THE ROLE OF ALTERED KNEE GAIT MECHANICS IN THE INITIATION OF TIBIOFEMORAL AND PATELLOFEMORAL OSTEOARTHRITIS AFTER ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

by

Jack R. Williams

A dissertation submitted to the Faculty of the University of Delaware in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Mechanical Engineering

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PREFACE

The three aims of this dissertation are currently in various stages of the publishing process. The contents of Aim 1 (Chapter 2) have been submitted to the American Journal of Sports Medicine as:

Williams JR, Neal K, Alfayyadh A, Capin JJ, Khandha A, Manal K, Snyder-Mackler L, Buchanan TS (2022). Asymmetric Gait Loading Patterns after ACL Reconstruction May Predispose Individuals to Knee Cartilage Degradation: A Quantitative MRI Study. *American Journal of Sports Medicine*. In Review.

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ABSTRACT

Post-traumatic knee osteoarthritis (OA) after anterior cruciate ligament reconstruction (ACLR) is common. Alterations in knee gait mechanics, which are commonly observed after surgery, are hypothesized to be a mechanism responsible for eventual disease development. Advanced quantitative magnetic resonance imaging (qMRI) techniques can provide insights into cartilage health prior to irreversible morphometric signs of cartilage deterioration. Recent evidence indicates that patellofemoral OA after ACLR is at least as common as medial tibiofemoral OA and is associated with worse patient reported outcomes. Despite this, little is known about the mechanisms for disease development within this compartment of the knee. Thus, the goal of this work was to assess the role that altered knee gait mechanics play in the initiation of tibiofemoral and patellofemoral knee OA after ACLR. This was accomplished through a combination of subject-specific EMG-driven neuromusculoskeletal modeling techniques and qMRI.

The first aim of this dissertation sought to assess how early changes in medial tibiofemoral interlimb loading patterns influenced long-term cartilage health. We found that loading patterns other than consistent interlimb symmetry may predispose medial tibiofemoral knee cartilage to long-term degradation. Thus, consistent interlimb loading symmetry may be an ideal target for explorative rehabilitation efforts aimed at preventing OA within this compartment of the knee. In the second aim of this dissertation, we characterized the loading environment of the patellofemoral compartment of the knee during walking gait at 3, 6, and 24 months after ACLR. We

found that the involved limb's patellofemoral compartment was underloaded, compared to the uninvolved limb, at 3 and 6 months after surgery. This underloading was resolved by 24 months. In the third aim of this dissertation, we assessed patellofemoral knee cartilage health 24-months after surgery and examined the associations between patellofemoral loading and other knee gait mechanics 3 months after surgery with these measures of long-term cartilage health. Alterations in knee cartilage health 24-months after ACLR were detected in the femoral trochlear cartilage of the involved limb but not in patellar cartilage. Smaller patellofemoral loads, smaller knee flexion angles and moments, and slower walking speeds 3 months after ACLR were associated with femoral trochlear cartilage degradation 24-months after surgery. This suggests that altered involved limb trochlear health is present 24-months after ACLR and may be related to how an individual walks 3 months after surgery. Altogether, the work of this dissertation furthers our understanding of the role altered knee gait mechanics play in the initiation of tibiofemoral and patellofemoral knee OA after ACLR. This information, in turn, may be used in the design of rehabilitation efforts aimed at preventing the onset of post-traumatic knee osteoarthritis.

Chapter 1

INTRODUCTION

ACL Injuries and Osteoarthritis

The anterior cruciate ligament (ACL) is one of the major knee ligaments. Its primary function is to prevent excessive anterior tibial translation, with respect to the femur, and plays an important role in maintaining knee joint stability during everyday tasks.[1] Unfortunately, ACL tears are one of the most common and devastating knee joint injuries.[2] Globally, it is estimated that upwards of two million individuals per year sustain an ACL injury.[3] These injuries can result in instability within the limb and can leave other tissues within the knee susceptible to further damage.[4,5] While some elect to live life without their ACL, focusing on rehabilitation to regain partial knee joint stability, others elect to undergo ACL reconstruction (ACLR) with the hope of restoring normal knee function while simultaneously protecting other tissues within the joint.[2,6] While successful at restoring stability within the injured limb, this procedure fails to prevent the development of post-traumatic knee osteoarthritis (OA).[7–9] Upwards of 50-90% of individuals who undergo this procedure develop radiographic OA within 10-20 years of surgery, predominantly within the medial tibiofemoral compartment of the injured limb.[8,9] Despite high incidence rates, little is known about the mechanisms behind disease development. Those who undergo an ACLR are typically young, active, and otherwise healthy; consequently, many develop OA 15-20 years earlier than those without a traumatic knee injury effectively becoming a “young patient with an old knee”.[8–12] Thus, there is a critical need to

understand the mechanisms behind OA development after ACLR so that preventative rehabilitation techniques can be designed and employed to delay disease development.

Knee Cartilage Structure and the Initiation of OA

To understand how knee OA develops after ACLR, it is first important to understand the biochemical and structural features of cartilage and their functional roles. Articular cartilage is designed to maintain low friction between the articulating surfaces of the joint and to absorb and distribute loads encountered during daily locomotion.[13] Cartilage is primarily composed of chondrocytes, water, and an extracellular matrix which itself contains both a collagen matrix and proteoglycans.[13–16] The presence of these components, and their interactions, are essential for maintaining normal cartilage function.[13–17]

Chondrocytes are mechanosensitive cells within the cartilage chiefly responsible for the maintenance of the extracellular matrix.[13,16,18,19] Within the extracellular matrix resides cartilage's collagen matrix which provides resistance to tensile loading.[17] Proteoglycans, themselves composed of glycosaminoglycans, are negatively charged proteins within the extracellular matrix which serve to attract water creating a swelling pressure within the cartilage.[13–16,18] This swelling pressure is balanced by the collagen matrix which is placed under tension and together these enable cartilage to resist compressive forces applied to the joint.[14,16,18] The last component, water, is abundant within cartilage. During compression water flows through the extracellular matrix and encounters frictional resistance which aides cartilage in dissipating energy and absorbing loads.[13,15,16]

Early, pre-morphometric, signs of knee osteoarthritis result in alterations to these crucial components of articular cartilage. This includes disorganization and

degradation of the collagen matrix, loss of proteoglycans, and an increase in water content.[14,20] These alterations can change the mechanical and functional properties of cartilage which, in turn, can lead to morphometric signs of degradation.[14,20,21] End stage OA is characterized by pain, limited mobility, and an overall reduced quality of life.[22] These, in turn, are associated with mental health challenges such as depression.[22]

Detection of Osteoarthritis

Knee OA is typically detected and diagnosed via radiographs.[21] However, detection of OA using radiography is limited to when irreversible morphometric signs of disease development, such as osteophyte formation and cartilage loss, have already occurred.[23] Thus, the use of radiographs as a tool to assess OA with the goal of preventing or delaying its onset is not feasible.

Recent advancements in magnetic resonance imaging (MRI) provide researchers with opportunities to monitor the onset and progression of knee OA prior to radiographic signs of disease development.[23]

One approach to monitoring OA via MRI is through the use of semi-quantitative scoring techniques such as the Whole Organ Magnetic Resonance Imaging Score (WORMS)[24], Knee Osteoarthritis Scoring System (KOSS)[25], Boston Leads Osteoarthritis Knee Score (BLOKS)[26], and the MRI Osteoarthritis Knee Score (MOAKS)[27]. The basic premise of these systems is that they assign a score based on the presence of some quality observed on the MRI scans. For example, the WORMS method examines 14 features within different regions of the knee (e.g., cartilage signal and morphology, integrity of each knee ligament…) each with its own scoring system. The cumulative score across these 14 features provides insights into the knee's health,

with a higher score indicative of pathology relating to OA.[24] Over the years this approach has become more and more common; with literature indicating that it is a reliable tool for the assessment of knee OA.[28] One of the key issues with this type of approach is that it requires a large number of scans from numerous points of view (i.e., sagittal, axial, and coronal) which can result in participants having to sit within the scanner for long periods of time. In addition, this type of analysis only utilizes standard MRI protocols focused on visualizing morphometric changes within the knee. Thus, they are incapable of identifying changes to the biochemical composition of cartilage, such as alterations to the collagen matrix or proteoglycan content, that occur prior to morphological changes.[14]

An alternative approach is the use of quantitative MRI (qMRI).[14,29] These advanced MRI techniques can provide unique insights into the biochemical and structural composition of cartilage during the early stages of OA, prior to morphometric degradation. There are several quantitative techniques that can be used to monitor early osteoarthritic changes in cartilage. These include: Delayed gadolinium enhanced MRI of cartilage (dGEMRIC), sodium MRI, $T1_\rho$ mapping, glycosaminoglycan chemical exchange saturation transfer (GagCEST), and T_2 mapping.[14,29] The dGEMRIC technique, which can detect glycosaminoglycan content, has been used in several longitudinal studies (including following ACL tears) but requires the use of an invasive contrast agent and thus is not ideal if other, non-invasive, techniques are available.[14,29–31] Sodium MRI can indirectly detect glycosaminoglycan content within cartilage but is limited to scanners with high field strengths and requires specialized equipment.[14,29,32,33] $T1_\rho$ mapping is thought to be related to proteoglycan content and has been utilized in several research studies after

ACLR; some, however, have found conflicting evidence regarding its association with proteoglycan content *in vivo*.[14,29,34] GagCEST is a noninvasive technique thought capable of monitoring the glycosaminoglycan, and thus proteoglycan, content of cartilage. The viability of this technique at low MRI field strengths, such as 3 tesla scanners, is questionable due to a variety of issues including: low signal-to-noise ratios, susceptibilities to B_0 inhomogeneities, issues with direct saturation effects, and relatively fast exchange rates.[14,29,35,36] T_2 mapping can monitor the collagen matrix structure and water content of cartilage and has been extensively validated.[14,15,29,32,37] A prolonged T_2 relaxation time is indicative of collagen matrix degradation and increased water content, both of which are hallmark signs of early knee OA. It should be noted that this technique is susceptible to the magic angle effect which can artificially inflate values based on the orientation of collagen fibers with respect to the B_0 field.[15,23,38]

These advanced MRI techniques have shown promise in being able to detect and monitor early signs of cartilage degradation and thus may be a viable tool in studies aiming to investigate the early onset of OA development. T_2 relaxation times will be used as a measure of knee cartilage health throughout this work. Other qMRI techniques, such as GagCEST and $T1_\rho$, were explored but ultimately not utilized due to issues with application at the available scanner strength (GagCEST) and limited sample sizes ($T1_\rho$).

Mechanisms for OA Development after ACLR

One mechanism thought responsible for the development of OA after ACLR is alterations in knee gait mechanics. These alterations are frequently observed after surgery and may represent an ideal target for explorative rehabilitative efforts, as gait

mechanics may be modifiable.[39–43] Commonly altered knee gait variables include: knee flexion angles[40,44,45], sagittal[40,46] and frontal[40,47] plane moments and impulses[48,49], and transverse plane rotations[40,47,50,51]. These alterations are usually observed in the involved limb compared to the uninvolved limb and healthy controls.[40,50] Alterations in gait mechanics are reported as early as 3 months[43] after ACLR and can persist past return-to-sport time points, sometimes failing to resolve until several years after surgery.[40–42,48,50,52,53] Mechanistically, these alterations may shift the location and magnitude of loading applied to the knee which, given cartilage's mechanosensitivity, may disrupt the biochemical and structural health of cartilage.[18,54]

Several studies have found associations between altered gait mechanics and variables reflective of the biological and structural health of the knee (assessed via qMRI variables).[11,55–57] These studies utilized surrogate measures of knee joint loading (knee flexion moment, knee adduction moment, knee adduction moment impulse)[58–60] that fail to account for complex neuromuscular phenomena such as knee muscle co-contraction, which is common after ACLR.[61] The use of more sophisticated models, such as an electromyography (EMG) informed neuromusculoskeletal model[58,59], can overcome these limitations and may provide more accurate estimates of knee loading. Using an EMG-informed neuromusculoskeletal model, Wellsandt et al. (2016)[48] found that those who underloaded their involved limb's medial tibiofemoral compartment 6 months after ACLR developed radiographic OA 5 years after surgery. This suggests that knee loading, as assessed by knee compartmental forces, may provide important insights into the transition to OA.

What is Unknown?

Investigators have extensively studied the development of osteoarthritis within the medial tibiofemoral compartment of the knee. While several studies have assessed the relationships between mechanics and qMRI variables after ACLR within the medial tibiofemoral compartment, few have examined how changes in gait mechanics over time influence osteoarthritis development.[49] Previous work suggests that interlimb symmetry in gait mechanics after ACLR may be a good target for rehabilitation.[11] Recent evidence indicates that there are large asymmetries in mechanics 3 months after surgery that tend to become more symmetric by 6 months.[43] However, it is unknown if early changes in asymmetry after ACLR are associated with long-term cartilage health and if a return to symmetry in the early months after surgery is associated with better cartilage health. This motivates the **1st Aim** of this dissertation, presented in Chapter 2, which seeks to assess T_2 relaxation times 24 months after ACLR based on changes in medial compartment force symmetry patterns from 3 to 6 months after surgery.

While medial tibiofemoral OA is common after ACLR and has been extensively investigated, recent evidence indicates that patellofemoral OA after ACLR is as common as, if not more prevalent than, tibiofemoral OA and linked to worse patient reported outcomes.[62–64] Despite this, the mechanisms leading to OA development within the patellofemoral compartment remain understudied. Those who develop medial tibiofemoral OA 5 years after ACLR underload their involved limb's medial tibiofemoral compartment (as assessed by peak medial compartment force) 6 months after surgery compared to those who do not develop OA.[48] Loading of the patellofemoral compartment after ACLR may similarly provide insights into OA development; however, little is known about the patellofemoral loading environment

after ACLR and how it changes after surgery. This motivates the **2nd Aim** of this dissertation, presented in Chapter 3, which seeks to examine patellofemoral contact forces during walking in the involved and uninvolved limbs at 3, 6, and 24 months after ACLR. Corresponding to a lack of information about the biomechanical environment of the patellofemoral compartment is a lack of knowledge regarding the biochemical health of patellofemoral cartilage after ACLR and its association with patellofemoral knee gait mechanics. This motivates the **3rd Aim** of this dissertation, presented in Chapter 4, which seeks to (1) examine patellofemoral T_2 relaxation times 24-months after ACLR and (2) to investigate the association between knee gait biomechanical variables 3 months after ACLR and 24-month T_2 relaxation times.

Thus, the overall goal of this dissertation is to understand the role of altered knee gait mechanics in the development of tibiofemoral and patellofemoral OA after ACLR. This work will provide insights into what movement strategies put cartilage at risk of OA and will be among the first to investigate the mechanisms of disease development within the patellofemoral compartment, which is an emerging area of interest. This, in turn, could help inform the development of rehabilitation techniques aimed at delaying or preventing the onset of OA; potentially giving younger individuals the chance to maintain a normal quality of life for a longer period of time.

Aim 1 (Chapter 2)

Questions

1. Are early changes in knee mechanics after ACLR associated with long-term cartilage health?
2. Is consistently symmetric loading better for long-term cartilage health?

3. Does achieving symmetry early after surgery, after an initial period of asymmetry, result in better long-term cartilage health?

Goal

Assess the biochemical health of tibiofemoral knee cartilage (via T_2 relaxation times) 24 months after ACLR in those who display consistent loading symmetry between limbs at 3 and 6 months after surgery, compared to those who display loading patterns going from asymmetry to symmetry or those who have some other change in loading symmetry pattern between these time points.

Hypothesis

Those who display interlimb loading symmetry at both 3 and 6 months (i.e., consistent loading symmetry) will have the shortest T_2 relaxation times, reflective of healthier cartilage, at 24 months.

Why is this Important?

Understanding knee loading patterns early after ACLR and how they relate to the long-term biochemical health of knee cartilage will provide unique insights into the mechanisms behind the development of OA. This information may be used to identify high-risk gait patterns early after ACLR, when interventions may be more effective, which in turn can help inform the development of rehabilitative techniques aimed at slowing, or even preventing, the onset of OA.

Aim 2 (Chapter 3)

Questions

1. Are there asymmetries in patellofemoral loading early after ACLR?
2. How do patellofemoral loads change over time after surgery?

Goal

Examine patellofemoral contact forces during walking in both the involved and uninvolved limbs at 3, 6, and 24 months after ACLR.

Hypotheses

1. The involved limb's patellofemoral contact force will be less than the uninvolved limb's at 3 and 6 months after ACLR, but not at 24 months.
2. The uninvolved limb's patellofemoral contact forces will remain relatively consistent over time.
3. The involved limb's patellofemoral contact forces will increase with time to match those of the uninvolved limb.

Why is this important?

Knee compartmental loading within the tibiofemoral compartment is associated with radiographic OA development. Thus, knee loading may be an important factor in the pathogenesis of post-traumatic knee OA. Few have examined patellofemoral knee loads after ACLR. Developing an understanding of the biomechanical loading environment of the patellofemoral compartment may provide important insights into the mechanisms for disease development within this compartment of the knee.

Aim 3 (Chapter 4)

Questions

1. Are alterations in patellofemoral cartilage health detectable 24 months after ACLR?
2. Are the mechanics of an individual's gait early after surgery associated with long-term measures of patellofemoral health?

Goal

1. Examine patellofemoral T_2 relaxation times 24 months after ACLR.
2. Investigate the association between knee gait biomechanical variables 3 months after ACLR and 24-month T_2 relaxation times.

Hypotheses

1. The involved limb will display prolonged (i.e., worse) T_2 relaxation times, compared to the uninvolved limb, in both patellar and trochlear cartilage 24 months after surgery.
2. Smaller values of the knee gait biomechanical variables of interest (e.g., smaller patellofemoral loads, smaller knee flexion angles…) 3 months after ACLR will be associated with prolonged (i.e., worse) involved limb patellofemoral T_2 relaxation times 24 months after surgery.

Why is this important?

Understanding which regions of the patellofemoral compartment exhibit early signs of OA and how long-term knee cartilage health is associated with early gait movement patterns may shed light into the mechanisms leading to disease development within this compartment of the knee. This information may open the

door to further investigations into how and why knee OA develops within the patellofemoral compartment and may help inform the development of preventative rehabilitation techniques.

Chapter 2

ASYMMETRIC GAIT LOADING PATTERNS AFTER ACL RECONSTRUCTION MAY PREDISPOSE INDIVIDUALS TO KNEE CARTILAGE DEGRADATION: A QUANTITATIVE MRI STUDY

Introduction

Osteoarthritis (OA) after anterior cruciate ligament reconstruction (ACLR) is common, especially within the medial tibiofemoral compartment of the knee.[8,9] Incidence rates of OA after ACLR vary between 50-90% within 10-15 years of surgery.[8,9] End stage OA is characterized by pain and limited mobility and is linked to mental health challenges such as depression.[22] Those who undergo ACLR are typically young, active, and otherwise healthy; consequently, many develop OA and suffer from its adverse effects early in life.[8,10] Thus, it is important to understand the pathogenesis of OA after ACLR so that those at high-risk of disease development can be identified, and preventative therapeutic techniques can be developed and employed to preserve their quality of life.

Crucial to understanding, and potentially preventing, the development of OA after ACLR is the ability to identify signs of OA early after surgery, prior to irreversible morphometric damage.[65] This early timeframe, termed "Pre-OA"[54,65–67], is not well understood. One proposed means to monitor and study this "Pre-OA" stage is through the systems-based framework championed by Andriacchi and Chu.[54,66,67] In this framework[54,67], the joint is viewed through the lens of three interconnected systems: biological, mechanical, and structural, all of which have set regions of

normal operation.[68] They theorized that when one of these systems is disrupted, causing it to stray from its normal operating range, the joint will enter a "Pre-OA" state and will progress to OA if no intervention occurs.[54,67] Techniques capable of monitoring cartilage's biological and structural health prior to irreversible morphometric degradation, such as quantitative magnetic resonance imaging (qMRI)[14,29], may be used to investigate "Pre-OA". The most commonly used of these techniques is T_2 relaxation time[14,15,29,69], which reflects collagen matrix structure. A prolonged T_2 relaxation time indicates increased water content and degradation of knee cartilage's collagen matrix, hallmark signs of early OA development.[15,29]

One of the most widely reported phenomena after ACLR is alterations in knee gait mechanics.[40] Commonly altered variables include: knee flexion angle (KFA)[40,44,45], knee flexion moment (KFM)[40,46], knee adduction moment (KAM)[40,47], and KAM impulse.[48,49] These alterations are reported as early as 3 months[43] after ACLR and can persist past return-to-sport time points, sometimes failing to resolve until several years after surgery.[40–42,48,50,52,53] In the context of the framework proposed by Andriacchi and Chu, these alterations represent a deviation from the normal operating range in the mechanical system of the knee and thus predisposes the joint to a state of "Pre-OA".[54,67] Several studies have found associations between altered gait mechanics and variables reflective of the biological and structural systems of the knee (assessed via qMRI variables).[11,55–57] These studies utilized surrogate measures of knee joint loading (KFM, KAM, KAM impulse)[58–60] that fail to account for complex neuromuscular phenomena such as knee muscle co-contraction, which is common after ACLR.[61] The use of more sophisticated models, such as an electromyography (EMG) informed neuromusculoskeletal model[58,59], can overcome these limitations and

may provide more accurate estimates of knee loading. Using an EMG-informed neuromusculoskeletal model, Wellsandt et al. (2016)[48] found that those who underloaded their involved limb's medial tibiofemoral compartment 6 months after ACLR developed radiographic OA 5 years after surgery. This suggests that knee loading, as assessed via peak medial compartment force (pMCF), may provide important insights into the transition to OA.

While several studies have assessed the relationships between mechanics and qMRI variables after ACLR, few have examined how changes in gait mechanics over time influence osteoarthritis development.[49] Previous work suggests that interlimb symmetry after ACLR may be a good target for rehabilitation.[11] Recent evidence indicates that there are large asymmetries in mechanics 3 months after surgery that tend to become more symmetric by 6 months.[43] However, it is unknown if early changes in asymmetry after ACLR are associated with long term cartilage health and if a return to symmetry in the early months after surgery is associated with better cartilage health. Thus, the purpose of this study was to assess T_2 relaxation times 24 months after ACLR based on changes in pMCF symmetry patterns from 3 to 6 months after surgery. We hypothesized that those who display interlimb loading symmetry at both 3 and 6 months (i.e., consistent loading symmetry) would have the shortest T_2 relaxation times, reflective of healthier cartilage, at 24 months.

Methods

Participants

Thirty-one participants (16 Female; Age: 22 ± 6 years) from a longitudinal cohort study were included in this study. Enrollment criteria included: primary

unilateral ACLR with no history of lower leg injury/surgery, no concomitant grade III ligament tears, no repairable meniscal injuries, no tibiofemoral osteochondral defects, no MRI contraindications, and between 16-45 years old. Additionally, participants needed to have completed motion analysis at both 3 and 6 months after ACLR and to have undergone qMRI 24 months after surgery. All data collections were completed at the primary institution after approval from an Institutional Review Board. Enrollment began in Spring 2016 and concluded in February 2020. All participants provided written informed consent prior to study participation. Minor assent and parental consent were acquired for individuals under the age of 18.

Motion Analysis

Participants completed motion analysis during overground walking at 3 (3.2 ± 0.5) and 6 (6.4 ± 0.7) months after ACLR. Each participant walked at a self-selected speed that was maintained (± 5%) across time points. Before walking, EMG electrodes (MA-300 EMG System, Motion Lab Systems) were placed over seven muscles on each leg after shaving/cleaning the regions over each muscle belly. These muscles included the rectus femoris, medial and lateral vasti, medial and lateral gastrocnemii, long head of the biceps femoris, and the semimembranosus.[53] Following electrode placement, participants completed maximal voluntary isometric contractions (MVICs) for each muscle group (gastrocnemii, quadriceps, and hamstrings) which were used to normalize EMG data obtained during walking.[48] EMG data were sampled at 1080 Hz.

After completing MVICs, each participant was outfitted with retroreflective markers placed bilaterally on bony landmarks (1st and 5th metatarsal heads, malleoli, femoral epicondyles, greater trochanters, and iliac crests).[43] Additionally, rigid shells containing multi-marker groupings were fixed to the shanks, thighs, and pelvis.[53]

Motion data were captured using an eight-camera infrared Vicon system (Oxford Metrics Limited) at a sampling rate of 120 Hz. During walking, ground reaction forces from a single embedded force plate (600 x 900 mm^2, Bertec Corporation) were acquired at a sampling rate of 1080 Hz.

Three trials for each leg were used for data analysis.[48,53] EMG data were high-pass filtered at 30 Hz (2^{nd} order Butterworth filter), rectified, low-pass filtered at 6 Hz, and normalized to the subject-specific MVIC values to create linear envelopes.[58,59] Following processes described by Buchanan et al. (2004)[58], linear envelopes were transformed into muscle activations. These muscle activations were used in a validated, subject-specific, neuromusculoskeletal model to calculate muscle forces.[58,59] These muscle forces, in conjunction with frontal plane moment arms (determined from each participant's anatomically scaled model), were used in a frontal plane moment balance to determine medial compartment force.[59,70] Of interest in this study was the first peak of medial compartment force (pMCF), which was normalized by bodyweight (BW).

Imaging

Twenty-four (24.5 ± 1.4) months after surgery, each participant underwent a supine bilateral knee MRI using a 3 Tesla magnet (Siemens) and a 15-channel transmit/receive knee coil (Siemens). All participants were constrained to knee extension within the coil. During the MRI a sagittal bilateral two-dimensional T_2 mapping sequence[11] [Field of View: 150 mm, Slice Thickness: 3 mm, Repetition Time: 3090 ms, Echo Times: 10-70 ms] was performed.

Images were analyzed using 3D Slicer (https://www.slicer.org/).[71] T_2 maps were calculated and analyzed using a previously described methodology.[11] During

calculation of the T_2 maps, the first echo was skipped to avoid stimulated echo artifacts.[72] Prior to image segmentation, both the involved and uninvolved limbs were registered to a T_2 weighted image of the participant's uninvolved limb [Field of View: 150 mm, Slice Thickness: 3 mm, Repetition Time: 3090 ms, Echo Time: 10 ms] obtained at the 3 month time point. All cartilage segmentations were performed on the first echo of the T_2 mapping sequence. Three slices corresponding to the center of the medial compartment were segmented into 6 regions of interest (ROI) based around the meniscus. These regions were further subdivided into deep and superficial layers to account for structural differences in these layers of cartilage (**Figure 1**[11]).[29] The T_2 relaxation time for each layer of each ROI was averaged across all three slices, resulting in 12 medial compartment T_2 relaxation times within each limb for each participant.

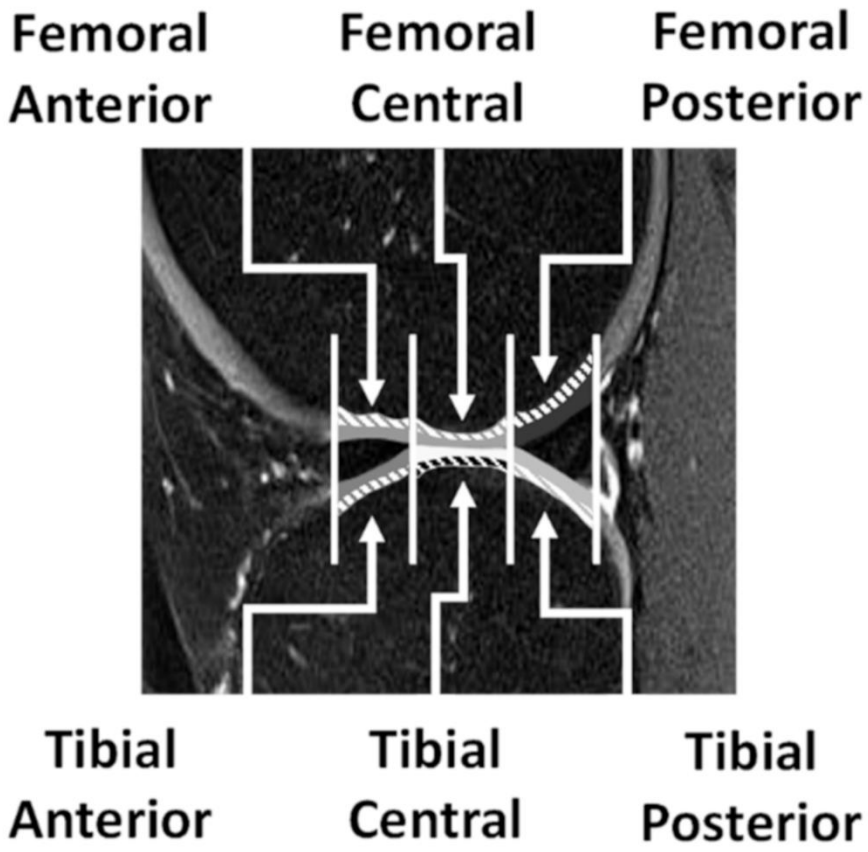

Figure 1 Sagittal knee scan depicting regions of interest, based on the meniscus boundaries. There were three on the femoral side: femoral anterior, femoral central, and femoral posterior and three on the tibial side: tibial anterior, tibial central, and tibial posterior. Each region of interest was further subdivided into deep (dashed lines) and superficial regions. (Figure and caption reproduced, with permission, from Williams et al.[11])

Loading Group

At each time point, the interlimb difference (involved – uninvolved) in pMCF was calculated. Using a meaningful interlimb difference threshold for pMCF[53] (0.4 BW) participants were classified as underloaders (involved – uninvolved $\leq$ -0.4 BW), symmetric loaders (-0.4 BW < involved – uninvolved < 0.4 BW), or overloaders

(involved – uninvolved ≥ 0.4 BW). These participants were then classified into different groupings based on their loading patterns at both 3 and 6 months (**Figure 2**).

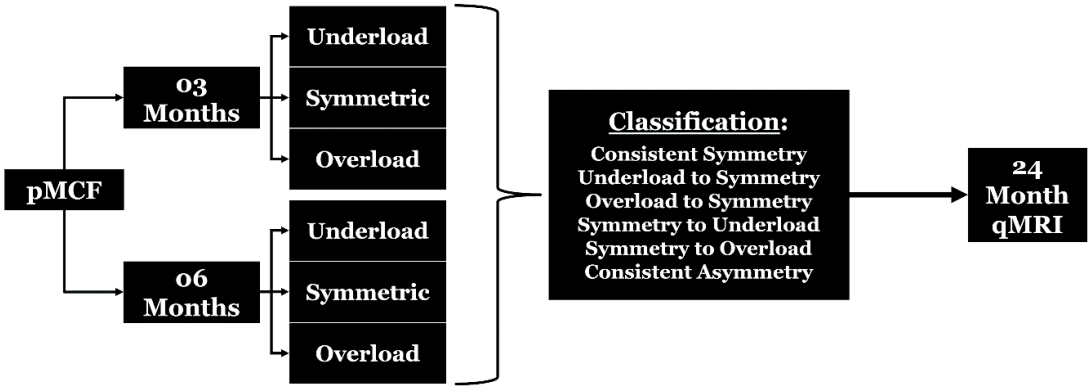

Figure 2 Schematic representing methodology for determining the groupings for loading patterns. pMCF was assessed at both 3 and 6 months after ACLR. The interlimb difference (involved – uninvolved) of pMCF was calculated at each time point. A meaningful interlimb difference threshold (0.4 BW) was used to determine if the participant underloaded, symmetrically loaded, or overloaded their involved limb (vs. uninvolved limb) at both time points. Based on their loading pattern at both 3- and 6-months participants were grouped into classifications that conveyed their loading pattern across these time points. The average T_2 relaxation time for each ROI was determined in both limbs of each loading group.

Statistical Analyses

Statistical analyses were performed in JMP (SAS, $\alpha = 0.05$). As this was an exploratory study, no adjustments for multiple comparisons were made.[73] Normality of the data was assessed using Shapiro-Wilks tests. Demographic characteristics were compared between groups using ANOVAs for continuous data and Chi-Square tests for descriptive data. The effect of loading group in each ROI was assessed using an ANOVA (for parametric data) or a Kruskal-Wallis test (for nonparametric data). If the

ANOVA/Kruskal-Wallis tests were significant, post-hoc Tukey HSD/Dunn's tests were used to compare groups within a ROI and the effect size was evaluated using η^2 values (small effect: $\eta^2 = 0.01$, medium effect: $\eta^2 = 0.06$, large effect: $\eta^2 = 0.14$).[74]

Results

Loading Groups

Five loading groups initially emerged from these data (**Figure 3**). The first group displayed symmetric pMCFs at both 3 and 6 months (**Consistent Symmetry**; n = 5), the second group underloaded at 3 months but went to symmetry at 6 months (n = 9), the third group overloaded at 3 months but went to symmetry at 6 months (n = 6), the fourth group had asymmetric pMCFs at both 3 and 6 months (n = 6), and the fifth group went from symmetry at 3 months to asymmetry at 6 months (n = 5). The T_2 relaxation times of the groups that started underloading/overloading but ended at symmetry did not differ from each other in any ROI of either leg. Thus, these groups were condensed into one group centered on going from asymmetry to symmetry (**Asymmetry to Symmetry**; n = 15). Similarly, the T_2 relaxation times of the consistently asymmetric group and the group that went from symmetry to asymmetry were not statistically different in any ROI of either limb. Thus, these groups were condensed into one group centered on ending with asymmetric pMCFs at 6 months (**End Asymmetric**; n = 11). Altogether, there were three final groupings: a consistently symmetric group, a group that went from asymmetry to symmetry, and a group that ended asymmetrically (**Figure 3**). Demographic information for the three groups can be found in **Table 1**.

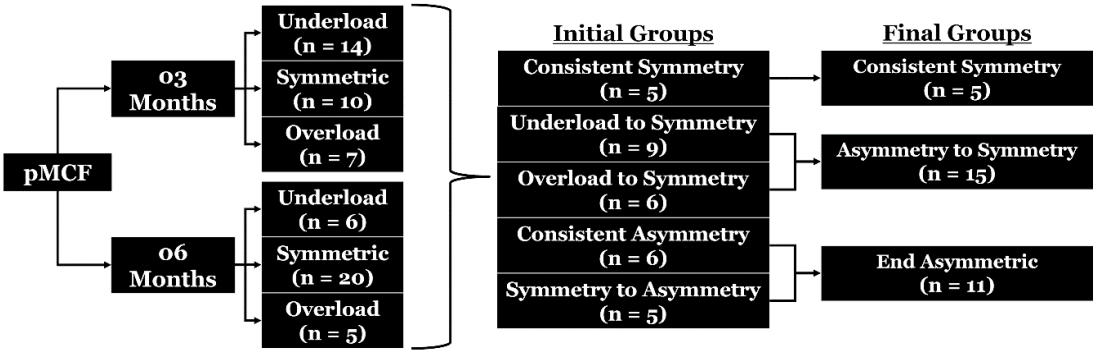

Figure 3 Schematic detailing methodology for determining the groupings for loading patterns with sample sizes at each stage. Five groups initially emerged from the data. After comparing 24-month T_2 relaxation times these five groups were further condensed into three final groups.

Table 1 Demographic Characteristics for each Loading Group

Group	Consistent Symmetry	Asymmetry to Symmetry	End Asymmetric	p-value
N	5	15	11	N/A
Sex	1 F, 4 M	9 F, 6 M	6 F, 5 M	0.274
Age (years)	21 ± 4	23 ± 7	22 ± 7	0.834
Mass (kg)	77.2 ± 15.6	70.4 ± 15.3	71.5 ± 14.5	0.679
BMI (kg/m^2)	24.5 ± 3.3	24.2 ± 4.3	24.4 ± 3.4	0.790
Graft Type	2 BPTB 3 Hamstring 0 Allograft	8 BPTB 6 Hamstring 1 Allograft	6 BPTB 1 Hamstring 4 Allograft	0.070
Meniscal Status	2 None 3 Meniscectomy	10 None 5 Meniscectomy	6 None 5 Meniscectomy	0.554
Walking Speed (m/s)	1.5 ± 0.1	1.6 ± 0.2	1.5 ± 0.1	0.041

Note: F = Female, M = Male, BPTB = Bone-Patellar Tendon-Bone Autograft

T_2 Relaxation Times – Deep Layer

The Consistent Symmetry group displayed the lowest deep layer T_2 relaxation times in 5 of the 6 regions of the involved limb (**Figure 4**). The T_2 relaxation times of the Asymmetry to Symmetry and End Asymmetric groups did not differ from each

other across all six regions. Significant effects of loading group were present in the femoral anterior ($p = 0.003$, $\eta^2 = 0.34$), femoral central ($p = 0.032$, $\eta^2 = 0.22$), and tibial anterior ($p = 0.021$, $\eta^2 = 0.24$) regions. In the femoral anterior region, the Asymmetry to Symmetry ($p = 0.006$) and End Asymmetric ($p = 0.003$) groups displayed significantly prolonged deep layer T_2 relaxation times compared to the Consistent Symmetry group. Similarly, in the femoral central region the Asymmetry to Symmetry ($p = 0.044$) and End Asymmetric ($p = 0.035$) groups displayed significantly prolonged deep layer T_2 relaxation times compared to the Consistent Symmetry group. In the tibial anterior region, the Asymmetry to Symmetry group displayed significantly prolonged T_2 relaxation times compared to the Consistent Symmetry group ($p = 0.019$), but the End Asymmetric group ($p = 0.248$) did not (**Figure 4**). No effect of loading group was present in the uninvolved limb (not shown).

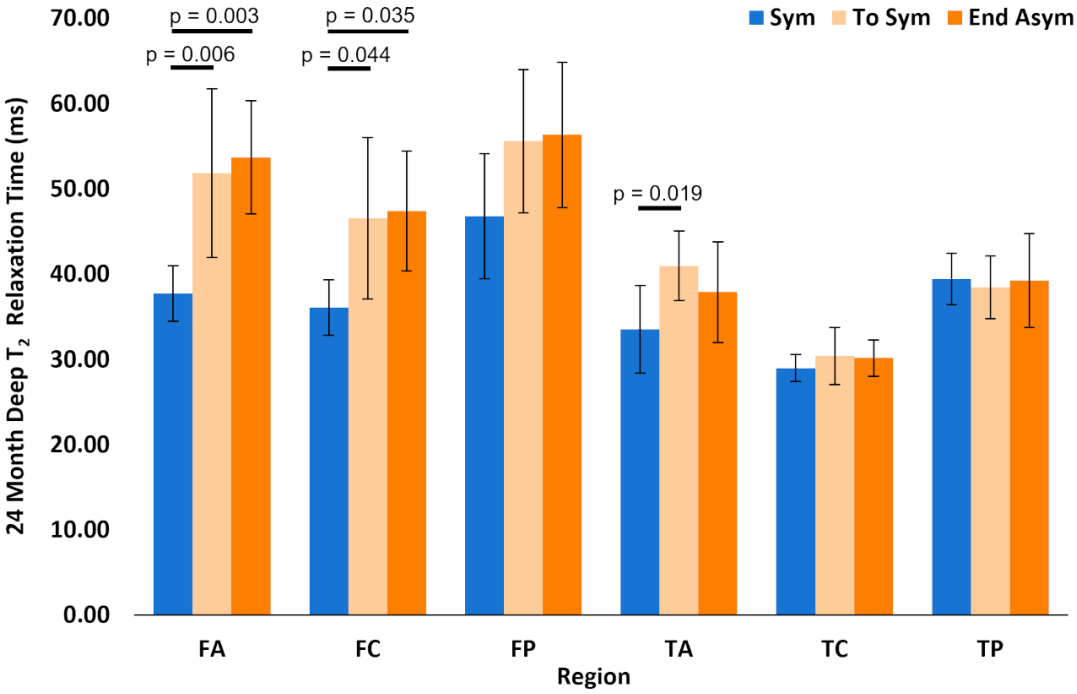

Figure 4 Average involved limb deep layer T_2 relaxation times for the six regions of interest separated by loading group (± 1 standard deviation). Within each region, the first blue bar indicates the Consistent Symmetry (Sym) group, the middle tan bar indicates the Asymmetry to Symmetry (To Sym) group, and the last orange bar indicates the End Asymmetric (End Asym) group. A prolonged T_2 relaxation time is indicative of collagen matrix degradation. A significant effect of loading group was present within the femoral anterior, femoral central, and tibial anterior regions of interest. The lines above each bar represent the significant pairings revealed from the post-hoc analyses. The beginning and ending points of each line represent the two groups being compared with the p-value of the comparison reported above each line. Regions: FA = femoral anterior, FC = femoral central, FP = femoral posterior, TA = tibial anterior, TC = tibial central, and TP = tibial posterior.

T_2 Relaxation Times – Superficial Layer

The Consistent Symmetry group displayed the lowest T_2 relaxation times in 3 of the 6 regions of the involved limb. However, these were not significant as there

were no main effects of loading group present within any region (**Figure 5**). No main effect of loading group was present in the uninvolved limb (not shown).

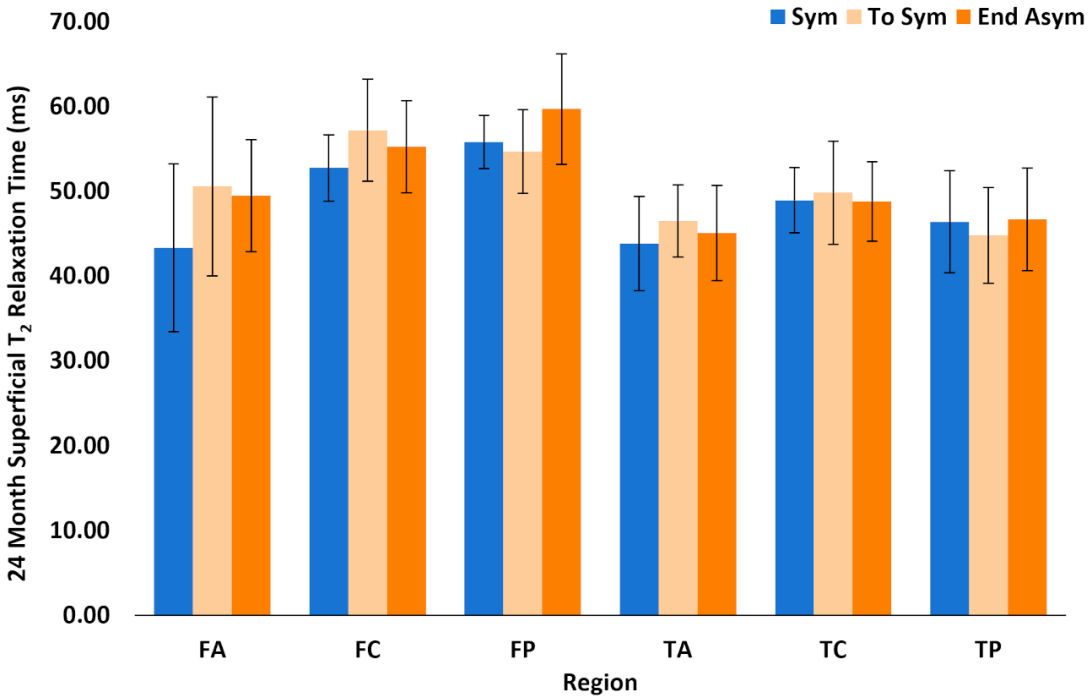

Figure 5 Average involved limb superficial layer T_2 relaxation times for the six regions of interest separated by loading group (± 1 standard deviation). Within each region, the first blue bar indicates the Consistent Symmetry (Sym) group, the middle tan bar indicates the Asymmetry to Symmetry (To Sym) group, and the last orange bar indicates the End Asymmetric (End Asym) group. A prolonged T_2 relaxation time is indicative of collagen matrix degradation. Regions: FA = femoral anterior, FC = femoral central, FP = femoral posterior, TA = tibial anterior, TC = tibial central, and TP = tibial posterior.

Discussion

Our hypothesis was partially supported. Those with consistent pMCF symmetry 3 and 6 months after ACLR displayed the shortest 24 month involved limb

T_2 relaxation times in the deep layer of cartilage, indicating the healthiest cartilage of the loading groups examined. The other two groups, one including those who were asymmetric at 3 months and symmetric at 6 months and the other including individuals with symmetry or asymmetry at 3 months but asymmetry at 6 months, both displayed similarly prolonged T_2 relaxation times (vs. the Consistently Symmetric group) within select regions of interest. No differences were detected in the superficial layers of involved limb cartilage or in any cartilage layer of the uninvolved limb. Overall, these results indicate that loading patterns other than consistent interlimb symmetry early after ACLR are associated with prolonged involved limb deep layer T_2 relaxation times 24 months after surgery, suggesting worse cartilage health. Interestingly, the group that was initially asymmetric at 3 months but became symmetric by 6 months still displayed significantly prolonged T_2 relaxation times compared to the Consistently Symmetric group. This suggests that even a return to interlimb symmetry in pMCF by 6 months after surgery may not prevent cartilage deterioration.

Central to Andriacchi and Chu's theory on how "Pre-OA" develops into OA after ACLR is that gait alterations after surgery could result in shifts in regions of cartilage to which load is being applied.[54,67] This newly loaded cartilage may not be capable of bearing the applied knee loads and thus cartilage degeneration may initiate, ultimately leading to OA. While there is evidence to support the idea that alterations in load location may initiate cartilage degeneration[75–78], alterations in load magnitude may have the same impact. As cartilage is mechanosensitive[18], the repeated occurrence of early underloading may decondition cartilage to typical loads. When individuals return to "normal" loading with time (i.e., to symmetric loading) they may

experience a relative overloading of their cartilage (compared to what it is structurally and biochemically able to sustain) which could lead to cartilage degradation. This idea is supported by a recent review of cartilage's mechanoadaptability[18] which suggests that underloading leads to cartilage atrophy, typically in the deeper layers of cartilage, and that cartilage overloading leads to OA. The authors of this study believed that atrophied cartilage may lose its mechanoprotective mechanisms and that "forced remobilization" of the cartilage results in OA-like alterations.[18] If this theory is true, it raises several questions such as "how long can altered gait patterns occur before the joint becomes damaged?" and "does the rate of joint reloading play a role in the initiation of cartilage degradation?". Regardless, the present findings indicate that potential biomechanical rehabilitation targets need to be carefully considered as a return to loading symmetry between 3 and 6 months after ACLR was not associated with good long-term cartilage health.

Kumar et al. (2018)[49] found that those who increase KAM impulse from pre-surgery to 6 months after ACLR also experience worsening cartilage health (assessed via $T_2/T_{1\rho}$ relaxation times) from pre-surgery to 6 months, compared to those without an increase. While they did not find a statistically significant interlimb difference in KAM impulse, likely a result of having all subjects walk at the same speed (1.35 m/s), Kumar and colleagues did see lower KAM impulse in the involved limb (vs. uninvolved) pre-surgery that increased with time until interlimb symmetry was achieved at 12 months. The increase in KAM impulse, thought reflective of medial knee loading, may be representative of reloading rather than overloading and thus a similar mechanism to that seen in our study could explain why the group that increased their KAM impulse displayed worse cartilage health.

Previous work[48] found that those who developed radiographic medial tibiofemoral OA 5 years after ACLR underloaded their involved limb (vs. those that did not develop OA) 6 months after surgery. They also examined pMCF over several time points including pre-surgery, 6 months, 1 year, and 2 years after ACLR.[48] While no statistical analyses were performed on limb loading over time, those who did not develop OA displayed relatively consistent involved limb loading over time while those that did develop OA had underloading of the involved limb early after injury and reconstruction that increased with time.[48] Thus, rather than just underloading at a cross-sectional time point, it could be the increasing loading with time (as athletes returned to sport) that was a driving mechanism leading to radiographic OA development.

The Asymmetry to Symmetry group also featured those who overloaded their involved limb at 3 months. Overloading of cartilage can result in damage to the collagen matrix and loss of proteoglycans, both of which are linked to irreversible cartilage degradation.[79] Thus, repeated overloading of cartilage during walking among this subgroup of participants may have exposed cartilage to degradation that could not be reversed by achieving symmetry at 6 months. The End Asymmetric group had similar T_2 relaxation times as the Asymmetry to Symmetry group. This group featured participants who had consistent interlimb asymmetry and participants who started symmetrically but progressed to asymmetry. It may be that these individuals achieved symmetry at some point after 6 months and thus could have experienced a similar pathway to cartilage degeneration as the Asymmetry to Symmetry group.

The effect of loading group was only present within the deep layers of cartilage. This aligns well with a previous cross-sectional study investigating knee

mechanics and T_2 relaxation times 3 months after ACLR which found associations only within the deep layers of cartilage.[11] This also aligns well with reports that, in animal models, the deeper layers of cartilage may be more sensitive to immobilization.[18,80] Future work needs to investigate the mechanisms behind these layer dependent associations. T_2 relaxation times are incapable of assessing the deepest, calcified, layers of cartilage. Future work should examine these loading patterns using qMRI techniques better suited to these deeper layers, such as UTE-T_2*.[66] We also do not know why only select regions of interest within the deep layer of cartilage had significant effects of loading group. It could be that alterations to other biomechanical variables, such as knee flexion angle or external tibial rotation, could influence which of these regions experienced effects of loading groups. Another explanation could be that these regions lacked the statistical power to detect any differences. Future work with a larger cohort of individuals is needed to explore this possibility.

While the results of this study were interpreted from the perspective of the involved limb compared to the uninvolved limb, it is possible changes in mechanics in the uninvolved limb could be driving the loading patterns seen here. A sub-analysis of changes in pMCF within both limbs in the 5 initial loading groups revealed no changes in uninvolved limb pMCFs in any group except for the group that went from overloading to symmetry ($p = 0.042$). While this group did see changes in the uninvolved limb, they experienced much larger changes in the involved limb ($p = 0.017$) and thus the interpretation of these results is likely still valid. This study relied on a grouping approach to data analysis rather than a continuous approach. This was done for two reasons. First, changes in interlimb differences are hard to interpret when

reported numerically as it provides no context for where the individual began and ended (i.e., there could be a large change in interlimb symmetry with time, but the individual may still be underloading or overloading). Second, centering the data around a meaningful interlimb difference threshold may be more clinically meaningful, as a target of interlimb difference in loading of < 0.4 BW is easier to define than a specific increase or decrease in interlimb symmetry with time.

There are several limitations that need to be considered when interpreting the results of this study. This study is an exploratory analysis; hence, the results should be interpreted with caution. The cohort study from which the data for this study were acquired was not designed for the analyses performed here. Thus, each grouping examined in this study had relatively small sample sizes which may have resulted in some regions of interest (i.e., those where no effect of loading group was detected) being underpowered. While the data collection and analysis described are time consuming and arduous, future work should incorporate a larger number of subjects for more definitive findings.

Individuals' rehabilitation was not controlled for in this study. While it is possible that rehabilitation could have influenced the outcomes seen here, this also makes the results of our study more generalizable as it is not feasible to control for this variable among the larger ACLR population. There were several other variables, such as age, sex, return to activity, and meniscal status, that may have explained the T_2 relaxation times observed. Sub-analyses (not shown) revealed that neither age nor sex were significantly associated with 24-month T_2 relaxation times. Among the participants in this study, only two did not return to sport. There was no difference in T_2 relaxation times between those that did/did not return to sport. When 24-month T_2

relaxation times were grouped based on meniscal status (instead of loading group) there were no differences between those with a meniscectomy vs. those without a meniscectomy regardless of region of interest or layer assessed, indicating a minimal effect of these variables on the 24-month T_2 relaxation times. The effect of meniscal status on pMCF interlimb difference was also assessed at the 3- and 6-month time points. Interlimb differences in pMCF did not differ between those who did/did not have a concomitant meniscectomy. It should be noted that individuals who underwent meniscal repairs were excluded from this study as those who undergo this type of procedure typically have an extended period of non-weight bearing after surgery which would have substantially influenced knee loading.

These analyses did not examine loading beyond 6 months. Changes in loading/loading patterns between 6 and 24 months may also be associated with the 24-month T_2 relaxation times reported here. Future work needs to examine loading patterns over a more consistent (i.e., month to month, rather than every three months) and longer duration of time. Additionally, this study was also not able to examine if the rate at which symmetry was achieved influences long-term cartilage health. A more gradual progression towards symmetry (compared to the 3-month difference examined here) may lead to better long-term cartilage health. Future work needs to explore this potential variable. This study only examined pMCF but it is likely that other biomechanical variables also influenced the T_2 relaxation times seen here. More comprehensive measures of the knee's biomechanical environment are needed to properly account for the complex nature of the knee. Finite element models may be one solution to this limitation as they can capture stress and strain distributions throughout cartilage. Recent work by Bolcos et al. (2020)[81] and Orozco et al. (2021)[82]

have shown promise in linking alterations in stresses and strains to qMRI variables after ACLR. While these approaches may be able to capture the complex biomechanical environment of the knee and be better tailored to patient specific analyses, they are time consuming to develop and thus are not currently a clinically feasible tool. Finally, the loading groups in this study were defined using a previously determined meaningful interlimb difference threshold.[53] While we believe this threshold is a relatively conservative estimate (0.4 BW), future work needs to assess the sensitivity of these results to changes in this value.

In conclusion, this study found that individuals with consistent interlimb symmetry in pMCF at both 3 and 6 months after ACLR demonstrated the lowest (i.e., healthiest) deep layer T_2 relaxation times 24 months after surgery. Interestingly, within the femoral anterior, femoral central, and tibial anterior regions of cartilage, even those who achieved knee loading symmetry by 6 months after surgery displayed significantly prolonged involved limb deep layer T_2 relaxation times when compared to the group displaying consistent symmetry. This trend towards symmetry could result in a relative overloading which may lead to cartilage breakdown and, eventually, OA. Future studies are needed to investigate this theory and to explore its potential implications for rehabilitation.

Chapter 3

PATELLOFEMORAL CONTACT FORCES AFTER ACL RECONSTRUCTION: A LONGITUDINAL STUDY

Introduction

Post-traumatic knee osteoarthritis (OA) after ACL reconstruction (ACLR) is common.[9] While OA is widely acknowledged as a consequence of ACLR, with many developing OA 15-20 years sooner than those without an ACLR[10,12], most efforts to understand disease development have been confined to the tibiofemoral compartment of the knee. Patellofemoral OA, however, is as prevalent as, if not more prevalent than, tibiofemoral OA.[62] Despite high incidence rates, the mechanisms leading to OA development within the patellofemoral compartment remain understudied.

One mechanism thought to be associated with OA development after ACLR is alterations in lower-limb biomechanics. Alterations to tibiofemoral knee biomechanics after ACLR have been extensively studied[40]; however, few have investigated alterations of patellofemoral mechanics. Biomechanical alterations seen after ACLR that may influence the patellofemoral compartment include: smaller peak knee flexion angles and moments, increases in internal knee rotation excursion, and less range of motion of the involved limb during gait, compared to the uninvolved limb and healthy controls.[62] These biomechanical disruptions may alter cartilage loading magnitude and/or shift loading to regions of cartilage that are not able to support the applied load which in turn may initiate changes to cartilage's biochemical structure and ultimately lead to OA.[54] Additionally, extensor strength deficits are common after ACLR and

have the potential to disrupt the patellofemoral biomechanical environment[83], likely resulting in reduced patellofemoral loads. Despite the influence of extensor strength on the patellofemoral compartment, studies are limited and provide mixed evidence regarding extensor weakness after ACLR and its relation to patellofemoral OA development.[84,85]

Those who develop medial tibiofemoral OA 5 years after ACLR underload their involved limb's medial tibiofemoral compartment (as assessed by peak medial compartment force) 6 months after surgery compared to those who do not develop OA.[48] Among this group, underloading of the medial tibiofemoral compartment was resolved (reloaded) by 2 years. Loading of the patellofemoral compartment after ACLR may similarly provide insights into OA development; however, little is known about the patellofemoral loading environment after ACLR. Herrington et al. (2017)[86] found that individuals had higher involved limb patellofemoral contact forces, compared to the uninvolved limb and healthy controls, during running 8 months after ACLR. Conversely, Sritharan et al. (2020)[87] and Bowersock et al. (2017)[88] found reduced involved limb patellofemoral contact forces, when compared to the uninvolved limb, during running 1-2 years and 4.5 years after ACLR, respectively. Recent work by Sritharan and colleagues found a similar underloading of the involved limb, compared to healthy controls, during a single leg hop task.[89] Thus, while some reports of patellofemoral loading after ACLR are available, the results are mixed and have not been assessed during activities of daily living, such as walking. Moreover, these studies are limited to models using static optimization or knee flexion moments to determine muscle forces and to later cross-sectional time points after surgery.

These previous analyses have also been limited to specific points within the movement pattern (i.e., peak patellofemoral contact force). Statistical parametric mapping (SPM) allows for statistical tests to be performed over the entirety of the biomechanical waveform thus avoiding biases associated with analyzing discreate points within the task.[90,91] Statistical inferences in these tests are based on the waveform characteristics of the test statistic, with p-values indicating the likelihood that the observed test statistic suprathreshold cluster resulted from chance.[91] This approach also adjusts the critical p-value ($\alpha = 0.05$) by considering the dependence of the biomechanical value at a point in time within the movement on the surrounding values rather than using an overly conservative approach, such as a Bonferroni correction for each point in the waveform (i.e., dividing α by 100 to account for each point of stance).[90]

The purpose of this study was to use an EMG-driven model to examine patellofemoral contact forces during walking in the involved and uninvolved limbs at 3, 6, and 24 months after ACLR using statistical parametric mapping. We hypothesized that: (1) the involved limb's patellofemoral contact force would be less than the uninvolved limb's at 3 and 6 months after ACLR but not at 24 months, (2) the uninvolved limb's patellofemoral contact forces would remain relatively consistent over time, and (3) the involved limb's patellofemoral contact forces would increase with time to match those of the uninvolved limb.

Methods

Participants

Twenty-seven individuals (**Table 2**) from a longitudinal cohort study were included in this study. Participants were included if they met the following criteria: underwent unilateral ACLR with no previous history of ACL injury/reconstruction within either limb, no prior history of major lower leg injury/surgery, no history of disease or illness that would influence the lower limb, no concomitant grade III ligament tears, no repairable meniscus injury, and between 16-45 years old. Additionally, participants needed to have completed motion analysis at all time points after surgery. Graft type and concomitant meniscal procedures are listed in Table 2.

Table 2 Demographic Characteristics (n=27)

Variable	**Mean ± Standard Deviation or Number (%)**		
Age at 3 Months (years)	23 ± 6		
Sex	13 Female (48%), 14 Male (52%)		
Height (m)	1.7 ± 0.1		
Weight (kg)	**3 Months**	**6 Months**	**24 Months**
	71.1 ± 14.1	75.4 ± 14.0	76.8 ± 14.2
BMI (kg/m^2)	**3 Months**	**6 Months**	**24 Months**
	23.9 ± 3.6	25.4 ± 3.7	25.8 ± 3.8
Graft Type	4 allograft (20%), 9 hamstring autografts (29%), 14 bone-patellar tendon-bone autografts (51%)		
Meniscal Status	15 None (56%), 12 Meniscectomy (44%)		

All data collections were performed at the University of Delaware following approval from the University's Institutional Review Board. Prior to study participation, all participants gave informed consent. Both minor assent and parental consent were obtained for individuals under the age of 18.

Motion Analysis

Each participant completed motion analysis testing during overground walking at three (3.2 ± 0.6), six (6.4 ± 0.6) and twenty-four (24.5 ± 1.5) months after ACLR; during which they walked down a 6-meter pathway at a self-selected speed that was maintained across time points (± 5%). Prior to walking, EMG electrodes (MA-300 EMG System, Motion Lab Systems, Baton Rouge, LA) were placed over seven muscles of interest on each leg after shaving and cleaning the regions above the muscle bellies. These muscles included extensors (rectus femoris, vastus medialis, and vastus lateralis) and flexors (medial and lateral gastrocnemii, semimembranosus, long head of the biceps femoris).[53] After placement of the electrodes, participants completed maximal voluntary isometric contractions (MVICs) for each muscle group (quadriceps, hamstrings, and gastrocnemii). The MVIC values were then used to normalize EMG data obtained during walking.[48] After electrode placement and MVICs, retroreflective markers were placed bilaterally on bony landmarks and rigid multi-marker shells were fixed to the shanks, thighs, and pelvis.[53]

Motion data during walking were recorded using an 8-camera infrared Vicon setup (Oxford Metrics Limited, London, UK) at a sampling rate of 120 Hz; EMG data were sampled at 1080 Hz. During walking, ground reaction forces from a single embedded force plate (600 x 900 mm^2, Bertec Corporation, Worthington, OH) were sampled at 1080 Hz. Three trials per leg were used for data analysis.

Kinematic and kinetic variables were calculated via inverse dynamics using Visual3D (C-Motion, Germantown, MD) after the data were low-pass filtered at 6 Hz and 25 Hz, respectively. To create linear envelopes, EMG data were high-pass filtered at 30 Hz using a 2nd order Butterworth filter, rectified, low-pass filtered at 6 Hz, and then normalized to the subject's MVIC values.[58,59] The EMG signal of the vastus intermedius was estimated by averaging the signals from the medial and lateral vasti.[59] Using processes outlined by Buchanan et al. (2004)[58], these linear envelopes were transformed into muscle activations which, in turn, were used in a validated, subject-specific neuromusculoskeletal model to determine muscle forces.[59] Subsequently, the forces of the rectus femoris, medial and lateral vasti, and vastus intermedius were summed to determine the net quadriceps muscle force.

Patellofemoral Contact Forces

Patellofemoral contact forces were calculated using similar methodologies as those of Yamaguchi and Zajac (1989)[92] and Shelburne and Pandy (1997)[93]. The femoral condyles, patella, and tibial plateau were approximated as a rigid 2-dimensional (2D) circle, box, and line, respectively. The sizes of the 2D femur, patella, and tibial plateau for each participant were determined using subject-specific SIMM models created during the muscle force estimation process at the three-month time point.[59] The relative position (x-y coordinates) of the insertion of the quadriceps tendon on the patella, and the insertion of the patellar ligament on both the patella and tibia were also determined using the subject-specific SIMM models. The coordinates of these positions were relative to the center of the femur which was defined as the origin of the coordinate system. The patellar ligament was assumed inextensible throughout.[92,93] The tibial plateau and patella moved relative to the femur during knee

flexion; the femur was held fixed throughout (**Figure 6**). The location of the contact point of the tibia on the femur as a function of knee flexion angle was determined using data from Nisell et al. (1986)[94]. Using these data, the tibial plateau (and subsequently the patellar ligament and patella) was shifted so that the tibiofemoral contact point at that knee flexion angle of interest was physiologically accurate. Likewise, the angle of the quadriceps tendon with respect to the femur (θ_q) as a function of knee flexion angle was determined using data from van Eijden et al. (1986)[95]. Following this, the angle of the patellar ligament with respect to the y-axis of the femur (β) was determined using Equation 1:

$$\beta = \tan^{-1}\frac{A_x - TT_x}{A_y - TT_y} \quad (1)$$

Where A_x and A_y are the x- and y-coordinates of the patellar ligament's attachment to the patella and TT_x and TT_y are the x- and y-coordinates of the patellar ligament's attachment to the tibia.

At each knee flexion angle, the patella was assumed to be in static equilibrium. Thus, the following must hold true:

$$\Sigma F_{PFx} = 0, \Sigma F_{PFy} = 0, \Sigma M_{PF} = 0 \quad (2)$$

Where F_{PFx} are the forces acting on the patella in the x-direction, F_{PFy} are the forces acting on the patella in the y-direction, and M_{PF} are the moments acting about the patellofemoral contact point. These lead to the following equations, as outlined in Appendix A of Shelburne and Pandy (1997)[93]:

$$\Sigma F_{PFx} = F_q \sin\theta_q + F_{pl} \sin\beta + F_{PF} \cos\alpha = 0 \quad (3)$$

$$\Sigma F_{PFy} = F_q \cos\theta_q - F_{pl} \cos\beta + F_{PF} \sin\alpha = 0 \quad (4)$$

$$\Sigma M_{PF} = F_{pl} M_{pl} - F_q M_q = \cos(\theta_q + \alpha) M_{pl} - \cos(\beta - \alpha) M_q = 0 \quad (5)$$

Where F_q is the quadriceps muscle force, F_{pl} is the patellar ligament force, F_{pf} is the patellofemoral contact force, α is the patellar flexion angle, M_{pl} is the moment arm of the patellar ligament force with respect to the patellofemoral contact point, and M_q is the moment arm of the quadriceps muscle force with respect to the patellofemoral contact point.

The patellar flexion angle (α), and thus the position and orientation of the patella relative to the femur, was solved iteratively by minimizing the sum of squared errors so that the moments generated around the patellofemoral contact point were balanced (i.e., so that Equation 5 held true). From this, the F_{pf}/F_q ratio was calculated using Equation 6, after combining and rearranging Equations 3 and 4:

$$\frac{F_{pf}}{F_q} = \frac{-\sin(\theta_q + \beta)}{\cos(\beta - \alpha)} \tag{6}$$

The subject-specific F_{pf}/F_q ratio from 0° to 90° of knee flexion was calculated at 5° intervals. A fourth-order polynomial was then fit to these data to create a subject-specific equation to calculate the F_{pf}/F_q ratio as a function of knee flexion angle. The subject's knee flexion angle throughout stance was then used as an input to this subject-specific equation to determine the F_{pf}/F_q ratio throughout stance, which was multiplied by the quadriceps muscle force throughout stance to determine the F_{pf}. The F_{pf}, henceforth referred to as PCF, was subsequently normalized by bodyweight (BW) to allow for direct subject-to-subject comparison.

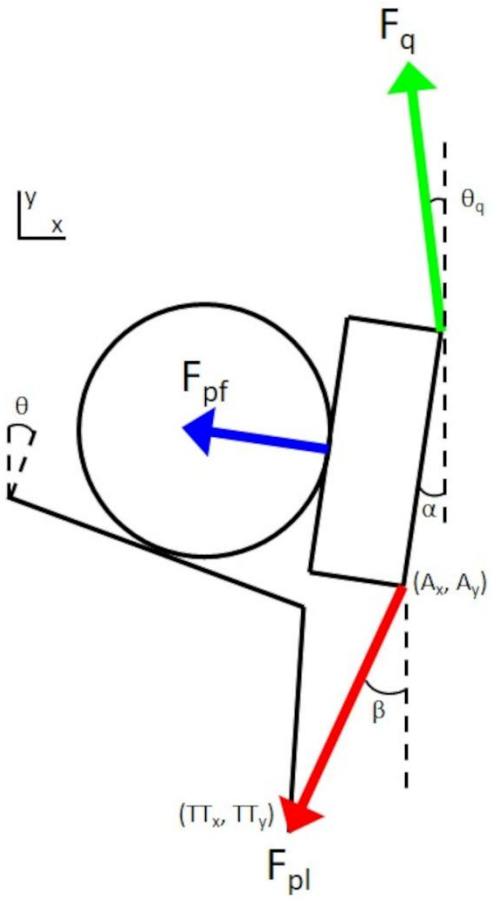

Figure 6 2D patellofemoral model at 20° of knee flexion. The circle is a subject-specific approximation of the femoral condyles, while the box and bottom lines are approximations of the patella and tibial plateau, respectively. F_q = quadriceps forces, F_{pl} = patellar ligament forces, F_{pf} = patellofemoral contact force, θ = knee flexion angle, θ_q = quadriceps muscle force angle, α = patellar flexion angle, β = patellar ligament angle, A_x and A_y = the x- and y-coordinates of the patellar ligament's attachment to the patella, and TT_x and TT_y = the x- and y-coordinates of the patellar ligament's attachment to the tibia.

Statistical Analyses

All statistical analyses were performed in MATLAB (MathWorks, Natick, MA, USA). Statistical Parametric Mapping (SPM1D[91]) was used to perform a 2 (limb)

x 3 (time) repeated measures ANOVA throughout stance with statistical significance defined as $\alpha < 0.05$. Additionally, SPM was used to perform post-hoc 2-tailed paired t-tests to assess patellofemoral contact forces between limbs (involved vs. uninvolved) at individual time points (3, 6, and 24 months) and to perform post-hoc 1 (limb) x 3 (time) repeated measures ANOVAs to assess how patellofemoral contact forces within each limb changed with time. For these post-hoc tests, statistical significance was adjusted using a Bonferroni correction to account for multiple comparisons.

Results

A significant main effect of limb ($p < 0.001$ from 5-35% of stance), main effect of time ($p < 0.001$ from 55-74% of stance), and limb x time interaction ($p = 0.007$ from 10-21% of stance) were present for patellofemoral contact forces (**Figure 7**).

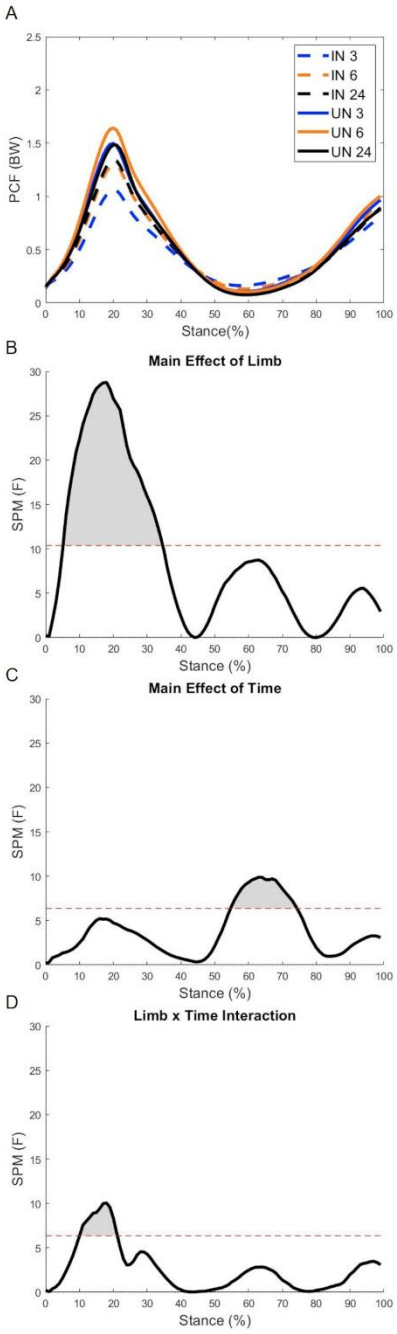

Figure 7 (A) 3 (blue), 6 (orange), and 24 (black) month average PCFs for the involved (dashed) and uninvolved (solid) limbs through 100% of stance; standard deviations omitted to help with clarity. (B) SPM main effect of limb, (C) SPM main effect of time, and (D) SPM limb x time interaction F-statistic over 100% of stance; red dashed line represents the critical F-value ($\alpha < 0.05$); shaded regions indicative of statistical significance.

Three months after ACLR, the PCF in the involved limb was significantly less than that of the uninvolved limb during the initial loading response of weight acceptance and into midstance ($p < 0.001$ from 7-30% of stance; **Figure 8A**). The average peak patellofemoral contact force (pPCF) in the involved and uninvolved limbs were 1.1 BW and 1.5 BW, respectively. Six months after surgery, the involved limb's patellofemoral compartment was still underloaded when compared to the uninvolved limb during the initial loading response of weight acceptance and into midstance ($p = 0.001$ from 11-23% of stance and $p = 0.025$ from 27-32% of stance; **Figure 8B**). The average pPCF in the involved and uninvolved limbs were 1.3 BW and 1.6 BW, respectively. Twenty-four months after surgery there was no significant difference between the involved and uninvolved limbs (**Figure 8C**). The average pPCF in the involved and uninvolved limbs were 1.3 BW and 1.5 BW, respectively. Overall, interlimb differences (involved limb – uninvolved limb) were largest at 3 months and decreased with time (**Figure 9**).

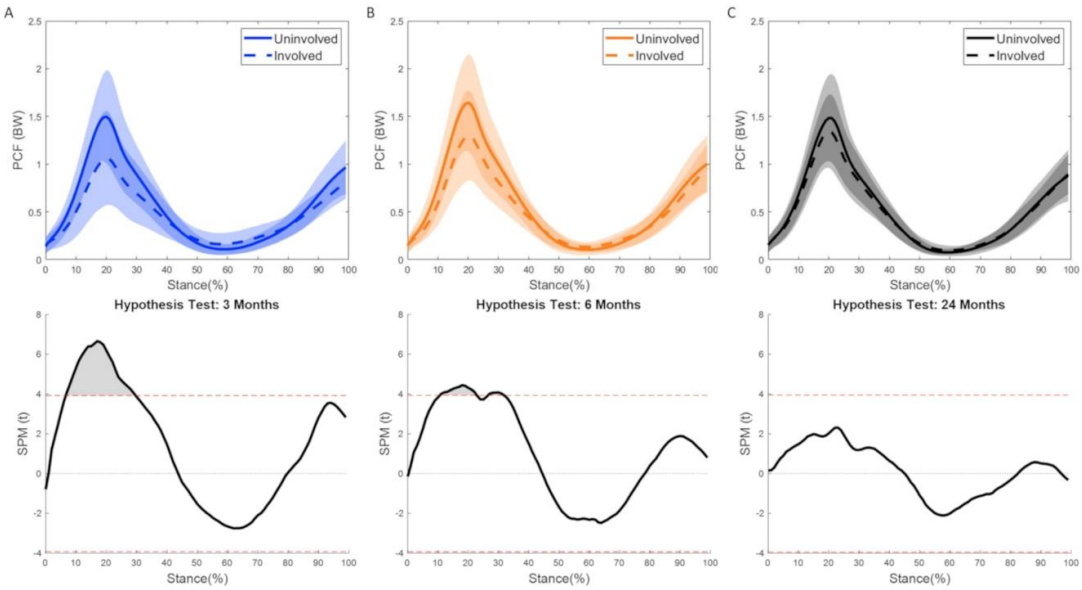

Figure 8 The top graphs show the average PCF through 100% of stance ± one standard deviation (shaded). The dashed lines represent the involved limb while the solid lines represent the uninvolved limb. The lower graphs show two-tailed paired t-tests using SPM with the red dashed line indicative of the critical t-threshold and the shaded regions indicative of areas of statistical significance. (A) PCF 3 months after ACLR. (B) PCF 6 months after ACLR. (C) PCF 24 months after ACLR.

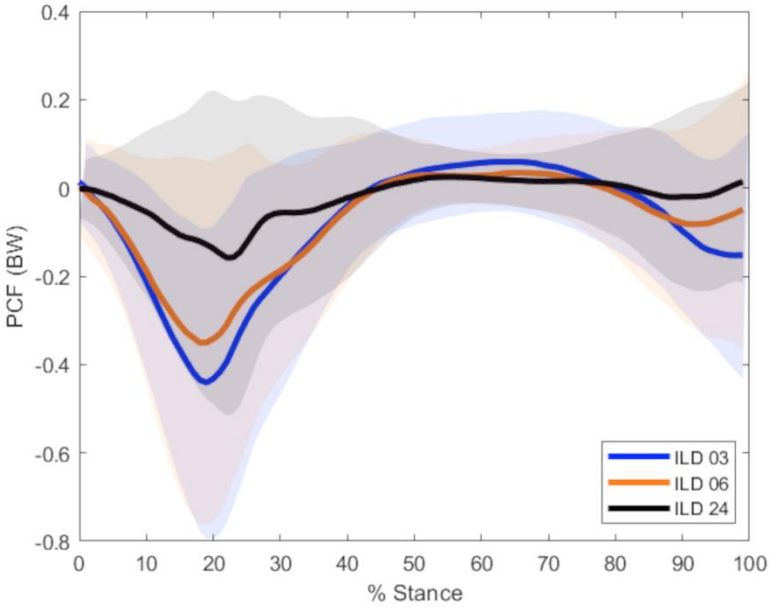

Figure 9 Average interlimb difference (ILD; involved limb – uninvolved limb) of patellofemoral contact force through 100% of stance ± one standard deviation (shaded). The blue line represents the 3-month time point, the orange line the 6-month time point, and the black line the 24-month time point. The average interlimb difference was largest at 3 months during weight acceptance (peak magnitude = -0.44 BW) and decreased with time until smallest at 24 months (peak magnitude = -0.16 BW).

The involved limb's PCF increased from 3 to 6 months and then remained relatively consistent from 6 to 24 months (**Figure 10A**). Significant effects of time were present during weight acceptance into midstance ($p = 0.031$ from 17-22%) and terminal stance ($p = 0.046$ from 63-65% of stance). There was no main effect of time in the uninvolved limb (**Figure 10B**); however, the uninvolved limb's patellofemoral contact force did increase from 3 to 6 months and then subsequently decrease from 6 to 24 months during the end of weight acceptance into midstance.

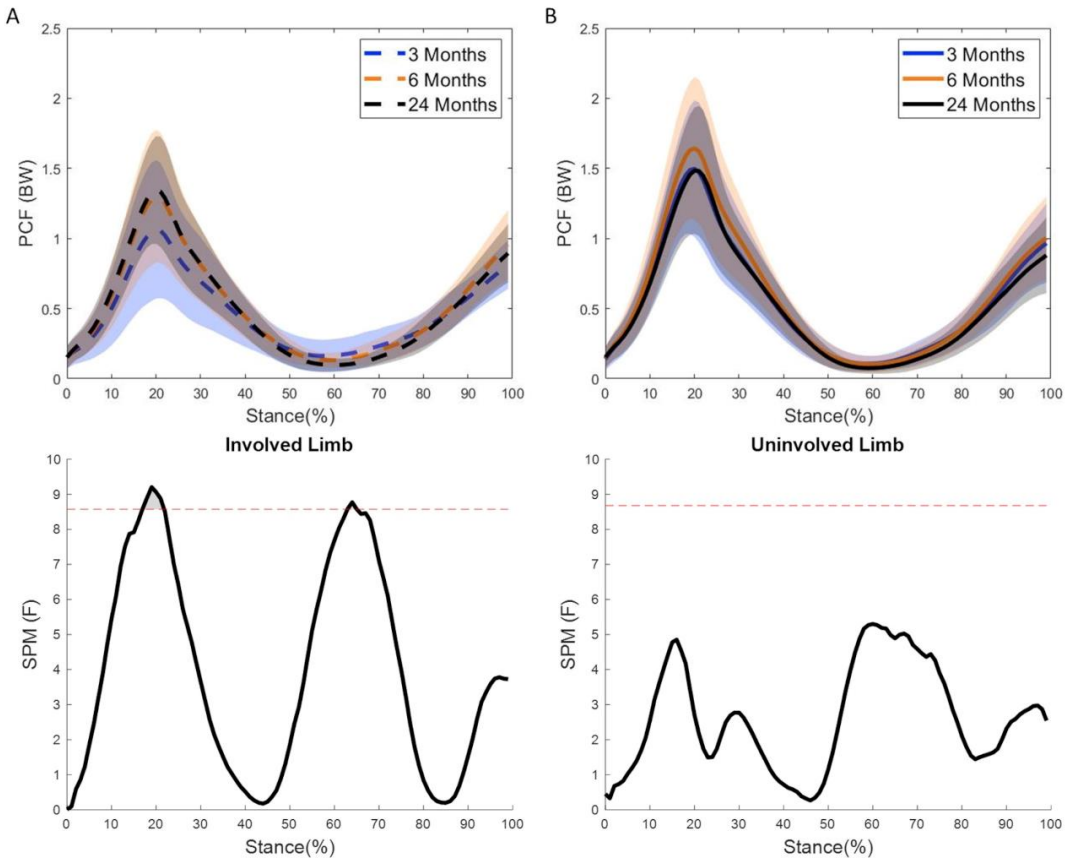

Figure 10 The top graphs show the average PCF through 100% of stance ± one standard deviation (shaded). The blue line represents the 3-month time point, the orange line the 6-month time point, and the black line the 24-month time point. The lower graphs show the F-statistic from a 1 (limb) x 3 (time) repeated measures ANOVA using SPM with the red dashed line indicative of the critical F-value and the shaded regions indicative of areas of statistical significance. (A) Involved limb. (B) Uninvolved limb.

Discussion

To the best of our knowledge, this is the first study to assess patellofemoral loading after ACLR during a repetitive, everyday task. Previous work on patellofemoral contact forces after ACLR have been limited to more dynamic tasks, such as running and single leg hops.[86–89] Reported pPCFs from these studies range

from 4.2-6.1 BW in the involved limb and 4.6-6.7 BW in the uninvolved limb during running and upwards of 10 BW during single leg hopping. Unsurprisingly, pPCFs during walking were lower than those of more dynamic tasks. Specifically, pPCFs in our study were 1.3 BW in the involved limb and 1.5 BW in the uninvolved limb 24 months after surgery. These values align well with Shelburne et al. (2005)[96] who found a pPCF of 1.3 BW in healthy limbs during gait. Previous analyses of patellofemoral contact forces after ACLR have been limited to later time points after surgery, after individuals returned to sport. This study is the first to examine patellofemoral contact forces during the early months after surgery (prior to 8 months). Recent work within the tibiofemoral compartment of the knee found associations between knee mechanics and measures of cartilage health 3 months after ACLR[11], highlighting the importance of examining early time frames after surgery when interventions may be more effective. This study is also the first to longitudinally assess patellofemoral contact forces after ACLR. Given cartilage's mechanosensitivity, an understanding of longitudinal changes in loading may provide better insights into the mechanisms of OA development. Additionally, this is the first to examine patellofemoral contact forces over the entirety of the movement pattern. While assessment of biomechanical variables at the peak of their movement patterns is common, analysis of 1D data from a 0D perspective introduces statistical bias and leaves room to overlook important information about the biomechanical variable analyzed. Finally, this study is also the first to incorporate EMG informed estimations of muscle forces in the calculation of patellofemoral contact forces after ACLR. Previous studies have relied on static optimization or knee flexion moment based approaches to estimate muscle forces which may have underestimated the magnitude

of the forces applied to the model.[86,87,89] The approach used here allows us to capture complex muscle patterns, such as muscle co-contraction, more accurately. Overall, this study adds to the existing literature by providing a comprehensive assessment of patellofemoral contact forces over the first 24 months after surgery during the most common locomotion pattern performed on a day-to-day basis.

Our first hypothesis, that the involved limb's patellofemoral contact force would be less than the uninvolved limb's at 3 and 6 months after ACLR but not at 24 months, was supported. This loading pattern is similar to the loading patterns we saw within the medial tibiofemoral compartment.[48] In that study reduced involved limb medial compartment force was present early after ACLR but was reloaded with time. Those with reduced involved peak medial compartment force 6 months after surgery developed radiographic osteoarthritis within the same compartment 5 years after surgery. Cartilage is a mechanosensitive tissue with essential processes within the tissue, such as chondrocyte stimulation, dependent on maintenance of a normal loading pattern. Immobilization of cartilage within animal models is associated with alterations to the structural and biochemical health of cartilage characteristic of early osteoarthritis.[97] Among human subjects, recent evidence indicates that both overloading and underloading may be mechanisms responsible for OA development.[98] Whether or not involved limb patellofemoral underloading seen here is linked to long term osteoarthritis development remains to be investigated.

The underlying cause of patellofemoral underloading during the early months after reconstruction is not known. Extensor muscle weakness, a commonly observed phenomenon after ACLR, is likely a large contributor to underloading. Extensor muscle forces followed a similar pattern as the PCFs in both limbs. Significant

asymmetries in extensor forces were present early after ACLR (involved less than uninvolved) but were resolved by 24 months (not shown). Conversely, hamstring muscle forces were consistent between limbs and across times (not shown). This suggests that the adaption of a quadriceps avoidance strategy, rather than a hamstring facilitation approach, may be responsible for the observed PCF patterns. While we did calculate extensor muscle forces in this study, we were not able to determine whether the differences in PCF between limbs are the result of strength deficits or alterations in muscle activation strategy, as both muscle strength and activation play a role in the muscle force calculation. A recent study by Arhos et al. (2021)[41] found that restoration of quadriceps strength symmetry alone after ACLR was not associated with full restoration of biomechanical symmetry, although this study did not examine patellofemoral contact forces. This may imply that both strength deficiency and sensorimotor control deficits are contributing to alterations in mechanics early after ACLR and that only by correcting both will biomechanical symmetry be achieved. Future work needs to examine the influence of extensor strength on patellofemoral contact forces and determine if restoration of extensor strength symmetry with time corresponds to PCF symmetry. Another possible explanation is that alterations in other biomechanical variables (e.g., knee flexion angles) could be influencing patellofemoral contact force locations and magnitudes.[62] For example, Sritharan et al. (2020)[87] found small anterior shifts in the center of pressure of the vertical ground reaction force of the involved limb during running. They hypothesized that this anterior shift could be subtly offloading the knee and thus could be a mechanism for patellofemoral underloading. Future work needs to assess the associations between other gait biomechanical variables and PCFs after ACLR. Asymmetries in PCFs

occurred during weight acceptance and into midstance. This is not surprising as this is the phase of stance when the knee absorbs load. Most individuals adopt a stiffened knee gait strategy to reduce the load to their involved limb after ACLR. This includes reduced vertical ground reaction forces, quadriceps avoidance, and flexing the knee less during the early parts of stance.[44] These strategies have been attributed to pain and psychological phenomena such as fear of movement and reinjury.[99,100] It may be that increased confidence with time could be a driving mechanism towards symmetry.

Our second hypothesis, that the uninvolved limb's patellofemoral contact forces would remain relatively consistent over time was partially supported. The uninvolved limb's PCF increased from 3 to 6 months during the end of weight acceptance into midstance and was followed by a subsequent decrease from 6 to 24 months back down to similar values as those seen at the 3-month time point. While there were changes with time, they were not statistically significant. The increases in PCF seen in the uninvolved limb may be a response to performing more high intensity dynamic activities (as is typical around 3-to-6 months after surgery). This is also around the time when more bilateral therapy techniques are utilized. This focus on bilateral conditioning may result in increases in uninvolved limb extensor strength[41] which subsequently could alter the biomechanical environment of the patellofemoral compartment. This increase in the uninvolved limb from 3 to 6 months could also be in response to the change that occurs in the involved limb from 3 to 6 months. That is, after surgery these individuals have learned to walk with a certain asymmetry and, as a result, as their involved limb increases in strength they may subconsciously adjust their uninvolved limb to maintain a degree of asymmetry until they re-learn a normal biomechanical pattern.

Our third hypothesis, that the involved limb's patellofemoral contact forces would increase with time to match those of the uninvolved limb, was supported. The involved limb's PCF increased with time towards that of the uninvolved limb but remained relatively consistent from 6 months onward. Interestingly, it appears as if lesser loading in the involved limb is resolved by 6 months after reconstruction, with the significant interlimb difference at 6 months most likely a result of the subsequent increase in the uninvolved limb's PCFs from 3 to 6 months. Sometime between 6 and 24 months, the uninvolved limb's PCF decreases and loading symmetry is achieved. This conflicts with the findings of Sritharan et al. (2020)[87] and Bowersock et al. (2017)[88], both of whom found patellofemoral underloading during running at later time points after ACLR. Differences between those studies and ours can likely be attributed to the differences in tasks (walking vs. running). This may imply that more dynamic tasks, such as running or single leg hops, could elucidate biomechanical patterns that otherwise appeared resolved during gait and that the repeated occurrence of such activities following ACLR may further increase the chance of eventual patellofemoral OA development. Future work needs to assess the relationship between the frequency of dynamic task occurrences after ACLR and patellofemoral OA development.

There are limitations to consider when interpreting the results of this study. First, there are several assumptions associated with the patellofemoral model. One is the usage of 2D approximations for the femur, tibia, and patella. While a 3D representation of the knee may provide increased accuracy, this 2D approach was able to produce patellofemoral contact forces similar to values reported of healthy walking gait.[96] Another limitation of the model was the usage of an inextensible patellar

ligament. Using a similar model, Yamaguchi and Zajac increased the patellar ligament length by 20% and found no meaningful changes in the resultant patellofemoral contact force, especially during lower knee flexion angles, as is seen during the stance phase of gait.[92,93] As the reported ultimate tensile strain at failure of the patellar ligament is 14 ± 6%[101], it is likely that the assumption of an inextensible patellar ligament does not meaningfully change the predicted contact forces. Patellofemoral kinematics, including increased patellar external rotation, lateral tilt, and lateral translation, are also altered following reconstruction.[102] More advanced techniques than the motion capture and modeling techniques employed here (such as fluoroscopic imaging) are needed to elucidate these potential alterations. Future studies incorporating these techniques may further shed light on potential alterations to the loading environment of the patellofemoral compartment after ACLR and how these alterations may predispose individuals to eventual OA development. This study featured participants with a variety of graft types and concomitant meniscal procedures which may have influenced the results. Future work needs to examine the effect of these variables on patellofemoral contact forces after ACLR. It should be noted that no power analysis was performed for this study as these analyses were secondary to the analyses of the primary study from which subjects were taken. Thus, regions where no significant differences were present may be so due to inadequate power rather than lack of true statistical difference. Finally, participants were recruited from a multitude of clinics and surgeons from the surrounding area. As a result, information regarding participants' rehabilitation after surgery were unavailable and thus could not be controlled for as a potential confounding variable in this study. While differing rehabilitation strategies may influence PCFs this also makes the

results of our study more generalizable as it is not feasible to control for this variable in the larger ACLR population. Future work needs to examine the influence of differing rehabilitation protocols on PCFs after ACLR.

In conclusion, our findings suggest that patellofemoral underloading during gait exists early after ACLR but is resolved by 2 years after surgery. This represents a first step towards understanding the loading environment of the patellofemoral compartment during walking and how it changes in the early months after ACLR. Future work is needed to determine if the patellofemoral loading patterns observed here are associated with signs of eventual patellofemoral osteoarthritis development.

Chapter 4

PATELLOFEMORAL CONTACT FORCES AND KNEE GAIT MECHANICS 3 MONTHS AFTER ACL RECONSTRUCTION ARE ASSOCIATED WITH CARTILAGE DEGRADATION 24 MONTHS AFTER SURGERY

Introduction

Over 50% of individuals who undergo anterior cruciate ligament reconstruction (ACLR) develop post-traumatic knee osteoarthritis (OA) 10-20 years after surgery.[8,9] Many of the individuals who undergo this procedure are young, active, and otherwise healthy; consequently, many develop knee OA and suffer from its adverse consequences early in life.[8,10] Investigations regarding the pathogenesis of OA after ACLR have mostly been confined to the medial tibiofemoral compartment of the knee. Recent evidence indicates that patellofemoral OA after ACLR is at least as common as medial tibiofemoral OA and is associated with worse patient reported outcomes.[62–64] Despite this, few have investigated the mechanisms leading to OA within the patellofemoral compartment of the knee.

Advanced magnetic resonance imaging (MRI) techniques, such as quantitative MRI (qMRI), can monitor OA-related biochemical alterations that occur prior to morphometric alterations to cartilage.[29] One of the most commonly used qMRI techniques is T_2 relaxation time, which provides insight into the collagen matrix structure of cartilage.[15,29] A prolonged T_2 relaxation time is indicative of increased water content and collagen matrix degradation, both of which are hallmark signs of early knee OA.[15,29] There is limited information on patellofemoral T_2 relaxation times

after ACLR. In exploratory studies, Kim et. al. (2018)[103] and Li et al. (2018)[104] both found prolonged involved limb femoral trochlear cartilage T_2 relaxation times (vs. uninvolved limb) 3 years after ACLR. We previously reported no difference in trochlear cartilage T_2 relaxation times between limbs 6 months after ACLR, however this may have been too early after surgery for alterations to have occurred.[105] Given the paucity of data, more investigations into patellofemoral T_2 relaxation times after ACLR are needed as these could provide insights into cartilage health prior to morphometric alterations when potential rehabilitative interventions may be more viable.

One mechanism thought responsible for OA development after ACLR is alterations in knee gait mechanics. These alterations are frequently observed after surgery and may represent an ideal target for explorative rehabilitative efforts, as gait mechanics may be modifiable.[39–43] Commonly reported alterations after ACLR that may influence the patellofemoral compartment include reduced involved limb knee flexion angles and knee flexion moments during gait.[40–45,62] These alterations are reported as early as 3 months after ACLR and persist past return-to-sport time points.[40–45] Mechanistically, these alterations may shift the location and magnitude of loading applied to the patellofemoral compartment which, given cartilage's mechanosensitivity, may disrupt the biochemical and structural health of cartilage.[18,54] Previous work from our lab found no association between knee gait biomechanical variables 3 months after ACLR and trochlear cartilage T_2 relaxation times 6 months after surgery.[105] We did, however, observe a significant negative association between participant walking speed and trochlear cartilage T_2 relaxation times, indicating that slower walking speed 3 months after ACLR was associated with prolonged (worse) T_2

relaxation times 6 months after surgery.[105] Recent evidence (from Chapter 3) suggests that underloading of the involved limb's patellofemoral compartment, compared to the uninvolved limb, is evident 3 months after surgery.[106] However, it is unknown if this underloading and other early gait alterations are associated with long-term signs of OA development within the patellofemoral compartment. Thus, the purpose of this study was (1) to examine patellofemoral cartilage T_2 relaxation times 24-months after ACLR and (2) to investigate the association between knee gait biomechanical variables 3 months after ACLR and 24-month T_2 relaxation times. We hypothesized that (1) the involved limb would display prolonged T_2 relaxation times, compared to the uninvolved limb, in both patellar and trochlear cartilage and (2) that smaller values of the knee gait biomechanical variables of interest at 3 months would be associated with prolonged involved limb patellofemoral T_2 relaxation times at 24 months (i.e., that a significant negative association would be present).

Methods

Participants

Thirty participants (**Table 3**) from a larger longitudinal cohort study were included in this study. Enrollment criteria for the general study included: primary unilateral ACLR with no history of lower leg injury or surgery, no concomitant grade III ligament tears, no repairable meniscal injuries, no contraindications for MRI, and between 16-45 years old. Eligibility criteria specific to this study included: no patellofemoral osteochondral defects, completion of motion analysis 3 months after ACLR, and completion of an MRI 24 months after surgery. All data were collected at the University of Delaware following approval from an Institutional Review Board.

All participants granted written informed consent with both minor assent and parental consent obtained for individuals under the age of 18.

Table 3 Demographic Characteristics of Participants 3 Months after ACLR (n = 30)

Variable	Mean ± Standard Deviation or Number (%)
Age (years)	23 ± 7
Sex	14 Female (47%), 16 Male (53%)
Mass (kg)	77.1 ± 14.9
Height (m)	1.7 ± 0.1
BMI (kg/m^2)	25.9 ± 3.8
Graft Type	15 BPTB (50%), 9 Hamstring (30%), 6 Allograft (20%)
Meniscal Status	14 Meniscectomy (46%), 16 None (53%)
Walking Speed (m/s)	1.55 ± 0.14

Motion Analysis and Musculoskeletal Modeling

Participants completed motion analysis during overground walking at a self-selected speed 3 months (3.2 ± 0.6) after ACLR. Prior to walking, surface electromyography (EMG) electrodes (MA-300 EMG System, Motion Lab Systems) were placed over seven muscles of interest on each leg after shaving and cleaning the regions over each muscle belly. Muscles of interest included the rectus femoris, vastus medialis, vastus lateralis, medial and lateral gastrocnemii, semimembranosus, and the long head of the biceps femoris.[48] After placement of the electrodes, participants completed maximal voluntary isometric contractions (MVICs) for each examined muscle group (quadriceps, gastrocnemii, and hamstrings).[107] Retroreflective markers were then placed bilaterally on bony landmarks (1st and 5th metatarsal heads, malleoli, femoral epicondyles, greater trochanters, and iliac crest) and rigid shells with multi-

marker groupings were fixed to the pelvis, thighs, and shanks with two additional markers attached to each calcaneus.[43]

Kinematic data during walking were captured using an eight-camera infrared Vicon system (Oxford Metrics Limited) at a sampling rate of 120 Hz. Kinetic data, recorded using a single embedded force plate (600 x 900 mm^2, Bertec Corporation), and EMG data were both sampled at 1080 Hz. Three trials for each leg were used for data analysis.[48,106] Kinematic and kinetic variables of interest were calculated using inverse dynamics in Visual 3D (C-motion) after low-pass filtering the data at 6 Hz and 25 Hz, respectively. EMG data were high-pass filtered (30 Hz using a 2^{nd} order Butterworth filter), rectified, low-pass filtered (6 Hz), and then normalized to the subject's MVIC values to create linear envelopes.[58,59] Linear envelopes of the semitendinosus and the short head of the biceps femoris were set equal to those of the semimembranosus and long head of the biceps femoris, respectively.[59] The linear envelope of the vastus intermedius was determined by averaging those of the vastus medialis and vastus lateralis.[59] Following processes outlined in Buchanan et al. (2004)[58], linear envelopes were transformed into muscle activations. These muscle activations, in turn, were used in a validated, subject-specific neuromusculoskeletal model to calculate muscle forces.[58,59] These muscle forces were input into a previously described model (Chapter 3) to calculate patellofemoral contact forces.[106]

Variables of interest in this study included: peak patellofemoral contact force (pPCF), peak knee flexion angle (pKFA), peak knee flexion moment (pKFM), and walking speed in both the involved and uninvolved limbs. Patellofemoral contact force was normalized by bodyweight (BW) and knee flexion moment was normalized to bodyweight and height (%BW*HT).[43]

Imaging

Twenty-four (24.6 ± 1.4) months after ACLR, these same participants underwent a supine bilateral knee MRI using a 3 Tesla magnet (Siemens) and a 15-channel transmit/receive knee coil (Siemens). During the MRI scan, a sagittal bilateral T_2 mapping sequence was performed [Field of View: 150 mm, Slice Thickness: 3 mm, Repetition Time: 3090 ms, Echo Times: 10 – 70 ms].[11]

Images were analyzed in 3D Slicer (https://www.slicer.org/).[71] T_2 maps were calculated using a monoexponential fit.[11] During the calculation of the T_2 map the first echo in each sequence was skipped in order to reduce stimulated echo artifacts.[72] Three slices corresponding to the center of the patellar ridge and three slices corresponding to the center of the femoral trochlear sulcus were used for patellar and trochlear analyses, respectively. For each slice, the entire patellar or trochlear cartilage was initially segmented. Each segmentation was then further subdivided into equal deep and superficial layers to account for structural differences in those layers of cartilage.[29] T_2 relaxation times were averaged across all three slices to provide an average patellar and trochlear T_2 relaxation time within each limb for each subject. Analyses involving T_2 relaxation times were done from both the total cartilage perspective and from the deep and superficial layer perspectives.

Statistical Analyses

Statistical analyses were performed in JMP (SAS) with statistical significance defined as $\alpha = 0.05$. Normality of the patellar and trochlear T_2 relaxation times in both limbs was assessed using a Shapiro-Wilks test. Two-tailed paired t-tests (for parametric data) or Wilcoxon Rank Sum tests (for nonparametric data) were used to compare T_2 relaxation times between limbs. This was done for the entirety of the

cartilage of interest as well as for the deep and superficial layers. Pearson correlation and simple linear regression were used to assess the association between each biomechanical variable of interest and the patellar and trochlear T_2 relaxation times. The assumptions of linear regression, (1) that the relationship is linear, (2) that the residuals are normally distributed, (3) residual homoscedasticity, and (4) independent observations, were confirmed valid for all tests. Effect sizes of the correlations were assessed using R^2 values and were described as a small ($R^2 > 0.02$), medium ($R^2 > 0.13$), or large ($R^2 > 0.26$).[108]

Results

24-Month T_2 Relaxation Times

The involved limb displayed significantly prolonged total trochlear cartilage T_2 relaxation times, compared to the uninvolved limb, 24-months after surgery ($p = 0.025$; Involved: 49.64 ± 3.85 ms; Uninvolved: 47.57 ± 3.40 ms; **Figure 11A**). When further subdividing trochlear cartilage into deep and superficial layers, it was found that the involved limb displayed significantly prolonged T_2 relaxation times compared to the uninvolved limb only in the deep layer ($p_{T,deep} = 0.005$, $Involved_{T,deep}$: 47.34 ± 4.40 ms, $Uninvolved_{T,deep}$: 44.40 ± 4.17 ms; $p_{T,superficial} = 0.245$, $Involved_{T,superficial}$: 51.76 ± 4.19, $Uninvolved_{T,superficial}$: 50.57 ± 3.28 ms; **Figure 11B**). There was no difference between limbs in T_2 relaxation times within the total patellar cartilage ($p = 0.725$; Involved: 41.67 ± 3.15; Uninvolved: 41.66 ± 3.71; **Figure 11A**). Further subdividing the patellar cartilage into deep and superficial layers again revealed no differences between limbs ($p_{P,deep} = 0.712$, $Involved_{P,deep}$: 36.50 ± 3.77 ms,

Uninvolved$_{P,Deep}$: 36.25 ± 3.73 ms; $p_{P,superficial}$ = 0.505, Involved$_{P,superficial}$: 46.91 ± 3.19 ms, Uninvolved$_{P,superficial}$: 47.43 ± 4.23 ms; **Figure 11B**).

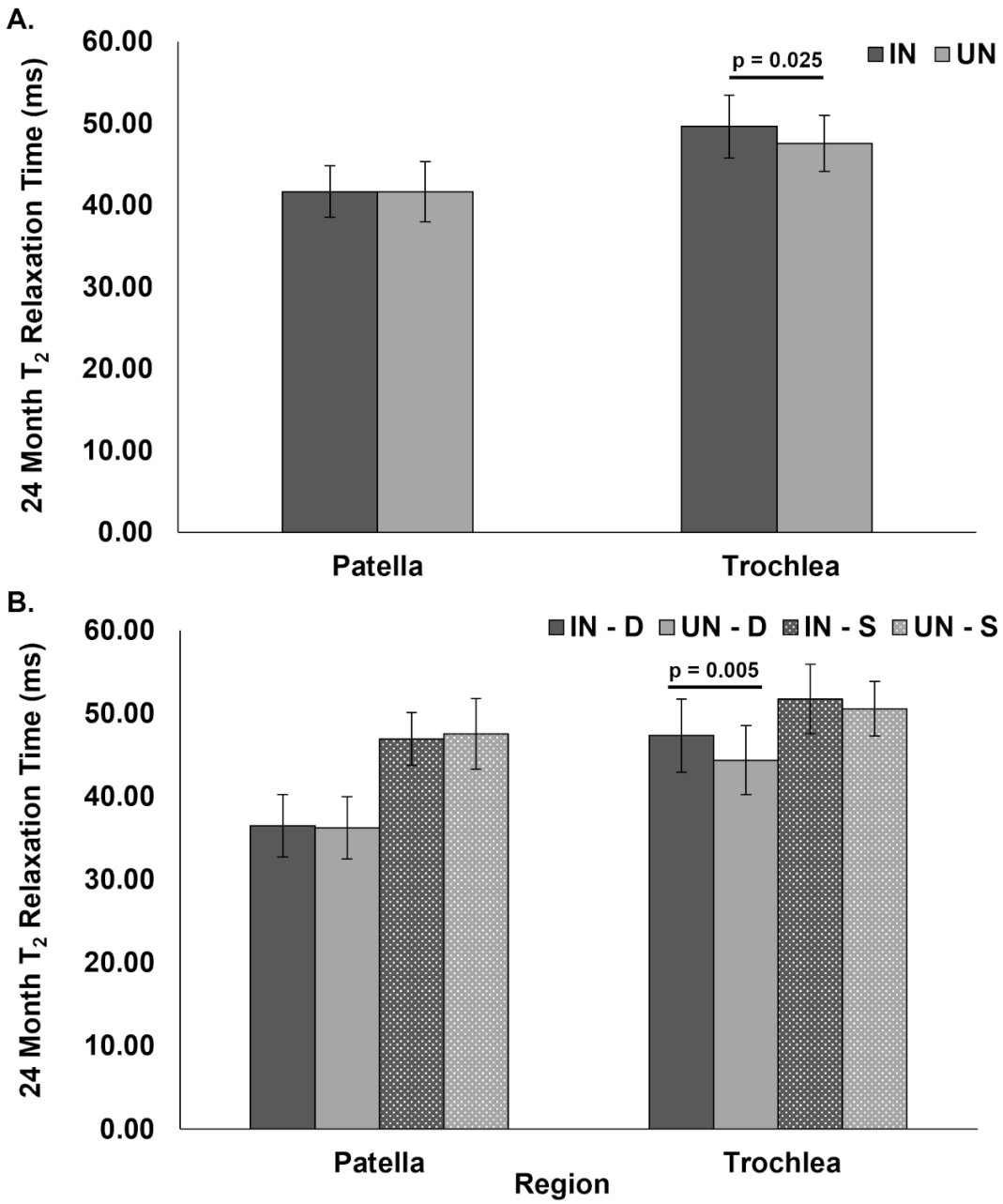

Figure 11 (A) Average 24-Month T_2 relaxation time in the involved (dark gray) and uninvolved (light gray) limbs of both total patella and trochlear cartilage (± 1 standard deviation). (B) Average 24-Month T_2 relaxation times in the involved (dark gray) and uninvolved (light gray) limbs of both deep (solid) and superficial (checkered) patella and trochlear cartilage (± 1 standard deviation). A prolonged T_2 relaxation time is indicative of collagen matrix degradation.

3 Month Gait Mechanics vs 24 Month T_2 Relaxation Times – Involved Limb

Significant negative correlations existed between all the biomechanical variables of interest and 24-month involved limb total trochlea cartilage T_2 relaxation times (**Table 4**).

Table 4 Involved Limb - Association between 3-month walking gait mechanics and 24-month total patellar and trochlear cartilage T_2 relaxation times. Significant associations are **bolded**.

Gait Variable	Region	r	Effect Size (R^2)	p Value
pPCF	Patella	- 0.089	0.008	0.636
	Trochlea	**- 0.549**	**0.301**	**0.002**
pKFA	Patella	- 0.158	0.025	0.409
	Trochlea	**- 0.550**	**0.303**	**0.002**
pKFM	Patella	- 0.063	0.004	0.752
	Trochlea	**- 0.470**	**0.221**	**0.009**
Walking Speed	Patella	- 0.318	0.101	0.226
	Trochlea	**- 0.428**	**0.183**	**0.019**

There was a significant negative association with a large effect between pPCF at 3 months and trochlear cartilage T_2 relaxation times at 24 months (**Figure 12**).

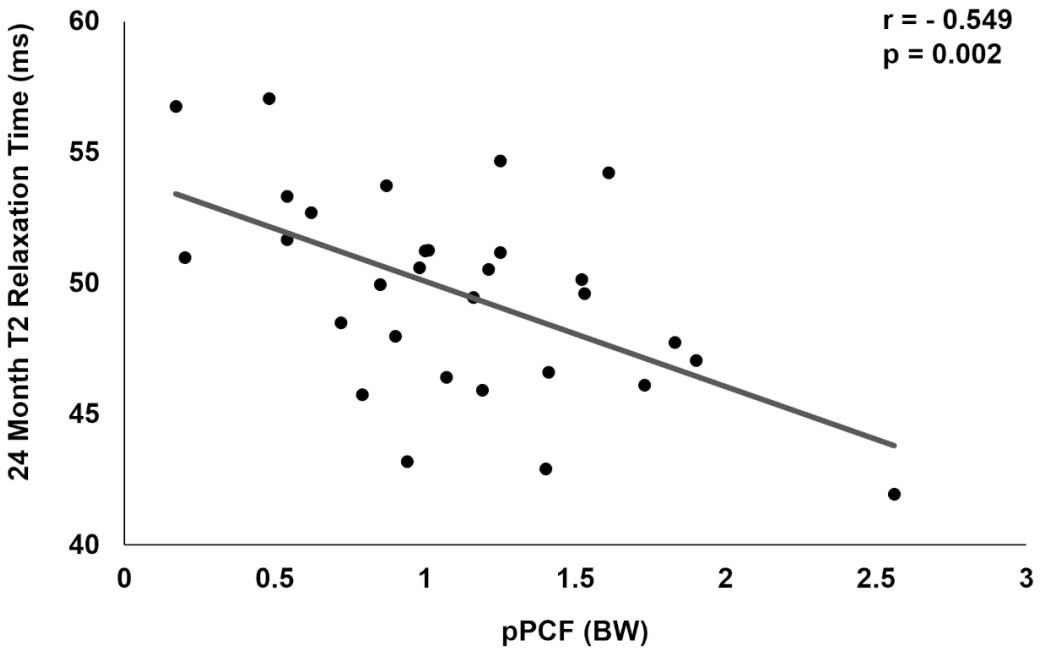

Figure 12 Association between 3-month peak patellofemoral contact force (pPCF) and 24-month total trochlear T_2 relaxation time. A prolonged T_2 relaxation time is indicative of collagen matrix degradation. Trochlear cartilage T_2 relaxation time was negatively associated with pPCF, suggesting that smaller patellofemoral loads 3 months after ACLR were associated with worse trochlear cartilage health 24-months after surgery. *Note*: Y-axis begins at 40 ms rather than 0 ms.

Similarly, there was a significant negative association with a large effect size between pKFA at 3 months and trochlear cartilage T_2 relaxation times at 24-months (**Figure 13**).

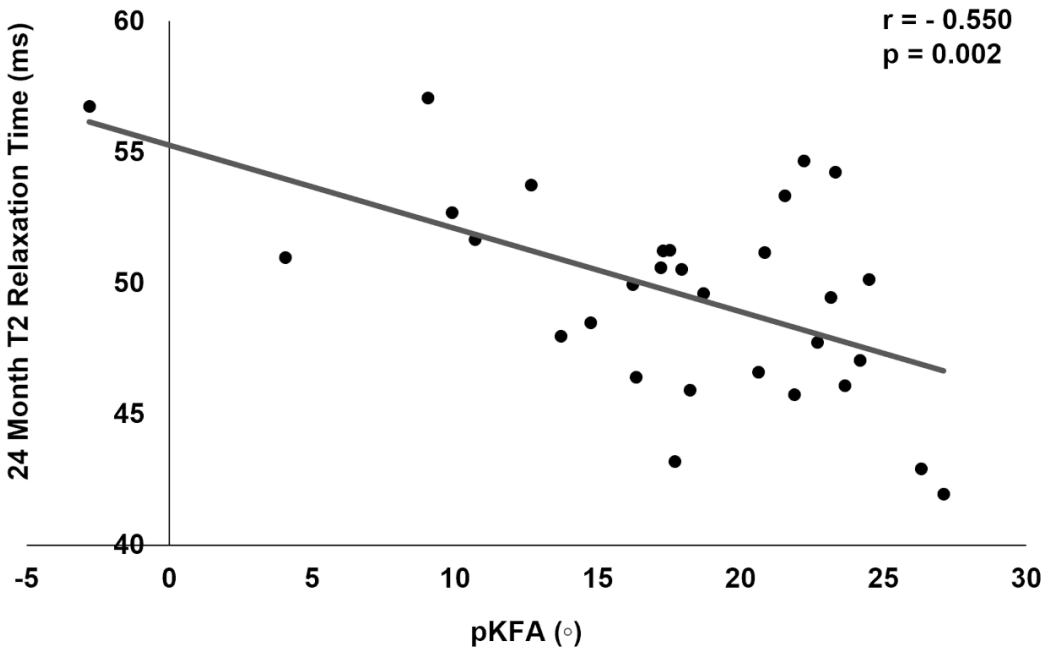

Figure 13 Association between 3-month peak knee flexion angle (pKFA) and 24-month total trochlear T_2 relaxation time. A prolonged T_2 relaxation time is indicative of collagen matrix degradation. Trochlear cartilage T_2 relaxation time was negatively associated with pKFA, suggesting that smaller pKFAs 3 months after ACLR were associated with worse trochlear cartilage health 24-months after surgery. *Note*: Y-axis begins at 40 ms rather than 0 ms.

The association between 3-month pKFM and 24-month trochlear cartilage T_2 relaxation times was similarly significant and negative but had a medium effect size (**Figure 14**).

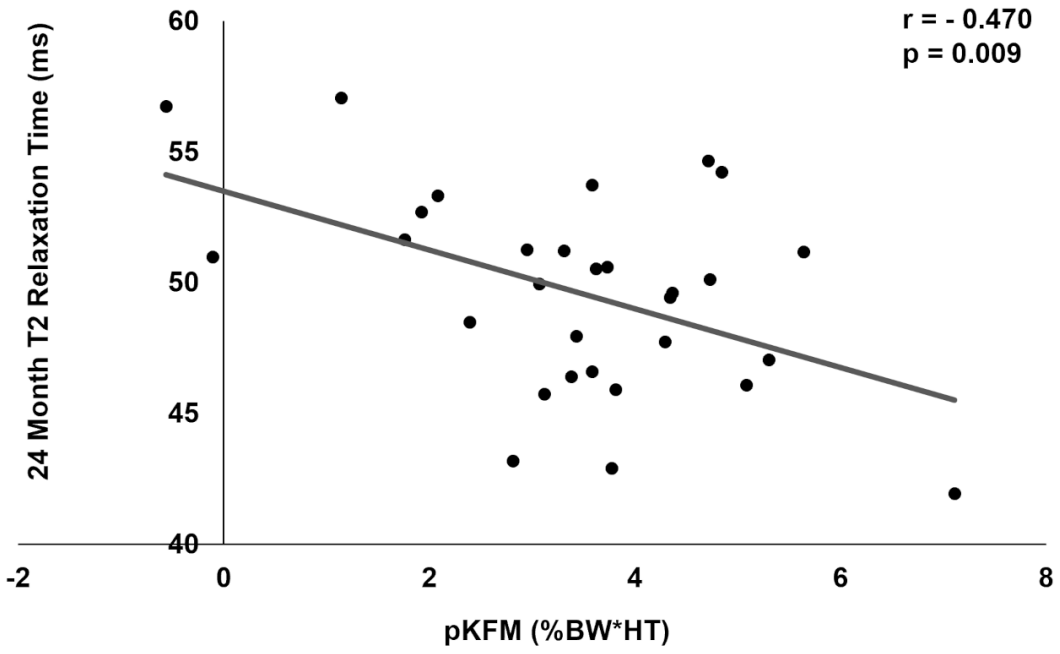

Figure 14 Association between 3-month peak knee flexion moment (pKFM) and 24-month total trochlear T_2 relaxation time. A prolonged T_2 relaxation time is indicative of collagen matrix degradation. Trochlear cartilage T_2 relaxation time was negatively associated with pKFM, suggesting that smaller pKFMs 3 months after ACLR were associated with worse trochlear cartilage health 24-months after surgery. *Note*: Y-axis begins at 40 ms rather than 0 ms.

Finally, the association between walking speed and trochlear cartilage T_2 relaxation times was significant, was negative, and had a medium effect size (**Figure 15**).

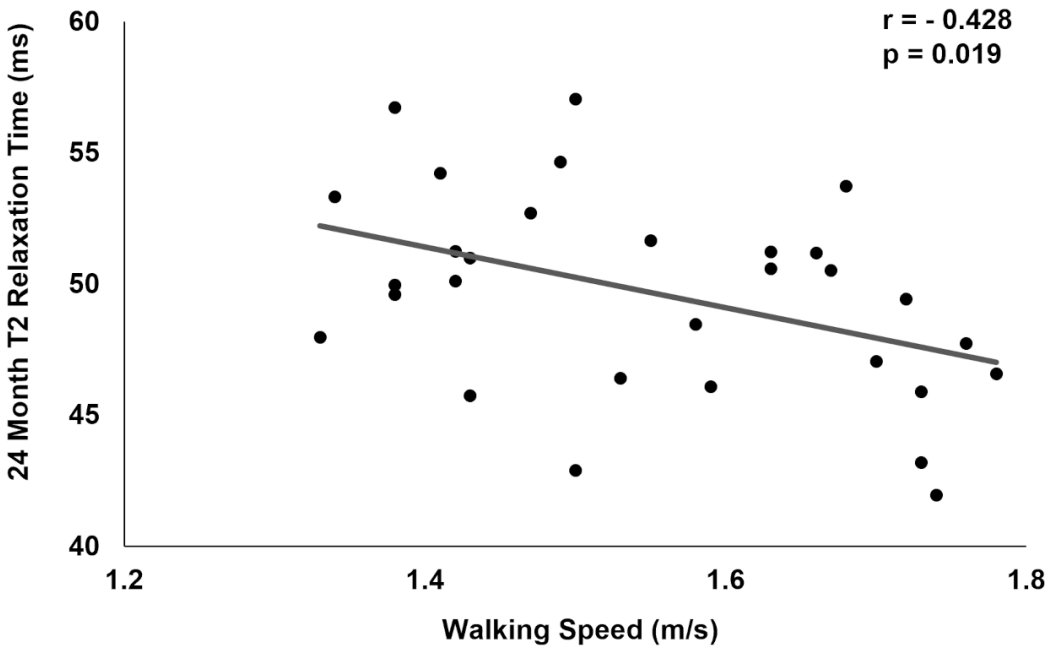

Figure 15 Association between 3-month walking speed and 24-month total trochlear T_2 relaxation time. A prolonged T_2 relaxation time is indicative of collagen matrix degradation. Trochlear cartilage T_2 relaxation time was negatively associated with walking speed, suggesting that slower walking speeds 3 months after ACLR were associated with worse trochlear cartilage health 24-months after surgery. *Note*: Y-axis begins at 40 ms rather than 0 ms and the X-axis begins at 1.2 m/s rather than 0 m/s.

These associations were mirrored within the deep and superficial layers, where every biomechanical variable of interest had a significant negative association with both deep and superficial T_2 relaxation times. The only exception to this was walking speed which was not significantly associated with deep layer trochlear T_2 relaxation times ($p = 0.097$, **Table 5**). No significant associations were seen between the biomechanical variables of interest and total patellar T_2 relaxation times (**Table 4**); however, small effect sizes were observed for the correlations involving pKFA and walking speed. When further subdivided into deep and superficial layers there was still

no association between the biomechanical variables and patellar T_2 relaxation times (**Table 5**).

Table 5 Involved Limb - Association between 3-month walking gait mechanics and 24-month deep and superficial patellar and trochlear cartilage T_2 relaxation times.

Deep Layer				
Gait Variable	**Region**	**r**	**Effect Size (R^2)**	**p Value**
pPCF	Patella	- 0.052	0.003	0.783
	Trochlea	**- 0.493**	**0.243**	**0.006**
pKFA	Patella	- 0.110	0.012	0.564
	Trochlea	**- 0.498**	**0.248**	**0.005**
pKFM	Patella	- 0.061	0.004	0.747
	Trochlea	**- 0.461**	**0.213**	**0.010**
Walking Speed	Patella	- 0.298	0.089	0.110
	Trochlea	- 0.309	0.095	0.097
Superficial				
Gait Variable	**Region**	**r**	**Effect Size (R^2)**	**p Value**
pPCF	Patella	- 0.100	0.010	0.598
	Trochlea	**- 0.485**	**0.235**	**0.007**
pKFA	Patella	- 0.166	0.028	0.380
	Trochlea	**- 0.492**	**0.242**	**0.006**
pKFM	Patella	0.032	0.001	0.866
	Trochlea	**- 0.382**	**0.146**	**0.037**
Walking Speed	Patella	- 0.231	0.053	0.220
	Trochlea	**- 0.450**	**0.203**	**0.013**

3 Month Gait vs 24 Month T_2 Relaxation Times – Uninvolved Limb

There were no significant associations between any biomechanical variable of interest and uninvolved limb total T_2 relaxation times, regardless of region of cartilage (**Table 6**).

Table 6 Uninvolved Limb - Association between 3-month walking gait mechanics and 24-month total patellar and trochlear cartilage T_2 relaxation times.

Gait Variable	Region	r	Effect Size (R^2)	p Value
pPCF	Patella	- 0.202	0.041	0.282
	Trochlea	0.084	0.007	0.660
pKFA	Patella	- 0.214	0.046	0.257
	Trochlea	0.011	< 0.001	0.952
pKFM	Patella	- 0.164	0.027	0.390
	Trochlea	- 0.052	0.003	0.786
Walking Speed	Patella	- 0.152	0.023	0.423
	Trochlea	- 0.128	0.016	0.500

When further subdivided into deep and superficial layers, there was still no significant associations between any of the variables assessed (**Table 7**)

Table 7 Uninvolved Limb - Association between 3-month walking gait mechanics and 24-month deep and superficial patellar and trochlear cartilage T_2 relaxation times.

Deep Layer				
Gait Variable	**Region**	**r**	**Effect Size (R^2)**	**p Value**
pPCF	Patella	- 0.225	0.051	0.232
	Trochlea	0.076	0.006	0.690
pKFA	Patella	- 0.219	0.048	0.246
	Trochlea	0.080	0.006	0.673
pKFM	Patella	- 0.184	0.034	0.329
	Trochlea	- 0.060	0.004	0.753
Walking Speed	Patella	- 0.142	0.020	0.452
	Trochlea	- 0.049	0.002	0.796
Superficial Layer				
Gait Variable	**Region**	**r**	**Effect Size (R^2)**	**p Value**
pPCF	Patella	- 0.204	0.042	0.279
	Trochlea	0.101	0.010	0.594
pKFA	Patella	- 0.256	0.065	0.173
	Trochlea	- 0.053	0.003	0.779
pKFM	Patella	- 0.198	0.039	0.295
	Trochlea	- 0.015	<0.001	0.938

Table 2 continued

Walking Speed	Patella	- 0.145	0.021	0.444
	Trochlea	- 0.183	0.034	0.333

Discussion

The purpose of this study was to examine patellofemoral cartilage health, as assessed by T_2 relaxation times, 24-months after ACLR and to determine if these measures of cartilage health were associated with patellofemoral load and other knee gait mechanics 3 months after surgery. We found that individuals displayed prolonged T_2 relaxation times in the trochlear cartilage of the involved limb 24-months after surgery, indicating worse cartilage health. We also found that patellofemoral loading and other knee gait mechanics 3 months after surgery were negatively associated with 24-month femoral trochlear cartilage T_2 relaxation times. This is one of only a few studies that have examined patellofemoral T_2 relaxation times after ACLR.[103–105] Additionally, this is the first study to examine how patellofemoral loading is associated with cartilage degradation after ACLR and the first to examine longitudinal associations between knee gait mechanics and patellofemoral qMRI variables post-surgery. Altogether these results add to the growing body of literature surrounding patellofemoral OA after ACLR and provide insight into how potentially modifiable mechanisms for disease development early after surgery are associated with long-term cartilage health.

Our first hypothesis, that the involved limb would display significantly prolonged patellofemoral T_2 relaxation times (vs. uninvolved) 24 months after ACLR, was partially supported. T_2 relaxation times were significantly prolonged within trochlear cartilage but not in patellar cartilage. These results agree with the findings of

Kim et al. (2018)[103] and Li et al. (2018)[104], both of whom observed prolonged T_2 relaxation times only within trochlear cartilage 3 years after surgery. These results also align well with reports that morphometric signs of patellofemoral OA after ACLR originate within trochlear cartilage.[109] While there were no differences between limbs in patellar cartilage, 23% of individuals displayed involved limb total T_2 relaxation times at least 2 ms greater than the uninvolved limb (equivalent to the average difference in trochlear cartilage). This may suggest that at least a subset of these individuals are at risk of long-term patellar cartilage degradation, however future follow up is needed to examine this possibility. When cartilage was further subdivided into deep and superficial layers, a significant difference between limbs was only present within the deep layer of trochlear cartilage. This contradicts the findings of Kim et al. (2018)[103] who found significant differences between limbs only in the superficial layers. The average T_2 relaxation times found in this study were also shorter than those found by Kim et al. (2018). This could be due to a variety of reasons including that our sample was younger (23 ± 7 years vs. 34 ± 8 years), had an earlier follow up (2 years vs. 3 years), had more participants (30 vs. 10), utilized different acquisition and processing techniques, and were analyzed using different slices of cartilage.[103] Comparisons with the magnitudes of Li et al. (2018)[104] were not possible as they only reported the interlimb differences in T_2 relaxation times. Overall, the results of this study provide new insights into the timeline of OA development after surgery and align well with reports of increased risk of OA development within trochlear cartilage following ACLR. Future work should examine longitudinal changes in patellofemoral T_2 relaxation times after ACLR and include longer-term follow-up.

Our second hypothesis, that smaller values of the knee gait biomechanical variables of interest at 3 months would be associated with prolonged involved limb patellofemoral T_2 relaxation times at 24 months, was largely supported.

To the best of our knowledge, this is the first study to examine the association between patellofemoral loading, as assessed by patellofemoral contact force, and knee cartilage health after ACLR. While many assume OA development stems from overloading of the joint, there is a growing body of evidence suggesting that underloading may be equally detrimental. Within the medial tibiofemoral compartment, underloading of the involved limb 6 months after ACLR is associated with radiographic osteoarthritis development 5 years after surgery.[48] Limited evidence suggests that underloading of the patellofemoral compartment occurs during everyday tasks, such as walking, and during more dynamic activities such as running and single leg hopping.[87,89,106] The results of this study indicate that underloading of the patellofemoral compartment during walking gait 3 months after surgery is associated with worse trochlear cartilage health 24-months after surgery. This may be explained by the fact that cartilage is a mechanosensitive tissue, with many critical processes within the joint dependent on the loading environment.[18,19] For example, chondrocytes, which are essential for cartilage matrix synthesis, rely on mechanical stimuli.[18,19] Without proper loading chondrocyte function could be disrupted leading to alterations in collagen matrix synthesis and consequently degradation.[19] Studies investigating cartilage immobilization in animal models support this notion as immobilization was associated with both structural and biochemical alterations typically seen in the initial stages of OA.[97] Thus, underloading of the patellofemoral compartment after ACLR, as seen here, has the potential to disrupt and degrade the

biochemical and structural components of cartilage. It should be noted that this study did not examine the influence of loading history on long-term cartilage degradation. Cumulative load over time may provide important insights into the mechanisms for OA development; thus, future work should examine this potential variable.

Smaller involved limb pKFAs during gait, compared to the uninvolved limb and healthy controls, are commonly reported after ACLR.[40,43–45] Our results suggest that smaller involved limb pKFAs 3 months after ACLR are associated with worse trochlear cartilage health 24-months after surgery. In the context of the patellofemoral compartment, alterations in pKFA could shift where load is applied to patellar and trochlear cartilage. Altered load location is hypothesized to be a potential mechanism for OA development as this may load cartilage not capable of sustaining typical day-to-day forces.[54,67,75,77,78] This, in turn, could result in a repeated relative overloading of patellofemoral cartilage that could lead to cartilage degradation. These results seemingly contradict the findings of Williams et al. (2021)[110] who found that greater knee flexion angle at heel-strike 2 years after surgery was associated with worse patellofemoral qMRI measures at the same time point. However, given differences in where knee flexion angle was examined in these two studies (pKFA vs. KFA at heel-strike), our results may actually be representative of the same phenomenon. Reduced pKFAs and greater knee flexion angles at heel-strike are both likely emblematic of reduced range of motion during gait (i.e., a “stiff-knee” gait), which is commonly reported after ACLR.[78,110,111] Thus, their observation at heel-strike may be in line with our observation at pKFA; suggesting that truncated sagittal plane range of motion during gait is associated with worse trochlear health two years after ACLR.

Alterations in knee flexion moment are also commonly reported after ACLR.[40,43] The results of our study indicate that a smaller pKFM during gait 3 months after ACLR is associated with prolonged trochlear T_2 relaxation times 24 months after surgery. This contradicts the findings of Williams et al. (2021)[110] who found that greater pKFM was associated with qMRI measures of trochlear degradation at 2 years after surgery. The disagreement of our results may stem from the differences of when pKFM was observed (3 months vs. 24 months). Early reductions in pKFM are common after ACLR and are thought to be adopted as a pain avoidance mechanism.[112] Conversely, evidence indicates that those with existing patellofemoral OA typically display increased pKFMs.[112,113] Thus, greater pKFMs at 24 months may be a consequence of, rather than a mechanism for, patellofemoral OA development. Given reports of MRI defined trochlear OA development as early as one year after ACLR, it may be that Williams et al. (2021)[110] were observing OA driven pKFMs rather than pKFM driven signs of OA degradation.[109] It should also be noted that some argue that KFMs are reflective of knee extensor muscle forces and thus may be proportional to patellofemoral joint contact forces.[113] This assumption fails to account for neuromuscular phenomena such as knee muscle co-contraction, which is commonly reported after ACLR.[61] This, in turn, has the potential to underestimate quadriceps muscle forces and patellofemoral loading. Nonetheless, early reductions in pKFM were associated with worse cartilage health 2 years after surgery, suggesting that pKFM may play an important role in the onset of eventual disease development.

Previous work from our lab found that walking speed 3 months after surgery was the sole biomechanical predictor of trochlear cartilage T_2 relaxation times 6 months after surgery.[105] The results of the present study reinforce this finding, as

walking speed 3 months after ACLR was significantly associated with trochlear cartilage T_2 relaxation times 24-months after surgery. Some believe walking speed is an important measure of function and that, given the relative ease in which it can be measured, it may be an ideal initial target in explorative rehabilitation efforts.[45,114] While slower walking speed was associated with prolonged T_2 relaxation times this does not necessarily mean that having individuals walk with increased speed after ACLR will preserve long-term cartilage health. In fact, increased speed may also be detrimental to cartilage. Numerous studies indicate that faster walking speed after ACLR is associated with increased biomechanical asymmetry between limbs.[115,116] Asymmetries in knee biomechanics are linked to prolonged tibiofemoral T_2 relaxation times after ACLR.[11] While walking speed may represent an easy to measure and modifiable mechanical feature of movement, more work is needed to fully understand its role in OA development after ACLR and its viability as a rehabilitation target.

There are several limitations that need to be considered when interpreting the results of this study. The presence of significant associations between these variables does not necessarily imply cause and effect. Other underlying factors within the knee, such as the inflammatory response after surgery, may be responsible for the mechanics and relaxation times observed.[66] We are not able to determine why patellar cartilage did not exhibit signs of degradation or associations with gait variables. It could be that the thicker patellar cartilage, compared to trochlear, may provide the patella with more protection from post-surgical biomechanical and biochemical alterations.[117] These results align well with prior work from Culvenor et. al. (2015)[109] who found that trochlear cartilage was the most affected region after ACLR. Future work needs to explore these region-specific differences. Linear regression is susceptible to outliers in

data. We assessed the influence of outliers on the associations examined and found that they did not meaningfully change the results, hence they were not removed. Participant surgical and rehabilitation factors, such as graft type, presence of meniscectomy, and rehabilitation approach were not controlled for in this study. While ideal, controlling for these variables across the broader ACLR population is not feasible and thus the results of our study may be more generalizable. We would like to note that participants with meniscal repairs were excluded from this study as this procedure is associated with a prolonged period of non-weight bearing post-surgery that would strongly influence the knee mechanics observed at 3 months.

In conclusion, alterations in involved limb femoral trochlear cartilage T_2 relaxation times are apparent 24-months after ACLR. Patellofemoral loading and other knee mechanics during walking gait 3 months after surgery were strongly associated with these T_2 relaxation times, where smaller loads, smaller knee flexion angles and moments, and slower walking speeds were all associated with worse cartilage health. This suggests that how an individual walks early after ACLR may influence the long-term health of their patellofemoral cartilage. Future studies should explore the viability of these potentially modifiable variables in rehabilitative efforts aimed at preventing long-term post-traumatic knee osteoarthritis.

Chapter 5

CONCLUSIONS AND FUTURE WORK

Aim 1

Conclusions

The results of this Aim indicate that loading patterns other than consistent interlimb symmetry early after ACLR are associated with prolonged involved limb deep layer T_2 relaxation times 24 months after surgery, suggesting worse cartilage health. Thus, consistent interlimb loading symmetry may be a viable target for explorative rehabilitation efforts aimed at preventing or delaying the long-term development of OA after ACLR. Interestingly, the group that was initially asymmetric at 3 months but became symmetric by 6 months still displayed significantly prolonged T_2 relaxation times compared to the consistently symmetric group. This suggests that even a return to interlimb symmetry in pMCF by 6 months after surgery may not prevent cartilage deterioration. These findings raise several questions and may have important implications for rehabilitation efforts.

Future Work

A limited number of participants completed this study; thus, the findings presented here could inform the design of a larger study directly aimed at assessing the influence of loading history on the long-term development of knee OA. This could include examining knee loading patterns over a longer duration of time rather than just

the two time points examined here. This could also feature the inclusion of complimentary qMRI assessments, such as $T1_{\rho}$ and UTE-T_2^* mapping techniques, which may provide deeper insights into alterations occurring in cartilage and include long-term radiographic assessments to verify the MRI findings. This could also be designed to incorporate recent advancements in how qMRI variables are assessed, such as voxel-based relaxometry. This technique is a fully automated approach to assessing qMRI maps that is also capable of identifying focal regions of altered cartilage health that may be missed in traditional ROI-based approaches.[118–120]

While loading history appears to be associated with signs of OA development few have explored interventions aimed at altering gait mechanics to prevent disease development. Tools such as split-belt treadmills[121], variable stiffness treadmills[122], modified footwear[123], and wearable exoskeletons[124] as well as techniques such as gait-based[125] biofeedback training may be useful in exploration of potential rehabilitative interventions. The viability of these tools and techniques in rehabilitation after ACLR and how they influence neuromuscular control and the mechanics of other regions of the body (e.g., hip and ankle mechanics) remains to be explored.

Additionally, more comprehensive measures are needed to capture the complex nature of the knee's biomechanical environment. Finite element models may be one solution to this as they can capture stress and strain distributions throughout cartilage. Recent work by Bolcos et al. (2020)[81] and Orozco et al. (2021)[82] have shown promise in linking alterations in stresses and strains to qMRI variables after ACLR. Further work using these models could explore the layer specific associations seen in the results presented in this dissertation. Additionally, long-term analysis of stress

patterns and how they change may provide better insights into the mechanisms behind OA development.

Aim 2

Conclusions

Our hypotheses were partially supported. Patellofemoral underloading during gait exists early after ACLR but is resolved by 2 years after surgery. The involved limb's patellofemoral contact forces increase with time towards those of the uninvolved limb, however it appears that most of the changes in the involved limb occur early after surgery. The uninvolved limb exhibited some changes with time; these changes, however, were small and not statistically significant. This work represents a first step towards understanding the loading environment of the patellofemoral compartment during walking after ACLR and how it changes in the early months after surgery. These loading patterns are similar to those observed in the medial tibiofemoral compartment of the knee which were linked to radiographic OA development.[48] Thus, the early loading patterns seen within this study may play a role in the development of patellofemoral OA, which is commonly reported after ACLR.

Future Work

There are several avenues in which the work in this study could be expanded. First and foremost, the use of traditional motion capture techniques and simplified models severely limit that amount of information that can be obtained regarding the patellofemoral compartment. More sophisticated tools, such as dynamic MRIs[126,127] or biplanar fluoroscopy[102,126], could provide insights into patellar tracking. This information, in turn, could more accurately reflect how load location and magnitude is

changed after ACLR. Additionally, these approaches would enable investigations into the role that subject-specific variations in patellofemoral geometry have in the onset of OA after ACLR.[126,128] It should be noted though, that these approaches are generally limited in their ability to capture typical human body motion and loads during activities of daily living such as gait. Finding a means to accurately characterize the complexities of the patellofemoral biomechanical environment after ACLR during day-to-day activities remains an area of high interest.

In addition, investigations into the influence of surgical factors and rehabilitation choices on patellofemoral biomechanics and loading are warranted. Limited evidence exists about the influence of concomitant meniscal[89] procedures on patellofemoral load after ACLR and no information exists on the influence of graft type on patellofemoral load. The impact of these variables on patellar tracking also warrants investigation. Furthermore, the influence of quadriceps strength, and how it changes after ACLR, on the patellofemoral compartment remains to be investigated. Other potential disrupting factors, such as tunnel placement and graft tensioning during surgery, also warrant exploration.

Finally, studies utilizing finite element models to investigate patellofemoral stresses and their distribution after ACLR may help further shed light on the mechanisms for OA development.

Aim 3

Conclusions

Alterations in involved limb femoral trochlear cartilage T_2 relaxation times are apparent 24-months after ACLR. This suggests that alterations in patellofemoral knee cartilage health are present and detectable 2 years after surgery. Patellofemoral loading and other knee mechanics during walking 3 months after surgery were strongly associated with these T_2 relaxation times, where smaller loads, smaller knee flexion angles and moments, and slower walking speed were all associated with worse cartilage health. This suggests that how an individual walks early after ACLR may influence the long-term health of their patellofemoral cartilage. These results are the first to establish a biomechanical basis for long-term patellofemoral cartilage degradation after ACLR. This information could have important implications for the design of post-surgical rehabilitation.

Future Work

There is a limited amount of information regarding patellofemoral T_2 relaxation times after ACLR, most of which have been confined to the later years after surgery. Investigations into these variables early after surgery may provide unique insights into how patellofemoral OA develops after ACLR. Additionally, to the best of our knowledge, prior studies on T_2 relaxation times have been confined to cross-sectional analyses. Longitudinal examination of patellofemoral T_2 relaxation times that encompass both early and long-term assessments may reveal more information about the pathogenesis of this disease within this region of the knee.

No study has assessed how changes in patellofemoral load over time influences long-term cartilage health. As shown in Chapter 2, loading history may play an important role in long-term disease development. Studies examining loading history

and measures of daily cumulative load may provide more insights into the mechanisms for disease development within this compartment of the knee.

While it appears that altered loading is connected to patellofemoral T_2 relaxation times, it is not known if alterations in patellar tracking are associated with these measures. Additionally, the influence of surgical choices and concomitant procedures on patellofemoral health are not understood. While it does not appear that graft type is related to patellofemoral OA development after ACLR[62], the influence of graft type and meniscal status on patellofemoral T_2 relaxation times should be examined. Finally, alterations in patellofemoral stresses after ACLR remain unexplored. Stress distribution patterns within the patellofemoral compartment after ACLR should be compared to qMRI maps to examine the role that altered stress distributions could have in the development of OA.

REFERENCES

1. Noyes FR. 2009. The function of the human anterior cruciate ligament and analysis of singleand double-bundle graft reconstructions. Sports Health 1(1):66–75.

2. Kiapour AM, Murray MM. 2014. Basic science of anterior cruciate ligament injury and repair. Bone Jt. Res. 3(2):20–31.

3. Renström PA. 2013. Eight clinical conundrums relating to anterior cruciate ligament (ACL) injury in sport: Recent evidence and a personal reflection. Br. J. Sports Med. 47(6):367–372.

4. Sanders TL, Pareek A, Kremers HM, et al. 2017. Long-term follow-up of isolated ACL tears treated without ligament reconstruction. Knee Surgery, Sport. Traumatol. Arthrosc. 25(2):493–500.

5. Sommerfeldt M, Raheem A, Whittaker J, et al. 2018. Recurrent Instability Episodes and Meniscal or Cartilage Damage After Anterior Cruciate Ligament Injury: A Systematic Review. Orthop. J. Sport. Med. 6(7):1–9.

6. Paschos NK, Howell SM. 2016. Anterior cruciate ligament reconstruction: Principles of treatment. EFORT Open Rev. 1(11):398–408.

7. Simon D, Mascarenhas R, Saltzman BM, et al. 2015. The Relationship between Anterior Cruciate Ligament Injury and Osteoarthritis of the Knee. Adv. Orthop. 2015:1–11.

8. Lohmander LS, Englund PM, Dahl LL, Roos EM. 2007. The long-term consequence of anterior cruciate ligament and meniscus injuries: Osteoarthritis. Am. J. Sports Med. 35(10):1756–1769.

9. Barenius B, Ponzer S, Shalabi A, et al. 2014. Increased risk of osteoarthritis after anterior cruciate ligament reconstruction: A 14-year follow-up study of a randomized controlled trial. Am. J. Sports Med. 42(5):1049–1057.

10. Roos H, Adalberth T, Dahlberg L, Lohmander LS. 1995. Osteoarthritis of the knee after injury to the anterior cruciate ligament or meniscus: the influence of time and age. Osteoarthr. Cartil. 3(4):261–267.

11. Williams JR, Neal K, Alfayyadh A, et al. 2022. Knee cartilage T2 relaxation times 3 months after ACL reconstruction are associated with knee gait variables linked to knee osteoarthritis. J. Orthop. Res. 40(1):252–259.

12. Li X, Kuo D, Theologis A, et al. 2011. Cartilage in Anterior Cruciate Ligament–Reconstructed Knees: MR Imaging T1 ρ and T2—Initial Experience with 1-year Follow-up. Radiology 258(2):505–514.

13. Sophia Fox AJ, Bedi A, Rodeo SA. 2009. The basic science of articular cartilage: Structure, composition, and function. Sports Health 1(6):461–468.

14. Matzat SJ, van Tiel J, Gold GE, Oei EHG. 2013. Quantitative MRI techniques of cartilage composition. Quant. Imaging Med. Surg. 3(3):162–174.

15. Mosher TJ, Dardzinski BJ. 2004. Cartilage MRI T2 relaxation time mapping: Overview and applications. Semin. Musculoskelet. Radiol. 8(4):355–368.

16. Cohen NP, Foster RJ, Mow VC. 1998. Composition and dynamics of articular cartilage: Structure, function, and maintaining healthy state. J. Orthop. Sports Phys. Ther. 28(4):203–215.

17. Maldonado M, Nam J. 2013. The role of changes in extracellular matrix of cartilage in the presence of inflammation on the pathology of osteoarthritis. Biomed Res. Int. 2013.

18. Vincent TL, Wann AKT. 2019. Mechanoadaptation: articular cartilage through thick and thin. J. Physiol. 597(5):1271–1281.

19. Sanchez-Adams J, Leddy HA, McNulty AL, et al. 2014. The Mechanobiology of Articular Cartilage: Bearing the Burden of Osteoarthritis. Curr. Rheumatol. Rep. 16(10):1–9.

20. Buckwalter J, Mankin H. 1998. Articular Cartilage: Degeneration and Osteoarthritis, Repair, Regeneration, and Transplantation. Instr Course Lect 47:487–504.

21. Kellgren J, JS L. 1957. Radiological Assessment of osteo-arthrosis. Ann. Rheum. Dis. 16(4):494–502.

22. MacKay C, Jaglal SB, Sale J, et al. 2014. A qualitative study of the consequences of knee symptoms: “It’s like you’re an athlete and you go to a couch potato.” BMJ Open 4(10):1–10.

23. Menashe L, Hirko K, Losina E, et al. 2012. The diagnostic performance of MRI

in osteoarthritis: a systematic reveiw and meta-analysis. Osteoarthr. Cartil. 20(1):13–21.

24. Peterfy CG, Guermazi A, Zaim S, et al. 2004. Whole-organ magnetic resonance imaging score (WORMS) of the knee in osteoarthritis. Osteoarthr. Cartil. 12(3):177–190.

25. Kornaat PR, Ceulemans RYT, Kroon HM, et al. 2005. MRI assessment of knee osteoarthritis: Knee Osteoarthritis Scoring System (KOSS) - Inter-observer and intra-observer reproducibility of a compartment-based scoring system. Skeletal Radiol. 34(2):95–102.

26. Hunter DJ, Lo GH, Gale D, et al. 2008. The reliability of a new scoring system for knee osteoarthritis MRI and the validity of bone marrow lesion assessment: BLOKS (Boston-Leeds Osteoarthritis Knee Score). Ann. Rheum. Dis. 67(2):206–211.

27. Hunter DJ, Guermazi A, Lo GH, et al. 2011. Evolution of semi-quantitative whole joint assessment of knee OA: MOAKS (MRI Osteoarthritis Knee Score). Osteoarthr. Cartil. 19(8):990–1002.

28. Roemer FW, Hunter DJ, Crema MD, et al. 2016. An illustrative overview of semi-quantitative MRI scoring of knee osteoarthritis: Lessons learned from longitudinal observational studies. Osteoarthr. Cartil. 24(2):274–289.

29. Argentieri EC, Burge AJ, Potter HG. 2018. Magnetic Resonance Imaging of Articular Cartilage within the Knee. J. Knee Surg. 31(2):155–165.

30. Neuman P, Tjörnstrand J, Svensson J, et al. 2011. Longitudinal assessment of femoral knee cartilage quality using contrast enhanced MRI (dGEMRIC) in patients with anterior cruciate ligament injury - comparison with asymptomatic volunteers. Osteoarthr. Cartil. 19(8):977–983.

31. Tjörnstrand J, Neuman P, Svensson J, et al. 2019. Osteoarthritis development related to cartilage quality-the prognostic value of dGEMRIC after anterior cruciate ligament injury. Osteoarthr. Cartil. 27(11):1647–1652.

32. Braun HJ, Gold GE. 2011. Advanced MRI of articular cartilage. Imaging Med. 3(5):541–555.

33. Bangerter NK, Tarbox GJ, Taylor MD, Kaggie JD. 2016. Quantitative sodium magnetic resonance imaging of cartilage, muscle, and tendon. Quant. Imaging Med. Surg. 6(6):699–714.

34. Theologis AA, Haughom B, Liang F, et al. 2014. Comparison of T1rho relaxation times between ACL-reconstructed knees and contralateral uninjured knees. Knee Surgery, Sport. Traumatol. Arthrosc. 22(2):298–307.

35. Watkins LE, Rubin EB, Mazzoli V, et al. 2020. Rapid volumetric gagCEST imaging of knee articular cartilage at 3 T: evaluation of improved dynamic range and an osteoarthritic population. NMR Biomed. 33(8):1–12.

36. Singh A, Haris M, Cai K, et al. 2012. Chemical Exchange Saturation Transfer Magnetic Resonance Imaging of Human Knee Cartilage at 3 T and 7 T. Magn. Reson. Med. 68(2):558–594.

37. David-Vaudey E, Ghosh S, Ries M, Majumdar S. 2004. T2relaxation time measurements in osteoarthritis. Magn. Reson. Imaging 22(5):673–682.

38. Bydder M, Rahal A, Fullerton GD, Bydder GM. 2007. The magic angle effect: A source of artifact, determinant of image contrast, and technique for imaging. J. Magn. Reson. Imaging 25(2):290–300.

39. Uhlrich SD, Silder A, Beaupre GS, et al. 2018. Subject-specific toe-in or toe-out gait modifications reduce the larger knee adduction moment peak more than a non-personalized approach. J. Biomech. 66:103–110.

40. Slater L V., Hart JM, Kelly AR, Kuenze CM. 2017. Progressive Changes in Walking Kinematics and Kinetics After Anterior Cruciate Ligament Injury and Reconstruction: A Review and Meta-Analysis. J. Athl. Train. 52(9):847–860.

41. Arhos EK, Capin JJ, Buchanan TS, Snyder-Mackler L. 2021. Quadriceps Strength Symmetry Does Not Modify Gait Mechanics After Anterior Cruciate Ligament Reconstruction, Rehabilitation, and Return-to-Sport Training. Am. J. Sports Med. 49(2):417–425.

42. Gokeler A, Benjaminse A, van Eck CF, et al. 2013. Return of normal gait as an outcome measurement in acl reconstructed patients. A systematic review. Int. J. Sports Phys. Ther. 8(4):441–451.

43. Neal K, Williams JR, Alfayyadh A, et al. 2022. Knee joint biomechanics during gait improve from 3 to 6 months after anterior cruciate ligament reconstruction. J. Orthop. Res..

44. Davis-Wilson HC, Pfeiffer SJ, Johnston CD, et al. 2020. Bilateral Gait Six and Twelve Months Post-ACL Reconstruction Compared with Controls. Med. Sci. Sport. Exerc. 52(4):785–794.

45. Capin JJ, Khandha A, Zarzycki R, et al. 2018. Gait mechanics and tibiofemoral loading in men of the ACL-SPORTS randomized control trial. J. Orthop. Res. 36(9):2364–2372.

46. Hooper DM, Morrissey MC, Drechsler WI, et al. 2002. Gait analysis 6 and 12 months after anterior cruciate ligament reconstruction surgery. Clin. Orthop. Relat. Res. (403):168–178.

47. Zabala ME, Favre J, Scanlan SF, et al. 2013. Three-Dimensional Knee Moments of ACL Reconstructed and Control Subjects during Gait, Stair Ascent, and Stair Descent. J. Biomech. 46(3):515–520.

48. Wellsandt E, Gardinier ES, Manal K, et al. 2016. Decreased knee joint loading associated with early knee osteoarthritis after anterior cruciate ligament injury. Am. J. Sport. Med. 44(1):143–151.

49. Kumar D, Su F, Wu D, et al. 2018. Frontal Plane Knee Mechanics and Early Cartilage Degeneration in People With Anterior Cruciate Ligament Reconstruction: A Longitudinal Study. Am. J. Sports Med. 46(2):378–387.

50. Hart HF, Culvenor AG, Collins NJ, et al. 2016. Knee kinematics and joint moments during gait following anterior cruciate ligament econstruction: A systematic review and meta-analysis. Br. J. Sports Med. 50(10):597–612.

51. Scanlan SF, Chaudhari AMW, Dyrby CO, Andriacchi TP. 2010. Differences in tibial rotation during walking in ACL reconstructed and healthy contralateral knees. J. Biomech. 43(9):1817–1822.

52. Kaur M, Ribeiro DC, Theis JC, et al. 2016. Movement Patterns of the Knee During Gait Following ACL Reconstruction: A Systematic Review and Meta-Analysis. Sport. Med. 46(12):1869–1895.

53. Khandha A, Manal K, Wellsandt E, et al. 2017. Gait mechanics in those with/without medial compartment knee osteoarthritis 5 years after anterior cruciate ligament reconstruction. J. Orthop. Res. 35(3):625–633.

54. Chu CR, Andriacchi TP. 2015. Dance Between Biology, Mechanics, and Structure: A Systems-Based Approach to Developing Osteoarthritis Prevention Strategies. J. Orthop. Res. 33(7):939–947.

55. Titchenal MR, Williams AA, Chehab EF, et al. 2018. Cartilage Subsurface Changes to Magnetic Resonance Imaging UTE-T2* 2 Years After Anterior Cruciate Ligament Reconstruction Correlate With Walking Mechanics Associated With Knee Osteoarthritis. Am. J. Sports Med. 46(3):565–572.

56. Pfeiffer SJ, Spang J, Nissman D, et al. 2019. Gait Mechanics and T1ρ MRI of Tibiofemoral Cartilage 6 Months after ACL Reconstruction. Med. Sci. Sports Exerc. 51(4):630–639.

57. Teng HL, Wu D, Su F, et al. 2017. Gait Characteristics Associated With a Greater Increase in Medial Knee Cartilage T1ρ and T2 Relaxation Times in Patients Undergoing Anterior Cruciate Ligament Reconstruction. Am. J. Sports Med. 45(14):3262–3271.

58. Buchanan TS, Lloyd DG, Manal K, Besier TF. 2004. Neuromusculoskeletal Modeling : Estimation of Muscle Forces and Joint Moments and Movements From Measurements of Neural Command. J. Appl. Biomech. 20(4):367–395.

59. Manal K, Buchanan TS. 2013. An Electromyogram-Driven Musculoskeletal Model of the Knee to Predict in Vivo Joint Contact Forces During Normal and Novel Gait Patterns. J. Biomech. Eng. 135(2):1–7.

60. Manal K, Gardinier E, Buchanan TS, Snyder-Mackler L. 2015. A more informed evaluation of medial compartment loading: the combined use of the knee adduction and flexor moments. Osteoarthr. Cartil. 23(7):1107–1111.

61. Blackburn T, Pietrosimone B, Goodwin JS, et al. 2019. Co-activation during gait following anterior cruciate ligament reconstruction. Clin. Biomech. 67:153–159.

62. Culvenor AG, Cook JL, Collins NJ, Crossley KM. 2013. Is patellofemoral joint osteoarthritis an under-recognised outcome of anterior cruciate ligament reconstruction? A narrative literature review. Br. J. Sports Med. 47(2):66–73.

63. Culvenor AG, Collins NJ, Guermazi A, et al. 2016. Early Patellofemoral Osteoarthritis Features One Year after Anterior Cruciate Ligament Reconstruction: Symptoms and Quality of Life at Three Years. Arthritis Care Res. 68(6):784–792.

64. Øiestad BE, Holm I, Engebretsen L, et al. 2013. The prevalence of patellofemoral osteoarthritis 12 years after anterior cruciate ligament reconstruction. Knee Surgery, Sport. Traumatol. Arthrosc. 21(4):942–949.

65. Chu CR, Williams AA, Coyle CH, Bowers ME. 2012. Early Diagnosis to Enable Early Treatment of Pre-Osteoarthritis. Arthritis Res. Ther. 14(3):1–10.

66. Chu CR, Williams AA, Erhart-Hledik JC, et al. 2021. Visualizing pre-osteoarthritis: Integrating MRI UTE-T2* with mechanics and biology to combat osteoarthritis—The 2019 Elizabeth Winston Lanier Kappa Delta Award. J.

Orthop. Res. 39(8):1585–1595.

67. Andriacchi TP, Favre J, Erhart-Hledik JC, Chu CR. 2015. A Systems View of Risk Factors for Knee Osteoarthritis Reveals Insights into the Pathogenesis of the Disease. Ann. Biomed. Eng. 43(2):376–387.

68. Dye SF. 1996. The knee as a biologic transmission with an envelope of function: A theory. Clin. Orthop. Relat. Res. (325):10–18.

69. Li X, Majumdar S. 2013. Quantitative MRI of articular cartilage and its clinical applications. J. Magn. Reson. Imaging 38(5):991–1008.

70. Winby CR, Lloyd DG, Besier TF, Kirk TB. 2009. Muscle and external load contribution to knee joint contact loads during normal gait. J. Biomech. 42(14):2294–2300.

71. Fedorov A, Beichel R, Kalphaty-Cramer J, et al. 2012. 3D Slicer as an image computing platform for the quantitative imaging network. Magn. Reson. Imaging 30(9):1323–1341.

72. Smith HE, Mosher TJ, Dardzinski BJ, et al. 2001. Spatial variation in cartilage T2 of the knee. J. Magn. Reson. Imaging 14(1):50–55.

73. Rothman KJ. 1990. No Adjustments Are Needed For Multiple Comparisons. Epidemiology 1(1):43–46.

74. Lakens D. 2013. Calculating and reporting effect sizes to facilitate cumulative science: A practical primer for t-tests and ANOVAs. Front. Psychol. 4(863):1–12.

75. Andriacchi TP, Koo S, Scanlan SF. 2009. Gait mechanics influence healthy cartilage morphology and osteoarthritis of the knee. J. Bone Jt. Surg. 91(SUPPL. 1):95–101.

76. Favre J, Erhart-Hledik JC, Chehab EF, Andriacchi TP. 2016. Baseline ambulatory knee kinematics are associated with changes in cartilage thickness in osteoarthritic patients over 5 years. J. Biomech. 49(9):1859–1864.

77. Koo S, Rylander JH, Andriacchi TP. 2011. Knee joint kinematics during walking influences the spatial cartilage thickness distribution in the knee. J. Biomech. 44(7):1405–1409.

78. Scanlan SF, Favre J, Andriacchi TP. 2013. The relationship between peak knee extension at heel-strike of walking and the location of thickest femoral cartilage

in ACL reconstructed and healthy contralateral knees. J. Biomech. 46(5):849–854.

79. Jørgensen AEM, Kjær M, Heinemeier KM. 2017. The effect of aging and mechanical loading on the metabolism of articular cartilage. J. Rheumatol. 44(4):410–417.

80. Kiviranta I, Jurvelin J, Tammi M, et al. 1987. Weight bearing controls glycosaminoglycan concentration and articular cartilage thickness in the knee joints of young beagle dogs. Arthritis Rheum. 30(7):801–809.

81. Bolcos PO, Mononen ME, Tanaka MS, et al. 2020. Identification of locations susceptible to osteoarthritis in patients with anterior cruciate ligament reconstruction: Combining knee joint computational modelling with follow-up T1ρ and T2 imaging. Clin. Biomech. 79:1–10.

82. Orozco GA, Bolcos P, Mohammadi A, et al. 2021. Prediction of local fixed charge density loss in cartilage following ACL injury and reconstruction: A computational proof-of-concept study with MRI follow-up. J. Orthop. Res. 39(5):1064–1081.

83. Huber R, Viecelli C, Bizzini M, et al. 2019. Knee extensor and flexor strength before and after anterior cruciate ligament reconstruction in a large sample of patients: influence of graft type. Phys. Sportsmed. 47(1):85–90.

84. Keays SL, Newcombe PA, Bullock-Saxton JE, et al. 2010. Factors Involved in the Development of Osteoarthritis after Anterior Cruciate Ligament Surgery. Am. J. Sports Med. 38(3):455–463.

85. Lee DW, Yeom CH, Kim DH, et al. 2018. Prevalence and predictors of patellofemoral osteoarthritis after anterior cruciate ligament reconstruction with hamstring tendon autograft. Clin. Orthop. Surg. 10(2):181–190.

86. Herrington L, Alarifi S, Jones R. 2017. Patellofemoral Joint Loads during Running at the Time of Return to Sport in Elite Athletes with ACL Reconstruction. Am. J. Sports Med. 45(12):2812–2816.

87. Sritharan P, Schache AG, Culvenor AG, et al. 2020. Between-Limb Differences in Patellofemoral Joint Forces During Running at 12 to 24 Months After Unilateral Anterior Cruciate Ligament Reconstruction. Am. J. Sports Med. 48(7):1711–1719.

88. Bowersock CD, Willy RW, DeVita P, Willson JD. 2017. Reduced step length reduces knee joint contact forces during running following anterior cruciate

ligament reconstruction but does not alter inter-limb asymmetry. Clin. Biomech. 43:79–85.

89. Sritharan P, Schache AG, Culvenor AG, et al. 2022. Patellofemoral and tibiofemoral joint loading during a single-leg forward hop following ACL reconstruction. J. Orthop. Res. 40(1):159–169.

90. Pataky TC, Robinson MA, Vanrenterghem J. 2013. Vector field statistical analysis of kinematic and force trajectories. J. Biomech. 46(14):2394–2401.

91. Pataky TC. 2012. One-dimensional statistical parametric mapping in Python. Comput. Methods Biomech. Biomed. Engin. 15(3):295–301.

92. Yamaguchi GT, Zajac FE. 1989. A planar model of the knee joint to characterize the knee extensor mechanism. J. Biomech. 22(1):1–10.

93. Shelburne KB, Pandy MG. 1997. A musculoskeletal model of the knee for evaluating ligament forces during isometric contractions. J. Biomech. 30(2):163–176.

94. Nisell R, Németh G, Ohlsén H. 1986. Joint forces in extension of the knee: Analysis of a mechanical model. Acta Orthop. 57(1):41–46.

95. van Eijden TMGJ, Kouwenhoven E, Verburg J, Weijs WA. 1986. A mathematical model of the patellofemoral joint. J. Biomech. 19(3):219–229.

96. Shelburne KB, Torry MR, Pandy MG. 2005. Muscle, ligament, and joint-contact forces at the knee during walking. Med. Sci. Sports Exerc. 37(11):1948–1956.

97. Vanwanseele B, Lucchinetti E, Stüssi E. 2002. The effects of immobilization on the characteristics of articular cartilage: Current concepts and future directions. Osteoarthr. Cartil. 10(5):408–419.

98. Voinier D, Neogi T, Stefanik JJ, et al. 2020. Using Cumulative Load to Explain How Body Mass Index and Daily Walking Relate to Worsening Knee Cartialge Damage Over Two Years: The MOST Study. Arthritis Rheumatol. 72(6):957–965.

99. Chmielewski TL, Jones D, Day T, et al. 2008. The association of pain and fear of movement/reinjury with function during anterior cruciate ligament reconstruction rehabilitation. J. Orthop. Sports Phys. Ther. 38(12):746–753.

100. Zarzycki R, Failla M, Capin JJ, Snyder-Mackler L. 2018. Psychological

readiness to return to sport is associated with knee kinematic asymmetry during gait following anterior cruciate ligament reconstruction. J. Orthop. Sports Phys. Ther. 48(12):968–973.

101. Johnson GA, Tramaglini DM, Levine RE, et al. 1994. Tensile and viscoelastic properties of human patellar tendon. J. Orthop. Res. 12(6):796–803.

102. Lin Z, Tang Y, Tan H, Cai D. 2019. Patellofemoral kinematic characteristics in anterior cruciate ligament deficiency and reconstruction. BMC Musculoskelet. Disord. 20(1):1–8.

103. Kim CW, Hosseini A, Lin L, et al. 2018. Quantitative analysis of T2 relaxation times of the patellofemoral joint cartilage 3 years after anterior cruciate ligament reconstruction. J. Orthop. Transl. 12:85–92.

104. Li G, Li JS, Torriani M, Hosseini A. 2018. Short-Term Contact Kinematic Changes and Longer-Term Biochemical Changes in the Cartilage After ACL Reconstruction: A Pilot Study. Ann. Biomed. Eng. 46(11):1797–1805.

105. Capin JJ, Williams JR, Neal K, et al. 2020. Slower Walking Speed Is Related to Early Femoral Trochlear Cartilage Degradation After ACL Reconstruction. J. Orthop. Res. 38(3):645–652.

106. Williams JR, Neal K, Alfayyadh A, et al. 2022. Patellofemoral contact forces after ACL reconstruction: A longitudinal study. J. Biomech. 134 Available from: https://doi.org/10.1016/j.jbiomech.2022.110993.

107. Capin JJ, Khandha A, Zarzycki R, et al. 2017. Gait mechanics and second ACL rupture: Implications for delaying return-to-sport. J. Orthop. Res. 35(9):1894–1901.

108. Cohen J. 1988. Statistical Power Analysis for the Behavioral Sciences, 2nd ed. New York: Routledge. 567 p.

109. Culvenor AG, Collins NJ, Guermazi A, et al. 2015. Early knee osteoarthritis is evident one year following anterior cruciate ligament reconstruction: A magnetic resonance imaging evaluation. Arthritis Rheumatol. 67(4):946–955.

110. Williams AA, Erhart-Hledik JC, Asay JL, et al. 2021. Patient-Reported Outcomes and Knee Mechanics Correlate With Patellofemoral Deep Cartilage UTE-T2* 2 Years After Anterior Cruciate Ligament Reconstruction. Am. J. Sports Med. 49(3):675–683.

111. Capin JJ, Zarzycki R, Arundale A, et al. 2017. Report of the Primary Outcomes

for Gait Mechanics in Men of the ACL-SPORTS Trial: Secondary Prevention With and Without Perturbation Training Does Not Restore Gait Symmetry in Men 1 or 2 Years After ACL Reconstruction. Clin. Orthop. Relat. Res. 475(10):2513–2522.

112. Favre J, Jolles BM. 2016. Gait analysis of patients with knee osteoarthritis highlights a pathological mechanical pathway and provides a basis for therapeutic interventions. EFORT Open Rev. 1(10):368–374.

113. Teng H-L, Calixto NE, Macleod TD, et al. 2016. Associations between patellofemoral joint cartilage T1p and T2 and knee flexion moment and impulse during gait in individuals with and without patellofemoral joint osteoarthritis. Osteoarthr. Cartil. 24(9):1554–1564.

114. Middleton A, Fritz SL, Lusardi M. 2015. Walking speed: The functional vital sign. J. Aging Phys. Act. 23(2):314–322.

115. Garcia SA, Brown SR, Koje M, et al. 2022. Gait asymmetries are exacerbated at faster walking speeds in individuals with acute anterior cruciate ligament reconstruction. J. Orthop. Res. 40(1):219–230.

116. Knobel RJ, Ito N, Arhos EK, et al. 2021. Patients walking faster after anterior cruciate ligament reconstruction have more gait asymmetry. Int. J. Sports Phys. Ther. 16(1):169–176.

117. Sidharthan S, Yau A, Almeida BA, et al. 2021. Patterns of Articular Cartilage Thickness in Pediatric and Adolescent Knees: A Magnetic Resonance Imaging–Based Study. Arthrosc. Sport. Med. Rehabil. 3(2):e381–e390.

118. Pedoia V, Li X, Su F, et al. 2016. Fully automatic analysis of the knee articular cartilage T1ρ relaxation time using voxel-based relaxometry. J. Magn. Reson. Imaging 43(4):970–980.

119. Pedoia V, Gallo MC, Souza RB, Majumdar S. 2017. Longitudinal study using voxel-based relaxometry: Association between cartilage T1p and T2 and patient reported outcome changes in hip osteoarthritis. J. Magn. Reson. Imaging 45(5):1523–1533.

120. Teng HL, Pedoia V, Link TM, et al. 2018. Local associations between knee cartilage T1ρ and T2 relaxation times and patellofemoral joint stress during walking: A voxel-based relaxometry analysis. Knee 25(3):406–416.

121. Reisman DS, McLean H, Bastian AJ. 2010. Split-Belt Treadmill Training Post-Stroke: A Case Study. J. Neurol. Phys. Therpay 34(4):202–207.

122. Skidmore J, Barkan A, Artemiadis P. 2015. Variable Stiffness Treadmill (VST): System Development, Characterization, and Preliminary Experiments. IEEE/ASME Trans. Mechatronics 20(4):1717–1724.

123. Shakoor N, Lidtke RH, Wimmer MA, et al. 2013. Improvement in Knee Loading After Use of Specialized Footwear for Knee Osteoarthritis Results of a Six-Month Pilot Investigation. Arthritis Rheum. 65(5):1282–1289.

124. Zhou X, Liu G, Han B, et al. 2021. Different Prevention and Treatment Strategies for Knee Osteoarthritis (KOA) with Various Lower Limb Exoskeletons – A Comprehensive Review. Robotica 39(8):1345–1367.

125. Shull PB, Silder A, Shultz R, et al. 2013. Six-Week Gait Retraining Program Reduces Knee Adduction Moment , Reduces Pain , and Improves Function for Individuals with Medial Compartment Knee Osteoarthritis. J. Orthop. Res. 31(7):1020–1025.

126. Wheatley MGA, Rainbow MJ, Clouthier AL. 2020. Patellofemoral Mechanics : a Review of Pathomechanics and Research Approaches. Curr. Rev. Musculoskelet. Med. 13(3):326–337.

127. Seisler AR, Sheehan FT. 2007. Normative Three-Dimensional Patellofemoral and Tibiofemoral Kinematics : A Dynamic , in Vivo Study. IEEE Trans. Biomed. Eng. 54(7):1333–1341.

128. Andrish JT. 2015. Biomechanics of the Patellofemoral Joint. Oper. Tech. Sports Med. 23(2):62–67.

Appendix A

INSTITUTIONAL REVIEW BOARD APPROVAL LETTER

Institutional Review Board
210H Hullihen Hall
Newark, DE 19716
Phone: 302-831-2137
Fax: 302-831-2828

DATE:	March 15, 2021
TO:	Thomas Buchanan, PhD
FROM:	University of Delaware IRB
STUDY TITLE:	[868724-15] Understanding the role of unloading in the knee in osteoarthritis (OA) following anterior cruciate ligament reconstruction (ACLR).
SUBMISSION TYPE:	Continuing Review/Progress Report
ACTION:	APPROVED
APPROVAL DATE:	March 15, 2021
EXPIRATION DATE:	March 15, 2022
REVIEW TYPE:	Expedited Review
REVIEW CATEGORY:	Expedited review category # *(9)*

Thank you for your Continuing Review/Progress Report submission to the University of Delaware Institutional Review Board (UD IRB). The UD IRB has reviewed and APPROVED the proposed research and submitted documents via Expedited Review in compliance with the pertinent federal regulations.

As the Principal Investigator for this study, you are responsible for and agree that:

- All research must be conducted in accordance with the protocol and all other study forms as approved in this submission. Any revisions to the approved study procedures or documents must be reviewed and approved by the IRB prior to their implementation. Please use the UD amendment form to request the review of any changes to approved study procedures or documents.
- Informed consent is a process that must allow prospective participants sufficient opportunity to discuss and consider whether to participate. IRB-approved and stamped consent documents must be used when enrolling participants and a written copy shall be given to the person signing the informed consent form.
- Unanticipated problems, serious adverse events involving risk to participants, and all non-compliance issues must be reported to this office in a timely fashion according with the UD requirements for reportable events. All sponsor reporting requirements must also be followed.

Oversight of this study by the UD IRB REQUIRES the submission of a CONTINUING REVIEW seeking the renewal of this IRB approval, which will expire on March 15, 2022. A continuing review/progress report form and up-to-date copies of the protocol form and all other approved study materials must be submitted to the UD IRB at least 45 days prior to the expiration date to allow for the required IRB review of that report.

If you have any questions, please contact the UD IRB Office at (302) 831-2137 or via email at hsrb-research@udel.edu. Please include the study title and reference number in all correspondence with this office.

Appendix B

INSTITUTIONAL REVIEW BOARD INFORMED CONSENT

INFORMED CONSENT/ASSENT/PARENTAL PERMISSION TO PARTICIPATE IN RESEARCH

Title of Project: Understanding the role of unloading in the knee in osteoarthritis (OA) following anterior cruciate ligament reconstruction (ACLR)

Principal Investigator(s): Dr. Thomas S. Buchanan

You or your child are being invited to participate in a research study. This consent form tells you about the study including its purpose, what you will be asked to do if you decide to take part, and the risks and benefits of being in the study. Please read the information below and ask us any questions you may have before you decide whether or not you want to participate as a volunteer or parent.

Participation is voluntary for your or your child and you can refuse to participate or withdraw at any time without penalty or loss of benefits to which you are otherwise entitled. If you decide to participate, you will be asked to sign this form and a copy will be given to you to keep for your reference.

WHAT IS THE PURPOSE OF THIS STUDY?

The purpose of this research study is understand the role of unloading in the knee in osteoarthritis (OA) following anterior cruciate ligament reconstruction (ACLR) surgery.

Though ACLR restores knee stability, it does not fully address abnormal knee movement and knee loading patterns, i.e. abnormal walking patterns where the ACLR knee is unloaded compared to the other non-surgical knee. Abnormal walking patterns are believed to be a mechanism leading to knee osteoarthritis (OA). Knee OA is a condition wherein the load bearing region of the knee, the cartilage, undergoes degradation. Reliable identification of knee OA requires the use of radiographs, commonly known as X-rays.

Motion analysis testing is the most common method used to analyze walking patterns. Motion analysis testing comprises of non-invasive walking experiments, often including surface electromyography (non-invasive muscle signal recording) to estimate muscle coordination patterns and force production.

In addition to walking patterns, biological and chemical changes (biochemical changes) in knee cartilage are also believed to affect the progression of OA. An imaging method, known as quantitative magnetic resonance imaging (MRI) allows for non-invasive estimation of these changes in knee cartilage. Quantitative MRI is being increasingly used over the past two decades. However, estimates of biochemical changes in knee cartilage, specific to an ACLR population, are not yet readily available in literature. It is also not known how these changes are related to walking patterns. Finally, changes in knee geometry, which can be studied using standard MRI, are also known to affect the progression of knee OA.

With that background, the purpose of this research project is to study changes in walking patterns and biochemical properties of knee cartilage after ACLR. Knee geometry measurements and OA related changes will also be evaluated. 75 subjects will be recruited 3 months after ACLR. Testing will be conducted for each subject at the following time points after ACLR:

Participant's Initials _____

- 3, 6, and 24 months

Motion analysis testing will be used to assess walking patterns. Quantitative MRI will be used to estimate biochemical changes in knee cartilage, while standard MRI will be used to construct a geometric representation of the knee. Finally, the presence/absence of knee OA and progression of OA will be verified using radiographs.

In addition, 30 subjects, in the same age groups as ACLR subjects, but with no history of knee injury will also be recruited, to allow for comparison against subjects with ACLR. Control subjects will only be required to complete motion analysis testing and imaging (quantitative and standard MRI), similar to subjects with ACLR, and at one time point only, i.e. immediately after recruitment.

The ultimate goal of this research project is to use a mathematical model to reveal conditions that can affect the knee cartilage negatively, and result in knee OA. We also hope that an improved understanding of these conditions will eventually contribute to preventative therapeutic protocols.

WHY ARE YOU OR YOUR CHILD BEING ASKED TO PARTICIPATE?

We are asking you or your child to be in the study because you or your child has undergone ACLR approximately three months ago, and can be part of the ACLR group, or because you have no history of knee injury, and can be part of the control group. The age range for participation, for both groups, is between 16 and 45 years.

Exclusion criteria for ACLR group:

You could be excluded from volunteering for the study if you have sustained major leg injury, have undergone major leg surgery that requires serious medical management (i.e. fracture or re-injury), or an ACL injury/repair prior to the most recent procedure in either knee. You could also be excluded if you sustained major tears to other knee ligaments, or repairable meniscus injuries.

Exclusion criteria for control group:

You could be excluded from volunteering for the study if you have sustained major leg injury, have undergone major leg surgery that requires serious medical management (i.e. fracture), knee ligament injuries or knee meniscus injuries.

Exclusion criteria common to both ACLR and control groups:

You could be excluded if you have any condition that prevents you from walking, or laying still on your back.

Additionally, the conditions listed below, if met, will be grounds for exclusion because of standard precautions for imaging. Pregnancy is not a contraindication to MRI of the knee, but our scans may be taken by community providers who screen for and do not perform MRI on pregnant women when it is not medically necessary.

Participant's Initials _____

- Joint replacement with metallic parts
- Surgical procedure that includes metallic components
- Extreme claustrophobia (fear of small, closed spaces)
- Pacemaker (a medical implant in the heart)
- Metal in the body (implants, screws, plates, shrapnel, etc.)
- Aneurysm clips (clips used to treat bulging blood vessels)
- Ear or Eye Implants

WHAT WILL YOU BE ASKED TO DO?

If you or your child want to participate, the information below lists the location and details about the study. All the procedures are non-invasive, i.e. nothing will be inserted in the body, and rather, components will be attached to the surface of the body, when required.

Motion analysis testing will be conducted at STAR campus at the University of Delaware (540 S College Avenue, Newark DE 19713).

MRI will be conducted at either of the following locations:

- University of Delaware's Center for Biomedical or Brain Imaging, located at 75 East Delaware Avenue, Newark DE 19716, OR
- Diagnostic Imaging Associates, located at L-6 Omega Drive, Newark DE 19713, OR
- Best Open MRI-Abby Medical Center, 1 Centurian Drive, Suite 107, Newark DE 19713

Finally, radiography (x-ray imaging) will take place at either of the following locations:

- Diagnostic Imaging Associates, located at L-6 Omega Drive, Newark DE 19713, OR
- Go-Care at Abby Medical Center, 1 Centurian Drive, Suite 106, Newark DE 19713, OR
- First State Orthopedics (4745 Ogletown Stanton Rd #225, Newark, DE 19713) OR

The information below provides a description of what the testing sessions will include.

Study questionnaire

Relevant time points: 3, 6 and 24 months

Participant's Initials _____

You or your child will fill out a survey form that will be used to capture information related to injury and functional capabilities. This will enable us to get information about the current status of the knee. It generally takes an average of 5 minutes for the survey form to be filled out.

Motion analysis testing

Relevant time points: 3, 6 and 24 months

Surface electrodes taped to your (or your child's) skin will be used to record the electrical activity of your muscles (electromyography). After all electrodes have been placed, you will perform a maximum contraction of each muscle (i.e. applying maximum effort that is comfortable), with straps applied to your ankles to provide resistance. Nine electrodes will be secured to each leg and then plugged into a small (6" x 4" x 3") transmitter box that will be attached to the back of a vest with Velcro. The transmitter sends the signal to the computer so we can determine when the muscles are contracting during the activities. These measurements will also be taken during the walking trials of motion analysis testing.

Markers will be attached to your skin and sneakers on both legs using adhesive skin tape. Shells with markers on them will be placed on your pelvis, thighs and calves and will be held in place with elastic wraps. These markers will allow the cameras to track your leg positions. You will be asked to perform several walking trials in our laboratory. Walking trials will give us information about the way your hips, knees, and ankles move while you walk. You will be asked to perform 7 trials of walking at a comfortable, self-selected speed, although additional trials may be required to obtain enough data. During the trials, you will also walk over a force plate that is embedded in the floor. The force plate enables collection of loading data during walking.

The electrodes and markers will be removed at the end of the testing session. Motion analysis testing is a safe, non-invasive process. The entire testing session will last approximately two (2) hours.

Quantitative and Standard MRI

Relevant time points: 3, 6 and 24 months

This study involves measuring anatomy and estimating biochemical properties of the knee using magnetic resonance imaging (MRI).

You (or your child) will be required to lie completely still on the scanner bed that will slide into the center (bore) of the MRI scanner. A knee coil will be placed around each leg, alternately, to measure the signal emitted from the knee. Pillows and other cushions may be used to make you more comfortable. Several scans will be taken and you will be required to remain still on the table for about 5-10 minutes at a time. You will be given periodic breaks in which they will be able to relax but will be asked to remain on the scanner bed for the duration of the session, which should last about 45-50 minutes. Another similar MRI session will also be conducted, which can be on the same day, or a different day, depending on your preference.

Participant's Initials _____

You (or your child) will be able to communicate with us via a built-in intercom. You will also be holding an emergency bulb that you can squeeze at any time to let us know you want to come out of the MRI scanner. If at any time you feel uncomfortable or unwilling to continue, no matter what the reason, you can request to immediately stop the study, and the operator will remove you from the scanner. All scans will be conducted by a certified MRI Technologist or other experienced personnel with relevant safety training.

These scans will provide information regarding biochemical and geometrical knee properties.

This is not a clinical evaluation

The images of the knee collected in this study are not intended to reveal illness, in part because this research protocol is not designed for clinical diagnosis. The images will not be routinely examined by a clinical radiologist. The personnel at the MRI Center are not qualified to medically evaluate these images. However, if, in the course of collecting images, we have any concerns, we may show scans to a clinical radiologist, who may suggest that you (or your child) obtain further diagnostic tests. Do not rely on this research MRI to detect or screen for abnormalities.

At our discretion, you may view their images and receive digital copies of them. These images will show the inside of the knee and you should be aware of the potential distress or discomfort that may occur by viewing these type of images.

Radiographs

Relevant time points: 3 and 24 months

Standing x-rays will be taken with the knee slightly bent. These x-rays will allow a radiologist to verify the presence or absence of OA, and to determine knee joint space width (JSW) measurements. This takes 5-10 minutes to be completed.

Radiographs at the 3 month time point will be useful for establishing a baseline, while radiographs at the 24 month time point will be useful to verify the presence/absence of knee OA, and OA progression. These x-rays will be locked in a cabinet for research purposes only.

If you (or your child) are part of the control group (i.e. no history of knee injury), you will only be required to complete motion analysis testing and imaging (quantitative and standard MRI), similar to subjects with ACLR, and at one time point only, i.e. immediately after recruitment.

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS? (WHAT ARE THE POSSIBLE BAD THINGS ABOUT THIS RESEARCH?)

A few things about this study that could make a volunteer uncomfortable are listed below.

Motion analysis testing

Participant's Initials _____

All motion analysis testing procedures involve a simple walking task that has been standardized at the University of Delaware. The risk of re-injury for the ACL-reconstructed population within the first 5 years after ACLR is approximately 5%. Of the hundreds of tests performed on ACLR individuals at the University of Delaware, no one has torn their surgical graft during testing. At the end of motion analysis testing, you may experience discomfort from the removal of tape holding markers and electrodes in place.

Quantitative and Standard MRI

MRI is an imaging technique that uses radio waves and magnetic fields to produce images of internal structures in the body. It is commonly used in hospitals. Unlike X-rays, the MRI does not use any ionizing radiation, and it does not use radioactivity, so there are no radiation related risks from having an MRI scan. Below there is a description of MRI related risks and what is being done to reduce any possible risks associated with them:

Metal: The MRI scanner produces a constant strong magnetic field, which may cause any metal implants, clips, or implanted medical devices within the body to shift position or malfunction. You (or your child) will not be allowed to participate in this study if you have any implanted metal, clips or devices. You will be screened to make sure that it is safe for you to enter a strong magnetic field. Please provide us with as much information as you can, for example if you had surgery in the past, so that we may decide whether it is safe for you to be a participant. Metallic objects brought into the MRI environment can become hazardous projectiles and can also interfere with the data quality. To minimize this risk, metal earrings, other piercings, necklaces and any other metal in contact with your body will be removed prior to the study. You will also be asked to remove all items from your pockets, including coins, electronics (including cell phones and hearing aids) and wallets. You will also be asked to remove belts with metal buckles, and may be asked to change into a gown that we will provide if your clothing contains significant metal, including metal underwire bras.

Pregnancy: Exposure to MRI scanning might be harmful to an unborn child. Although there are no established guidelines at this time regarding MRI and pregnancy, you (or your child) should be informed that there is a possibility of a yet undiscovered pregnancy related risk. If you know or suspect you may be pregnant or if you do not want to expose yourself to this risk, you will be excluded from participating in this study.

Inner ear damage: MRI scanning produces loud noises that can cause damage to the inner ear if appropriate hearing protection is not used. Earplugs and/or headphones will be provided to protect your (or your child's) ears.

Claustrophobia: When you (or your child) is inside the MRI scanner, the "bore" of the scanner will surround the knee that is being scanned. You will be positioned so that their knee is centered in the bore of the scanner. If you feel anxious in confined, spaces, you may not want to participate. If you are unsure, you can try a "mock" scanner when available, to evaluate the comfort level with the enclosed space of the

Participant's Initials _____

magnet bore. If you decide to participate and begin to feel claustrophobic, you will be able to tell us via the intercom or the squeeze ball and we will discontinue the study immediately.

Burns: In rare cases, contact with the MRI transmitting and receiving coil, conductive materials such as wires or other metallic objects, or skin-to-skin contact that forms conductive loops may result in excessive heating and burns during the experiment. The operators of the MRI scanner will take steps, such as using foam pads when necessary, to minimize this risk. Tattoos with metallic inks can also potentially cause burns. In addition, you (or your child) are requested to let the MRI operator know immediately if you experience any heating or burning sensations during a scan. The scanning session will be stopped as soon as you tell the operator.

Nerve or muscle stimulation: While the scanner is operating, there is a small chance that the rapidly changing magnetic fields could cause a slight tingling sensation or a muscle twitch, usually felt in the upper arms or torso. While these sensations may be startling, they are not dangerous or a health risk, and they have no lasting consequences. The sensations should stop when the scan ends. Because these sensations may nevertheless be distracting or even possibly uncomfortable, you (or your child) will be able to squeeze the signal bulb to alert the scanner operator if you feel tingling or muscle twitching, and we will immediately stop the scan. You will then have the opportunity to choose to withdraw from the study or to continue.

Other Risks: Besides the risks listed above, there are no other known risks from the magnetic field or radio waves at this time. Although MRI scanning has been used for more than 20 years, long-term effects are unknown.

Radiographs

This research study involves exposure to radiation from a standard radiograph (x-ray). This radiation exposure is not necessary for your medical care and is for research purposes only. At each time point that the radiograph is obtained, the total amount of radiation that you will receive in this study is about 0.12 mSv (mili-Silvert) and is approximately equivalent to a uniform whole body exposure of 15 days of exposure to natural background radiation. This use involves minimal risk per National Institutes of Health guidelines, and is necessary to obtain the research information desired. To reduce exposure, you (or your child) will wear a lead apron to cover the rest of your body while the x-rays of your leg are captured.

WHAT IF YOU OR YOUR CHILD ARE INJURED DURING PARTICIPATION IN THE STUDY?

If you or your child are injured during research procedures, you will be offered first aid at no cost to you. If additional medical treatment is needed, the cost of this treatment will be your responsibility or that of your third-party payer (for example, your health insurance). By signing this document, you are not waiving any rights that you may have if injury was the result of negligence of the university or its investigators.

Participant's Initials _____

WHAT ARE THE POTENTIAL BENEFITS? (WHAT ARE THE POTENTIAL GOOD THINGS ABOUT THIS RESEARCH?)

The proposed motion analysis testing procedure aims to study walking patterns after ACLR, and the change in these patterns over time. The data collected will be used to propose a mechanism for OA, and distinguish between abnormal versus normal walking patterns. A link between abnormal patterns and OA has not yet been established and validated. Hence, the proposed motion analysis testing procedure, by itself, cannot identify OA, and as such, no direct benefit to you is expected.

Similarly, the proposed MRI imaging procedure only aims to estimate biochemical properties of the knee cartilage, which has not yet been shown to predict OA. These properties will be used in a mathematical model to reveal conditions that can affect the knee cartilage negatively, and may result in knee OA. The proposed MRI imaging procedure, by itself, cannot predict OA, and as such, no direct benefit to you is expected.

However, we do hope that an improved understanding of the effect of the study measurements will provide information about knee OA in an ACLR population, and contribute to preventative therapeutic protocols in the future.

NEW INFORMATION THAT COULD AFFECT YOUR PARTICIPATION:

During the course of this study, we may learn new information that could be important to you. This may include information that could cause you to change your mind about participating in the study. We will notify you as soon as possible if any new information becomes available.

HOW WILL CONFIDENTIALITY BE MAINTAINED? (WHO MAY KNOW WHO PARTICIPATED IN THIS RESEARCH?)

No one other than the investigators will know that you or your child were in this study. If we tell other people about the research, we will not use names.

More details for adult participants and for parents/guardians of adolescent participants are provided below.

All information obtained during the study will be held in strict confidence to the fullest extent possible by law. In no case will personal identifiable information be shared with any other individuals or groups without your expressed written consent. Your (or your child's) images will be stored on secured computer servers and will be archived indefinitely. Non-identifiable images of your scans may be used for teaching purposes, be presented at meetings, published, and also shared in databases accessible to other researchers for further research and educational purposes. Your names or other identifying information will not be used in any publication or teaching materials without your specific permission.

Identities will be kept confidential by coding them with a subject identification number stored on a password protected computer. Only the investigators and research coordinator will have access to that file on the secure server.

Participant's Initials _____

All data will be electronically encrypted and archived indefinitely for comparative analyses of scientific and clinical questions related to the ACL injury, surgery and knee OA. All research findings will be compared to knee cartilage properties, knee loading patterns and knee movement patterns reported via peer-reviewed academic journals and conferences that emphasize outcomes after ACLR.

While rare, an accidental breach of confidentiality is a risk. Should an accidental breach of confidentiality occur, the event will be reported to the institutional review board (IRB) immediately, and appropriate follow up steps will be taken based on IRB recommendations.

HIPAA AUTHORIZATION

State and federal privacy laws protect your PHI. These laws say that, in most cases, your health care provider can release your PHI for the purpose of conducting research only if you give permission by signing an Authorization.

The research team would like and appreciate access to your PHI, specifically regarding any knee injury and or surgery, to make the study as complete as possible; however, if you do not sign this Authorization, you may still participate in the research study.

Who May Disclose and Who may Use and/or Receive my PHI?

By signing this document, you are hereby permitting your physicians, medical care providers, and UD's physical therapy clinic to disclose the PHI described in this Authorization to the research team involved in this project; the study sponsor and its employees; the Institutional Review Board (IRB) and other regulatory agencies responsible for overseeing research.

Once your PHI is shared with these persons, you understand that the PHI may no longer be protected by federal or state privacy laws.

What PHI Will Be Disclosed and Used, and for What Purpose?

The following PHI may be disclosed to, collected by, used by, and shared with those listed above:

Operative report (about an operation) and Physical therapy records.

This only pertains to medical records related to your ACL injury and surgery.

This Authorization will expire at the conclusion of the research study. You may cancel this Authorization at any time before, during, or after your participation in this study by giving a written request with your signature on it to the Principal Investigator at buchanan@udel.edu. If you cancel this Authorization, your PHI obtained before that date may still be used for this research study.

Participant's Initials _____

I hereby authorize the disclosure and use of **my Personal Health Information**

_____ _____

Signature of Patient or Authorized Representative Date

Printed Name of Person Signing: _____

Relationship to Patient: _____

WILL THERE BE ANY COSTS TO YOU FOR PARTICIPATING IN THIS RESEARCH?

There are no costs associated with participating in the study.

WILL YOU RECEIVE ANY COMPENSATION FOR PARTICIPATION?

Participants will be compensated 50 USD for motion analysis testing, 50 USD for qMRI, and 50 USD for a radiograph (x-ray). Thus, there will be a total of 150 USD compensation associated with each time point, i.e. 3, 6 and 24 month time points.

DO YOU HAVE TO TAKE PART IN THIS STUDY? (CAN YOU CHANGE YOUR MIND ABOUT BEING IN THE STUDY?)

You do not have to say yes. Taking part in this research study is up to you or your child. If you choose to take part, you can change your mind and stop at any time. If, at any time, you decide to stop, please let us know by telling one of the researchers.

If you are a student volunteer and decide not to take part in this research, your choice will not affect your grades or your relationship with your classmates and your teachers.

We may ask you to stop participating if any leg injury that requires serious medical management (i.e. fracture or re-injury) has occurred before the testing session.

WHO SHOULD YOU CALL IF YOU HAVE QUESTIONS OR CONCERNS?

If you have any questions about this study, please contact the Principal Investigator, Dr. Thomas S Buchanan at buchanan@udel.edu or (302) 831-2410.

If you have any questions or concerns about your rights as a research participant, you may contact the University of Delaware Institutional Review Board at hsrb-research@udel.edu or (302) 831-2137.

Participant's Initials _____

For adult participants (at least 18 years old):

Your signature below means that: 1) you are at least 18 years old; 2) you have read and understand the information given in this form; 3) you have asked any questions you have about the research and those questions have been answered to your satisfaction; 4) you accept the terms in the form and volunteer to participate in the study. You will be given a copy of this form to keep.

_____	_____	_____
Printed Name of Participant	Signature of Participant	Date

For adolescent participants (less than 18 years old):

If you want to participate, and we have answered all of your questions about it, please sign below.

_____	_____	_____
Printed Name of Participant	Signature of Participant	Date

For parents/guardians of adolescent participants (less than 18 years old):

You are making a decision whether or not to have your child participate in this study. Your signature indicates that you have read the information provided above and decided to allow your child to participate.

_____	_____	_____
Printed Name of Parent/Guardian	Signature of Parent/Guardian	Date
_____	_____	_____
Person Obtaining Consent (PRINTED NAME)	Person Obtaining Consent (SIGNATURE)	Date

---

OPTIONAL CONSENT TO BE CONTACTED FOR FUTURE STUDIES:

Do we have your permission to contact you regarding participation in future studies? Please write your initials next to your preferred choice.

_____ YES _____ NO

Participant's Initials _____

Appendix C

AIM 1 (CHAPTER 2) PERMISSION

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Appendix D

AIM 2 (CHAPTER 3) PERMISSION

Patellofemoral Contact Forces after ACL Reconstruction: A Longitudinal Study

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Journal	Journal of Biomechanics
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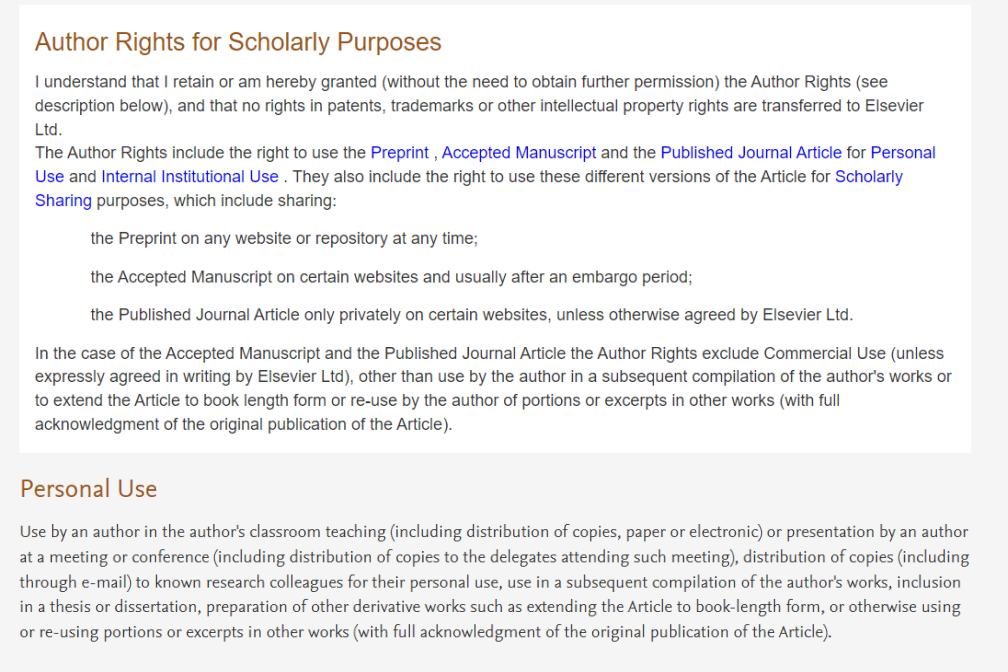
Appendix E

AIM 3 (CHAPTER 4) PERMISSION



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Appendix F

FIGURE 1 PERMISSION

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