hypertrophy is possible.

Tibia and femur morphology (specifically lateral tibial slope, medial tibial depth, and notch width index) can also influence peak ACL strain according to our findings. However, we do not currently understand how training and puberty can affect these risk factors. It is unlikely that a clinical intervention like a tibial osteotomy or notchplasty would be utilized to alter the posterior slope or femoral notch because of the invasiveness of the procedure. While altering the posterior slope could be beneficial for the ACL, it may also be detrimental to the posterior cruciate ligament[21]. Instead, it is more practical to use these bone morphologic risk factors as a screening tool for ACL injury risk.

Knee Extensor Strength Training in ACL Injury Prevention Programs

Active quadriceps tensile stiffness is upwards of 40% less in females than males[22]. While many ACL injury prevention programs include knee extensor strength training[30, 46, 56], there is a current knowledge gap regarding if an increase in quadriceps stiffness can aid females in protecting their ACL during a dynamic landing. Since quadriceps tensile stiffness is a function of muscle size and muscle activation, the stiffness properties of muscle is modifiable with training. Previous studies have shown that females land with greater quadriceps activation than males[49, 66]. However, it is unlikely that the females can achieve similar muscle stiffness as males due to their lower muscle mass[37].

The results of this dissertation show that increasing quadriceps tensile stiffness by 33% will lead to a 16% reduction in peak AM-ACL relative strain during a 2*BW simulated pivot landing (Chapter 3). Since the ACL can undergo a fatigue failure (Chapter 4), the 16% reduction in peak AM-ACL relative strain from increased quadriceps stiffness should extend the number of cycles to ACL failure. Therefore, the results of this dissertation would support knee extensor strength training as a beneficial for ACL injury prevention programs. Similar testing within the same apparatus found hamstrings lengthening could decrease peak AM-ACL relative strain by 70% during a 2*BW jump landing[89]. However, increasing quadriceps tensile stiffness via knee extensor strength training may be easier to accomplish *in vivo* than hamstrings lengthening[62], making it a more feasible method to reduce ACL strain. Developing an ACL injury prevention program that could combine knee extensor strength training with a jump landing strategy concentrating on hamstrings lengthening would be ideal combination for reducing *in vivo* ACL strain.

We feel that a 33% increase in muscle stiffness is realistic in female athletes through muscle hypertrophy. A 3 day/week progressive resistance training program in young females can produce a 8% increase in rectus femoris volume in 9 weeks[36] and a 38% increase in knee extensor strength in 16 weeks[42]. We can see similar gains in young males undergoing a 12-week knee extensor strength training, with a 6-8% increase in muscle volume and a 32-34% increase in muscle strength[43, 44]. These gains in muscle mass and strength produce a 30-58% gain in musculo-tendon stiffness. Similarly, muscle stiffness can also be increased with more muscle activation. Young males undergoing a 4-week explosive knee extensor training program produced a 34% increase in musclo-tendon stiffness which can be attributed to their 42% greater muscle activation[82]. There are no current studies on the effect of training on quadriceps tensile stiffness in females. Based on the training data in males and the assumption that the female muscle can undergo the same percentage increases in knee extensor strength and activation as males, it seems that a 33% increase in quadriceps tensile stiffness is achievable, but it is likely the maximum level achievable with a 3-month training program.

Clinical Measurements of Lateral Tibial Slope

This dissertation has shown that a greater lateral tibial slope is associated with increased AM-ACL relative strain during a pivot landing (Chapters 2 and 6). Therefore, future researchers may be interested in using lateral tibial slope for ACL injury risk screening, especially since it is also associated with a greater risk of ACL injury[28]. Because there is only a small range of variation in lateral tibial slope[28] (0°-14°), an accurate, repeatable method to measure lateral tibial slope is needed to use tibial slope for ACL injury risk screening. Using magnetic resonance imaging, the two most common ways to measure lateral tibial slope with a knee coil are the midpoint method[28] (as used in Chapter 4) and the circle method[33] (used in Chapters 2, 3, and 6). However, there is still a knowledge gap regarding the consistency of lateral tibial slope measurements from different measurement techniques, and ultimately how both these methods utilizing the proximal tibia compare to a method using the full tibia.

By examining the magnetic resonance imaging scans of 40 knees from age-, height-, and weight-matched donors (11 of which had full tibia scans performed), this dissertation demonstrates that the midpoint method will produce a lateral tibial slope measurement that is 3 degrees larger than the circle method, on average. Furthermore, we demonstrate that the lateral tibial slope measurements using the midpoint method are sensitive to the length of proximal tibia. Previous studies have not controlled for the length of tibia used for the midpoint measurement[28], so future studies should control the length of the tibia if the midpoint method is utilized. Furthermore, using less than 10 cm of proximal tibia to make a lateral tibial slope measurement is not recommended. The presence of the tibial tuberosity on the central axis image used to define the tibial proximal anatomic axis could bias the slope measurements.

On the contrary, a major benefit of the circle method is that lateral tibial slope measurements are independent to the length of proximal tibia imaged, which may have made it the more repeatable method according to inter- and intra-observer correlations. We did find that lateral tibial slope measurements with the midpoint method (especially with 15 cm of proximal tibia) were a better representation of measurements with the full tibia anatomic axis than the circle method. Overall, we conclude that lateral tibial slope measurements, even using the same method, are not all alike. This makes it difficult to define an absolute degree of inclination of the lateral tibial plateau that is most dangerous. Therefore, future screening studies that seek to evaluate ACL injury risk that utilize lateral tibial slope measurements as a component need to carefully select the best method for their purposes.

7.3 Innovation

A Novel-Method for Modeling *in vivo* Muscle Behavior within a *in vitro* Apparatus

This dissertation introduces a novel bi-linear spring to model the rapid lengthening of the quadriceps muscle during a jump landing (Appendix A). The quadriceps will be the primary muscle that stretches during a jump landing; any stretch in the gastrocnemius muscle from plantarflexion and in the hamstrings from hip flexion will be offset by knee flexion[35, 61]. Previous iterations of the Withrow – Oh testing apparatus used in this dissertation have modeled quadriceps behavior using a linear stiffness using aircraft cable[87-89] or nylon string[63, 64]. Other cadaveric testing frames have simulated a jump landing using no muscle forces[55] or quasi-static forces[27]. However, all of these approaches ignore the true behavior of striated muscle under rapid stretch.

Muscle fibers on the plateau region of the sarcomere length-tension curve will exhibit a high initial stiffness followed by little to no force increase as the fiber continues to stretch[17, 18, 38]. These same studies show that when a muscle fiber lies on the descending limb of the sarcomere length-tension curve, the fiber will show residual force enhancement as the muscle is stretched beyond the initial high stiffness. This bi-linear stiffness behavior has also been shown in whole muscle in rabbit tibialis anterior muscle[24], as well as human knee extensors[74] and knee flexors[26]. The novel bi-linear stiffness springs was developed using the methods of Jutte and Koda[39, 40]. As shown in Appendix A, these titanium springs can model both the non-linear stretch behavior of *in vivo* as well as the gender difference in quadriceps tensile stiffness[22]. Since quadriceps tensile stiffness plays an important role in how the ACL is loaded during a dynamic landing (as seen in Chapter 3), we believe the ability to model *in vivo* muscle function within an *in vitro* testing frame is a major advance in cadaveric research of ACL injury mechanisms.

7.4 Limitations

Since the onset of ACL injuries begins at age 12 and peaks following puberty[69], this dissertation is limited by the use of older cadavers ranging in age from 30 to 90 years old. The older donors were screened for prior lower extremity injury history and excluded if they had moderate to severe osteoarthritis. Specimens were generally grouped by gender and then donors matched by age, height, and weight to lower the variability between groups. However, these methods cannot control for the fact that tensile properties of the ACL will decrease significantly with age[90], in addition to changes to the other ligamentous knee structures, cartilage, and bone. Age will affect the ligament's *in vivo* ability to repair and re-model from repetitive loading, due to reduced vascularization of the ligament's proximal end in older adults[67]. While we did match the donors of the male and female knees used in Chapter 2 by height and weight, the male knees still had a significantly larger femoral bicondylar width.

The testing apparatus may seem to oversimplify a pivot landing since it only models the lower extremity as two segments comprising the knee joint, and two universal joints are used to represent the ankle and hip. During an *in vivo* landing, the position of the foot and hip may be important for attenuating the ground reaction forces[5]. In addition, the position of the trunk during a jump landing can be important[70]. Regardless of the orientation and position of the torso and pelvis, as well as landing foot and shank, the 3-D dynamic knee loads are ultimately transmitted to the knee joint by the tibia and the femur bones and trans-knee muscle forces. So, as long as the forces and moments transmitted to the test knee are realistic, then the knee loading imposed by the modified Withrow-Oh apparatus is realistic.

This dissertation utilized a specific impulsive load (compression force + knee flexion moment + internal tibial torque) in the modified Withrow-Oh apparatus. However, these results may not translate to other external loading patterns of the knee joint. This loading pattern was chosen because it is the worst-case scenario for the ACL in terms of AM-ACL strain within the current testing apparatus[64]. An increase in knee abduction is commonly noticed in video analyses of ACL injuries[6, 7, 65]. While a knee abduction moment was not added to the present loading, the knees were potted with their natural frontal plane alignment. When the compression force is applied, this natural frontal plane alignment, which was valgus in most knees tested, will induce a knee abduction moment. However, this knee abduction moment was small in comparison to the applied internal tibial torque.

The testing apparatus was updated in this dissertation to include a novel non-linear quadriceps spring to model the rapid lengthening of the muscle during the first 100 ms. However, the spring was optimized for a 2*BW landing. In Chapter 4, nylon string with a linear stiffness was used instead of the non-linear spring because the quadriceps response within the testing apparatus during a 3 - 5*BW simulated pivot landing was unknown. The specific non-linear springs used in Chapter 2 and 3 would have saturated the quadriceps force, as well as the landing forces. In order to use the non-linear spring with higher landing forces, the in-plane and out-of-plane thicknesses of the spring will need to be altered.

A differential variable reluctance transducer (DVRT) was utilized during the cadaveric testing by inserting its two bards on the distal 3rd of the anteromedial bundle of the ACL. Markolf et al. have previously shown that measuring strain on the anteromedial bundle is predictive of the ACL force throughout the entire ligament[51]. However, we know that ACL strain, as well as the material modulus of elasticity, are heterogeneous throughout the ligament[8, 48]. The posterolateral and anteromedial bundles of the ACL reciprocally share the load on the ligament with the posterolateral bundle carrying the load more near extension[2, 19]. Since the ligament fatigue failures in Chapter 4 show more damage to the posterolateral bundle than the anteromedial bundle in the failed knees, the posterolateral bundle may be undergoing greater strain during the application of internal tibial torque than the anteromedial bundle, or the posteromedial bundle. Therefore, it may be insufficient to only monitor strain on the anteromedial bundle when simulating a pivot maneuver. In addition, it cannot be ruled out that damage will occur to the ligament when inserting one or both DVRT bards into the ACL that could influence ACL strain and potentially ACL failure. Finally, the DVRT can only be used to monitor relative changes in ACL strain[51]. Since the pre-tensioned muscle forces will place a load on the ligament prior to testing, it is likely that the ACL strain is greater on the anteromedial bundle than measured with the DVRT.

The ACL was failed within our testing apparatus using varying landing forces of 3 – 5*BW. While these landing forces are higher than previous 2*BW landings simulated with our testing apparatus (Chapter 2 and 3), drop landings can reach peak forces from 6 – 10*BW[1]. In addition, we considered the ACL to have failed with our simulated pivot landing if it suffered a complete tear, a partial tear, a tibial avulsion, or became permanently elongated by increasing its anterior tibial translation by 3 mm from the first pivot trial. Tibial avulsions may be caused by poor bone quality in an older cadaver knee; however, tibial avulsions can occur in adolescents and young adults[23]. While the permanently elongated ACLs did not show macroscopic damage, there has been a clear functional change in the ligament due to the increased anterior tibial translation. Daniel et al. found a minimum 3-mm increase in anterior tibial translation in 85% of complete tears in ACL injured subjects under anesthesia[12], and multiple studies have shown than microscopic damage of thin and thick collagen fibrils will proceed macroscopic tearing of the ACL[41, 58, 92].

A large landing force (leading to greater ACL force) combined with a smaller ACL cross-sectional area will produce a greater peak ACL stress. We decided to use landing force as a surrogate for stress in Chapter 4 (as well as the modified S-N curve in Figure 7.1) because of the difficulties in tracking ACL stress, both *in vivo* and within our *in vitro* testing apparatus. During an *in vivo* landing, landing forces can be tracked using a force plate on the ground or with a device built into a shoe. However, ACL force, and ultimately ACL stress, cannot be determined because numerous combinations of muscle forces which can occur during a jump landing[86], and ultimately affect how much the ACL is loaded. Within our *in vitro* testing apparatus, we cannot track changes in ACL cross-sectional area during testing, which should decrease as the ligament lengthens prior to failure. Furthermore, we were concerned that *in vitro* methods to track ACL force[50] would be too intrusive, affecting our ability to investigate fatigue failures in the ACL. Therefore, we concentrated on measuring ACL strain in Chapter 4 as a surrogate measurement for ACL stress and ACL force.

Magnetic resonance imaging was utilized in this dissertation to visual the tibia, femur, and ACL, prior to any biomechanical testing, with good spatial resolution. A strength was that a blinded observer with good test-retest reliability was utilized to make measurements of ACL cross-sectional area, medial and lateral tibial slope, medial tibial depth, and notch width index. However, these measurements are prone to some subjectivity. For example, lateral tibial slope and medial tibial depth were measured at the tibial center of articulation of the lateral and medial tibial plateaus, as proposed by Hashemi et al.[28]. However, there is no true center of articulation for the tibia and it is ultimately up to the observer to determine this from an axial view of the tibia. In addition, the tibial slope measurements were measured using the subchondral bone line to define the posterior-inferior slope of the tibial plateau and does not consider potential effects of cartilage or meniscus.

While we only measured ACL cross-sectional area at one location (30% ligament length from tibial origin), we did not measure the entire ACL volume. Segmenting each slice of the MR images would give a more comprehensive view of ACL size as well as the tibial slopes across the entire plateau. However, this would be computationally costly to perform, thereby making it unlikely to be adopted by clinicians without further advances in imaging segmentation. We feel that the imaging measurement protocols used in this dissertation provide a quick, accurate, and repeatable method to assess an individual's knee morphology for potential ACL injury risk screening and therefore have clkinical applicability in a research setting.

In summary, this dissertation provides valuable insights into the gender differences in ACL injuries that could not ethically be reproduced in an *in vivo* experiment. The installation of a DVRT on a human subject's ACL is an invasive procedure and, of course, it would be unethical to cause ACL failure during human subjects testing. While magnetic resonance imaging screening of knee morphology in human subjects is realistic, the high cost of lower extremity MRIs is a deterrent for clinicians and researchers. Office MR scanners (or even portable MR scanners in the future) might offer a good alternative. The relationships between knee morphology and peak AM-ACL relative strain identified in this dissertation should help spur future morphology screening for ACL injury prevention.

7.5 References

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CHAPTER 8

CONCLUSIONS

Innovation

This dissertation addresses both ACL injury mechanism [Conclusions (1) – (7)] and ACL injury prevention and screening [Conclusions (2) – (4), (8), and (9)]. In addition, this dissertation adds a significant improvement to our current *in vitro* testing apparatus by simulating *in vivo* bi-linear muscle stretch behavior [Conclusion (10)].

The most novel findings in this dissertation include that the female ACL is prone to greater ACL strain than the male ACL during a dynamic maneuver, primarily due to their smaller ACL cross-sectional area and larger lateral tibial slope [Conclusions (1) – (3)]. Another novel finding is the ACL is susceptible to low-cycle fatigue failures like other collagenous structures under repeated high-intensity loading [Conclusions (5) – (7)]. These novel findings suggest the need to monitor the frequency and magnitude of pivot landing forces, as well as an individual's knee morphology, to reduce ACL injury risk.

Conclusions

1) In a convenience sample of 20 age-, height-, and weight-matched human donors, the female ACL exhibited 95% greater peak AM-ACL relative strain than the male ACL during a 2*BW simulated pivot landing involving compression, flexion moment, and internal tibial torque at an initial knee flexion angle of 15° (Chapter 2).

2) In a convenience sample of 18 age-, height-, and weight-matched human donors, the gender difference in peak AM-ACL relative strain can be attributed to females having a 39% smaller ACL cross-sectional area and a 23% larger lateral tibial slope. ACL cross-sectional area and lateral tibial slope accounted for 59% of variance in peak AM-ACL relative strain (Chapter 2).

3) In a convenience sample of 29 age-, height-, and weight-matched human donors, ACL cross-sectional area, the interaction of ACL cross-sectional area and lateral tibial slope, medial tibial depth, and the interaction of lateral tibial slope and notch width index were all negatively associated with peak AM-ACL relative strain during a 2*BW simulated pivot landing, accounting for 66% of the variance (Chapter 6).

4) In a convenience sample of 12 human female donors of similar age, height, and weight, an increase in quadriceps bi-linear tensile stiffness of 33% resulted in a 16% reduction in peak AM-ACL relative strain for a 2*BW simulated pivot landing. This reduction in peak AM-ACL relative strain was associated with a smaller increase in knee flexion and knee abduction (Chapter 3).

5) The human ACL is susceptible to low-cycle fatigue failures under cyclic loading replicating repeated pivot landings. The fatigue failures included complete ACL tears, partial ACL tears, tibial avulsions, and an increase of anterior tibial translation greater than 3-mm (Chapter 4).

6) In five female and five male matched-pair knees of age-, height-, and weight-matched human donors, a reduction in the number of cycles to ACL failure was associated with a larger pivot landing force and a smaller ACL cross-sectional area. No effect was observed for gender or lateral tibial slope in this small sample. (Chapter 4).

7) At 20° of initial knee flexion, the posterolateral ACL bundle is vulnerable to fatigue failure and injury under simulated 3 to 5 BW pivot landings (Chapter 4).

8) The tibial proximal anatomic axis can be defined with the circle method (two circles fit within the proximal tibia) or the midpoint method (two anteroposterior lines spaced 5 cm apart) using MRI. These methods will provide significantly different measurements of lateral tibial slope (Chapter 5).

9) The tibial proximal anatomic axis defined with the midpoint method is sensitive to the length of tibia used for the measurement, but is the best representation of the full tibial anatomic axis. On the contrary, the circle method is independent of tibial length, making it a more reproducible method than the midpoint method (Chapter 5).

10) The *in vivo* bi-linear quadriceps resistance to stretch can be modeled with an *in vitro* testing apparatus using novel J-shaped titanium springs placed in parallel within a custom aluminum housing. The number of parallel springs was adjusted to simulate the known gender difference in quadriceps tensile stiffness (Appendix A).

CHAPTER 9

RECOMMENDATIONS FOR FUTURE RESEARCH

1) The results of Chapter 4 suggest isolated tears of the posterolateral bundle are more likely to occur than isolated tears of the anteromedial bundle during 3 – 5*BW pivot landings with the knee initially at 20° flexion. Since isolated tears of anteromedial bundle are more commonly reported in the literature[23, 29] and the anteromedial bundle handles more load than the posterolateral bundle as the knee is flexed[1], it would be useful to replicate our Chapter 4 failure study at 30° and 45° knee flexion to determine whether isolated tears of the anteromedial bundle or complete tears of the ACL are more likely to occur at these greater knee flexion angles.

2) Since knee abduction is commonly associated with ACL injury during video analyses[4, 25], it would be beneficial to investigate whether the gender difference in peak ACL strain found in Chapter 2 is enhanced when a knee valgus frontal plane moment is added to our compound loading of 2*BW compression, flexion, and internal tibial torque. While previous experimental work suggests internal tibial torque, regardless of the direction of frontal plane moment, is the worst-case loading scenario for the ACL[24], the same study showed with a biomechanical model that valgus, rather than varus, frontal plane moment is the worst combination with internal tibial torque. Likewise, an investigation of whether adding a valgus moment to the dynamic compound load we used

to cause fatigue failure would reduce the number of cycles to ACL failure would be useful.

3) The non-linear quadriceps spring was utilized in Chapters 2 and 3 to simulate the quadriceps's *in vivo* response to rapid stretch during a 2*BW pivot landing. However, we did not utilize the non-linear spring in Chapter 4 because the non-linear spring will saturate quadriceps force during the low final stiffness region. Since we now know how much quadriceps force is generated within the testing apparatus during a 3 – 5*BW pivot landing, future research should adjust the in-plane and out-of-plane thickness of the non-linear spring to be optimized for higher landing forces.

4) We found that a steeper lateral tibial slope, especially when combined with a smaller ACL cross-sectional area, was associated with greater peak ACL strain during a pivot landing in Chapters 2 and 6. However, the Cox regression in Chapter 4 was unable to include lateral tibial slope as a significant predictor of the number of cycles to ACL failure. Other studies have found lateral tibial slope to be important, as it is associated with a greater risk of ACL injury[13], as well as greater anterior tibial translation and ACL force[26, 27]. It is plausible that lateral tibial slope may not have been significant in Chapter 4 due to the small sample size, so future studies should continue to monitor lateral tibial slope as a putative risk factor for ACL injury.

5) The findings that lateral tibial slope and ACL cross-sectional area were the best predictors of peak AM-ACL relative strain during a pivot landing (Chapters 2 and 6),

combined with the finding that a smaller ACL cross-sectional area reduces the number of cycles to ACL failure (Chapter 4), underline the practical importance of measuring these morphologic characteristics to assess an athlete's risk for ACL injury. In this study, we utilized a 3-Tesla MRI protocol; use of cadaver limbs eliminated the risk of a movement artifacts during the 15-20 minute scan. It is possible that a small in-office MR scanner (such as the eSaote S-Scan, Fonar mpExtremity MRI, or GE Lunar Artoscan) might make it cheaper to screen at-risk athletes using the particular imaging planes we used.

6) Rather than determining ACL size from an MR scan (as described above), another strategy may identify if a surrogate extra-articular tissue is predictive of ACL size. We speculate that the patellar ligament diameter may be predictive of ACL diameter since prior studies have found quadriceps strength is correlated with ACL cross-sectional area[2]. Patellar ligament measurements could be performed with a simple caliper measurement, potentially allowing for a quick assessment of an individual's ACL diameter.

7) While there are a growing number of publications on the effect of knee morphologic characteristics on ACL injury risk (see Section 7.1), these studies were all performed retrospectively. There is a need for a prospective study that tracks individuals with high-risk morphologies (i.e., small ACL cross-sectional area, larger lateral tibial slope, small notch-width index, shallow concavity of the medial tibial plateau), as well as height- and weight-matched controls with low-risk morphologies to determine if the high-risk individuals had a disproportionate number of ACL injuries over the controls over the course of multiple seasons. Furthermore, a longitudinal study of how these

morphologic characteristics change throughout puberty, and potentially how high-intensity activity affects these pubescent changes, seems warranted.

8) The role of the quadriceps in ACL injuries remains controversial. On one hand, a large quadriceps force can cause ACL injuries in cadaveric simulators of ACL injury[6, 30]. However, these same studies may be adopting loading scenarios that go above and beyond physiological loads during an *in vivo* landing, both in terms of the quadriceps force[7] and compressive forces[33]. On the other hand, studies performed at sub-failure loads, including in Chapter 3 of this dissertation, suggest that higher quadriceps tensile stiffness (or higher quadriceps pre-activation loads[12]) are beneficial for the ACL by reducing strain during dynamic maneuvers, even if knee flexion is reduced. This is because the reduced quadriceps tensile stiffness will produce greater pure rolling of the femur, relative to the tibia, thus increasing ACL strain. Future research might investigate the potential benefits of the quadriceps during landing tasks, as well as determining whether a threshold exists at a certain level of quadriceps force that places the ACL at greater risk for injury from the quadriceps muscle.

9) The partial tears of the ACL in this dissertation primarily occurred on the posterolateral bundle near the femoral attachment, as seen in other cadaveric failure studies[19, 20]. Histological studies of the ACL are currently limited, although they show that collagen disruption proceeds macroscopic tearing visible to the human eye[15, 22, 32]. None of these studies have focused on the mechanics of the enthesis of the ACL at its femoral attachment. Is it a feature of the morphology of the posterolateral enthesis that

causes it to fail there and not elsewhere under large tensile loads? Or did the particular combination of compound loading and 20 degree knee initial angle that we used induce an uneven stress distribution across the posterior ACL that caused it to fail at the posterolateral, and not anteromedial, bundle enthesis with the femur? Future research might test both of these hypotheses. Certainly, our research has demonstrated that partial posterolateral tears of the ACL can occur, leading to a partially damaged ACL state which may or may not go undetected clinically. It might be worthwhile to develop special imaging techniques to screen subjects for potential partial ACL tears to better prevent a future complete ACL tear.

10) We identified four knees within our fatigue failure experiment that underwent a 3-mm increase in anterior tibial translation during testing without macroscopic damage. While anterior tibial translation can increase an average of 1.2 mm (range: 0.2 mm to 4.6 mm) during a muscle fatigue protocol[31], it is unknown how long the ligament takes to recover from high levels of activity. The time the ligament needs to recover may be important for the prevention of ACL fatigue failures. It may also be important for insuring an athlete is not unfairly removed from practice and competition for a longer time than the ligament needs to recover.

11) The non-linear *in vivo* lengthening behavior of the quadriceps muscle during a pivot landing is modeled using a novel spring within our *in vitro* testing apparatus (Appendix A). This non-linear behavior occurs as a result of residual force enhancement, as seen in muscle fibers[9, 14] and rabbit tibialis anterior muscle[11]. However, this behavior

has only been recently observed in the human knee extensor muscles at a slow eccentric velocity (30 °/s) between 70° and 100° knee flexion[28]. Residual force enhancement was not found at 40° knee flexion; however, this may be occurring because the muscle is at the plateau of the sarcomere force-tension curve where there is non-linear stretch behavior but no residual force enhancement[9, 14]. Since this non-linear lengthening behavior is stretch rate dependent[11, 18] and muscle length dependent[8, 9, 14], a more comprehensive study of eccentric residual force enhancement in the human quadriceps muscle is warranted.

12) Quadriceps stiffness is modifiable with training, and may be beneficial for the ACL, as seen in Chapter 3. However, there are only a limited number of studies on the effect of training on muscle stiffness in females[3], and none of these studies have examined its effect on the quadriceps. Since measurements of musculo-tendon unit stiffness have been established using ultrasonography[16] or oscillatory pertubations[10], a training study on the gains in musculo-tendon unit stiffness from knee extensor strength training in young females seems feasible.

13) The insights that ligament fatigue failures can occur (Chapter 4) means that one could monitor the magnitude and frequency of high-intensity pivot landings in athletes in high-risk sports like soccer and basketball during practice and competition, similar to the monitoring of cumulative head impacts in football practice and competition to prevent concussions[5]. This could be accomplished using lower extremity instrumentation. Given the slow rate of adaptation, healing and remodeling in collagenous tissues like the ACL[21],

one would need to limit the number of pivot landings of a given severity within a certain timeframe, similar to the pitch count in Little League baseball to limit elbow fatigue injuries[17]. However, this would require *a priori* knowledge of the distribution of compound knee loading typically induced by practice and competition at each age, gender and athlete skill level within the given time period. Armed with that information and the lower extremity instrumentation, it would be possible to warn an individual, or their parent, coach or trainer, that they have reached the limit for the number of pivot landings that can be accomplished safely within that time period without risk of ACL failure.

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