KNEE GAIT MECHANICS AND CARTILAGE STRESS IN THOSE WITH/WITHOUT MEDIAL COMPARTMENT KNEE OSTEOARTHRITIS FIVE YEARS AFTER ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

by

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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 Biomedical Engineering

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ABSTRACT

Premature knee osteoarthritis (OA) after anterior cruciate ligament reconstruction (ACLR) surgery is a growing concern. Aberrant knee gait mechanics and joint loads are thought to affect cartilage stress distribution and the incidence of knee OA after ACLR. Knee OA occurs more frequently in the medial compartment, compared to the lateral compartment. All subjects with medial compartment knee OA demonstrate a radiographic osteophyte near the medial joint margin. However, not all subjects get knee OA five years after ACLR. Comparing knee gait mechanics and joint loads in subjects with and without knee OA may be key in establishing rehabilitation and treatment strategies to delay the progression of the disease.

The first question this proposal evaluates is "**what** are the differences in knee gait mechanics and joint loads in those with/without medial compartment knee OA after ACLR, and **when** are these differences present?" To that end, knee OA was evaluated five years after ACLR, while knee gait mechanics and joint loads were evaluated at multiple time points, i.e. before ACLR, six months, one year and five years after ACLR. All parameters were evaluated at the first peak of vertical ground reaction force during the stance phase of gait. Gait analysis and electromyography (EMG)-informed neuromusculoskeletal (NMS) modeling methods were used for this aim. Six months after ACLR, subjects with knee OA demonstrated inter-limb differences in flexion angle/moment, adduction moment and joint loads, with lower values for the involved knee, compared to the uninvolved knee. These inter-limb differences ceased to exist at later time points. These results indicate that an initial

period of under-loading of the involved knee is followed by an extended period of symmetrical loading, in subjects who get medial compartment knee OA five years after ACLR. For the involved knee, five years after ACLR, subjects with knee OA demonstrated lower values for flexion angle/moment, higher value for adduction moment (not statistically significant, but with large effect size) and similar joint loads, compared to subjects without knee OA. These results indicate that while both groups show inter-limb symmetry five years after ACLR, knee gait mechanics are different between these groups. Hence, the uninvolved knee (of subjects with knee OA in the involved knee) may also be at risk of developing knee OA at future time points.

The second question this proposal evaluates is "**how** is cartilage stress distribution near the medial joint margin (region of radiographic osteophyte, under the medial meniscus) affected due to knee gait mechanics and joint loading, in those with/without medial compartment knee OA after ACLR?" Utilizing a combination of knee gait mechanics, joint load and load distribution between deformable knee joint structures is necessary to estimate cartilage stress distribution. Hence, finite element (FE) modeling was used for this aim. Medial tibial cartilage stresses were evaluated at multiple time points, i.e. six months, one year and five years after ACLR, using knee gait mechanics and joint loads from the first aim as inputs. For the involved knee, five years after surgery, subjects with knee OA demonstrated higher values for peak effective stress in the region near the medial joint margin. These results show that stresses are indeed higher in the region where radiographic osteophytes are observed five years after ACLR in subjects with knee OA, compared to subjects without knee OA. These results help to reinforce the link between altered gait and knee OA.

The third question this proposal explores is "**how soon** can changes in cartilage tissue be detected, and is there a relation between joint loading and cartilage tissue level changes?" For inter-limb differences in subjects who get medial compartment knee OA five years after ACLR, evidence of under-loading was present at early time points (six months) after ACLR. Also, cartilage tissue level changes, which may be present at early time points after ACLR, would precede the appearance of radiographic osteophytes. To explore the changes in cartilage at early time points, T2 maps (using quantitative magnetic resonance imaging, or qMRI) were established for two additional subjects, one with evidence of under-loading in the involved knee, and one with symmetric loading. Both subjects had completed gait analysis one year after ACLR. The subject with under-loading of the involved knee did demonstrate higher T2 values (indicative of potential collagen matrix degradation) in the involved knee, compared to the uninvolved knee, and also greater inter-limb differences, compared to the subject with symmetric loading. These results, while from a very small number of subjects, warrant further investigation to establish or reject a potential correlation between early inter-limb loading differences and early cartilage tissue level changes. The sooner that the presence of OA related changes is detected, either directly or indirectly, the greater the potential for intervention to delay the progression of OA.

Future studies that implement a combination of the above methodologies (NMS + FE + qMRI) can aid in early detection, prediction and treatment of knee OA.

Chapter 1

INTRODUCTION

1.1 Dissertation Topic Overview and Organization

Approximately 200,000 individuals sustain an anterior cruciate ligament (ACL) injury annually in the United States [1]. ACL injuries primarily occur in young individuals who participate in sports involving pivoting and cutting activities [2]. At least 100,000 individuals undergo anterior cruciate ligament reconstruction (ACLR) with a tendon graft each year [1,3,4]. While the lateral knee compartment typically endures initial insult during an ACL injury, knee osteoarthritis (OA) of the medial knee compartment is the most frequently occurring pathology after ACLR [5,6]. Estimates of knee OA five to seven years after ACLR range from 12% to over 60 % [7–9], and as high as 74 % at ten to fifteen years after ACLR [10]. These estimates indicate that premature knee OA occurs in an active population despite ACLR.

Subjects who get medial compartment knee OA five years after ACLR demonstrate aberrant knee gait mechanics and decreased knee joint loading, or under-loading, six months to one year after ACLR. These aberrations are observed, compared to their contralateral knee, and compared to subjects who do not get knee OA [11]. Inter-limb and inter-group (non-OA versus OA) differences tend to diminish in magnitude or cease to exist two years after ACLR [11]. In animal studies, lack of loading due to immobilization has been shown to negatively impact the knee cartilage [12–14]. Hence, early under-loading (six months to one year after ACLR) is thought be related to degeneration of knee cartilage in subjects who eventually get medial compartment knee OA (five years after ACLR).

Animal studies have also shown that excessive joint loading, or over-loading is injurious for the cartilage and results in chondrocyte death [15]. In knee OA that is not specific to an ACLR population, body weight has been identified as one of the most important modifiable risk factors [16]. Excessive weight increases the knee joint compressive forces, and combined with repetitive loading, detrimental changes in the knee cartilage can occur [16,17]. Along the same lines, excessive loading is considered to be a risk for knee OA in a typically younger ACLR population [18].

Thus, both knee joint under-loading and over-loading could be involved in the onset and progression of knee OA after ACLR. Based on multiple in vivo and in vitro studies, a mechanism has been proposed for the initiation of knee OA after an ACL injury [19]. The mechanism suggests that drastic changes in knee joint mechanics and loading occur after an ACL injury and degeneration of the cartilage is initiated. Following this initial change, aberrant knee joint mechanics and over-loading lead to more degeneration. Given that ACLR does not mitigate the risk of knee OA, a similar mechanism may be involved in subjects who get knee OA after ACLR.

Taking all of the information above into consideration, an initial period (six months to one year after ACLR) of aberrant knee gait mechanics and under-loading is followed by a period of relatively normal loading (two years after ACLR), in subjects who get knee OA after ACLR. Based on the proposed mechanism of cartilage degeneration, aberrant knee gait mechanics may be present five years after ACLR, with joint over-loading in subjects who get knee OA. A normal joint load magnitude, in the presence of aberrant knee gait mechanics, could still impact load distribution within the joint and increase stresses in the knee joint cartilage.

While altered knee gait mechanics and joint loading are thought to be related to premature knee OA development [20–22], not all subjects with ACLR develop knee OA. Comparing knee gait mechanics and joint loading in non-OA versus OA ACLR groups may be key in developing rehabilitation strategies to delay OA progression. Hence, the first aim of the study evaluates knee gait mechanics and joint loading in those with/without medial compartment knee OA five years after ACLR. This aim is discussed in chapter 2.

Next, while altered knee gait mechanics and joint loading initiate knee OA after ACLR, it is the resultant load distribution within the knee joint and cartilage stress that ultimately results in cartilage degeneration [15]. The changes that occur in knee cartilage stress distribution due to altered knee gait mechanics are not clearly understood [23]. Specifically, it is not clear whether cartilage stresses are higher near the location of osteophytes observed in subjects who get medial compartment knee OA five years after ACLR. Therefore, the second aim of the study evaluates the impact of knee gait mechanics and joint loading on medial tibial cartilage stress in those with/without medial compartment knee OA five years after ACLR. This aim is discussed in chapter 3.

Finally, although osteophytes can be observed on radiographs five years after ACLR, the same is not true for OA related cartilage tissue level changes that precede osteophytic formation. Quantitative magnetic resonance imaging (qMRI) can aid in discerning tissue level changes in the cartilage that precede radiographic OA [24]. The sooner the changes related to knee OA are detected, the greater the potential for rehabilitative intervention to delay disease progression. However, it is not clear whether cartilage tissue level changes are associated with inter-limb loading differences that are observed at early time points (six months to one year) after ACLR [11]. Verifying the relation between joint loading and tissue level changes can further solidify the link between joint loading and knee OA after ACLR [25]. Hence, the third aim of the study explores cartilage tissue level changes for subjects that demonstrate inter-limb loading differences at early time points after ACLR. This aim in discussed in chapter 4.

Chapter 5 summarizes the conclusions from each of the three aims, and includes recommendations for future work.

Specific hypotheses will be included within individual chapters after introduction of background and rationale for each of the relevant aims (chapters 2, 3 and 4). For ease of reference and navigation, the hypotheses are also included below.

Chapter 2: Aim 1: Knee gait mechanics in those with/without medial compartment knee OA five years after ACLR surgery

Knee gait parameters are evaluated at the first and second peaks of vertical ground reaction force (vGRF) during gait, at the following time points: before ACLR (after injury), six months after ACLR, one year after ACLR and five years after ACLR. Each hypothesis listed below is evaluated at the first peak of vGRF during the stance phase of gait.

Hypothesis 1.1. For the ACLR knee, subjects with OA (versus non-OA) will exhibit a smaller knee flexion angle at all time points

Hypothesis 1.2. For the ACLR knee, subjects with OA (versus non-OA) will exhibit a smaller knee flexion moment at all time points

Hypothesis 1.3. For the ACLR knee, subjects with OA (versus non-OA) will exhibit a smaller knee adduction moment up to one year post-surgery, and a greater knee adduction moment five years post-surgery

Hypothesis 1.4. For the ACLR knee, subjects with OA (versus non-OA) will exhibit a smaller medial compartment load up to one year post-surgery, and similar medial compartment loads five years post-surgery

Hypothesis 1.5. For the ACLR knee, subjects with OA (versus non-OA) will exhibit a smaller total joint load up to one year post-surgery, and similar total joint loads five years post-surgery

Hypothesis 1.6. For each of the parameters in the above hypotheses, subjects with OA will exhibit inter-limb asymmetry at all time points

Chapter 3: Aim 2: Cartilage stress during gait in those with/without medial compartment knee OA five years after ACLR surgery

Medial tibial cartilage stresses are evaluated at the first and second peaks of vGRF during gait, at the following time points: six months after ACLR, one year after ACLR and five years after ACLR. The hypothesis listed below is evaluated at the first peak of vGRF during the stance phase of gait.

Hypothesis 2. Near the medial margin of the medial tibial cartilage for the ACLR knee, subjects with OA (versus non-OA) will exhibit a smaller peak stress up to one year post-surgery, and a greater peak stress five years post-surgery

Chapter 4: Exploratory Aim 3: Cartilage tissue level changes in those with/without asymmetric medial compartment knee joint load during gait after ACLR surgery

Knee cartilage T2 maps were established for two subjects, one with symmetric medial compartment knee joint load between six months and one year after ACLR, and the other with asymmetric loading. Hence, while the following hypothesis could not be verified due to the limited sample size, it has been included based on literature review, and to guide future work. The medial compartment knee joint load for assessing inter-limb asymmetry is evaluated at the first peak of vGRF during the stance phase of gait.

Hypothesis 3. Subjects with asymmetric knee joint loads will exhibit higher cartilage T2 values in the ACLR versus contralateral knee

Additionally, the current chapter introduces the following background topics in the sections below:

- The role of ACL during knee joint motion,
- The mechanism of non-contact ACL injury and the ACLR procedure, and
- Medial compartment knee osteoarthritis (OA) after ACLR.

1.2 Anterior Cruciate Ligament during Knee Joint Motion

On an average, each knee joint undergoes one million loading cycles annually [26]. The anterior cruciate ligament (ACL) plays a critical role in preventing excessive motion of the knee joint. The knee joint is highly mobile with six degrees of freedom (Figure 1, ACL highlighted).

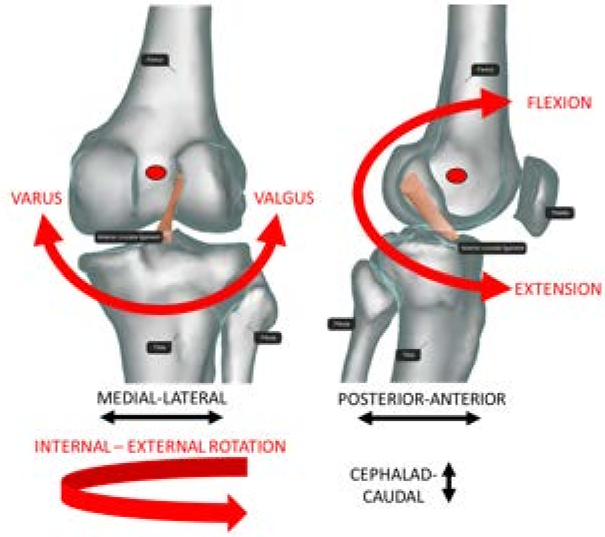

Figure 1. Posterior and lateral views of right knee with six degrees of freedom at the knee joint

(Source: http://www.primalpictures.com/)

The ACL is subjected to lengthening and slackening through the knee joint range of motion [27]. In the sagittal plane (figure 1: right – sagittal view), anterior tibial translation stretches (loads) the ACL, and ACL is the primary restraint against anterior tibial translation [28,29]. The ACL load is maximum near full extension, and loading decreases with an increasing flexion angle [28,30,31]. Cephalad-caudal translation (figure 1) is limited during activities of daily living, however, distraction of the joint increases the load seen by the ACL.

In the frontal plane (figure 1: left – posterior view), medial translation of the tibia increases the load on the ACL. Loads that induce medial translation during injury (in an accident, or during sports) have been shown to load the ACL excessively [32]. Also in the frontal plane (figure 1: left – posterior view), the effect of varus-valgus rotation, by itself, on ACL loading is negligible. In fact, loads that tend to induce varus-valgus rotation (i.e. frontal plane moments) reduce ACL load, when compared to loading due to anterior tibial translation alone [28]. However, when combined with anterior tibial translation, both varus and valgus moments increase ACL loading, when compared to loading due to anterior tibial translation alone. The increase in ligament load due to a valgus moment is more pronounced, compared to a varus moment [28].

In the transverse plane, the ACL is twisted along its length during internal-external rotation of the tibia, and acts as a restraint against excessive transverse plane motion [27].

During sports, a combination of aberrant knee kinetics and kinematics can result in injury to the structures surrounding the knee. The most common injury sustained by active individuals is an anterior cruciate ligament rupture during sports [33]. The non- contact mechanism of this injury and surgical treatment is discussed in the next section.

1.3 Non-Contact Anterior Cruciate Ligament Injury and Reconstruction

Most ACL injuries are non-contact in nature and are associated with high external loads during running and cutting maneuvers [34–37]. These loads induce a combination of knee joint motions shown below (figure 2). With the knee in a flexed position, the tibia translates anteriorly (figure 2: right – sagittal view). In the frontal plane (figure 2: left – anterior view), a dynamic valgus motion occurs along with internal tibial rotation. This combination results in excessive loading of the ACL, causing it to rupture.

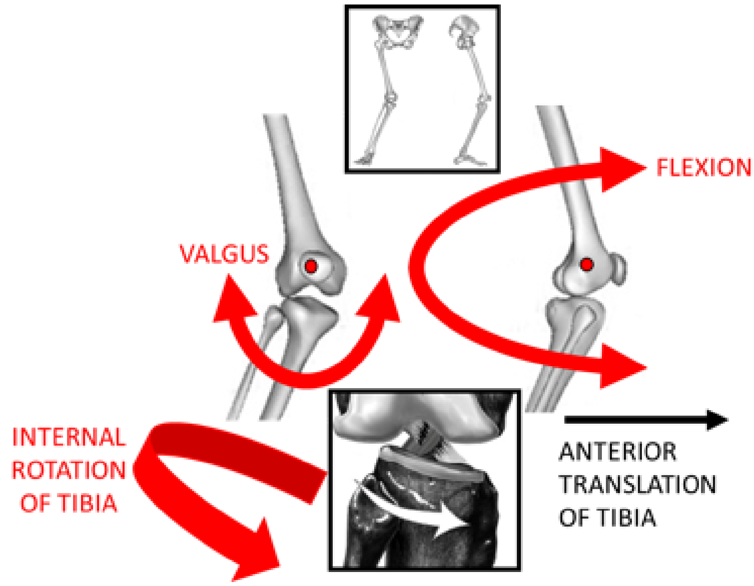

Figure 2. Anterior and lateral views of the right knee demonstrating the non-contact anterior cruciate ligament injury mechanism

(Source: http://scholar.harvard.edu/kiapour/publications/type/thesis)

The injury illustrated above occurs more commonly in women, and is affected by anatomical, hormonal and neuromuscular factors [36,38–40]. Within the knee joint, the site of insult is most commonly located in the lateral knee compartment [6]. Anterior cruciate ligament reconstruction (ACLR) surgery aims to minimize future damage to surrounding structures, and to impart stability to the knee joint [41–44]. ACLR is performed using either patellar tendon grafts, hamstring grafts or allografts [45,46]. Anatomical hamstring tendon grafts have been shown to provide better knee stability and function [46,47]. The ACLR procedure is performed using a medial and lateral portal with a medial parapatellar tendon incision. Figure 3 below shows ACLR reconstruction using hamstring tendon grafts, wherein portions of the semitendinosis and gracilis tendons are used to replace the native ACL.

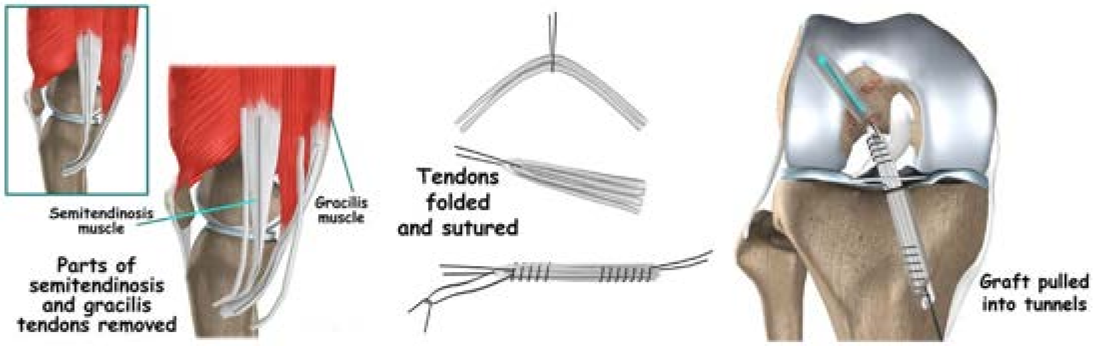

Figure 3. Medial and anterior views of right knee

(Source: http://www.sportsarthroscopyindia.com/acl_recons.html)

1.4 Medial Compartment Knee Osteoarthritis after Anterior Cruciate Ligament Reconstruction

The primary goal of anterior cruciate ligament reconstruction (ACLR) is to impart knee joint stability. A secondary goal is to prevent damage to the other structures surrounding the knee joint, including the knee joint cartilage [44]. While the risk of secondary injury to menisci is reduced after ACLR, the risk of degenerative changes in the knee cartilage, or knee osteoarthritis (OA) is not reduced [48–50]. Premature development of knee OA despite ACLR is a growing concern [3,10]. Multiple biological and mechanical factors have been correlated to onset and development of premature knee OA after ACL injury and surgery (ACLR) [51]. While the lateral knee compartment endures initial insult during injury, OA of the medial knee compartment is the most frequently occurring pathology after ACLR [5,6]. Figure 4 below shows evidence of knee OA in the medial knee compartment, determined by the presence of a marginal osteophyte (protrusion seen at the knee joint periphery in radiographs) five years after ACLR.

Figure 4. Onset of osteoarthritis: Posterior view of right knee five years after anterior cruciate ligament reconstruction demonstrating presence of osteophyte near the medial joint margin

While the exact mechanism leading to premature knee OA remains yet to be identified, altered knee gait mechanics after surgery is believed to be one of the causes that can lead to degeneration of cartilage [3,20,21,29].

Given that not all subjects develop knee OA after ACLR, comparing the nature and progression of knee gait biomechanics in non-OA versus OA ACLR groups may be the key to developing rehabilitation strategies, to delay the progression of the disease. The first aim of the study evaluates knee gait mechanics and joint loading in those with/without medial compartment knee OA five years after ACLR. This aim is discussed in chapter 2 below.

Chapter 2

AIM 1: KNEE GAIT MECHANICS IN THOSE WITH/WITHOUT MEDIAL COMPARTMENT KNEE OSTEOARTHRITIS FIVE YEARS AFTER ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION SURGERY

2.1 Introduction

It is estimated that approximately 100,000 anterior cruciate ligament reconstruction (ACLR) procedures are performed in the United States annually [52]. While the primary objective of ACLR is to reestablish function and stability in the knee joint, a secondary objective is also to prevent subsequent damage to the articular cartilage that can result in knee osteoarthritis (OA) [53]. Estimates of knee OA five to seven years after ACLR surgery range from 12% to over 60 % [7–9], and as high as 74 % at ten to fifteen years after surgery [10], with knee OA most commonly occurring in the medial knee compartment [5]. The prevalence of medial compartment knee OA, compared to lateral compartment knee OA, has been explained, at least in part, by the greater load in the medial versus lateral knee compartment during gait [5,54].

Multiple biological and mechanical factors have been correlated to onset and development of premature medial compartment knee OA after an anterior cruciate ligament (ACL) injury and surgery (ACLR) [51]. One of the mechanical factors associated with premature medial compartment knee OA in subjects after ACLR is altered knee gait kinematics and kinetics after surgery [20–22,55]. Analysis of knee gait mechanics also provides indirect information about internal knee joint loads [56]. Peak parameters during the weight acceptance phase, which tend to temporally coincide with the first peak of vertical ground reaction force (vGRF) [57,58], are most frequently used to assess knee joint kinematics/kinetics after anterior cruciate ligament reconstruction (ACLR) [55].

In the sagittal plane, subjects with unilateral ACLR demonstrate a smaller peak knee flexion angle in the ACLR versus contralateral knee during the weight acceptance phase of gait [59]. Also in the sagittal plane, a reduced peak knee flexion moment after ACLR has been correlated to unfavorable morphological changes in the medial tibial cartilage [60]. Changes in peak sagittal plane kinematic/kinetic values are observable at early (six months post-ACLR) as well as later (three years post-ACLR) post-surgery time points [55].

In the frontal plane, an increased peak knee adduction moment during gait has been suggested as a potential mechanism for increased medial compartment loading and OA development after ACLR [29]. Knee adduction moment based measures have been shown to predict medial compartment knee OA [54,61]. However, a systematic review and meta-analysis reported no differences in peak knee adduction moment at three years post-ACLR, compared to healthy controls [55]. Studies have also shown a reduction in peak knee adduction moment during gait, instead of an increase [20], comparing the ACLR versus contralateral knee two years after surgery. A combination of sagittal and frontal plane moments using neuromusculoskeletal (NMS) models provides a more accurate estimate of medial compartment load, than either measure alone [62]. While knee flexion moment influences the magnitude of the total knee joint load, knee adduction moment modulates the distribution of the total knee joint load between medial and lateral knee compartments [63,64]. When both knee flexion and adduction moments are simultaneously high or low (in the ACLR versus contralateral knee, for instance), the medial compartment load magnitude is likely higher or lower, respectively. However, if the flexion moment is lower and the adduction moment is higher (in the ACLR versus contralateral knee), as is observed in some studies after ACLR [29,55], the medial compartment load magnitude may not be different between the two knees.

Finally, transverse plane (internal tibial) rotation has been shown to be over-constrained due to ACLR surgical techniques, and evidence of the same is presented through cadaveric work [44] and running experiments [65]. There is also evidence of differences in transverse plane moment during gait, comparing the ACLR knee to healthy controls [20]. However, transverse plane parameters are most difficult to estimate reliably using traditional gait analysis methods at normal walking speeds. Hence, conclusions that can be drawn about changes in transverse plane parameters after ACLR during gait are limited [55].

NMS models that utilize information derived from electromyography (EMG) signals during gait have further enhanced the capability of traditional gait analysis, by allowing an estimation of loading in the medial compartment of the knee joint [66,67]. Recent evidence utilizing NMS models indicates that subjects with medial compartment knee OA five years after ACLR demonstrate some of the sagittal and frontal plane knee gait aberrations mentioned above, as well as decreased knee joint loading, or under-loading, six months to one year after ACLR [11]. These aberrations are observed, compared to the contralateral knee, and compared to subjects who do not get knee OA [11]. Inter-limb and inter-group (non-OA versus OA) differences tend to diminish in magnitude or cease to exist two years after ACLR [11]. In animal studies, under-loading and immobilization has been shown to negatively impact the knee cartilage [12–14]. Hence, early under-loading (six months to one year after ACLR) is thought be related to degeneration of knee cartilage in subjects who eventually get medial compartment knee OA (five years after ACLR).

Animal studies have also shown that excessive joint loading, or over-loading is injurious for the cartilage and results in chondrocyte death [15]. In knee OA that is not specific to an ACLR population, body weight has been identified as one of the most important modifiable risk factors [16]. Excessive weight increases the knee joint compressive forces, and combined with repetitive loading, detrimental changes in the knee cartilage can occur [16,17]. Along the same lines, excessive loading is considered to be a risk for knee OA in a typically younger ACLR population [18].

Thus, both knee joint under-loading and over-loading could be involved in the onset and progression of knee OA after ACLR. Based on multiple in vivo and in vitro studies, a mechanism has been proposed for the initiation of knee OA after an ACL injury [19]. The mechanism suggests that drastic changes in knee joint mechanics and loading occur after an ACL injury and degeneration of the cartilage is initiated. Following this initial change, aberrant knee joint mechanics and over-loading lead to more degeneration. Given that ACLR does not mitigate the risk of knee OA, a similar mechanism may be involved in subjects who get knee OA after ACLR.

Taking all of the information above into consideration, an initial period (six months to one year after ACLR) of aberrant knee gait mechanics and under-loading is followed by a period of relatively normal loading (two years after ACLR), in subjects who get knee OA after ACLR. Based on the proposed mechanism of cartilage degeneration, aberrant knee gait mechanics may be present five years after ACLR, with joint over-loading in subjects who get knee OA. A normal joint load magnitude, but in the presence of aberrant knee gait mechanics, could still impact load distribution within the joint and increase stresses in the knee joint cartilage.

While altered knee gait mechanics and joint loading are thought to be related to premature knee OA development [20–22], not all subjects with ACLR develop knee OA. Comparing knee gait mechanics and joint loading in non-OA versus OA ACLR groups may be key in developing rehabilitation strategies to delay OA progression.

With that background, the aim of the study is to evaluate knee gait mechanics and joint loading in those with/without medial compartment knee OA five years after ACLR. Knee gait parameters are evaluated at the following time points: before ACLR (after injury), six months after ACLR, one year after ACLR and five years after ACLR. Each hypothesis listed below is evaluated at the first peak of vGRF during the weight acceptance stance phase of gait.

Hypothesis 1.1. For the ACLR knee, subjects with OA (versus non-OA) will exhibit a smaller knee flexion angle at all time points

Hypothesis 1.2. For the ACLR knee, subjects with OA (versus non-OA) will exhibit a smaller knee flexion moment at all time points

Hypothesis 1.3. For the ACLR knee, subjects with OA (versus non-OA) will exhibit a smaller knee adduction moment up to one year post-surgery, and a greater knee adduction moment five years post-surgery

Hypothesis 1.4. For the ACLR knee, subjects with OA (versus non-OA) will exhibit a smaller medial compartment load up to one year post-surgery, and similar medial compartment loads five years post-surgery

Hypothesis 1.5. For the ACLR knee, subjects with OA (versus non-OA) will exhibit a smaller total joint load up to one year post-surgery, and similar total joint loads five years post-surgery

Hypothesis 1.6. For each of the parameters in the above hypotheses, subjects with OA will exhibit inter-limb asymmetry at all time points

While limited and not specific to an ACLR population, there is some evidence related to aberrant knee gait parameters during the late stance phase in subjects with knee OA [64,68,69]. Frontal plane moments and joint loads that coincide with the second peak of vGRF during gait are almost similar in magnitude to the values at the first peak of vGRF. There is also some evidence of differences in peak sagittal plane moments during the late stance phase of gait, between subjects with ACLR and healthy controls [20]. Hence, knee gait parameters that coincide with the second peak of vGRF are also reported here.

2.2 Methods

2.2.1 Study population

The study population was part of a larger trial of 55 individuals with unilateral ACL injury who had undergone progressive, pre-operative rehabilitation training [70]. Out of the 26 subjects with radiographs five years after unilateral ACLR, one subject was missing knee gait data at all time points, while another subject demonstrated signs of radiographic OA only in the lateral knee compartment (and not the medial knee compartment). These two subjects were excluded from the current analysis. Thus, 24 subjects, each of whom had knee gait data for at least one time point, were included in the final analysis (Figure 5).

Each subject was a regular participant in level I-II cutting and pivoting activities prior to ACL injury [71,72]. The study was approved by the Institutional Review Board at the University of Delaware (Appendices A and B). All subjects were provided with written consent forms for the study.

2.2.2 Inclusion-Exclusion criteria

Resolution of knee joint effusion, full knee range of motion and quadriceps strength criteria of at least 70 % of the contralateral limb were used for inclusion [73]. Exclusion criteria encompassed concomitant repairable meniscus injuries, grade III injury to other knee ligaments, and full-thickness articular cartilage lesions greater than 1 cm^2.

2.2.3 ACLR surgery

The ACLR procedure was performed using a medial and lateral portal with a medial parapatellar tendon incision by a single board-certified orthopedic surgeon. Either a four-bundle semitendinosus-gracilis autograft or soft tissue allograft was used for surgery.

2.2.4 Evaluation of knee OA

Signs of knee OA were evaluated from posterior-to-anterior bent knee (30°) radiographs five years after unilateral ACLR. SigmaView software (Agfa HealthCare Corporation, Greenville, SC) and the Kellgren-Lawrence (KL) system were used to grade levels of OA in each tibiofemoral compartment [74]. The presence of OA was operationally defined as a KL grade greater than or equal to 2.

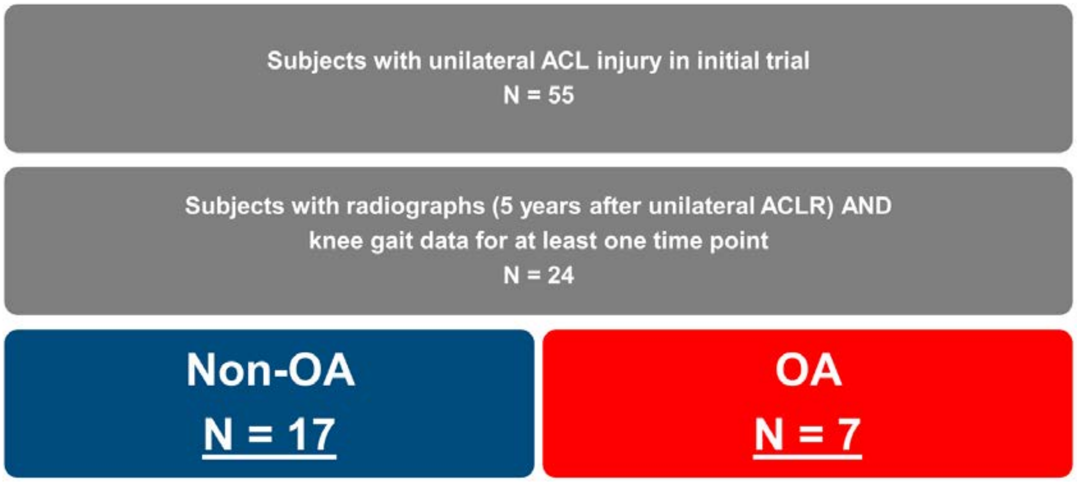

Figure 5. Study population of subjects with/without medial compartment knee OA five years after unilateral ACLR

(ACL = anterior cruciate ligament, ACLR = anterior cruciate ligament reconstruction, OA = osteoarthritis)

17 out of 24 subjects did not have medial compartment knee OA in the ACLR knee five years after surgery, and were included in the non-OA group. 7 out of 24 subjects demonstrated signs of medial compartment knee OA in the ACLR knee five years after surgery, and were included in the OA group. Non-OA versus OA group characteristics at the pre-surgery time point are included in table 1 below. For all subjects with medial compartment knee OA, the osteophyte was located near the medial margin of the medial compartment (i.e. the thinner cartilage region close to midline of the body [19])

Table 1. Non-OA (n = 17) versus OA (n = 7) group characteristics at the pre-surgery time point

Parameter	Non-OA (Mean ± SD)	OA (Mean ± SD)	P	d
Sex	12 men, 5 women	3 men, 4 women	.202	N/A
Graft type	7 autografts, 10 allografts	3 autografts, 4 allografts	.939	N/A
Age (years)	31 ± 11	35 ± 13	.443	0.35
Mass (kg)	85 ± 19	75 ± 15	.417	0.54
Height (m)	1.7 ± 0.1	1.7 ± 0.1	.602	0.34
Walking speed (m/s)	1.6 ± 0.1	1.5 ± 0.1	.666	0.28

- OA = osteoarthritis, SD = standard deviation, kg = kilogram, m = meter, s = second
- *P < .05, significant (chi-square test or independent t-test, as applicable),
- d = effect size, d > 0.8, large effect

2.2.5 Time points

Gait analysis experiments were conducted at the following time points: Before surgery (unilateral ACL injury within 7 months from the time of the gait experiment), six months after ACLR, one year after ACLR and five years after ACLR

2.2.6 Knee kinematic, kinetic and electromyography data analysis

At each time point, subjects performed multiple gait trials. Kinematic parameters were recorded using an eight infrared camera setup (Vicon, Oxford Metrics Limited, London, UK) and retroreflective markers at a sampling rate of 120 Hz. Retroreflective markers were placed on bony landmarks at each lower extremity, with rigid marker shells placed at the pelvis, thighs and shanks [75]. Subjects walked at a self-selected speed along a six meter walkway. Walking speed was established at the pre-surgery time point and maintained within ± 5 % during testing sessions at later time points. Kinetic parameters during gait were recorded using a force platform (Bertec Corporation, Worthington, OH) at a sampling rate of 1080 Hz. Stance phase knee joint angles and moments were processed using inverse dynamics in Visual3D (C-Motion, Germantown, MD). For data analysis, knee joint angles and moments were time-normalized to 100 % of stance phase and knee moments were normalized to % Body Weight x Height (% BW*HT) [76]. The moments reported are external moments in the tibial coordinate system.

The testing protocol also included surface electromyography (EMG) data collection during gait [77]. EMG data was band-pass filtered (20-500 Hz) prior to sampling. EMG data was sampled at 1080 Hz using a MA-300 EMG system (Motion Lab Systems, Baton Rouge, LA). EMG electrodes were placed over the muscle bellies of seven muscles crossing the knee joint, for each limb. The flexor muscles included semimembranosus, long head of biceps femoris and medial/lateral gastrocnemii, while the extensor muscles included rectus femoris and medial/lateral vasti. For each muscle, EMG data was high-pass filtered (2nd order Butterworth, cutoff = 30 Hz), rectified, low-pass filtered (cutoff = 6 Hz) to create linear envelopes, and normalized to maximum EMG found during maximum voluntary isometric contractions or gait trials. EMG for semitendinosus and short head of biceps femoris were set to be equal to linear envelopes of semimembranosus and long head of biceps femoris respectively. EMG for vastus intermedius was calculated as the average of medial and lateral vasti linear envelopes. Next, the linear envelopes from the 10 muscles crossing the knee were used as input in a previously validated EMG-informed neuromusculoskeletal (NMS) model [66,78]. EMG-informed NMS modeling involves subject-specific anatomical scaling (for muscle moment arm estimation) and calibration (for muscle force estimation) to minimize the squared difference between net internal and external sagittal plane knee moments. The workflow is shown in figure 6 below. Subject-specific anatomical scaling is based on retroreflective marker data from a standing trial, and it enables muscle-tendon length and moment arm estimations using stance phase kinematics (SIMM 6.0, Musculographics Inc., Chicago, IL). Subject-specific calibration involves adjustment of parameters in the muscle activation and muscle contraction sub-components. The muscle activation sub-component transforms the EMG signal to a muscle activation measure, and is characterized by four adjustable parameters (2 recursive filter coefficients, 1 electromechanical delay term and 1 non-linear shape factor). The muscle contraction sub-component transforms muscle activation to muscle force. It is a modified Hill-type representation of a muscle fiber in series with a tendon, and is characterized by adjustable time-invariant parameters in the equation below. Muscle force, $F^m(t)$, is a function of the following parameters [66]:

$$\mathbf{F^m(t) = f\ \{a(t),\ l^m(t),\ v^m(t),\ \varnothing(t),\ l^m_o,\ l^t_s,\ F^m_o\}}$$

In the above equation, the time-varying parameters are a (t) = muscle activation, $l^m(t)$ = fiber length, $v^m(t)$ = velocity, $\varnothing(t)$ = pennation angle, and the time-invariant parameters are l^m_o = optimal fiber length, l^t_s = tendon slack length, F^m_o = maximum isometric muscle force. The time-varying parameters are dependent on kinematics during gait, while the time-invariant parameters are based on data derived from literature [79]. The adjustable parameters are modified using simulated annealing [80] to minimize the squared difference between net internal and external sagittal plane knee moments. This process allows for the estimation of optimized muscle forces. Finally, optimized muscle force estimates and frontal plane moment arms are used to balance the external frontal plane knee moment [81]. This is done for each individual time point during the gait cycle, by assuming frontal plane equilibrium and contact at ± 25% of tibial plateau width, in relation to the knee joint center. This allows for subject-specific prediction of medial compartment, lateral compartment and total joint loads, averaged for three predicted walking trials. The medial compartment and total joint loads thus obtained were normalized to body weight (BW).

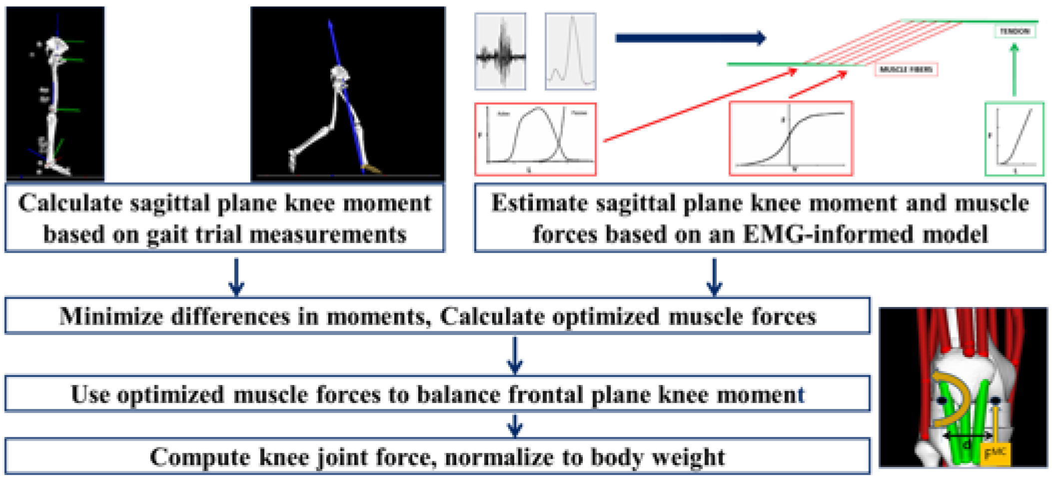

Figure 6. Electromyography (EMG)-informed neuromusculoskeletal modeling workflow

2.2.7 Statistical analysis

Independent t-tests (and chi-square tests, where applicable) were used to test non-OA versus OA group differences in terms of sex, graft type, age, mass, height and walking speed during gait trials (Table 1 above). For the weight acceptance phase of gait, the key parameters of interest at the first peak of vertical ground reaction force (vGRF) were knee flexion angle, knee flexion moment, knee adduction moment, medial compartment load and total joint load. These parameters were also evaluated at the second peak of vGRF. Independent t-tests were performed to test for differences in each of the key parameters, between non-OA versus OA groups. Mean ± standard deviations (SD) and effect size (Cohen's d) have been reported for each parameter.

Statistical analysis was conducted using Excel (Microsoft, Redmond WA) and JMP (Cary, NC). Statistical significance for all tests was set at $\alpha < 0.05$. Gait data from 12 healthy control subjects was used to determine meaningful inter-limb difference (MILD) thresholds for the key parameters of interest, using the methodology for estimating minimum detectable change [77]. The control group consisted of 5 women and 7 men, who actively participated in level I/II cutting and pivoting sports. The control group had the following subject characteristics (Mean ± standard deviation): age = 21 ± 3 years, mass = 75 ± 18 kg, height = 1.73 ± 0.1 m, walking speed = 1.6 ± 0.2 m/s. An inter-limb difference that was greater than the MILD threshold was interpreted as a reliable indication of inter-limb asymmetry.

2.3 Results

2.3.1 Knee kinematics, kinetics and joint load at the first peak of vertical ground reaction force during the stance phase of gait

2.3.1.1 Knee flexion angle (hypothesis 1.1)

For the ACLR knee, subjects with medial compartment knee OA exhibited a significantly smaller knee flexion angle five years after surgery, compared to the non-OA group (figure 7). At the one year time point, this difference approached significance, indicated by the large effect size. The differences at other time points were not significant.

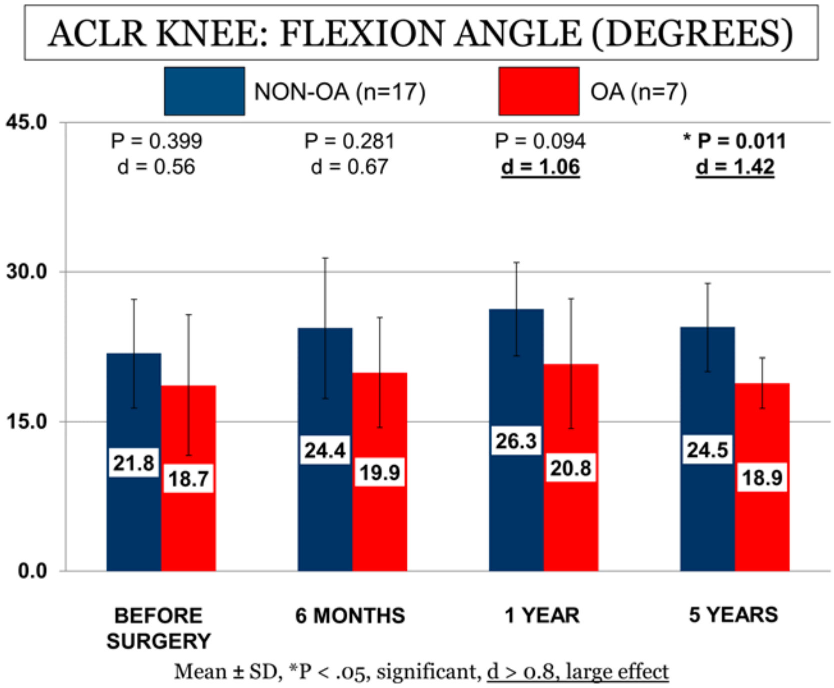

Figure 7. Knee flexion angle at the first peak of vertical ground reaction force

(ACLR = anterior cruciate ligament reconstruction, OA = osteoarthritis, SD = standard deviation, d = effect size)

2.3.1.2 External knee flexion moment (hypothesis 1.2)

For the ACLR knee, subjects with medial compartment knee OA exhibited a significantly smaller knee flexion moment five years after surgery, compared to the non-OA group (figure 8). At the six month time point, this difference approached significance, indicated by the large effect size. The differences at other time points were not significant.

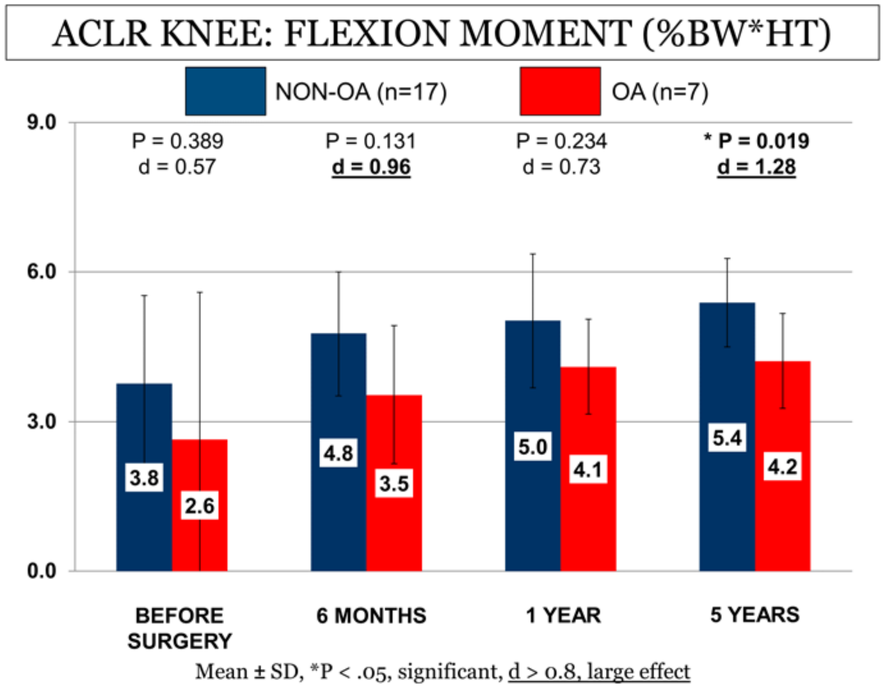

Figure 8. External knee flexion moment at the first peak of vertical ground reaction force

(ACLR = anterior cruciate ligament reconstruction, OA = osteoarthritis, BW = body weight, HT = height, SD = standard deviation, d = effect size)

2.3.1.3 External knee adduction moment (hypothesis 1.3)

For the ACLR knee, there were no significant differences in adduction moment between the non-OA versus OA groups (figure 9). However, the differences before surgery and at five years after surgery approached significance, indicated by the large effect size. Before surgery, subjects with medial compartment knee OA exhibited a smaller knee adduction moment, compared to the non-OA group. At five years after surgery, the OA group exhibited a larger knee adduction moment.

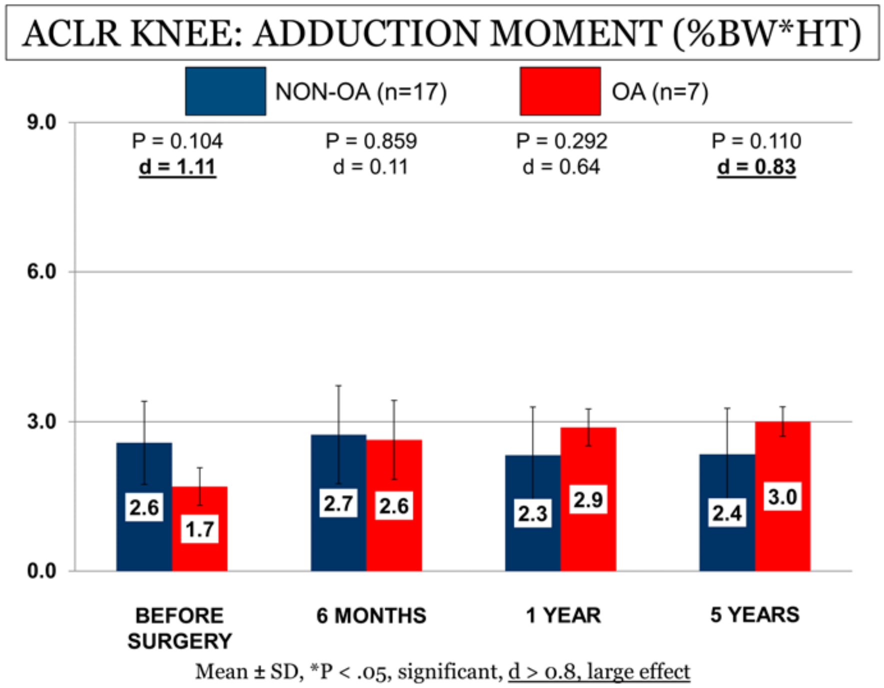

Figure 9. External knee adduction moment at the first peak of vertical ground reaction force

(ACLR = anterior cruciate ligament reconstruction, OA = osteoarthritis, BW = body weight, HT = height, SD = standard deviation, d = effect size)

2.3.1.4 Medial compartment load (hypothesis 1.4)

For the ACLR knee, there were no significant differences in medial compartment load between the non-OA versus OA groups (figure 10). However, the differences at six months approached significance, indicated by the large effect size. Six months after surgery, subjects with medial compartment knee OA exhibited a smaller medial compartment load, compared to the non-OA group.

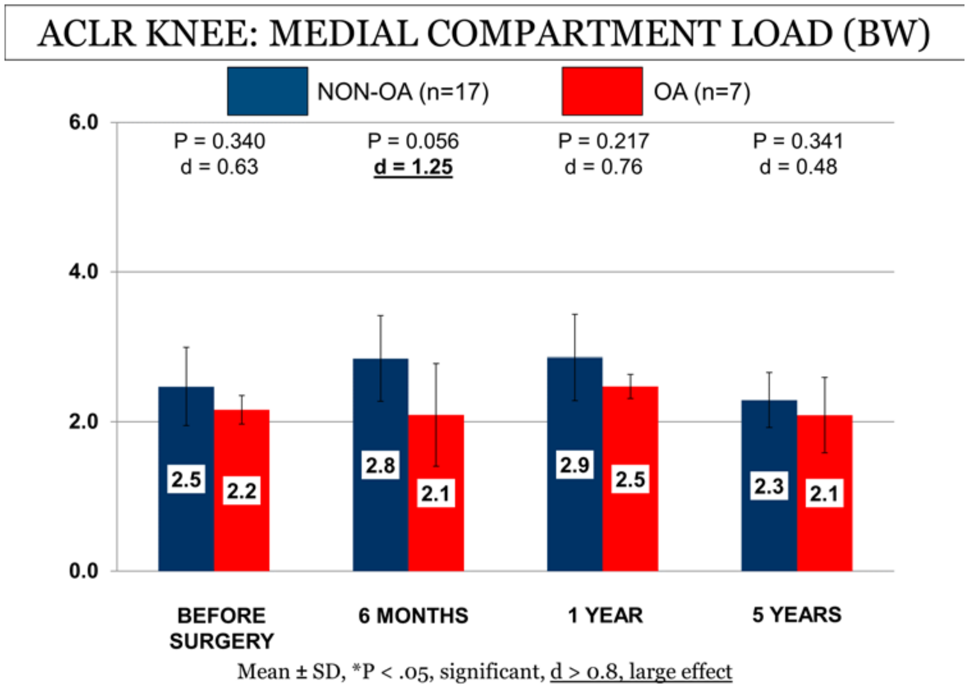

Figure 10. Medial compartment load at the first peak of vertical ground reaction force

(ACLR = anterior cruciate ligament reconstruction, OA = osteoarthritis, BW = body weight, SD = standard deviation, d = effect size)

2.3.1.5 Total joint load (hypothesis 1.5)

For the ACLR knee, there were no significant differences in total joint load between the non-OA versus OA groups (figure 11). However, the differences at six months and one year after surgery approached significance, indicated by the large effect size. At both time points, subjects with medial compartment knee OA exhibited a smaller total joint load, compared to the non-OA group.

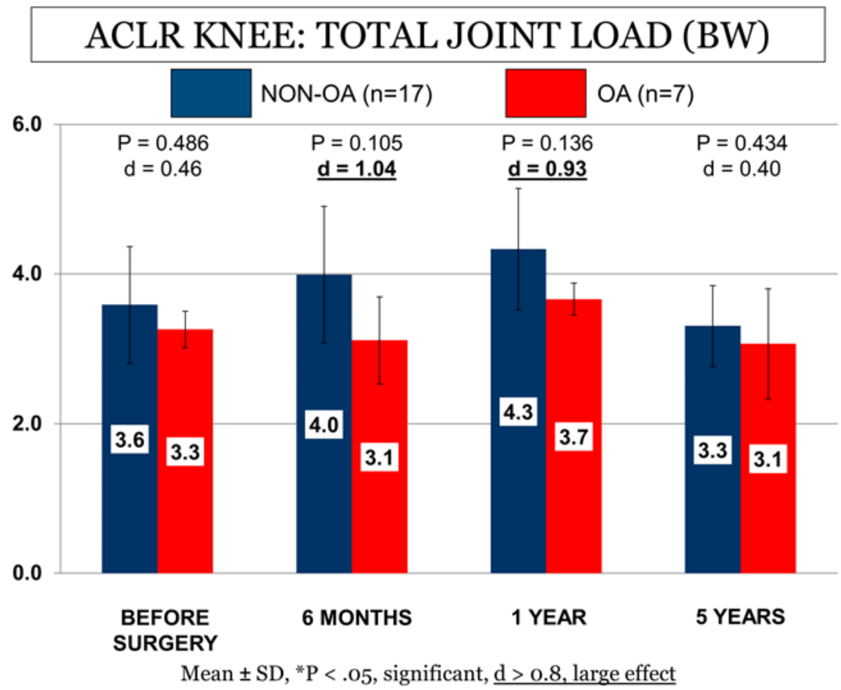

Figure 11. Total joint load at the first peak of vertical ground reaction force

(ACLR = anterior cruciate ligament reconstruction, OA = osteoarthritis, BW = body weight, SD = standard deviation, d = effect size)

2.3.1.6 Inter-limb difference in knee flexion angle (hypothesis 1.6)

Comparing the mean values of each group to the minimum inter-limb difference (MILD) threshold, both the OA and non-OA groups demonstrated a smaller knee flexion angle in the ACLR versus contralateral knee, six months after surgery (figure 12). There were no differences at other time points.

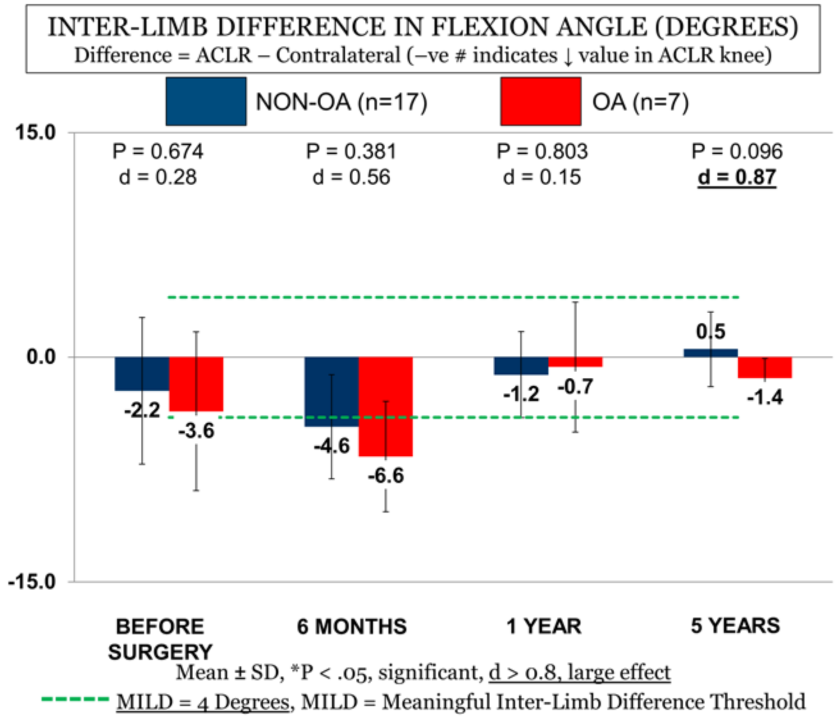

Figure 12. Inter-limb difference in knee flexion angle at the first peak of vertical ground reaction force

(ACLR = anterior cruciate ligament reconstruction, OA = osteoarthritis, SD = standard deviation, d = effect size)

2.3.1.7 Inter-limb difference in external knee flexion moment (hypothesis 1.6)

Comparing the mean values of each group to the minimum inter-limb difference (MILD) threshold, both the OA and non-OA groups demonstrated a smaller knee flexion moment in the ACLR versus contralateral knee, before surgery (figure 13). The OA group also demonstrated a smaller knee flexion moment in the ACLR versus contralateral knee six months after surgery, while the non-OA group demonstrated a smaller knee flexion moment in the ACLR versus contralateral knee one year after surgery. There were no differences at other time points.

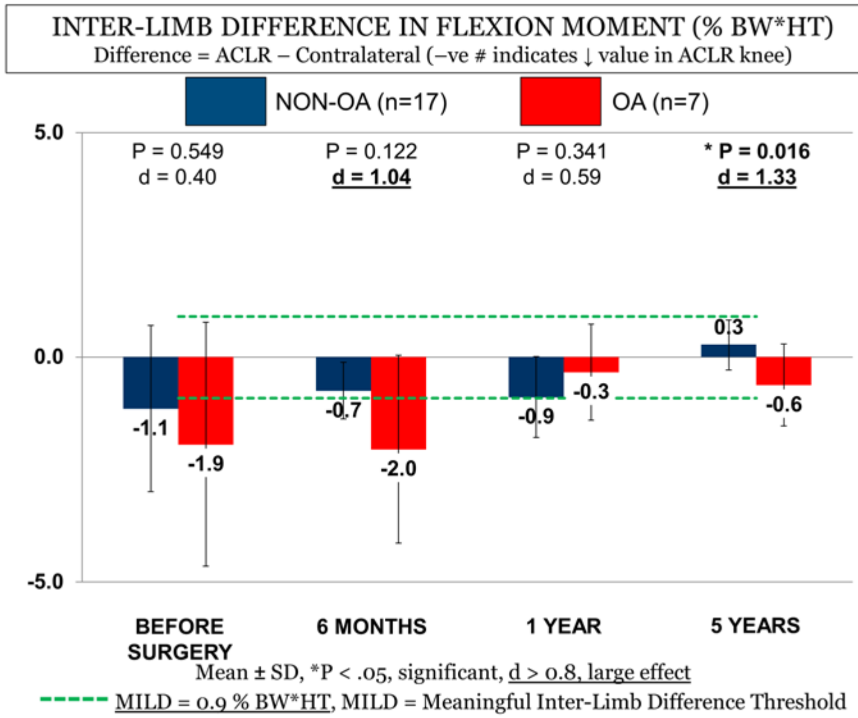

Figure 13. Inter-limb difference in external knee flexion moment at the first peak of vertical ground reaction force

(ACLR = anterior cruciate ligament reconstruction, OA = osteoarthritis, BW = body weight, HT = height, SD = standard deviation, d = effect size)

2.3.1.8 Inter-limb difference in external knee adduction moment (hypothesis 1.6)

Comparing the mean values of each group to the minimum inter-limb difference (MILD) threshold, the OA group demonstrated a smaller knee adduction moment in the ACLR versus contralateral knee, before surgery and at six months after surgery (figure 14). There were no differences at other time points.

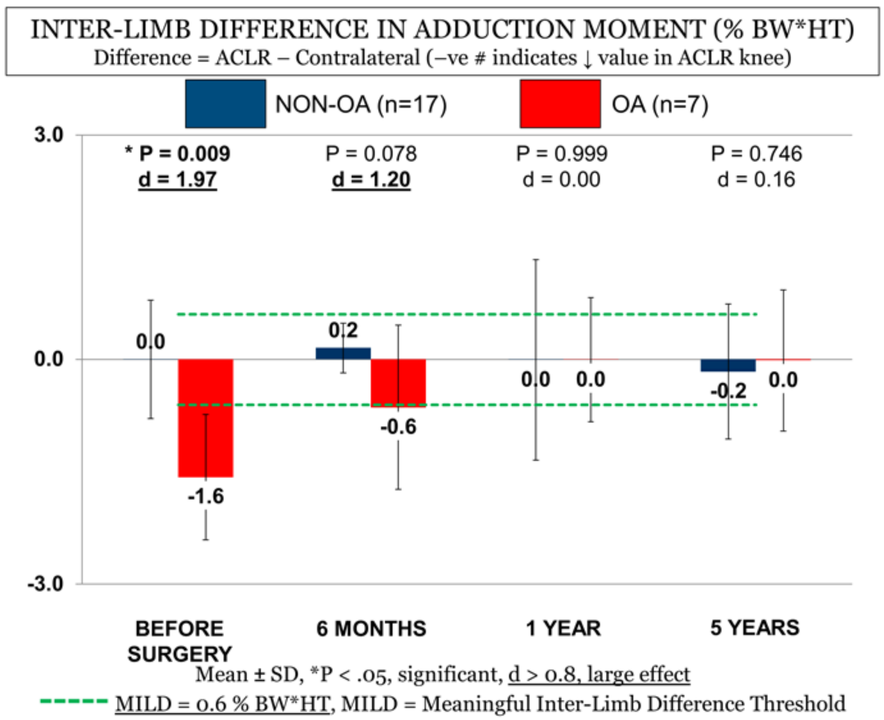

Figure 14. Inter-limb difference in external knee adduction moment at the first peak of vertical ground reaction force

(ACLR = anterior cruciate ligament reconstruction, OA = osteoarthritis, BW = body weight, HT = height, SD = standard deviation, d = effect size)

2.3.1.9 Inter-limb difference in medial compartment load (hypothesis 1.6)

Comparing the mean values of each group to the minimum inter-limb difference (MILD) threshold, both the OA and non-OA groups demonstrated a smaller medial compartment load in the ACLR versus contralateral knee, before surgery (figure 15). The OA group also demonstrated a smaller medial compartment load in the ACLR versus contralateral knee six months after surgery. There were no differences at other time points.

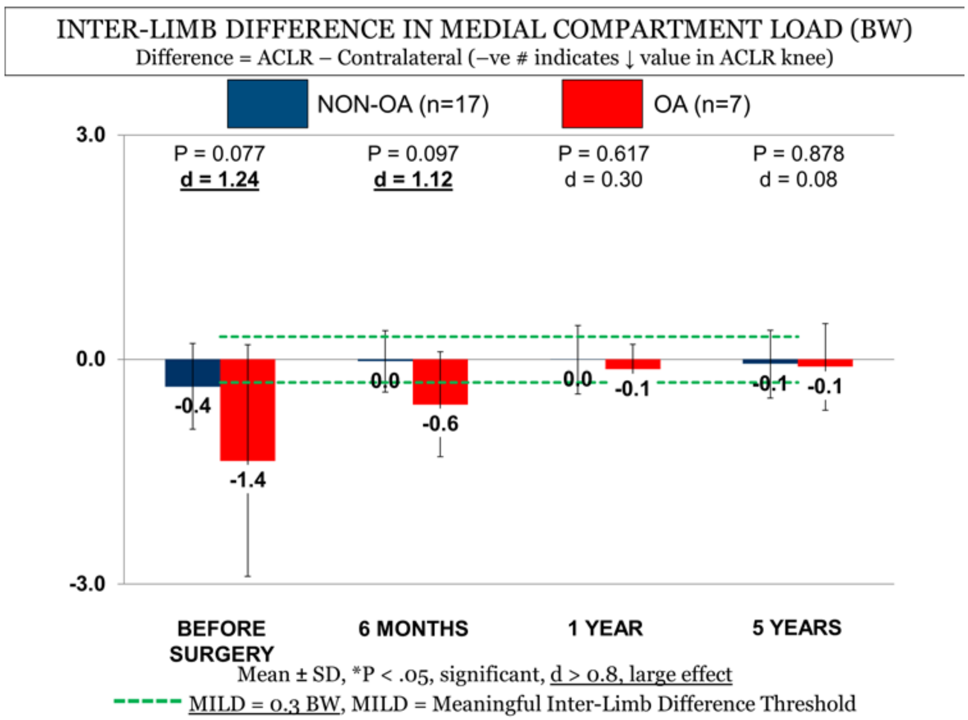

Figure 15. Inter-limb difference in medial compartment load at the first peak of vertical ground reaction force

(ACLR = anterior cruciate ligament reconstruction, OA = osteoarthritis, BW = body weight, SD = standard deviation, d = effect size)

2.3.1.10 Inter-limb difference in total joint load (hypothesis 1.6)

Comparing the mean values of each group to the minimum inter-limb difference (MILD) threshold, both the OA and non-OA groups demonstrated a smaller total joint load in the ACLR versus contralateral knee, before surgery (figure 16). The OA group also demonstrated a smaller total joint load in the ACLR versus contralateral knee six months after surgery. There were no differences at other time points.

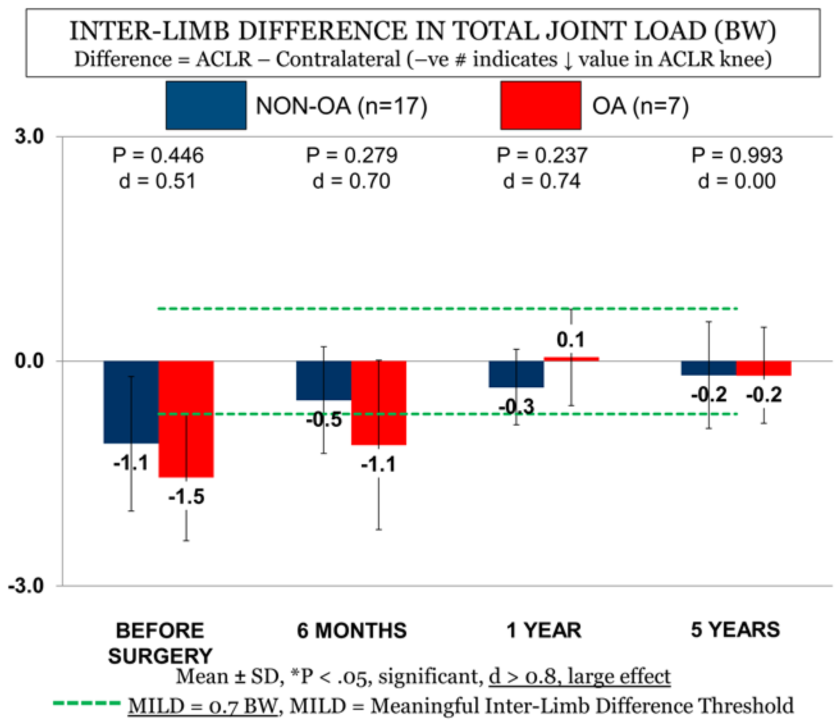

Figure 16. Inter-limb difference in total joint load at the first peak of vertical ground reaction force

(ACLR = anterior cruciate ligament reconstruction, OA = osteoarthritis, BW = body weight, SD = standard deviation, d = effect size)

2.3.2 Knee kinematics, kinetics and joint load at the second peak of vertical ground reaction force during the stance phase of gait

In general, the results at the second peak of vertical ground reaction force (vGRF) tended to have smaller magnitudes and larger standard deviations, compared to the results at the first peak of vGRF. The results for each of the parameters are included below.

2.3.2.1 Knee flexion angle

For the ACLR knee, there were no significant differences between non-OA versus OA groups. Six months after surgery, subjects with medial compartment knee OA exhibited a greater knee flexion angle, compared to the non-OA group (figure 17), and this difference approached significance, indicated by the large effect size.

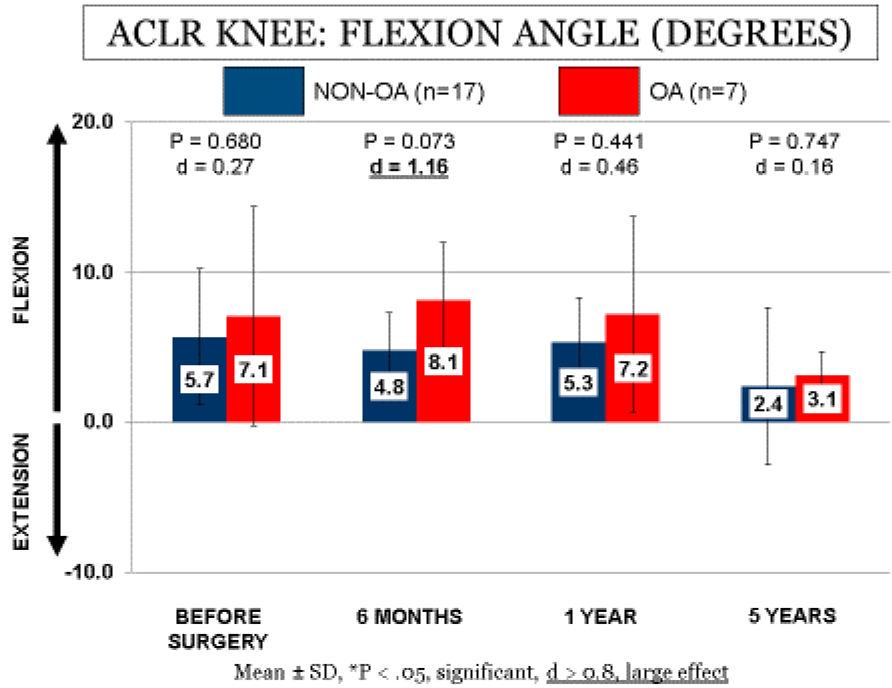

Figure 17. Knee flexion angle at the second peak of vertical ground reaction force

(ACLR = anterior cruciate ligament reconstruction, OA = osteoarthritis, SD = standard deviation, d = effect size)

2.3.2.2 External knee extension moment

At the second peak of vGRF, the external sagittal plane moments were predominantly extension moments (indicated by negative values in figure 18). For the ACLR knee, there were no significant differences between non-OA versus OA groups. Six months and one year after surgery, subjects with medial compartment knee OA exhibited a greater knee extension moment, compared to the non-OA group (figure 18), and this difference approached significance, indicated by the large effect size.

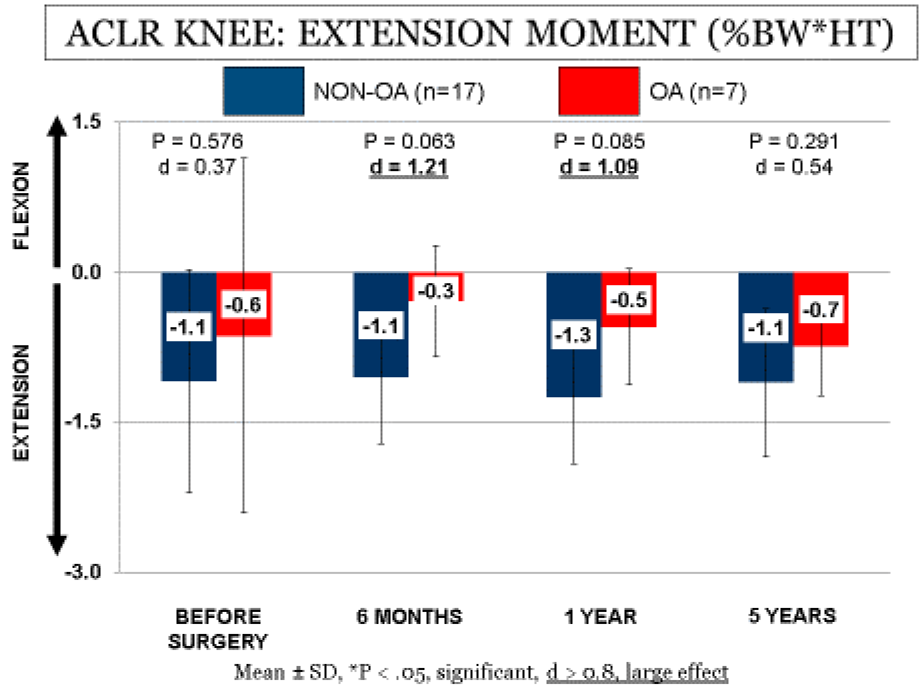

Figure 18. External knee extension moment at the second peak of vertical ground reaction force

(ACLR = anterior cruciate ligament reconstruction, OA = osteoarthritis, BW = body weight, HT = height, SD = standard deviation, d = effect size)

2.3.2.3 External knee adduction moment

For the ACLR knee, there were no significant differences between non-OA versus OA groups. Before surgery, subjects with medial compartment knee OA exhibited a smaller knee adduction moment, compared to the non-OA group (figure 19), and this difference approached significance, indicated by the large effect size.

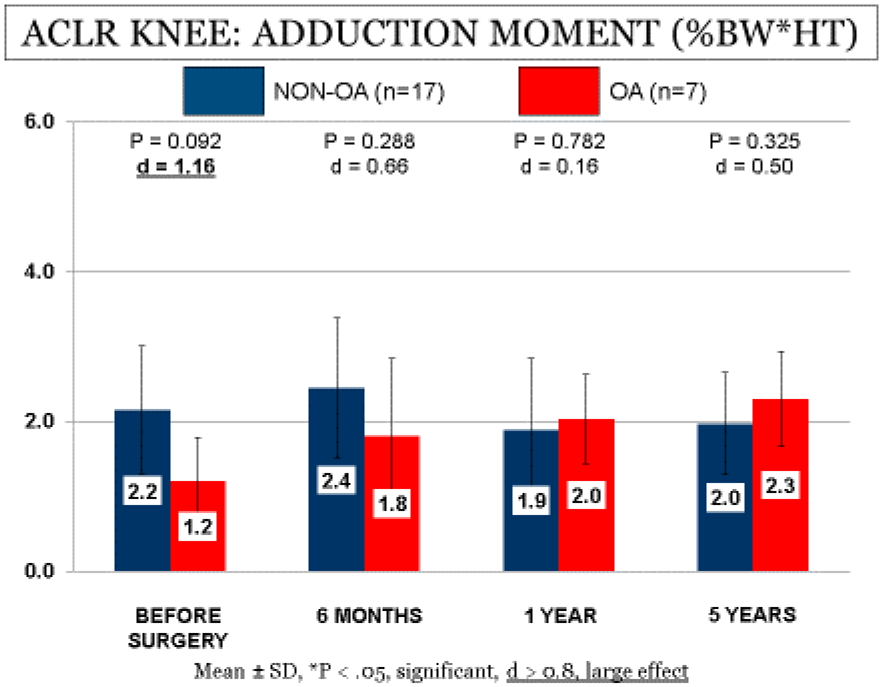

Figure 19. External knee adduction moment at the second peak of vertical ground reaction force

(ACLR = anterior cruciate ligament reconstruction, OA = osteoarthritis, BW = body weight, HT = height, SD = standard deviation, d = effect size)

2.3.2.4 Medial compartment load

For the ACLR knee, there were no significant differences between non-OA versus OA groups. Six months after surgery, subjects with medial compartment knee OA exhibited a smaller medial compartment load, compared to the non-OA group (figure 20), and this difference approached significance, indicated by the large effect size.

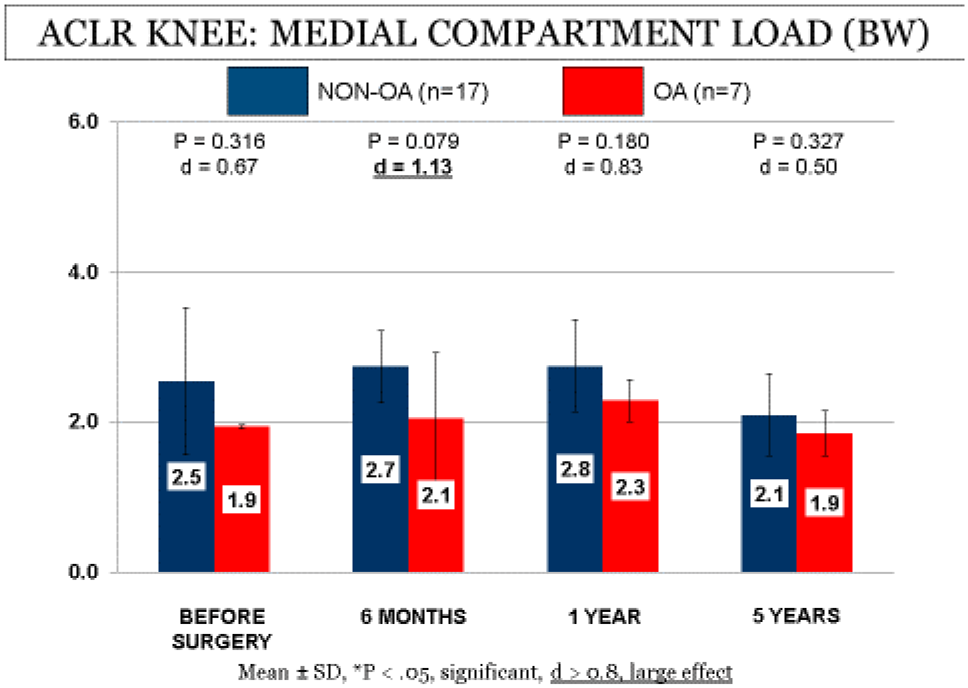

Figure 20. Medial compartment load at the second peak of vertical ground reaction force

(ACLR = anterior cruciate ligament reconstruction, OA = osteoarthritis, BW = body weight, SD = standard deviation, d = effect size)

2.3.2.5 Total joint load

For the ACLR knee, there were no significant differences between non-OA versus OA groups. Six months after surgery, subjects with medial compartment knee OA exhibited a smaller total joint load, compared to the non-OA group (figure 21), and this difference approached significance, indicated by the large effect size.

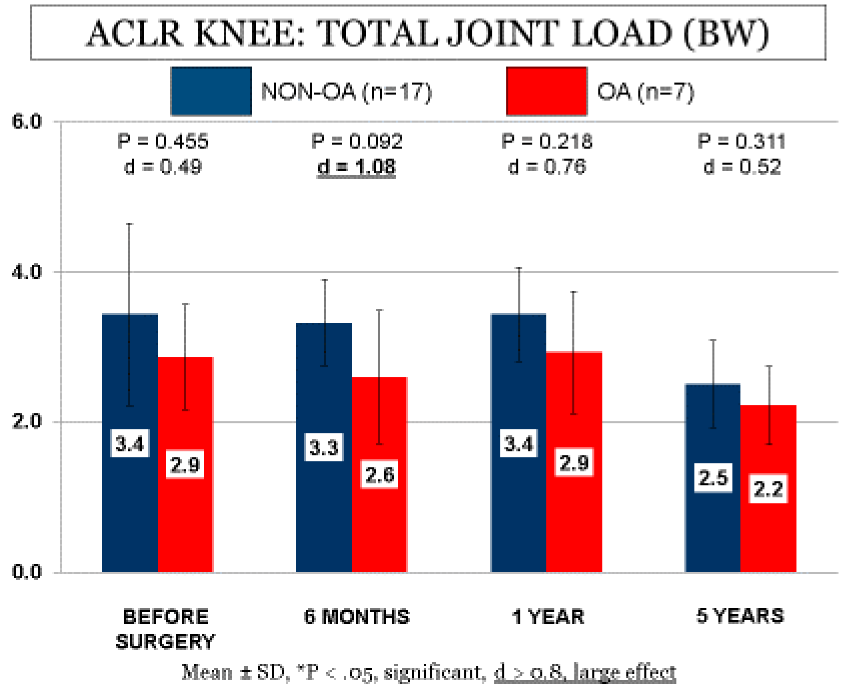

Figure 21. Total joint load at the second peak of vertical ground reaction force

(ACLR = anterior cruciate ligament reconstruction, OA = osteoarthritis, BW = body weight, SD = standard deviation, d = effect size)

2.3.2.6 Inter-limb difference in knee flexion angle

Comparing the mean values of each group to the minimum inter-limb difference (MILD) threshold, the non-OA group demonstrated a greater knee flexion angle in the ACLR versus contralateral knee before surgery (figure 22). One year after surgery, the OA group demonstrated a greater flexion knee angle in the ACLR versus contralateral knee. There were no differences at other time points.

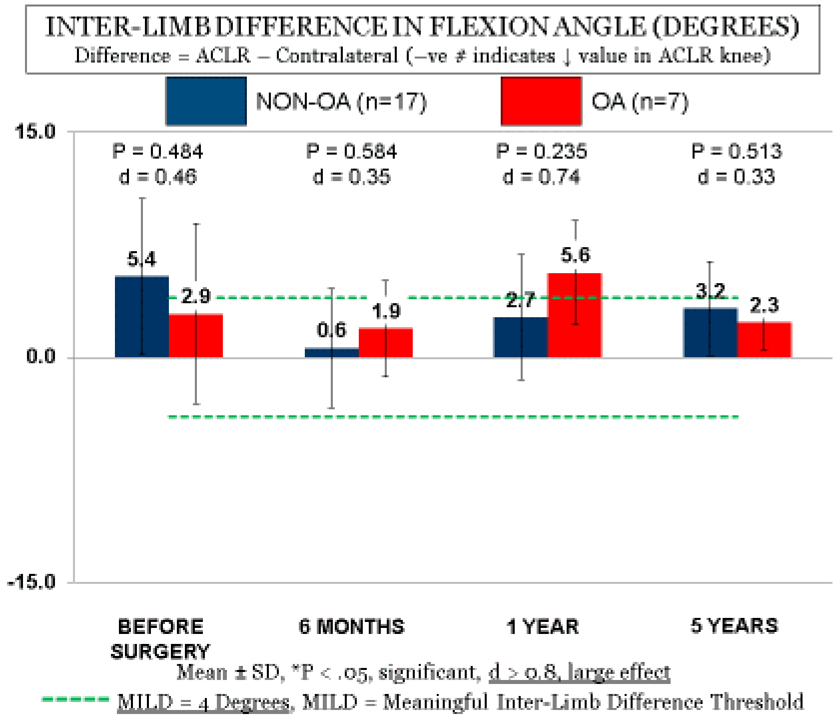

Figure 22. Inter-limb difference in knee flexion angle at the second peak of vertical ground reaction force

(ACLR = anterior cruciate ligament reconstruction, OA = osteoarthritis, SD = standard deviation, d = effect size)

2.3.2.7 Inter-limb difference in external knee extension moment

At the second peak of vGRF, the external sagittal plane moments were predominantly extension moments. A positive value in the figure 23 indicates that the ACLR knee had a smaller knee extension moment, compared to the contralateral knee. This clarification has also been included in the title block of the figure. Comparing the mean values of each group to the minimum inter-limb difference (MILD) threshold, there were no differences between limbs for either the non-OA or OA groups, at any time point.

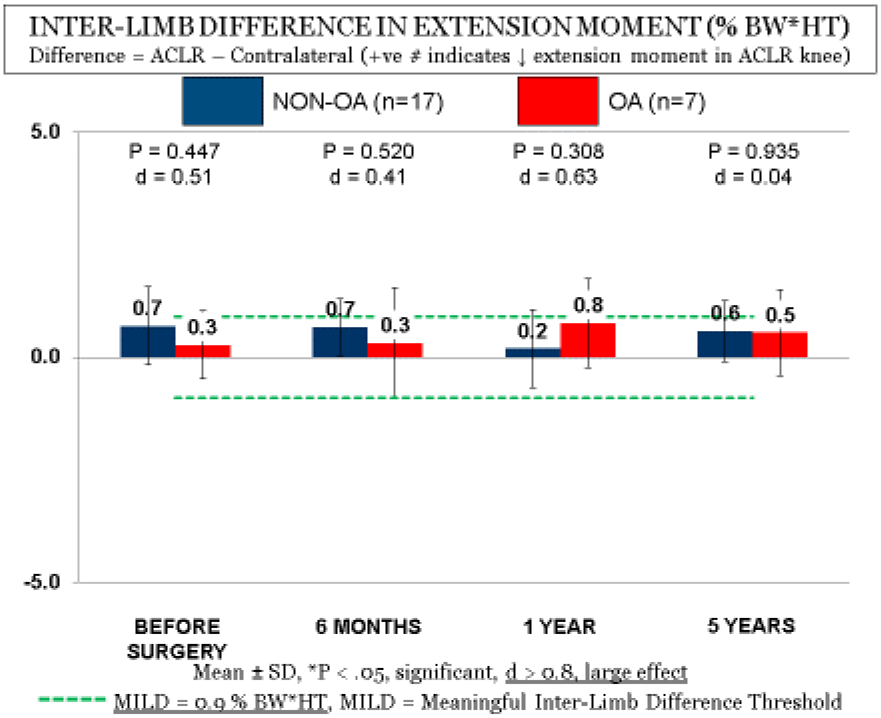

Figure 23. Inter-limb difference in external knee extension moment at the second peak of vertical ground reaction force

(ACLR = anterior cruciate ligament reconstruction, OA = osteoarthritis, BW = body weight, HT = height, SD = standard deviation, d = effect size)

2.3.2.8 Inter-limb difference in external knee adduction moment

Comparing the mean values of each group to the minimum inter-limb difference (MILD) threshold, the OA group demonstrated a lower knee adduction moment in the ACLR versus contralateral knee before surgery (figure 24). There were no differences at other time points.

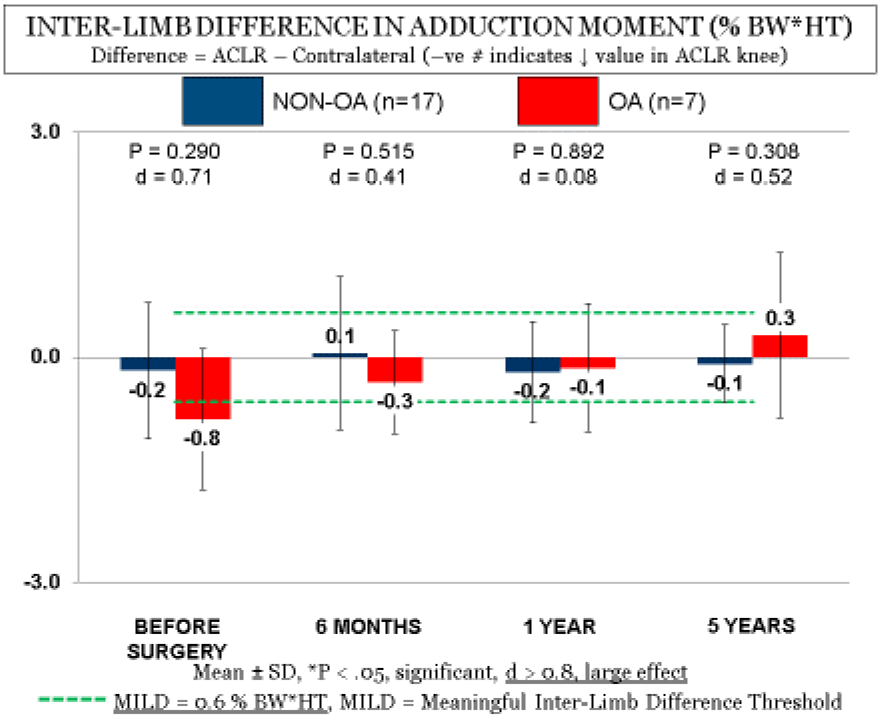

Figure 24. Inter-limb difference in external knee adduction moment at the second peak of vertical ground reaction force

(ACLR = anterior cruciate ligament reconstruction, OA = osteoarthritis, BW = body weight, HT = height, SD = standard deviation, d = effect size)

2.3.2.9 Inter-limb difference in medial compartment load

Comparing the mean values of each group to the minimum inter-limb difference (MILD) threshold, the OA group demonstrated a lower medial compartment load in the ACLR versus contralateral knee, before surgery and one year after surgery (figure 25). There were no differences at other time points.

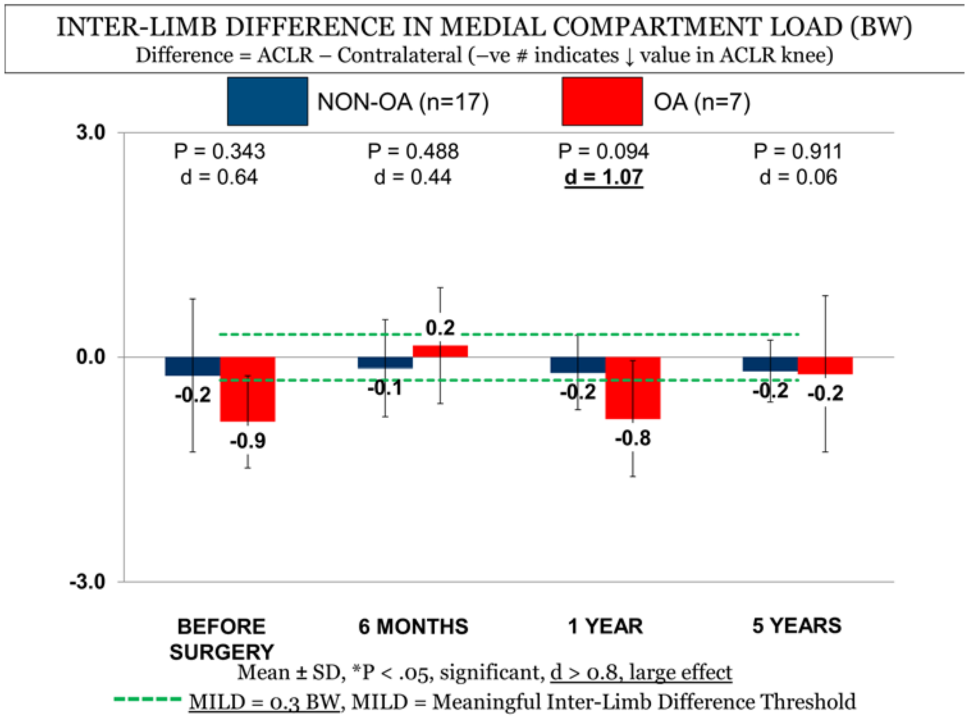

Figure 25. Inter-limb difference in medial compartment load at the second peak of vertical ground reaction force

(ACLR = anterior cruciate ligament reconstruction, OA = osteoarthritis, BW = body weight, SD = standard deviation, d = effect size)

2.3.2.10 Inter-limb difference in total joint load

Comparing the mean values of each group to the minimum inter-limb difference (MILD) threshold, the OA group demonstrated a lower total joint load in the ACLR versus contralateral knee, before surgery and one year after surgery (figure 26). There were no differences at other time points.

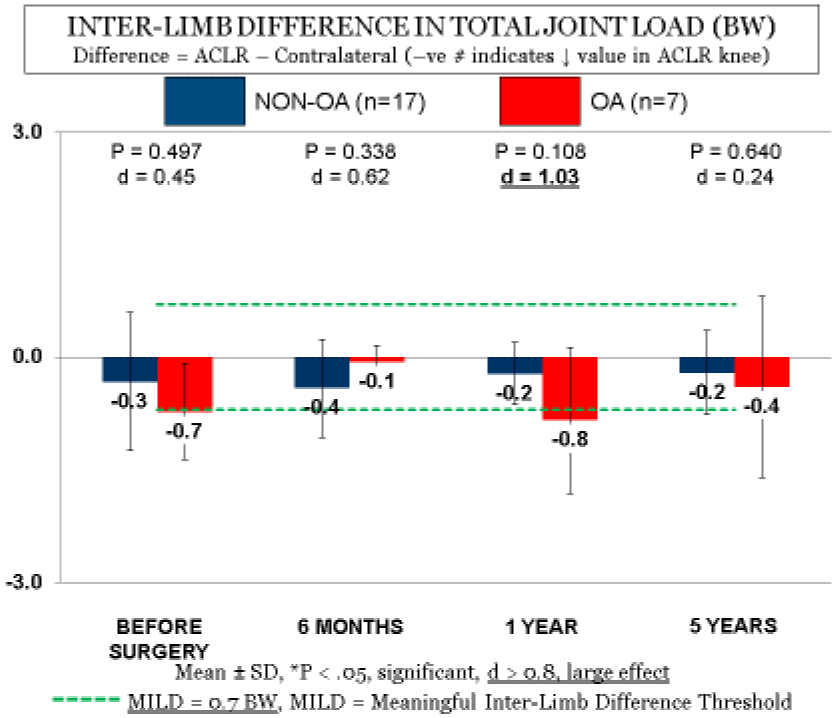

Figure 26. Inter-limb difference in total joint load at the second peak of vertical ground reaction force

(ACLR = anterior cruciate ligament reconstruction, OA = osteoarthritis, BW = body weight, SD = standard deviation, d = effect size)

2.4 Discussion

The purpose of this study was to evaluate knee gait parameters in subjects who get knee medial compartment knee OA five years after ACLR, versus those who do not, at multiple time points (before surgery, six months after surgery, one year after surgery and five years after surgery).

Sagittal plane kinematics influence tibiofemoral contact location within the knee joint [82]. For the ACLR knee, the OA (versus non-OA) group demonstrated a lower knee flexion angle at the first peak of vGRF (during the weight acceptance phase of gait). This difference approached significance one year after surgery, and was statistically significant five years after surgery. This observation is in line with previous reports that investigated the changes in sagittal plane kinematics in relation to OA [83]. A lower knee flexion angle has also been observed for subjects who undergo ACLR and demonstrate quadriceps weakness, when compared to uninjured controls [84]. A potential reason as to why a smaller knee flexion angle during weight acceptance could be detrimental for the cartilage is the shift in contact location. Between 0-30 ° of knee flexion, joint contact in the medial compartment shifts posteriorly with an increasing knee flexion angle [85,86]. Hence, the smaller the knee flexion angle, the more anterior the contact location in the medial compartment of the knee. Knowing that the medial tibial cartilage in the anterior region is thinner compared to the weight bearing region [87], even a low or normal medial compartment load magnitude can induce high stresses in the thinner anterior region of the cartilage.

Sagittal plane kinetics influence the medial compartment load magnitude. For external flexion knee moment during gait, studies have shown smaller values during weight acceptance in relation to OA progression, based on inter-group (non-OA versus OA) and inter-limb differences, up to one year after surgery [55,83,84,88]. These differences tend to diminish in magnitude and are often not found three years after surgery [55]. In the current study, the OA (versus non-OA) group demonstrated a smaller external knee flexion moment at the first peak of vGRF, for the ACLR knee. This difference approached significance six months after surgery, and was statistically significant five years after surgery. A lower value for external knee flexion moment could be due to quadriceps avoidance, reduced quadriceps strength, hamstrings facilitation, or a combination of those factors [84,89,90]. While reduced quadriceps strength lowers the tibiofemoral force, hamstrings facilitation can have the opposite effect [89]. Insufficient quadriceps strength at early time points after ACLR has been documented [84]. Hence, for the current study, it is plausible that the lower knee flexion moment for the OA (versus non-OA) group six months after ACLR results in a lower medial compartment load magnitude. Given that the net external flexion moment does not consider the impact of muscle co-contraction, a direct estimation of medial compartment load magnitude that utilizes muscle activation levels is more useful, and is discussed further.

In the frontal plane, external knee adduction moment modulates the distribution of the total joint load between medial and lateral compartments of the knee [20]. A larger knee adduction moment increases the medial compartment load, and is often used as an indirect indicator for medial compartment load [68]. Compared to healthy controls, individuals who develop knee OA demonstrate greater knee adduction moments [54,91]. However, up to three years after surgery, there is limited and conflicting evidence about the knee adduction moment being higher in the ACLR knee, compared to the contralateral knee and healthy controls [20,29,55]. In the current study, the differences in knee adduction moment at the first peak of vGRF approached significance at two time points, between the non-OA versus OA groups. At baseline, the value was lower for the OA (versus non-OA) group, while at five years after surgery, the value was higher. These results suggest that the degeneration mechanism proposed after an ACL injury [19] and surgery may involve initial under-loading after injury, followed by over-loading at five years after surgery.

A more direct and reliable estimate of medial compartment load magnitude can be made by including muscle activation and neuromusculoskeletal (NMS) modeling. In the current study, estimates of medial compartment load at the first peak of VGRF revealed that the magnitude was lower for the OA (versus) non-OA group at six months after surgery, and this difference approached significance. There were no differences in the medial compartment load magnitude at later post-surgery time points. Five years after surgery, the OA (versus non-OA) group demonstrated a lower knee flexion moment, but a higher knee adduction moment, for the ACLR knee. Knowing that both knee flexion and adduction moments impact medial compartment load magnitude [62,92], the combination of a lower knee flexion moment and higher knee adduction moment likely maintains the magnitude of the medial compartment load in subjects with OA to near normal levels. However, if the location is shifted to the thin cartilage region, a normal medial compartment load magnitude could still induce high cartilage stresses.

For total joint load estimates at the first peak of vGRF for the ACLR knee, the OA (versus) non-OA group demonstrated lower values at six months and five years after surgery, and these differences approached significance. Similar to the medial compartment load magnitude, the values for the two groups were similar at five years after surgery.

Pertaining to inter-limb asymmetry, smaller knee flexion angles during the weight acceptance phase have been reported in the ACLR versus contralateral knee six to twelve months after ACLR [59]. In the current study, six month inter-limb differences were observed for both (non-OA and OA) groups at the first peak of VGRF, using the minimum inter-limb difference (MILD) threshold. However, no differences were observed at any other time points. These data suggest that inter-limb differences during weight acceptance are resolved over time. However, at noted earlier, the OA (versus non-OA) group demonstrated a smaller knee flexion angle during weight acceptance, five years after ACLR. Hence, it is possible that inter-limb symmetry in non-OA versus OA groups is achieved in different ways after ACLR. Subjects without knee OA may achieve symmetry by matching the ACLR knee to the uninjured contralateral knee, while subjects with knee OA may achieve symmetry by matching the uninjured contralateral knee to the ACLR knee. A similar argument could apply to inter-limb symmetry observed for all other gait parameters five years after ACLR. For the OA group, this could imply an increased risk of knee OA in the uninjured contralateral knee, in addition to the ACLR knee, over time. Hence, rather than evaluating just the inter-limb symmetry, it may be necessary to differentiate between good versus bad inter-limb symmetry, when evaluating knee gait parameters. While there is some evidence of contralateral knee OA in subjects after unilateral ACLR, more long term follow-up evidence is required to verify this possibility [5].

Frontal plane moments and joint loads that coincide with the second peak of vGRF during gait are almost similar in magnitude to the values at the first peak of vGRF. There is also some evidence of differences in sagittal plane moments during the late stance phase of gait, between subjects with ACLR and healthy controls [20]. In the current study, no significant differences between the non-OA versus OA groups were observed at any time point for the ACLR knee, at the second peak of vGRF (section 2.3.2). However, large effect sizes and inter-limb differences were noted for each knee gait parameter, at various time points. Most notably, for the ACLR knee, the OA (versus non-OA) group demonstrated a smaller medial compartment and total joint load at the second peak of vGRF, and this difference approached significance at six months after surgery. This result was similar to differences for the ACLR knee seen at the first peak of vGRF. For inter-limb symmetry, the OA group under-loaded their ACLR knee (versus the contralateral knee), before surgery and at one year after surgery, at the second peak of vGRF during gait. There were no inter-limb differences five years after ACLR for either group, similar to observations made at the first peak of vGRF. The potential impact of knee gait kinematics, kinetics and joint loads at the second peak of vGRF on cartilage stresses is not clear. Given that the knee is a near neutral (sagittal plane) position at the second peak of vGRF during gait, the joint load is likely distributed over a larger area of menisci and cartilage, in both the medial and lateral knee compartments. Hence, the resultant knee cartilage stresses may be significantly lower at the second peak of vGRF (compared to the first peak of vGRF), due to better joint conformity. In evaluation of knee prosthesis conformity, mathematical simulations have shown that with better conformity, the stresses are indeed, significantly lower [93]. However, the impact of differences in sagittal plane knee gait kinematics on knee cartilage stresses, still need to be verified in vivo, for a normal (non-prosthetic) knee joint.

Further work also needs to be done, possibly using a combination of modalities used for studying the knee, including magnetic resonance imaging (MRI) [94,95], finite element (FE) modeling [40] , and dynamic stereo x-ray studies [96]. This would help verify whether the knee gait kinematic, kinetic and joint load magnitudes observed in subjects with medial compartment OA impact knee cartilage stress close to the region of clinically observed osteophytes. In the current study, we used radiographs, and not MRI, to detect the presence of OA, which is a limitation. Compared to radiographs, OA related changes in knee cartilage can be located and detected sooner using MRI [97] . Another limitation pertains to sex-based differences. It has been shown that women are more likely than men to demonstrate dynamic knee instability after injury [98]. In the current study, the sample size was small and differences based on sex were not considered. However, sex does not appear to be a determining factor in the development of knee OA, specifically after ACLR [5]. Lastly, frontal and transverse plane kinematics are impacted by ACLR [99]. A reliable measurement of frontal and transverse plane knee kinematics requires the use of dynamic stereo x-ray. Because our current experimental setup does not include dynamic stereo x-ray, the impact of frontal and transverse plane knee kinematics could not be considered.

In conclusion, five years after ACLR, the OA (versus non-OA) group demonstrated a significantly lower knee flexion angle and moment in the ACLR knee, at the first peak of vGRF. Also in the ACLR knee, the medial compartment and total joint loads for the two groups were similar. Given the presence of inter-group differences (non-OA versus OA) for the ACLR knee, but an absence of inter-limb asymmetry at five years for either group, it may be necessary to differentiate between good versus bad inter-limb symmetry, when evaluating knee gait parameters.

Chapter 3

AIM 2: CARTILAGE STRESS DURING GAIT IN THOSE WITH/WITHOUT MEDIAL COMPARTMENT KNEE OSTEOARTHRITIS FIVE YEARS AFTER ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION SURGERY

3.1 Introduction

Radiographs of subjects with unilateral anterior cruciate ligament reconstruction (ACLR) who go on to develop medial compartment knee OA five years after ACLR demonstrate an osteophyte near the medial joint margin (i.e. close to the midline of the body, Figure 27). Presence of osteophytes (a fibrocartilage-capped bony outgrowth) [100] in radiographs is commonly used to ascertain that a subject has knee osteoarthritis (OA). These osteophytes arise in the periosteum overlying the bone at the junction between cartilage and bone [101]. It has been shown that osteophyte formation due to subchondral bone remodeling plays an important role in the pathogenesis of OA [102]. For an untreated anterior cruciate ligament (ACL) injury, OA related cartilage degradation is primarily observed near the lateral tibial plateau, which is the site of initial injury, or near the postero-medial region of the tibial plateau [103,104]. The postero-medial osteophyte is likely a response to prevent excessive anterior tibial translation, in the absence of the passive ACL. However, the location of the osteophyte in subjects with unilateral anterior cruciate ligament reconstruction (ACLR) cannot be attributed to excessive anterior tibial translation, as functional stability in the knee joint is restored by the ACLR procedure [18,105].

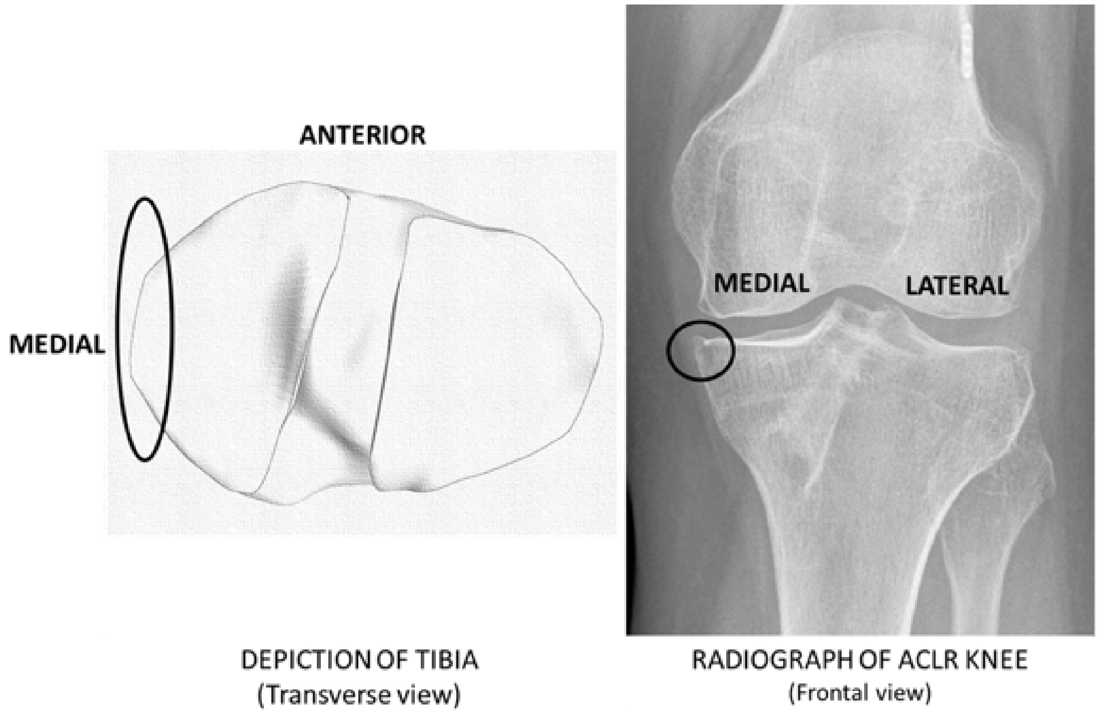

Figure 27. Posterior view of right knee five years after anterior cruciate ligament reconstruction demonstrating presence of osteophyte near the medial joint margin (onset of osteoarthritis)

Multiple biological and mechanical factors have been correlated to onset and development of premature medial compartment knee OA after an ACL injury and ACLR [51]. One of the mechanical factors associated with premature medial compartment knee OA in subjects after ACLR is altered knee gait kinematics and kinetics after surgery [20–22,55]. Peak parameters during the weight acceptance phase, which tend to temporally coincide with the first peak of vertical ground reaction force (vGRF) [57,58], are most frequently used to assess knee joint kinematics/kinetics after anterior cruciate ligament reconstruction (ACLR) [55].

Neuromusculoskeletal (NMS) models that utilize information derived from electromyography (EMG) signals during gait have enhanced the capability of traditional gait analysis, by allowing an estimation of loading in the medial compartment of the knee joint [66,67]. Recent evidence utilizing validated NMS models indicate that subjects with medial compartment knee OA five years after ACLR demonstrate sagittal and frontal plane knee gait aberrations, as well as decreased knee joint loading, or under-loading, six months to one year after ACLR [11]. In animal studies, under-loading and immobilization has been shown to negatively impact the knee cartilage [12–14]. Animal studies have also shown that excessive joint loading, or over-loading is injurious for the cartilage and results in chondrocyte death [15]. Thus, both knee joint under-loading (at early time points, i.e. up to one year after ACLR), and over-loading (at later time points, i.e. five years after ACLR) could be involved in the onset and progression of knee OA after ACLR [11,19]. A normal joint load magnitude, but in the presence of aberrant knee gait mechanics, could still impact load distribution within the joint and increase stresses in the knee joint cartilage. Moreover, while altered knee gait mechanics and joint loading are thought to be related to premature knee OA development [20–22], not all subjects with ACLR develop knee OA. Comparing knee gait mechanics and the resultant cartilage stress distribution in non-OA versus OA ACLR groups and the impact on resultant cartilage stresses may help solidify the link between aberrant knee gait mechanics and OA. While altered knee gait mechanics and joint loading are thought to initiate knee OA after ACLR, it is the resultant load distribution within the knee joint structures and cartilage stress that would play a role in subchondral bone remodeling and ultimately result in cartilage degeneration [15]. However, the changes that occur in knee cartilage stress distribution due to altered knee gait mechanics are not clearly understood [23]. Specifically, it is not clear whether cartilage stresses are higher near the location of osteophytes observed in subjects who get medial compartment knee OA five years after ACLR (Figure 27 above).

Finite element (FE) modeling techniques, combined with in vivo biomechanical data obtained using electromyography (EMG)-based neuromusculoskeletal (NMS) models can serve a valuable function to evaluate stresses within the knee joint [40,106–112]. Direct in vivo validation of knee joint stresses predicted by FE simulations is challenging. While knee joint loads can be directly estimated in vivo, it requires a knee joint replacement implant made of metal and plastic components, wherein cartilage, menisci and the ligament structures are violated [113]. Moreover, knee joint kinematics and kinetics are dictated by the implant geometry and material properties. Hence, knee joint replacement implants may not serve as a suitable surrogate to evaluate stresses in a joint with ACLR. Due to these reasons, validation of FE models primarily relies on cadaveric experiments performed under quasi-static loading conditions [106,109,114,115].

With that background, the aim of the study is to replicate knee joint experiments published in literature in a FE model, and to use the model to investigate the impact of knee gait biomechanics on knee cartilage stress distribution. Specifically, the model will be used to evaluate knee cartilage stresses near the medial joint margin (location of clinically observed osteophytes) in those with/without knee OA five years after ACLR. The hypothesis listed below is evaluated at the first peak of vGRF during the stance phase of gait.

Hypothesis 2. Near the medial margin of the medial tibial cartilage for the ACLR knee, subjects with OA (versus non-OA) will exhibit a smaller peak stress up to one year post-surgery, and a greater peak stress five years post-surgery

While limited and not specific to an ACLR population, there is some evidence related to aberrant knee gait parameters during the late stance phase in subjects with knee OA [64,68,69]. Frontal plane moments and joint loads that coincide with the second peak of vGRF during gait are almost similar in magnitude to the values at the first peak of vGRF. There is also some evidence of differences in peak sagittal kinetics during the late stance phase of gait, between subjects with ACLR and healthy controls [20]. Hence, medial tibial cartilage stresses at the second peak of vGRF are also reported here.

3.2 Methods

3.2.1 Clinical data description

3.2.1.1 Study population

The study population is described in section 2.2.1. 24 subjects were included in the final analysis (Figure 28). The study was approved by the Institutional Review Board at the University of Delaware (Appendices A and B). All subjects were provided with written consent forms for the study.

3.2.1.2 Inclusion-Exclusion criteria

The inclusion-exclusion criteria is described in section 2.2.2.

3.2.1.3 ACLR surgery

The ACLR procedure is described in section 2.2.3

3.2.1.4 Evaluation of knee OA

The procedure to determine presence/absence of knee OA is described in section 2.2.4.

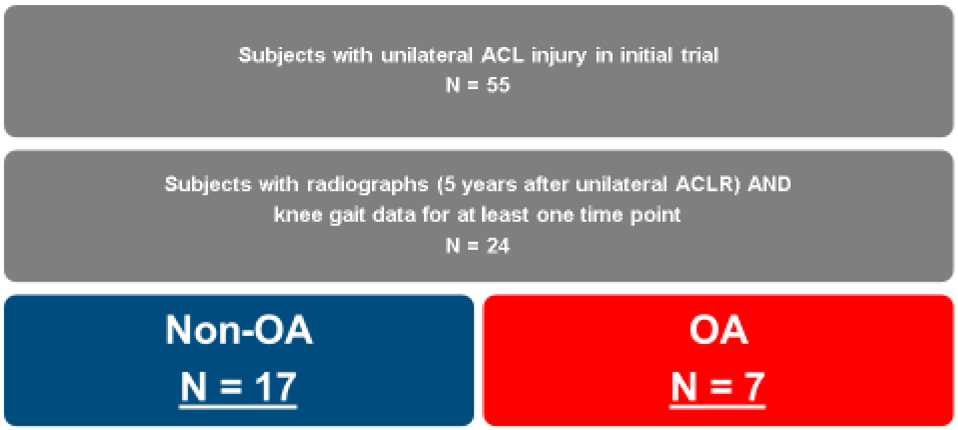

Figure 28. Subjects with/without medial compartment knee OA five years after unilateral ACLR

(ACL = anterior cruciate ligament, ACLR = anterior cruciate ligament reconstruction, OA = osteoarthritis)

17 out of 24 subjects did not have medial compartment knee OA in the ACLR knee five years after surgery, and were included in the non-OA group. 7 out of 24 subjects demonstrated signs of medial compartment knee OA in the ACLR knee five years after surgery, and were included in the OA group. Non-OA versus OA group characteristics at the pre-surgery time point are included in table 2 below. For all subjects with medial compartment knee OA, the osteophyte was located near the medial margin of the medial compartment (i.e. the thinner cartilage region close to midline of the body)

Table 2. Subject parameters for non-OA versus OA group at the pre-surgery time point

Parameter	Non-OA (Mean ± SD)	OA (Mean ± SD)	P	d
Sex	12 men, 5 women	3 men, 4 women	.202	N/A
Graft type	7 autografts, 10 allografts	3 autografts, 4 allografts	.939	N/A
Age (years)	31 ± 11	35 ± 13	.443	0.35
Mass (kg)	85 ± 19	75 ± 15	.417	0.54
Height (m)	1.7 ± 0.1	1.7 ± 0.1	.602	0.34
Walking speed (m/s)	1.6 ± 0.1	1.5 ± 0.1	.666	0.28

- OA = osteoarthritis, SD = standard deviation, kg = kilogram, m = meter, s = second
- *P < .05, significant (chi-square test or independent t-test, as applicable),
- d = effect size, d > 0.8, large effect

3.2.1.5 Post-surgery time points

Gait analysis data from the following post-surgery time points was utilized: six months after ACLR, one year after ACLR and five years after ACLR

3.2.2 Knee kinematic, kinetic and electromyography data analysis

The testing and data analysis methodology is described in section 2.2.6, and the workflow is shown in figure 29 below.

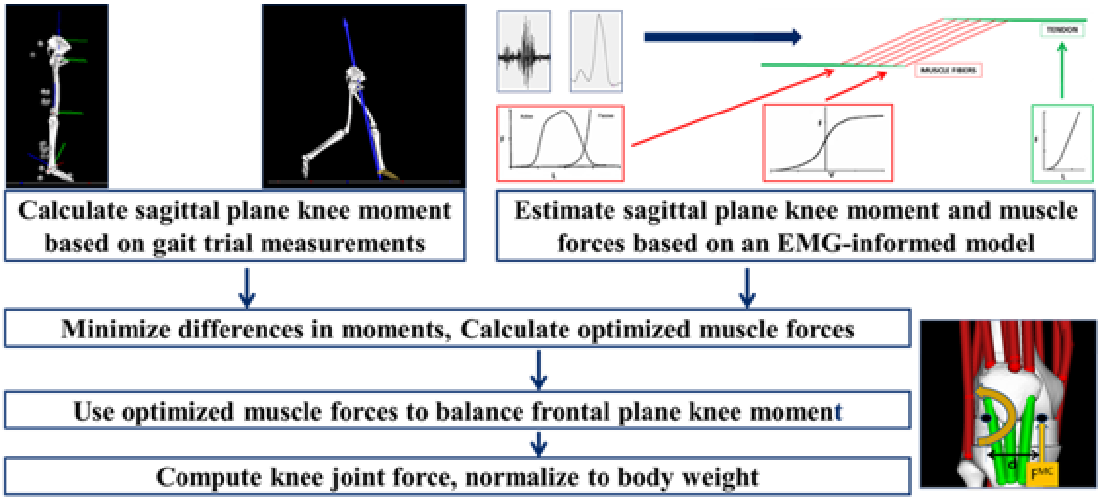

Figure 29. Workflow for neuromusculoskeletal modeling

The knee kinematic, kinetic and joint loading data thus obtained was be used as input for a finite element model, to run quasi-static simulations at the first and second peak of vertical ground reaction force.

3.2.3 Open Knee finite element model

3.2.3.1 Model description and material properties

An open source finite element mesh, the Open Knee, was used for analysis [116] using FEBiO [117,118] (Musculoskeletal Research Laboratories, University of Utah). The Open Knee project is aimed to provide access to three-dimensional finite element representations of the knee joint (Figures 30 and 31) [116].

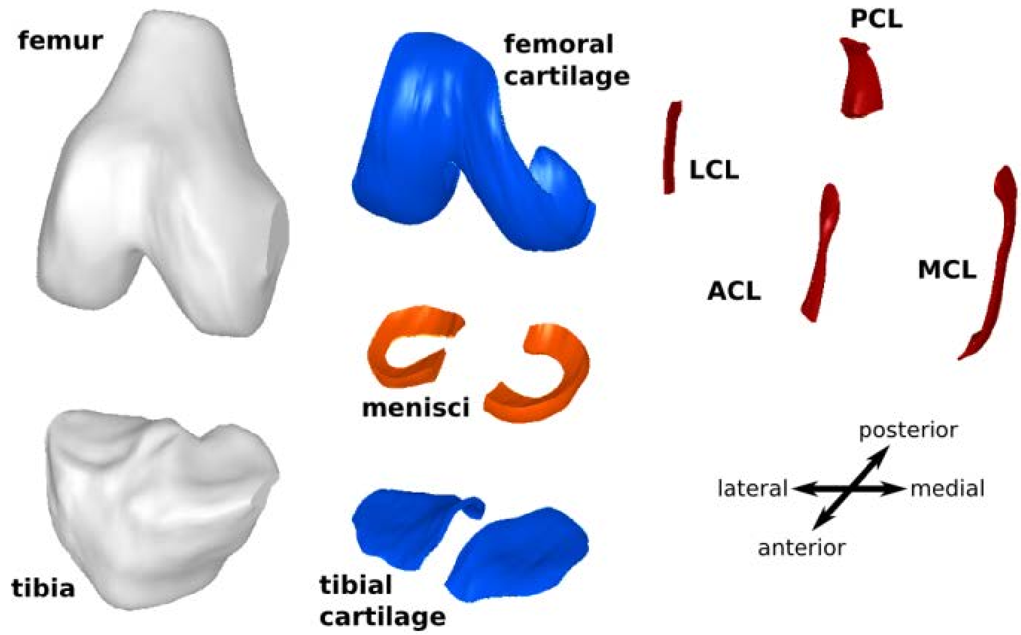

Figure 30. Knee joint structural representations in the Open Knee finite element model

(Source: http://simtk.org/home/openknee)

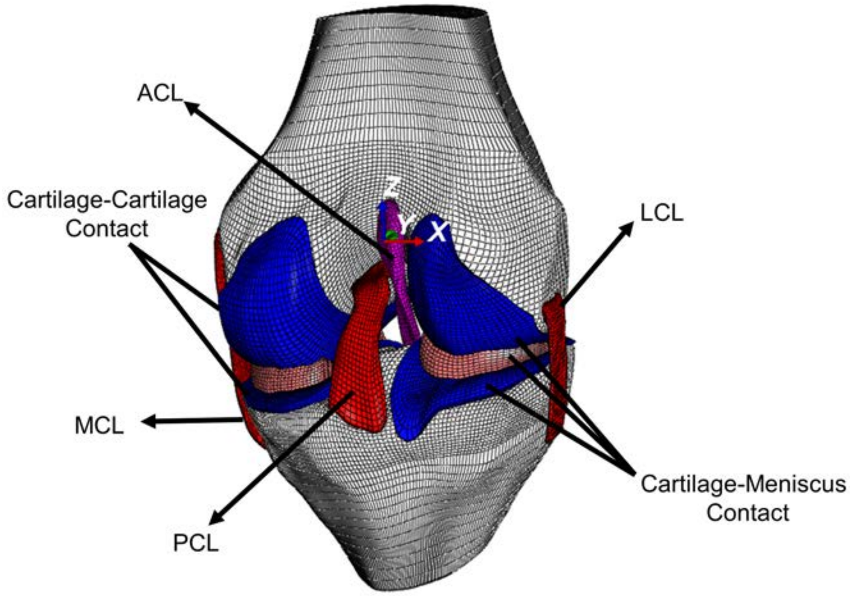

Figure 31. Postero-lateral view of Open Knee finite element mesh

(ACL = anterior cruciate ligament, PCL = posterior cruciate ligament, LCL = lateral collateral ligament, MCL = medial collateral ligament)

Table 3 below lists the assigned material properties to the different knee joint structures. Material properties are assigned based on literature [37,106,109,119], with the mesh density comparable to published knee models [109,120,121].

Table 3. Description of Open Knee joint representation and assigned material properties

Structure	# Elements	Element Type	Material Description	Material Properties (MPa, where applicable)
Femur	13860	shell	rigid body	N/A
Tibia	11360			
Femoral cartilage	17226	hexahedral	linear elastic, isotropic	$E = 15$, $\upsilon = 0.475$
Tibial cartilage	8847			
Lateral meniscus	4620		linear elastic, transversely isotropic	$E_1 = 20$, $E_2 = 120$, $E_3 = 20$ $\upsilon_{12} = 0.3$, $\upsilon_{13} = 0.45$, $\upsilon_{23} = 0.3$
Medial meniscus	4620			
ACL	4096		transversely isotropic hyperelastic, with mooney-rivlin ground substance	$c_1 = 1.95$, $c_2 = 0$, $c_3 = 0.0139$, $c_4 = 116.22$, $c_5 = 535.039$, $k = 73.2$, $\lambda_m = 1.046$
PCL	5248			$c_1 = 3.25$, $c_2 = 0$, $c_3 = 0.1196$, $c_4 = 87.178$, $c_5 = 431.063$, $k = 122$, $\lambda_m = 1.035$
MCL	5120			$c_1 = 1.44$, $c_2 = 0$, $c_3 = 0.57$, $c_4 = 48$, $c_5 = 467.1$, $k = 397$, $\lambda_m = 1.063$
LCL	6656			

(ACL = anterior cruciate ligament, PCL = posterior cruciate ligament, MCL = medial collateral ligament, LCL = lateral collateral ligament, E = Young's modulus, υ = Poisson's ratio, c_1-c_2 = Mooney-Rivlin coefficients, c_3-c_6 = fiber material coefficients, k = bulk modulus, λ_m = straightened fiber stretch)

3.2.3.2 Subject-specific scaling based on radiographic measurements

The Open Knee FE mesh was scaled based on subject-specific posterior-anterior (PA) radiographic measurements that were available at the five year time point after ACLR surgery. In the medial-lateral direction, the Open Knee model was scaled to match the distal femoral width measurement (dimension a) from the posterior-anterior radiograph, using PreView (Musculoskeletal Research Laboratories, University of Utah). In the anterior-posterior direction, the model was scaled based on the gender-specific dimensional relationship between the distal femoral width measurement (dimension a) and the posterior-anterior width of the lateral femoral condyle (dimension b) [122]. For men, the ratio of dimension b to dimension a was 0.867, while for women, the ratio was 0.904 [122]. Based on the anatomic axis measurement from the PA radiograph, the mechanical axis was calculated using a gender-specific offset (6.4 ° for men, 3.5 ° for women) [123] and reproduced in the Open Knee model by inducing a rotation in the frontal plane. Magnetic resonance imaging data was not available for any subject, hence subject-specific femoral and tibial cartilage thicknesses could not be reproduced. However, radiographic medial compartment joint space width measurement (JSW, measured at ~ 25 % of the medial-lateral distance, from the medial edge of femur) was available from PA radiographs. This JSW measurement was used as a surrogate for total cartilage thickness (femoral cartilage thickness + tibial cartilage thickness) in the center of the medial compartment. To accommodate this measurement in the Open Knee model, knee joint structure nodes were offset and scaled. This process allows incorporation of JSW measurement in the Open Knee model. However, it maintains the relative proportional cartilage thickness distribution per the original Open Knee model. Hence, femoral and tibial cartilage thicknesses incorporated are not truly subject-specific. Assumptions and limitations pertaining to scaling procedure defined here are included in the discussion section. The procedure outlined above was repeated for each subject, for each limb.

3.2.3.3 Constraints and loading conditions for simulations at the first and second peak of vertical ground reaction force during the stance phase of gait

Constraints were chosen to ensure a stable response of the tibiofemoral knee joint under in vivo kinematics and kinetics during gait. In the original Open Knee model, the meniscal horn attachment definitions allow excessive medial-lateral translation and anterior-posterior translation of the menisci under physiologic in vivo loading conditions (i.e. despite the horn attachment definitions, the menisci displace out of the joint) [124]. This necessitated the use of constraints at meniscal horn attachment nodes. All the meniscal horn attachment nodes were constrained in the medial-lateral direction. Additionally, the nodes representing the interior corner edge of the meniscal horn attachments were also constrained in the anterior-posterior direction. Translational motion of the meniscal horn attachment nodes in the cephalad-caudal direction was not constrained. This constraint definition allows for compression, and for motion of the whole menisci structure in all directions, while keeping the menisci from displacing out of the joint during in vivo gait simulations. While similar constraints have been used in other studies [109,124,125], this constraint definition is not truly physiologic. Assumptions and limitations pertaining to the meniscal horn attachment constraint defined here are included in the discussion section.

Rigid interfaces defined between bone-cartilage and bone-ligament structures in the original Open Knee model were maintained [119]. Similarly, contact definitions between cartilage-cartilage and cartilage-menisci structures in the Open Knee model were maintained (Figure 31). Contact is assumed to be frictionless. Contact definition relies on the finite sliding contact formulation in FEBiO [117], implemented with a two-pass facet-to-facet contact algorithm and penalty stiffness definition [119].

For the femur and tibia, rigid body reference points are coincident with the origin of the finite element model coordinate system [112,116,126]. With the tibia fully constrained, kinematic (sagittal plane: knee flexion angle), total joint load and kinetic (frontal plane: knee adduction moment) input was applied to the femur (figure 32) [112]. The kinematic, kinetic and total joint load data was obtained from gait and electromyography analysis. Quasi-static simulations at the first and second peak of vertical ground reaction force during the stance phase of gait were modeled. For isotropic material modeling, von Mises stress (effective stress), based on distortion energy criteria for multiaxial stresses, is considered useful for comparing stress values [127] under different loading conditions, and was used in the current study. The output variable of interest was peak effective stress in the medial tibial cartilage. The effective stress is given by the formula below, with subscripts representing components of the orthogonal coordinate system.

$$Stress_{effective} = \sqrt{\frac{(\sigma_{11} - \sigma_{22})^2 + (\sigma_{22} - \sigma_{33})^2 + (\sigma_{33} - \sigma_{11})^2 + 6(\sigma_{12}^2 + \sigma_{23}^2 + \sigma_{31}^2)}{2}}$$

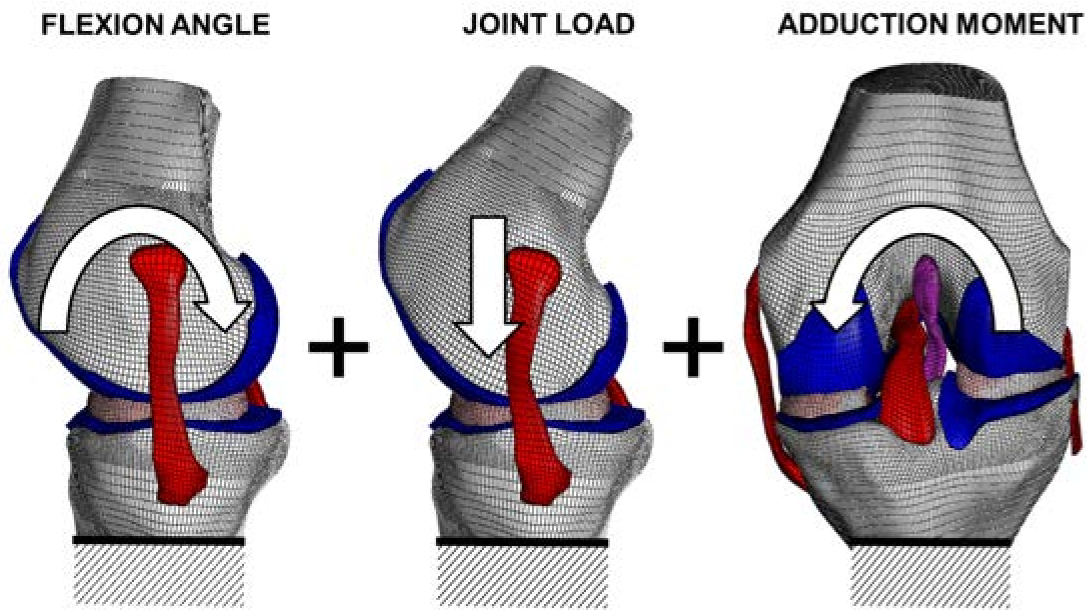

Figure 32. Medial and posterior view of the Open Knee model with loading and boundary conditions

3.2.4 Partitioning of medial tibial cartilage regions

To facilitate comparison of peak effective stress in different regions of medial tibial cartilage, the cartilage was divided into three equally spaced regions in the anterior-posterior direction, i.e. the anterior region, the central region and the posterior region. The central region was further subdivided into three equally spaced regions in the medial-lateral direction (figure 33). Region 1 represented the area near the medial joint margin, region 2 represented the central load-bearing area, and region 3 represented the area near the inter-condyloid eminence. Region 1 is the area of interest, i.e. the region near the medial joint margin where osteophytes are observed in radiographs. Peak von Mises stress values for regions 2 and 3 are also reported here.

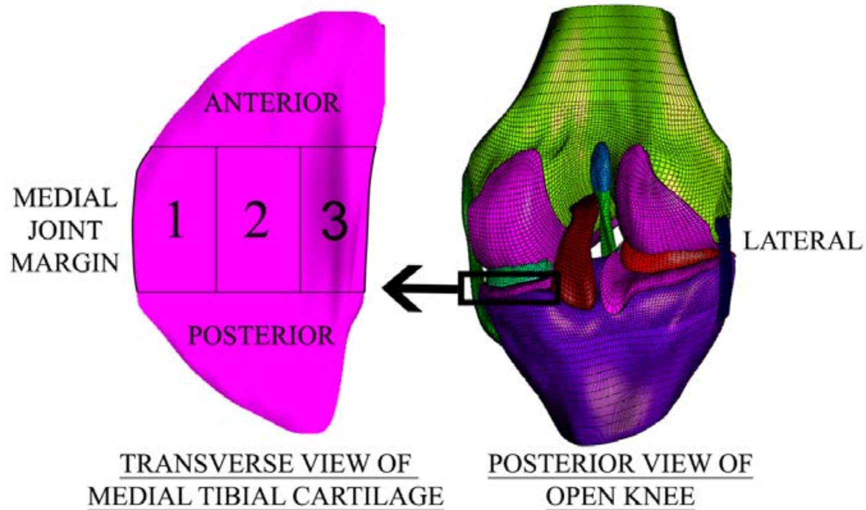

Figure 33. Partitioning of the medial tibial cartilage

3.2.5 Statistical analysis

Independent t-tests (and chi-square tests, where applicable) were used to test non-OA versus OA group differences in terms of sex, graft type, age, mass, height and walking speed during gait trials (Table 2 above). For the weight acceptance phase of gait, peak von Mises stress in the medial tibial cartilage (region 1) at the first peak of vertical ground reaction force (vGRF) was the key parameter of interest. Peak von Mises stress values were also evaluated for regions 2 and 3, and also at the second peak of vGRF. Independent t-tests were performed to test for differences between non-OA versus OA groups. Mean ± standard deviations (SD) and effect size (Cohen's d) have been reported for each parameter. Statistical analysis was conducted using Excel (Microsoft, Redmond WA) and JMP (Cary, NC). Statistical significance for all tests was set at $\alpha < 0.05$. Gait data from 12 healthy control subjects was used to determine meaningful inter-limb difference (MILD) thresholds for the key parameter of interest, using the methodology for estimating minimum detectable change [77]. The control group consisted of 5 women and 7 men, who actively participated in level I/II cutting and pivoting sports. The control group had the following subject characteristics (Mean ± standard deviation): age = 21 ± 3 years, mass = 75 ± 18 kg, height = 1.73 ± 0.1 m, walking speed = 1.6 ± 0.2 m/s. An inter-limb difference that was greater than the MILD threshold was interpreted as a reliable indication of inter-limb asymmetry.

3.2.6 Open Knee model simulation of published experimental studies

The Open Knee model, scaled per details in the previous section, was used to replicate a series of experiments reported in literature. The experimental conditions used and results are described in the next section.

Since most published experiments used for the current study report a mean age range of 40 to 50 years [37,128,82], the Open Knee FE model used was scaled based on radiographic measurements from a 45 year old male subject (Mass = 96 kg, Height = 1.83 m). Also, the Open Knee model does not include muscle representations, and the total joint loads need to be specified for simulation. Hence, for quasi-static cadaveric experiments that report known muscle forces (applied through isolated quadriceps and hamstring tendons), sagittal plane equilibrium [36] was used to estimate the total joint load for Open Knee simulation. For this purpose, a scaled lower extremity SIMM model (SIMM 6.0, Musculographics Inc., Chicago, IL) for the same 45 year old male subject was imported into OpenSim (simtk.org) [129]. Next, muscle force directions were calculated, based on kinematic conditions from cadaveric experiments. For the known quadriceps tendon force, the proportional patellar ligament force was also calculated [130], based on kinematic conditions specified in cadaveric experiments. This approach enabled the calculation of the total joint load, which was used as input for the Open Knee model.

3.2.6.1 Frontal plane kinematics and anterior cruciate ligament strain from cadaveric experiment reported in literature

In an experiment conducted using 20 fresh frozen cadaveric lower limbs (10 women, 10 men, age = 46 ± 6 years), the sagittal plane knee angle was held fixed (25 ° flexion) [37]. Additionally, the quadriceps and hamstring tendons were isolated to apply fixed muscle forces (quadriceps: 400 N, hamstrings: 200 N). Finally, knee abduction moment was applied to each specimen, and the resultant frontal plane kinematics and ACL strain were measured. This experiment was simulated using the Open Knee model, and the model predictions were compared to results from the cadaveric experiment. Experimental ACL strain was measured using a differential variable reluctance transducer (DVRT) placed on the distal third of the ACL. Accordingly, two nodes on the distal third of the ACL (~ 11.5 mm apart, per transducer length) were used to estimate strain in the Open Knee model. In figures 34 and 35 below, lines represent ± one standard deviation reported in the cadaveric experiment, while the bar graph represents the Open Knee estimates.

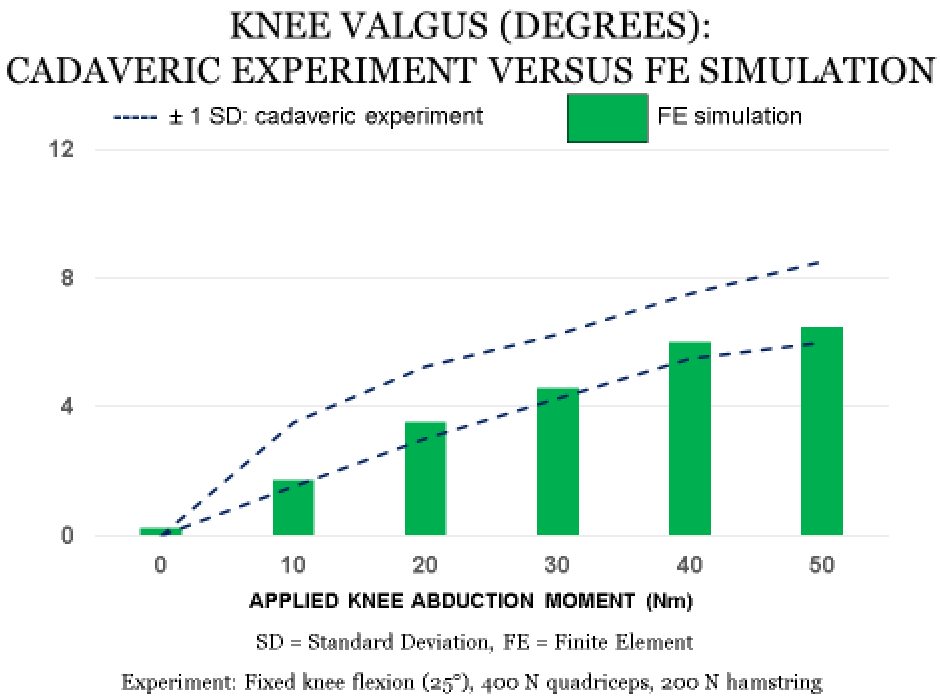

Figure 34. Knee valgus (degrees): Comparison of results from cadaveric experiment versus finite element simulation

Kiapour AM. Non-Contact ACL Injuries during Landing: Risk Factors and Mechanisms. Vasa. 2013;(August 2013)

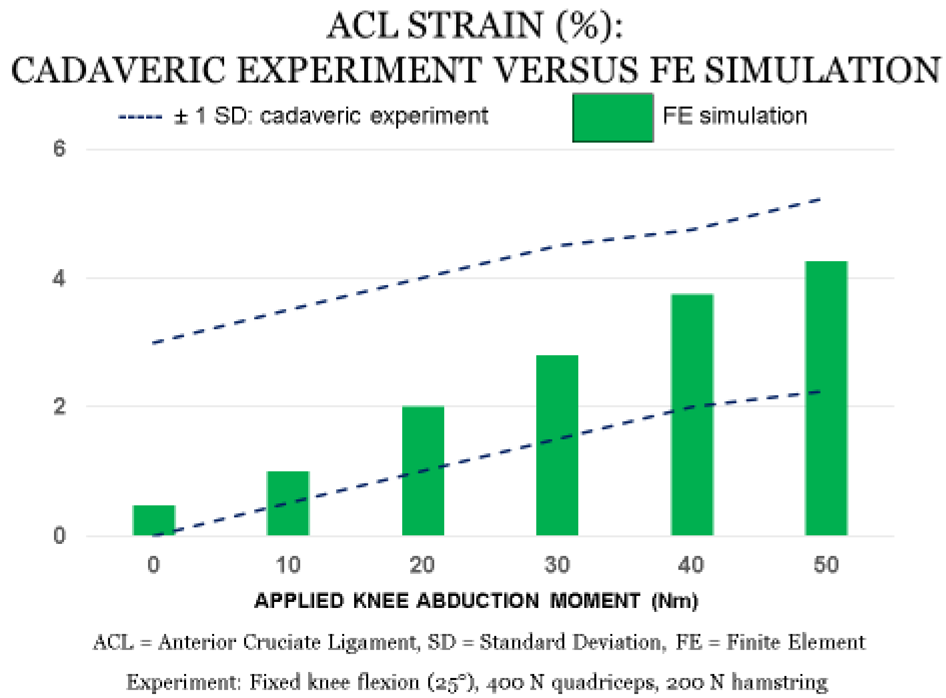

Figure 35. ACL strain (%): Comparison of results from cadaveric experiment versus finite element simulation

Kiapour AM. Non-Contact ACL Injuries during Landing: Risk Factors and Mechanisms. Vasa. 2013;(August 2013)

3.2.6.2 Tibiofemoral contact area and peak contact pressure from cadaveric experiment reported in literature

In an experiment conducted using 19 fresh-frozen cadaveric knees (age = 47 ± 17 years), a fixed compressive load (1000 N) was applied, while the sagittal plane knee angle was varied (0°, 15°, 30° and 45 ° flexion) [128]. The resultant tibiofemoral contact area (including the area covered by menisci) and peak tibiofemoral contact pressure were recorded. This experiment was simulated using the Open Knee model, and the model predictions were compared to results from the cadaveric experiment. In the Open Knee model, the tibiofemoral contact area was measured using a threshold value of 0.25 MPa (i.e. elements with values greater than threshold were included for calculation of contact area). In figures 36 through 39 below, lines represent ± one standard deviation reported in the cadaveric experiment, while the bar graph represents the Open Knee estimates.

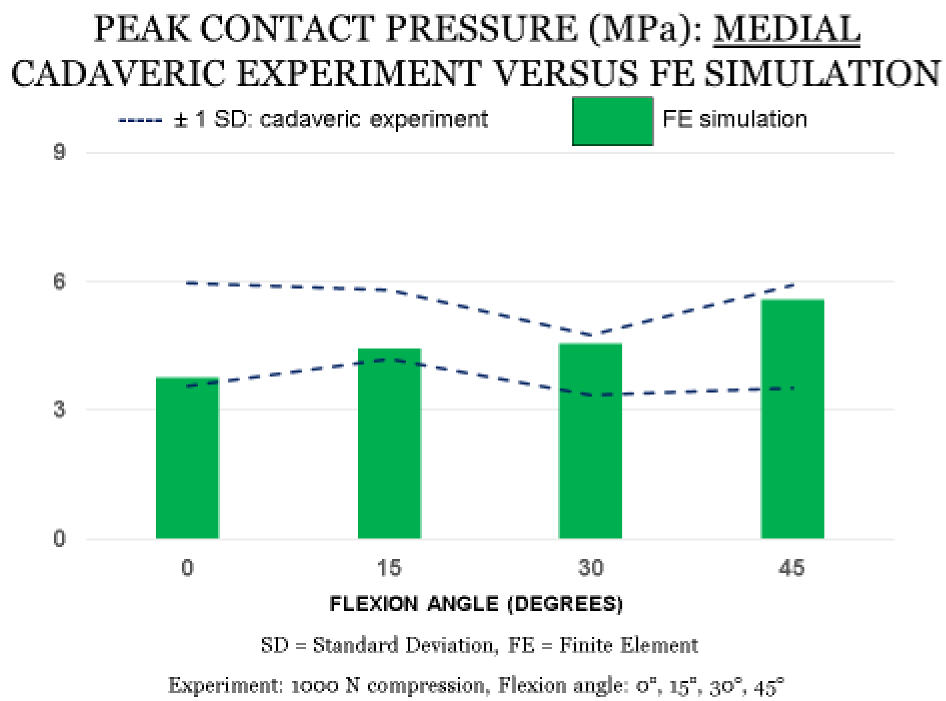

Figure 36. Peak contact pressure in medial tibiofemoral compartment: Comparison of results from cadaveric experiment versus finite element simulation

Morimoto Y, Ferretti M, Ekdahl M, Smolinski P, Fu FH. Tibiofemoral joint contact area and pressure after single- and double-bundle anterior cruciate ligament reconstruction. Arthroscopy. 2009;25(1):62-69.

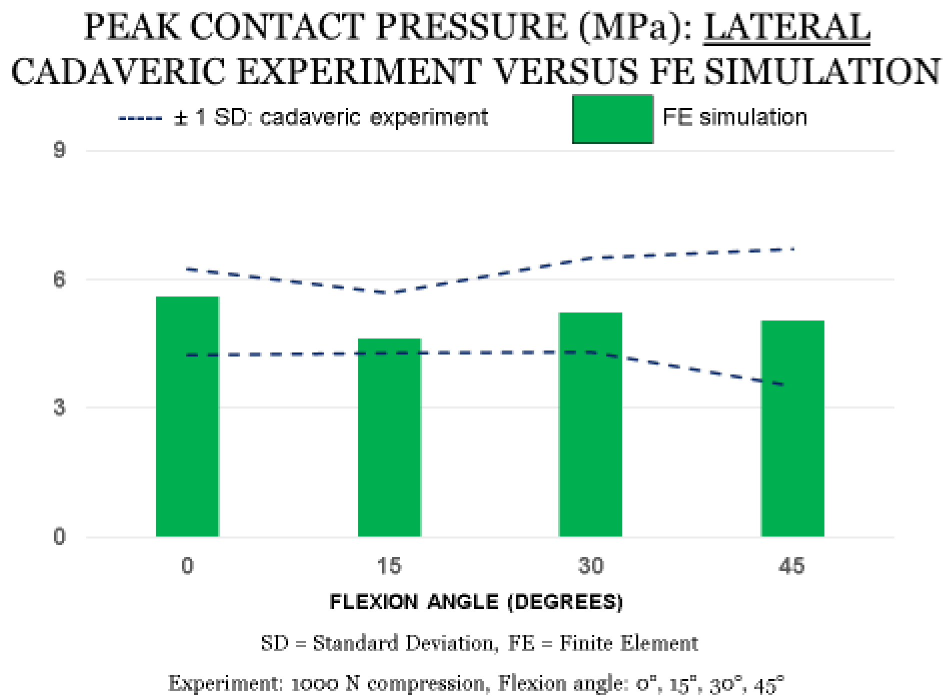

Figure 37. Peak contact pressure in lateral tibiofemoral compartment: Comparison of results from cadaveric experiment versus finite element simulation

Morimoto Y, Ferretti M, Ekdahl M, Smolinski P, Fu FH. Tibiofemoral joint contact area and pressure after single- and double-bundle anterior cruciate ligament reconstruction. Arthroscopy. 2009;25(1):62-69.

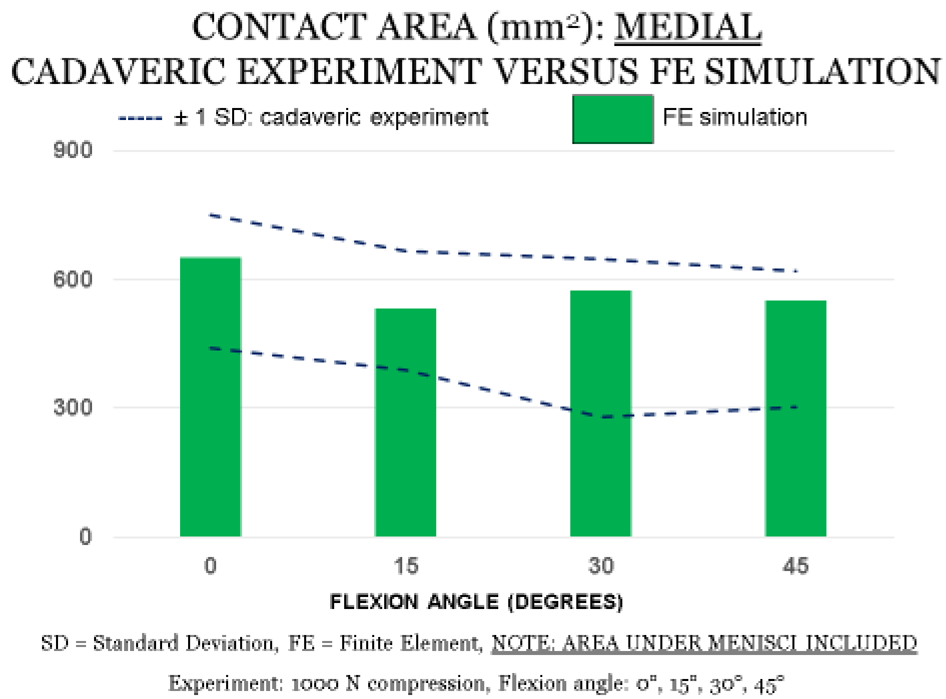

Figure 38. Contact area in medial tibiofemoral compartment: Comparison of results from cadaveric experiment versus finite element simulation

Morimoto Y, Ferretti M, Ekdahl M, Smolinski P, Fu FH. Tibiofemoral joint contact area and pressure after single- and double-bundle anterior cruciate ligament reconstruction. Arthroscopy. 2009;25(1):62-69.

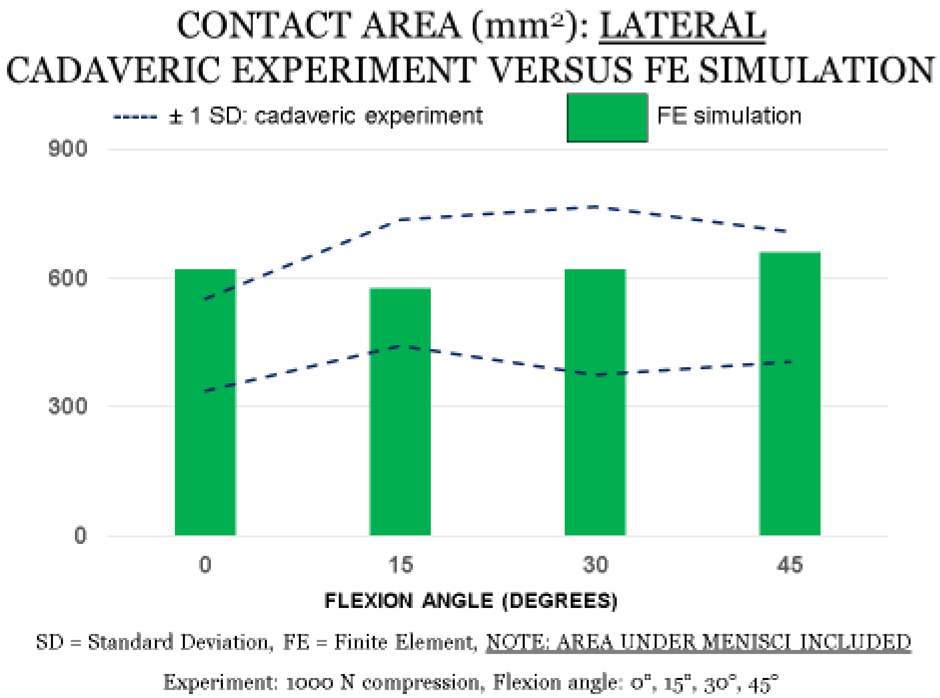

Figure 39. Contact area in lateral tibiofemoral compartment: Comparison of results from cadaveric experiment versus finite element simulation

Morimoto Y, Ferretti M, Ekdahl M, Smolinski P, Fu FH. Tibiofemoral joint contact area and pressure after single- and double-bundle anterior cruciate ligament reconstruction. Arthroscopy. 2009;25(1):62-69.

3.2.6.3 Transverse plane kinematics from cadaveric experiment reported in literature

In an experiment conducted using 20 fresh frozen cadaveric lower limbs (10 women, 10 men, age = 46 ± 6 years) [37], the quadriceps and hamstring tendons were isolated to apply fixed muscle forces (quadriceps: 400 N, hamstrings: 200 N). The resultant internal tibial rotation was measured at varying flexion angles (0-50°)

This experiment was simulated using the Open Knee model, and the model predictions were compared to results from the cadaveric experiment. In figure 40 below, lines represent ± one standard deviation reported in the cadaveric experiment, while the bar graph represents the Open Knee estimates.

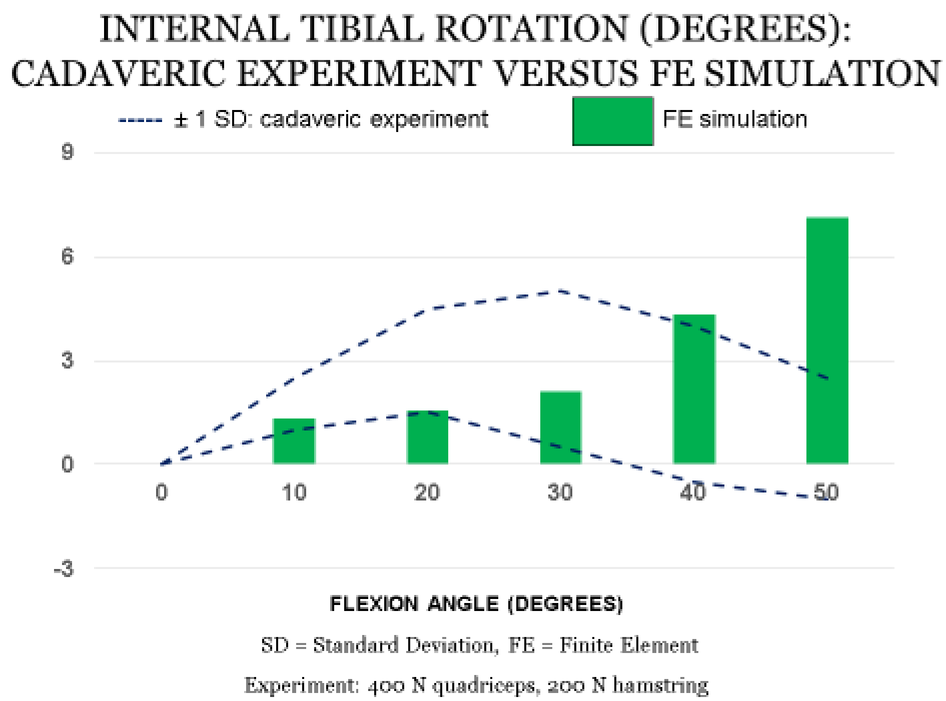

Figure 40. Internal tibial rotation (degrees): Comparison of results from cadaveric experiment versus finite element simulation

(A negative number on the graph above represents external tibial rotation)

Kiapour AM. Non-Contact ACL Injuries during Landing: Risk Factors and Mechanisms. Vasa. 2013;(August 2013)

3.2.6.4 Cartilage contact area during gait from in vivo experiment reported in literature

In an in vivo experiment conducted using 8 healthy subjects (6 men, 2 women, age range = 32 to 49 years), tibiofemoral contact area (excluding the area covered by menisci) was estimated during the stance phase of gait, using a combined dual fluoroscopic imaging system and magnetic resonance imaging [82]. However, the knee kinetic and joint loading data were not reported in the study. Hence, knee kinematics, kinetics and joint loading information from our database that were available for the 45 year old male subject (Mass = 96 kg, Height = 1.83 m) were used. Using the available information as input, quasi-static simulations were run at the first and second peaks of vertical ground reaction force (vGRF) during the stance phase of gait. Specifically, the sagittal plane knee angle, the external frontal plane moment and total joint load were used as inputs for the Open Knee model. The model predictions were compared to results from the in vivo experiment, at 20 % and 80 % of the stance phase, which approximately coincide with the first and second peaks of vertical ground reaction force. In the Open Knee model, the tibiofemoral contact area was measured using a threshold value of 0.25 MPa (i.e. elements with values greater than threshold were included for calculation of contact area). In figures 41 and 42 below, lines represent ± one standard deviation reported in the in vivo experiment, while the bar graph represents the Open Knee estimates.

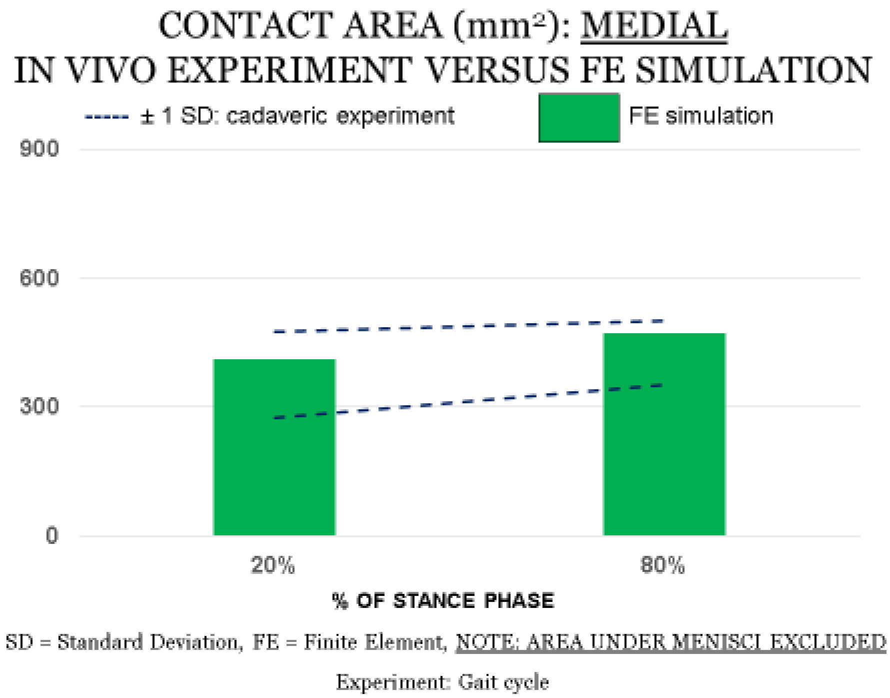

Figure 41. Contact area in medial tibiofemoral compartment: Comparison of results from in vivo experiment versus finite element simulation

Liu F, Kozanek M, Hosseini A, et al. In vivo tibiofemoral cartilage deformation during the stance phase of gait. J Biomech. 2010;43(4):658-665.

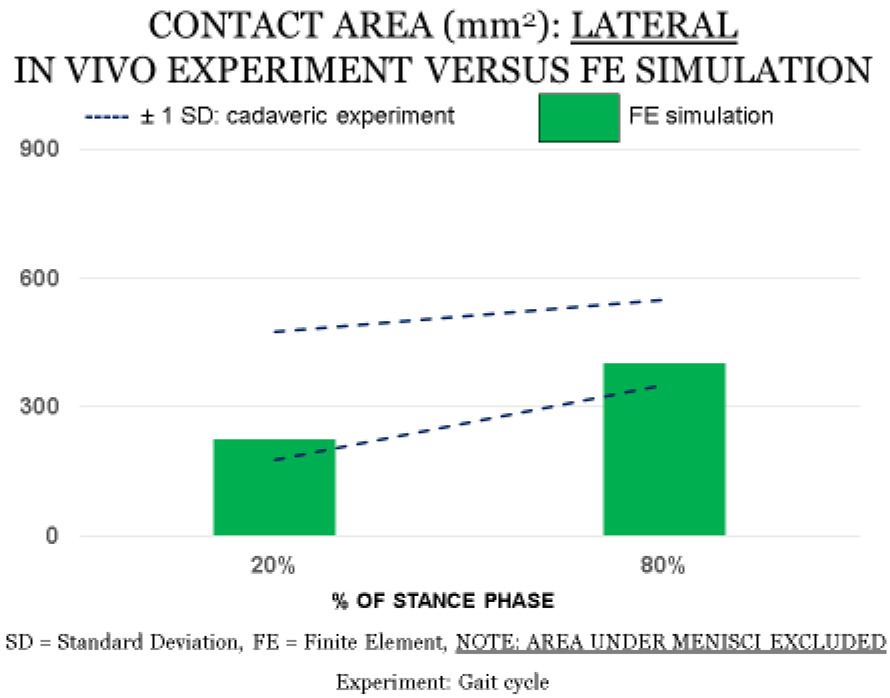

Figure 42. Contact area in lateral tibiofemoral compartment: Comparison of results from in vivo experiment versus finite element simulation

Liu F, Kozanek M, Hosseini A, et al. In vivo tibiofemoral cartilage deformation during the stance phase of gait. J Biomech. 2010;43(4):658-665.

3.2.6.5 Summary of FE predicted results against published experimental studies

Except transverse plane kinematics beyond 40° flexion, most estimates predicted by the Open Knee finite element model compared well with experimental values reported in literature. All structures of the knee joint are not represented in the Open Knee model, which likely affect transverse plane kinematics more than translations and rotations in other planes. Assumptions and limitations pertaining to transverse plane kinematics are included in the discussion section.

3.3 Results

The OA versus non-OA group differences in knee gait biomechanics and joint loading have been reported in the previous aim (Aim 1: Chapter 2). Utilizing subject-specific knee gait and loading parameters as input, finite element modeling simulations were conducted for the knee joint structure. The results below pertain to simulations at the first and second peaks of vertical ground reaction force during the stance phase of gait.

3.3.1 Peak medial tibial cartilage stress at the first peak of vertical ground reaction force during the stance phase of gait

3.3.1.1 Medial tibial cartilage stress distribution pattern

Figure 43 below shows the typical von Mises stress distribution in the medial tibial cartilage five years after unilateral ACLR. The stress distribution patterns between the subjects with/without medial compartment knee OA were distinctly different. The subject with medial compartment knee OA demonstrated high stresses near the medial joint margin. It is in this region that osteophytes are observed in radiographs.

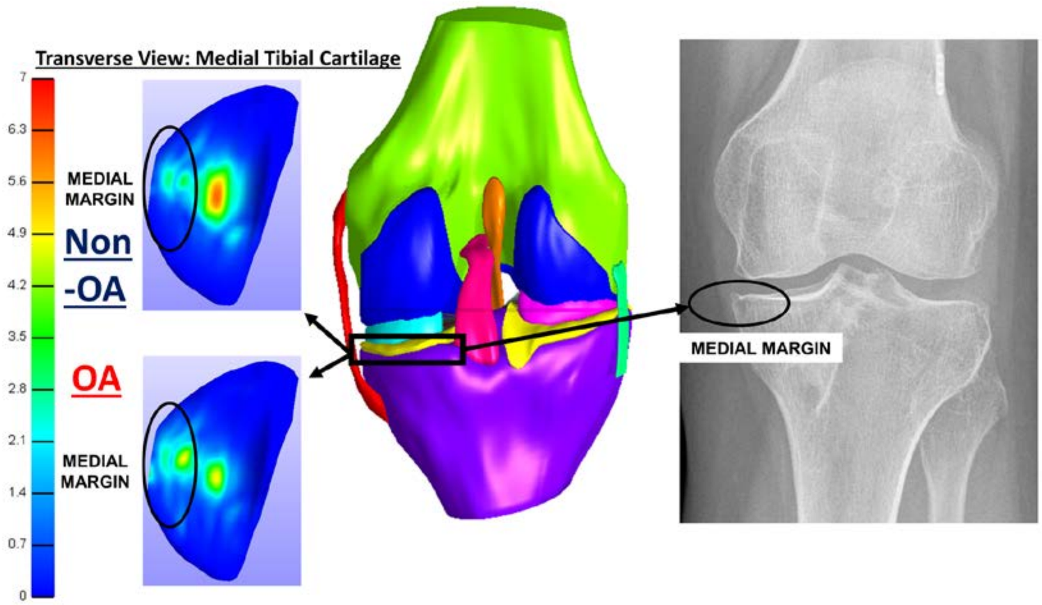

Figure 43. Von Mises stress distribution in the medial tibial cartilage at the first peak of vertical ground reaction force, five years after ACLR

(OA = osteoarthritis, ACLR = anterior cruciate ligament reconstruction)

3.3.1.2 Peak medial tibial cartilage stress: Near medial margin (region 1, hypothesis 2)

At the five year post-surgery time point, the peak von Mises stress value was significantly higher for the OA (versus non-OA) group (figure 44) near the medial joint margin. There were no significant differences are earlier time points.

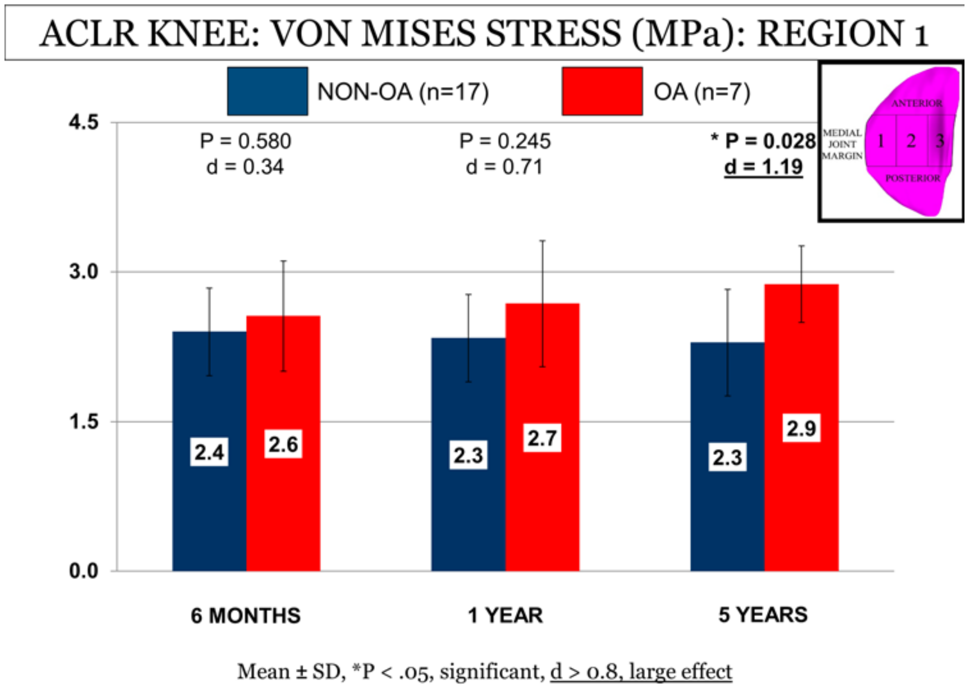

Figure 44. Peak von Mises stress near the medial margin of medial tibial cartilage (region 1) at the first peak of vertical ground reaction force

(ACLR = anterior cruciate ligament reconstruction, OA = osteoarthritis, SD = standard deviation, d = effect size)

3.3.1.3 Peak medial tibial cartilage stress: Central region (region 2)

In the central region, the peak von Mises stress value was lower for the OA (versus non-OA) group (figure 45) at the six month post-surgery time point. This difference approached significance, as indicated by the effect size. There were no significant differences at other time points.

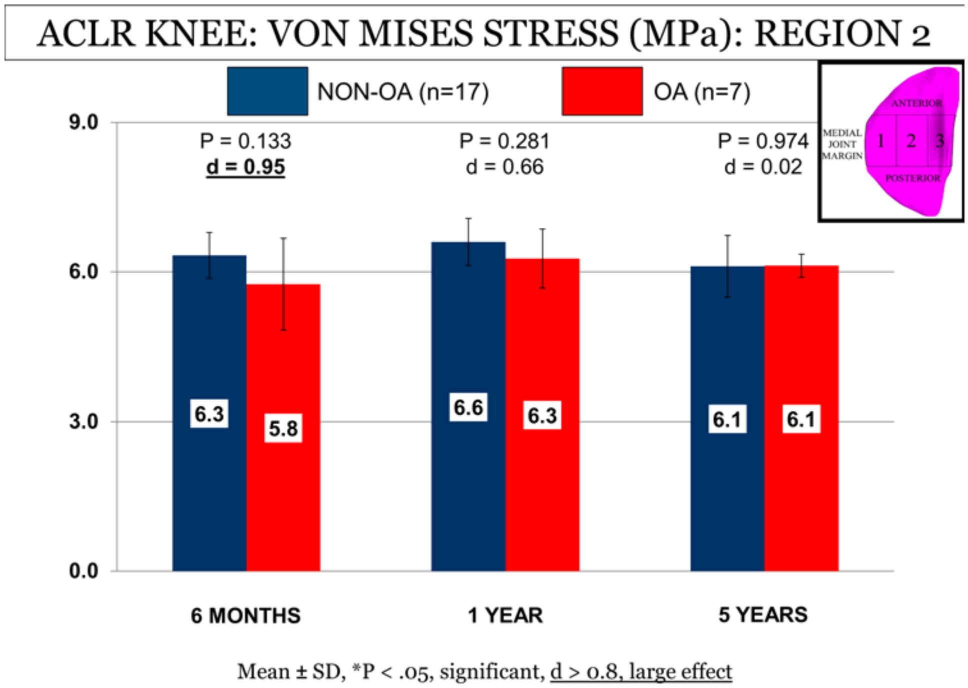

Figure 45. Peak von Mises stress in the central region of medial tibial cartilage (region 2) at the first peak of vertical ground reaction force

(ACLR = anterior cruciate ligament reconstruction, OA = osteoarthritis, SD = standard deviation, d = effect size)

3.3.1.4 Peak medial tibial cartilage stress: Near inter-condyloid eminence (region 3)

In the region near the inter-condyloid eminence, the peak von Mises stress value was lower for the OA (versus non-OA) group. This difference approached significance at the six month and one year post-surgery time points, as indicated by the large effect sizes. There were no differences at the five year post-surgery time point.

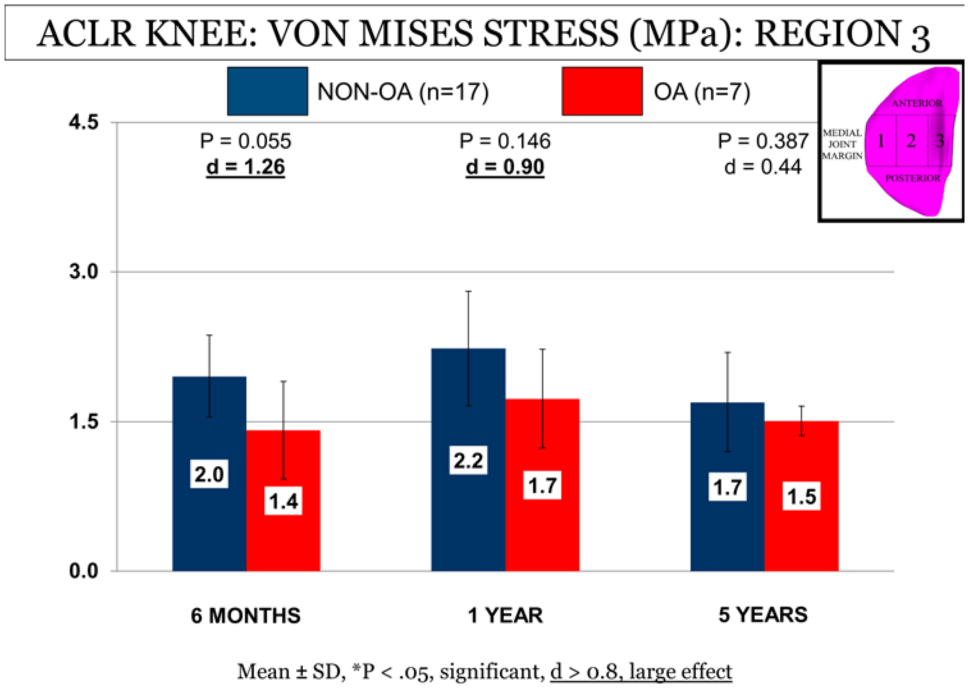

Figure 46. Peak von Mises stress near the inter-condyloid eminence of medial tibial cartilage (region 3) at the first peak of vertical ground reaction force

(ACLR = anterior cruciate ligament reconstruction, OA = osteoarthritis, SD = standard deviation, d = effect size)

3.3.1.5 Inter-limb difference in peak medial tibial cartilage stress: Near medial margin (region 1)

Comparing the mean values of each group to the minimum inter-limb difference (MILD) threshold, both the OA and non-OA groups did not demonstrate an inter-limb difference in the peak von Mises stress value near the medial joint margin, at any time point.

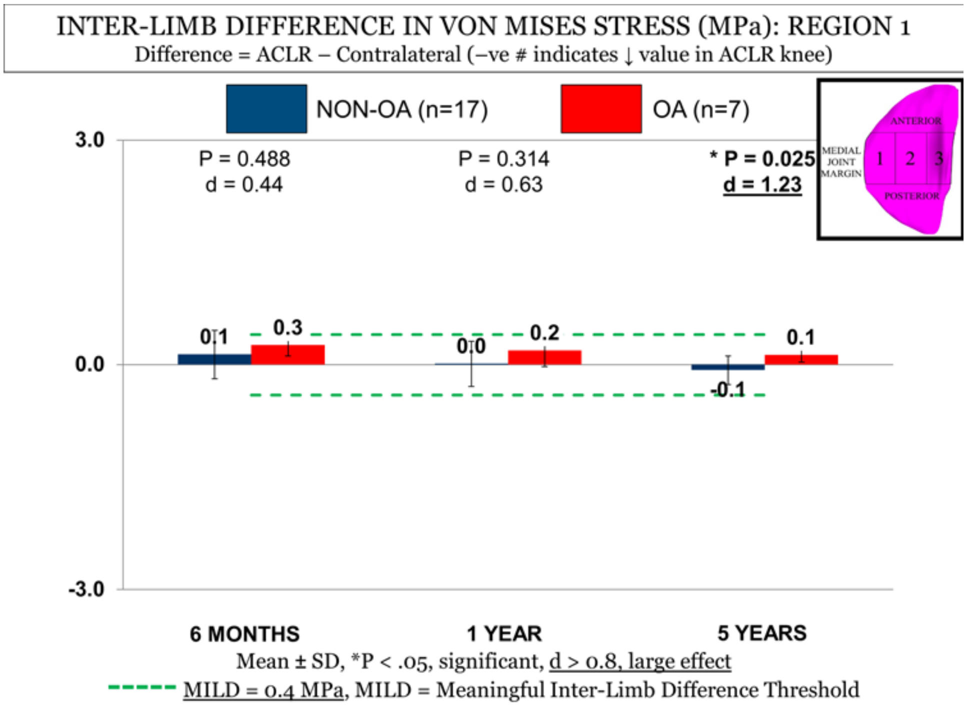

Figure 47. Inter-limb difference in peak von Mises stress near the medial margin of medial tibial cartilage (region 1) at the first peak of vertical ground reaction force

(ACLR = anterior cruciate ligament reconstruction, OA = osteoarthritis, SD = standard deviation, d = effect size)

3.3.1.6 Inter-limb difference in peak medial tibial cartilage stress: Central region (region 2)

Comparing the mean values of each group to the minimum inter-limb difference (MILD) threshold, both the OA and non-OA groups did not demonstrate an inter-limb difference in the peak von Mises stress value in the central region, at any time point.

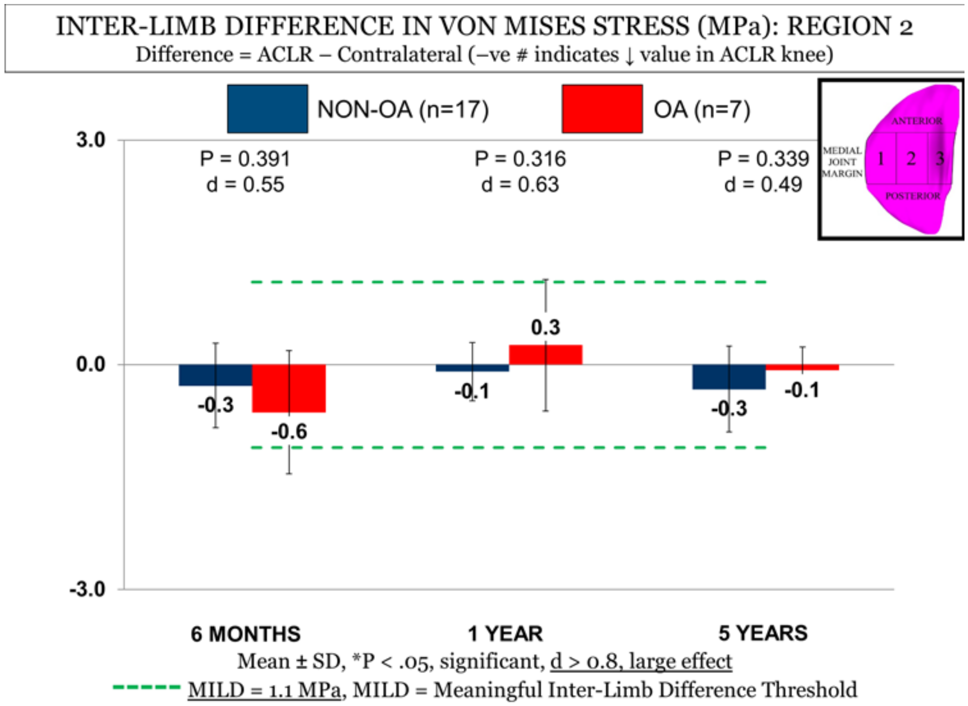

Figure 48. Inter-limb difference in peak von Mises stress in the central region of medial tibial cartilage (region 2) at the first peak of vertical ground reaction force

(ACLR = anterior cruciate ligament reconstruction, OA = osteoarthritis, SD = standard deviation, d = effect size)

3.3.1.7 Inter-limb difference in peak medial tibial cartilage stress: Near inter-condyloid eminence (region 3)

Comparing the mean values of each group to the minimum inter-limb difference (MILD) threshold for the region near the inter-condyloid eminence, the peak von Mises stress value in the ACLR knee was lower than the contralateral knee, for the OA group, at the six month post-surgery time point.

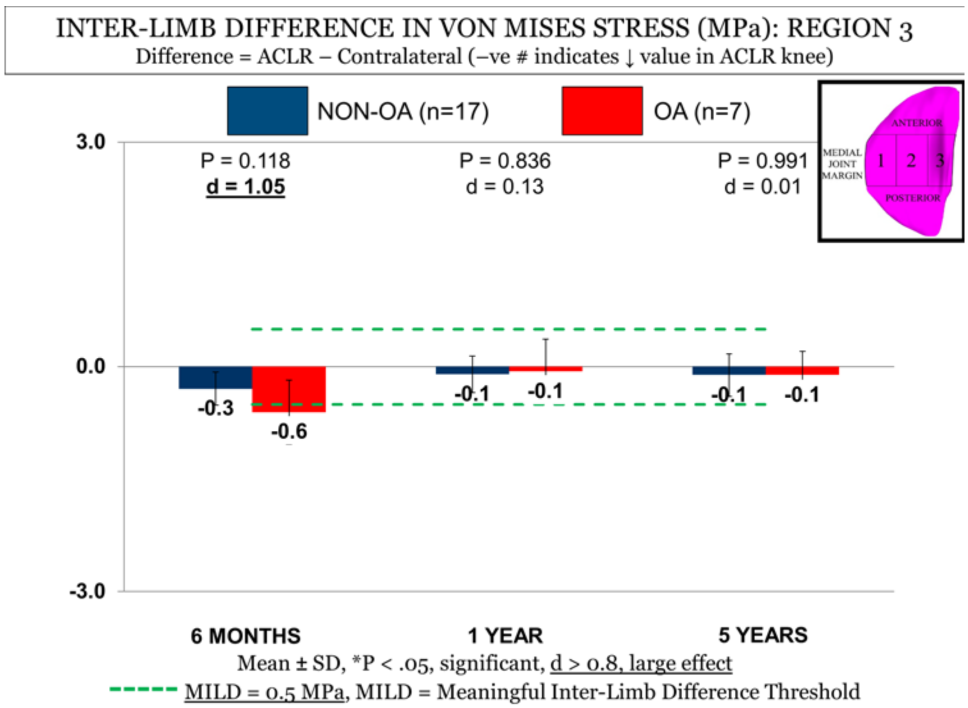

Figure 49. Inter-limb difference in peak von Mises stress near the inter-condyloid eminence of medial tibial cartilage (region 3) at the first peak of vertical ground reaction force

(ACLR = anterior cruciate ligament reconstruction, OA = osteoarthritis, SD = standard deviation, d = effect size)

3.3.2 Peak medial tibial cartilage stress at the second peak of vertical ground reaction force during the stance phase of gait

Figure 50 below shows the typical von Mises stress distribution in the medial tibial cartilage five years after unilateral ACLR. The stress distribution patterns between the subjects with/without medial compartment knee OA were not different. Compared to the first peak of vertical ground reaction force (vGRF), the overall peak stress value (typically in the central region, i.e. region 2) was lower. This was likely due to the fact that at the second peak of vGRF during the stance phase of gait, the knee is in near neutral position, i.e. limited or no flexion. Hence, better surface conformance and a larger contact area (compared to the first peak) would enable the load to be distributed over a larger area of the menisci and cartilage, both in the medial and lateral compartments. The larger contact area at a neutral position (compared to contact area at a greater flexion angle) was also evidenced in simulations comparing FE model predictions to published experimental studies (Figures 38, 39, 40 and 41). However, near the medial margin (region 1), the peak stress values at the second peak of vGRF were similar to values recorded at the first peak of vGRF.

3.3.2.1 Medial tibial cartilage stress distribution pattern

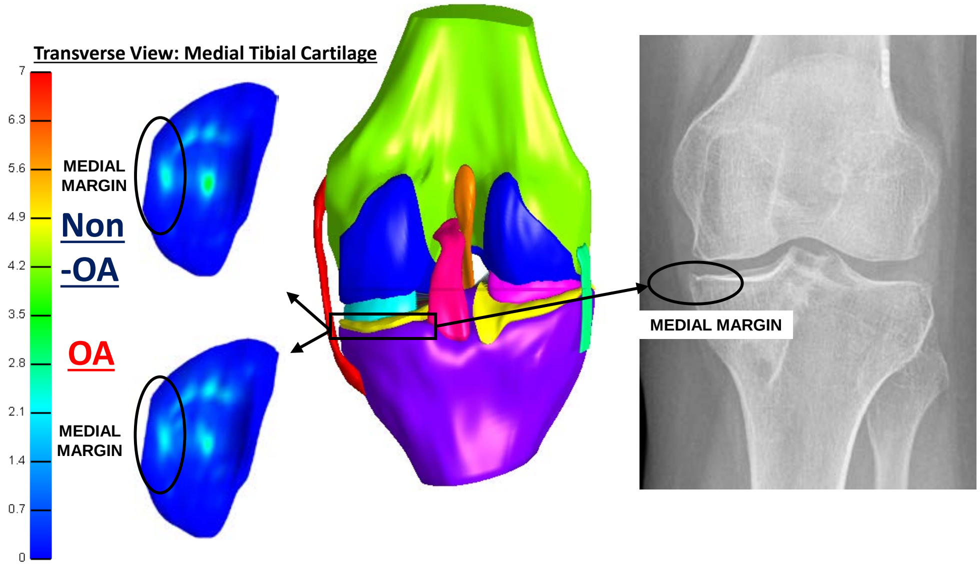

Figure 50. Von Mises stress distribution in the medial tibial cartilage at the second peak of vertical ground reaction force

(OA = osteoarthritis)

3.3.2.2 Peak medial tibial cartilage stress: Near medial margin (region 1)

Between the non-OA versus OA group, there were no significant differences in the peak von Mises stress value at any time point (figure 51), near the medial margin of the medial tibial cartilage (region 1).

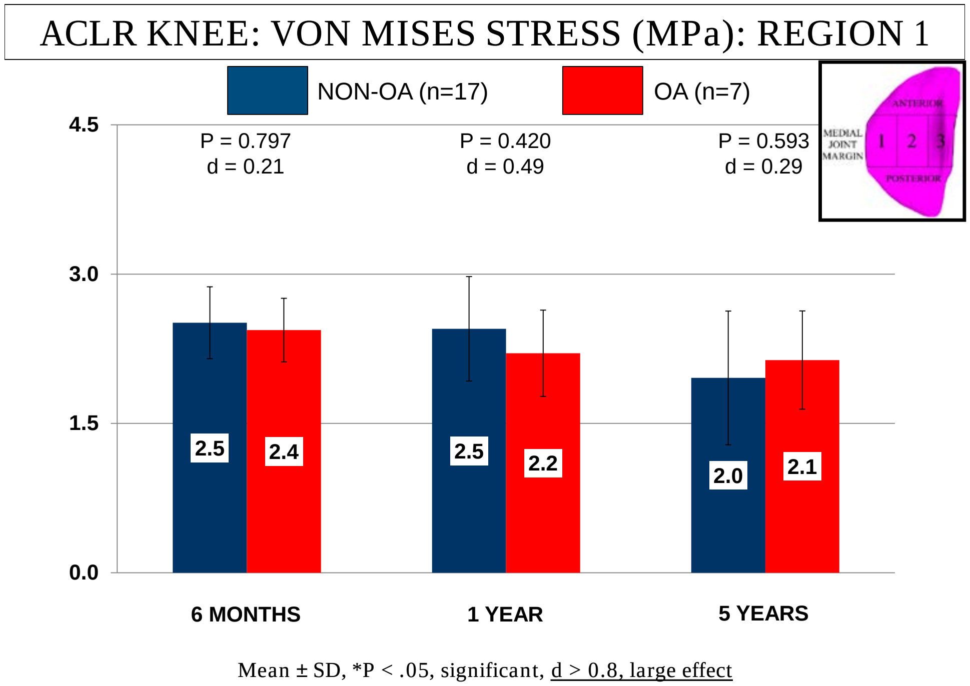

Figure 51. Peak von Mises stress near the medial margin of medial tibial cartilage (region 1) at the second peak of vertical ground reaction force

(ACLR = anterior cruciate ligament reconstruction, OA = osteoarthritis, SD = standard deviation, d = effect size)

3.3.2.3 Peak medial tibial cartilage stress: Central region (region 2)

Between the non-OA versus OA group, there were no significant differences in the peak von Mises stress value at any time point (figure 52), in the central region of the medial tibial cartilage (region 2).

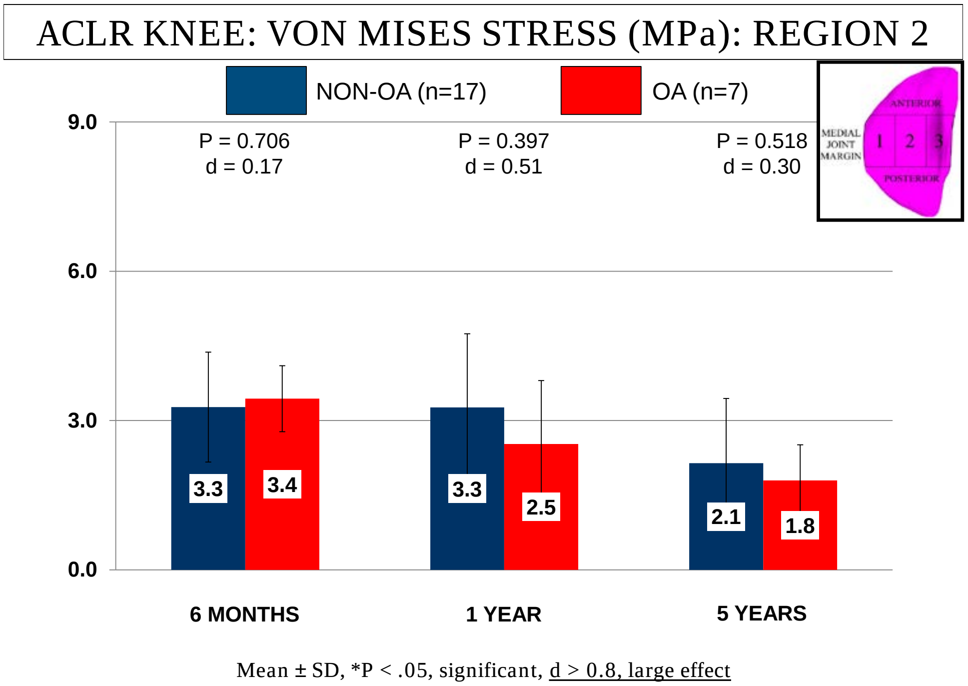

Figure 52. Peak von Mises stress in the central region of medial tibial cartilage (region 2) at the second peak of vertical ground reaction force

(ACLR = anterior cruciate ligament reconstruction, OA = osteoarthritis, SD = standard deviation, d = effect size)

3.3.2.4 Peak medial tibial cartilage stress: Near inter-condyloid eminence (region 3)

Between the non-OA versus OA group, there were no significant differences in the peak von Mises stress value at any time point (figure 53), near the inter-condyloid eminence region of the medial tibial cartilage (region 3).

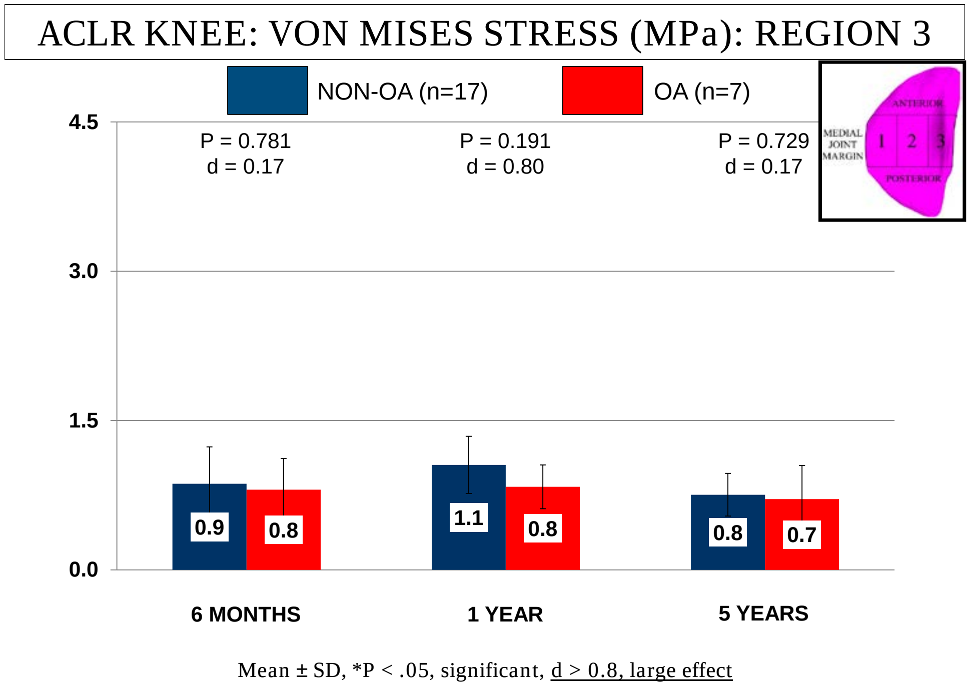

Figure 53. Peak von Mises stress near the inter-condyloid eminence of medial tibial cartilage (region 3) at the second peak of vertical ground reaction force

(ACLR = anterior cruciate ligament reconstruction, OA = osteoarthritis, SD = standard deviation, d = effect size)

3.3.2.5 Inter-limb difference in peak medial tibial cartilage stress: Near medial margin (region 1)

Comparing the mean values of each group to the minimum inter-limb difference (MILD) threshold for the region near the medial joint margin, the peak von Mises stress value in the ACLR knee was higher than the contralateral knee, for the OA group, at the five year post-surgery time point.

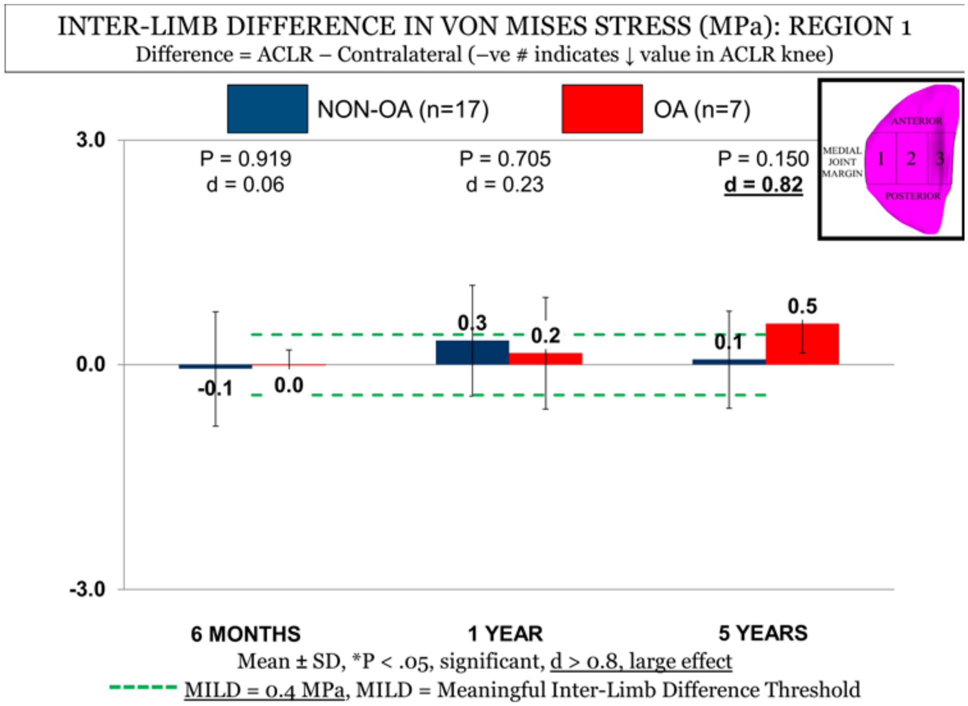

Figure 54. Inter-limb difference in peak von Mises stress near the medial margin of medial tibial cartilage (region 1) at the second peak of vertical ground reaction force

(ACLR = anterior cruciate ligament reconstruction, OA = osteoarthritis, SD = standard deviation, d = effect size)

3.3.2.6 Inter-limb difference in peak medial tibial cartilage stress: Central region (region 2)

Comparing the mean values of each group to the minimum inter-limb difference (MILD) threshold, both the OA and non-OA groups did not demonstrate an inter-limb difference in the peak von Mises stress value in the central region, at any time point.

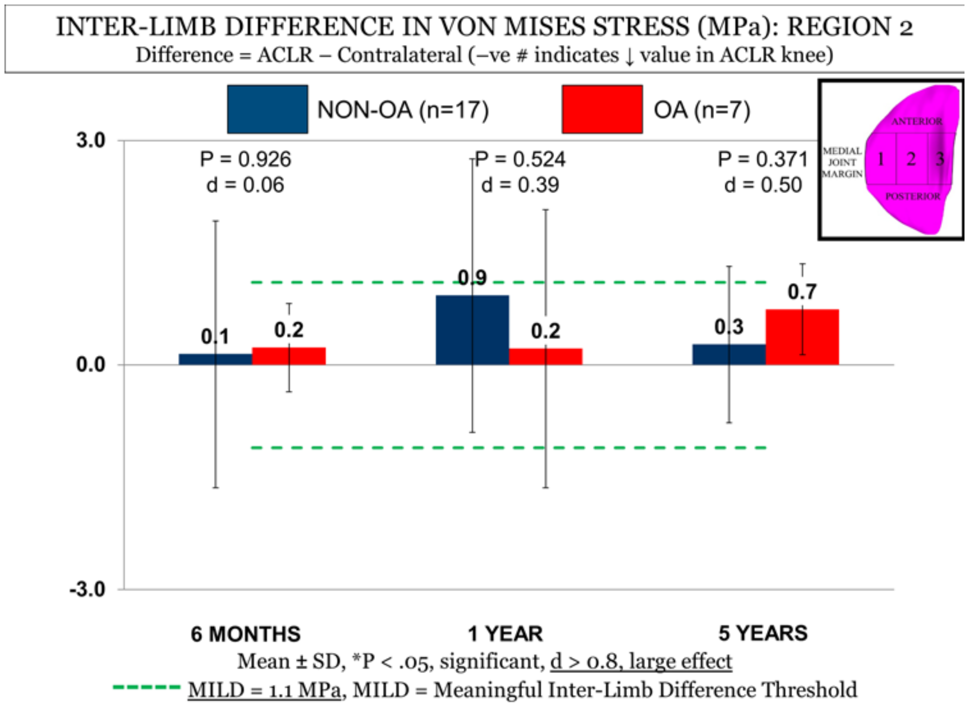

Figure 55. Inter-limb difference in peak von Mises stress in the central region of medial tibial cartilage (region 2) at the second peak of vertical ground reaction force

(ACLR = anterior cruciate ligament reconstruction, OA = osteoarthritis, SD = standard deviation, d = effect size)

3.3.2.7 Inter-limb difference in peak medial tibial cartilage stress: Near inter-condyloid eminence (region 3)

Comparing the mean values of each group to the minimum inter-limb difference (MILD) threshold, both the OA and non-OA groups did not demonstrate an inter-limb difference in the peak von Mises stress value near the inter-condyloid eminence, at any time point.

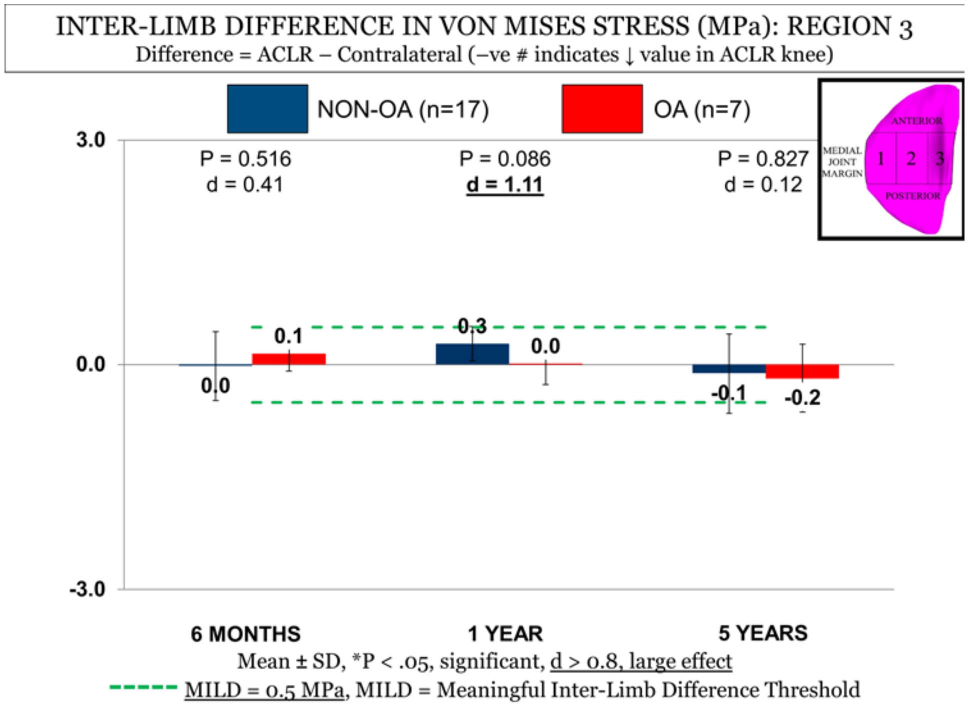

Figure 56. Inter-limb difference in peak von Mises stress near the inter-condyloid eminence of medial tibial cartilage (region 3) at the second peak of vertical ground reaction force

(ACLR = anterior cruciate ligament reconstruction, OA = osteoarthritis, SD = standard deviation, d = effect size)

3.4 Discussion

Altered knee gait mechanics and joint loading are thought to contribute to onset and progression of knee OA after ACLR [11,55]. The resultant load distribution within the knee joint structures and cartilage stresses play a role in subchondral bone remodeling, and ultimately result in cartilage degeneration [15]. However, the changes that occur in knee cartilage stress distribution due to altered knee gait mechanics are not clearly understood [23]. Specifically, it is not clear whether cartilage stresses are higher near the location of osteophytes in subjects who get medial compartment knee OA five years after ACLR. The aim of the study was to use a finite element (FE) knee model to investigate the impact of knee gait biomechanics on cartilage stress distribution. The differences in knee gait biomechanics and joint loading between OA versus non-OA groups have been reported in the previous aim (Aim 1: Chapter 2), while the resultant medial tibial cartilage stresses are discussed in the current chapter.

At the first peak of vGRF, for the ACLR knee, the OA (versus non-OA) group demonstrated a significantly higher peak effective (von Mises) stress value in the tibial cartilage near the medial joint margin, five years after ACLR. This is also the region where radiographic osteophytes were observed for the OA group. While the total joint load was similar for the two groups five years after ACLR, the sagittal plane knee kinematics were significantly different. The differences in frontal plane kinetics between the two groups also approached significance. A combination of these parameters resulted in a higher peak effective stress value near the medial joint margin five years after surgery, but not at other time points (six months and one year after surgery). Also, inter-limb asymmetry in knee gait mechanics and joint loading six months after ACLR in the OA group did not translate to a meaningful inter-limb difference in peak effective knee cartilage stress. These results suggest that not all combinations of altered knee gait mechanics and joint load magnitudes necessarily result in alterations of peak knee cartilage stresses [23], at least near the medial joint margin, which is covered by the medial meniscus.

Also near the medial joint margin, the peak effective knee cartilage stress values were similar at the first and second peaks of vGRF simulations. But the same was not true for the central region of the medial tibial cartilage. At the first peak of vGRF, the average peak effective stress in the central region was approximately 6 MPa, while at second peak of vGRF, it was approximately half that value. Even though the frontal plane moment and total joint load magnitudes are similar at the first and second peaks of vGRF, the knee flexion angle is not similar. At the second peak of vGRF, the knee is less flexed, compared to the first peak. A smaller knee flexion angle results in a larger contact area, for both the medial and lateral compartments. Hence, even though the total joint load magnitudes are similar at the first and second peaks of vGRF, the larger contact area at the second peak of vGRF results in lower stresses, compared to the first peak. This difference is specifically evident is the cartilage region that is not covered by menisci, i.e. the central region of the medial tibial cartilage, and also the region near the inter-condyloid eminence.

These results should be interpreted in the context of assumptions and limitations of the study. The cartilage was modeled as a linear elastic isotropic material, and not a biphasic, fibril reinforced material [127]. Considering the viscoelastic time constant of cartilage and the loading time duration during gait, this is a reasonable assumption [40] for the current simulations. Meniscal horn attachment was simplified by imposing boundary conditions on the menisci horn attachment nodes. While similar boundary conditions have been used in other studies [109,124,125] , there is a potential for localized cartilage stress concentrations due to this boundary condition, particularly in the anterior and posterior regions of medial tibial cartilage close to the center of the knee joint. Consequently, these regions were excluded when evaluating peak effective stress. The FE model also does not include the patellar structures and posterior capsule representations. Absence of one or both of these structures was likely the reason for poor confirmation of experimental results for transverse plane kinematics beyond 40 ^{o} flexion. Given that the simulations conducted in the current study were at the first and second peak of vGRF, the flexion angle was always less than 40 ^{o}. Hence, lack of these structures may not have an impact of peak effective cartilage stress values. However, the same needs to be verified after inclusion of the patellar interface and posterior capsule representations. It has been shown that orientation of the ACL graft is not similar to the original structure [131,132], and the material properties of an autograft/allograft can also be different [133,134], compared to the original ACL. For the current simulations, only radiographs were available, and determination of three-dimensional ACL graft orientation was not possible. The graft orientation and material properties from the original Open Knee model were retained, hence the simulations were not truly subject-specific. Also, while the Open Knee model was scaled based on available subject-specific radiographic dimensions, data pertaining to region-specific variation of cartilage thickness within the knee joint was not possible. While this is an important limitation, it was beneficial in that we could evaluate the direct impact of altered gait parameters only, by assuming similar region-specific variation of cartilage thickness within the knee joint, for all subjects.

Numerous in vitro and simulation studies have reported cartilage stresses and contact pressures varying from 2 – 34 MPa [37,121,128,135–137], depending on various loading modalities. Chondrocyte cell death has been reported to occur at high stress levels (~25 MPa) based on in vitro studies [138]. However, based on the conditioning hypothesis [139], the fatigue values that cause degeneration are likely much lower [112]. While degeneration of cartilage appears to be a mechanically driven process, it is not clear whether failure is dominated by tensile or shear stresses [140]. For isotropic material modeling, von Mises stress, based on distortion energy criteria for multiaxial stresses, is considered to useful for comparing stress values [127] under different loading conditions, and was used in the current study. To our knowledge, this is the first simulation study to show evidence of higher medial tibial cartilage stresses near the medial joint margin (for the OA versus non-OA group), due to altered knee gait mechanics after ACLR. This is the location where osteophytes are observed radiographically five years after ACLR, in subjects who get medial compartment knee OA. Further work is required to incorporate truly subject-specific knee structure material properties, cartilage morphometry and the variation of these parameters over time [141–143]. Incorporation of these parameters in FE simulations, potentially by utilizing quantitative magnetic resonance imaging (qMRI) techniques [103,144,145], can aid in early detection, prediction and treatment of knee OA.

Chapter 4

EXPLORATORY AIM 3: CARTILAGE TISSUE LEVEL CHANGES IN THOSE WITH/WITHOUT ASYMMETRIC KNEE JOINT LOAD DURING GAIT AFTER ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION SURGERY

4.1 Introduction

Recent evidence utilizing neuromusculoskeletal (NMS) models indicates that subjects with medial compartment knee osteoarthritis (OA) five years after anterior cruciate ligament reconstruction (ACLR) demonstrate decreased knee joint loading, or under-loading, six months to one year after ACLR [11]. These aberrations are observed, compared to the contralateral knee, and compared to subjects who do not get knee OA [11]. Inter-limb and inter-group (non-OA versus OA) differences tend to diminish in magnitude or cease to exist two years after ACLR [11]. In animal studies, under-loading and immobilization has been shown to negatively impact the knee cartilage [12–14]. Hence, early under-loading (six months to one year after ACLR) is thought be related to degeneration of knee cartilage in subjects who eventually get medial compartment knee OA (five years after ACLR). However, it is not clear whether cartilage tissue level changes are associated with inter-limb loading differences that are observed at early time points (six months to one year) after ACLR [11]. Verifying the relation between joint loading and tissue level changes can further solidify the link between joint loading and knee OA after ACLR [25].

Articular cartilage has very few cells (~4 % of wet weight), and its main components are water, and an extracellular matrix, composed of type II collagen and proteoglycans (PG) [146]. The PG protein cores are lined by glycosaminoglycans (GAG) which attract sodium and other positively charged ions, which, in turn, draw in water, resulting in swelling pressure of healthy cartilage tissue [24]. Early signs of cartilage OA at the tissue level include decreased collagen matrix organization, decreased PGs and increased water content, ultimately resulting in loss of normal function and cartilage degeneration [147,148].

Radiography has been the gold standard to detect OA, most commonly assessed by evidence of osteophytic lipping, sclerosis, deformity of bone contour and loss of joint space width [74,149]. However, these changes occur at a very late stage of the disease, when intervention options are limited [150]. Conventional magnetic resonance imaging (MRI) offers a means to directly assess the cartilage, and interpretation techniques of cartilage findings based on conventional MRI are evolving [151]. More recently, investigating tissue pathology using conventional MRI is being used as an aid to study the progression of the disease [152–154]. While conventional MRI is better than radiography for documenting OA progression, it is still limited to evaluation of morphometric OA changes [145]. For early detection of the disease, the subtle tissue level changes that precede morphometric level changes need to be quantified [24]. Advanced MRI techniques that utilize novel MRI pulse sequences are increasingly being used for early detection of tissue level cartilage degeneration [24,103,145]. The most prominent among these advanced MRI techniques include delayed gadolinium-enhanced MRI of cartilage (dGEMRIC), sodium imaging, T1ρ mapping and T2 mapping [24].

T1ρ mapping is used to estimate PG and GAG content. A higher T1ρ relaxation time compared to healthy tissue is indicative of reduced PG and GAG content [155]. The inverse correlation of T1ρ with PG/GAG content has been validated using in vitro and ex vivo experiments [156,157]. Changes in PG and GAG content are followed by changes in collagen matrix composition. T2 mapping is used to estimate collagen content and orientation [158]. A longer T2 relaxation time compared to healthy tissue is indicative of collagen matrix degradation. Though susceptible to the magic angle effect, T2 mapping has been validated using both in vitro and in vivo experiments [159–162], and it has proven to be useful in many clinical studies [163,164], including studies involving anterior cruciate ligament (ACL) injury/ACLR [103,165,166] and OA [167–169].

A longitudinal study in an ACL injury population utilizing T2 mapping has shown prolongation of T2 relaxation times in the cartilage over time [103]. These changes are indicative of collagen matrix degradation that lead to premature knee OA. Spatially, longitudinal degradation signs are observed in the site of original injury (most commonly the postero-lateral tibial plateau), in the weight bearing regions, particularly in the deep layer of the medial compartment cartilage [103,166,167,170]. Another group has evaluated an ACL injury population six months after surgery [165]. Their results show that even though no morphometric (cartilage volume and thickness) differences existed, prolongation of T2 relaxation times in the cartilage at six months was evident.

Animal studies have confirmed that chronic unloading of cartilage via immobilization results in degenerative OA changes [14]. More recently, this phenomenon was demonstrated in human studies using T2 mapping [170,171], and these studies indicate that a lack of mechanical stimulation can potentially be detrimental to cartilage health [172]. More importantly, the human study demonstrated substantial tissue level changes in response to loading and unloading. Unloading in a majority of these studies was achieved by using splints or crutches. During day-to-day gait activities, ACL subjects after surgery do not experience the large amount of unloading that is introduced by crutches, but it is possible that a relatively smaller amount of unloading over a larger amount of time can cause similar detrimental effects in the knee cartilage.

With that background, the following hypothesis was developed.

Hypothesis 3. Subjects with asymmetric knee joint loads will exhibit higher cartilage T2 values in the ACLR versus contralateral knee

The medial compartment knee joint load for assessing inter-limb asymmetry was evaluated at the first peak of vGRF during the stance phase of gait. Knee cartilage T2 maps were established for two subjects, one with symmetric medial compartment knee joint load between six months and one year after ACLR, and the other with asymmetric medial compartment knee joint load. Hence, while the hypothesis could not be verified based on the limited sample size, it has been included based on literature review, and to guide future work.

4.2 Methods

4.2.1 Subject selection

Two subjects with unilateral ACLR from a larger, randomized clinical trial were used for the study (Subject 1: Sex = male, age = 30 years, weight = 108 kg, height = 1.92 m, Subject 2: Sex = female, age = 37 years, weight = 70 kg, height =

1.68 m). Each subject had undergone progressive, pre-operative rehabilitation training [70] and also completed gait analysis at the one year post-operative time point. Each subject was a regular participant in level I-II cutting and pivoting activities prior to ACL injury [71,72]. The study was approved by the Institutional Review Board at the University of Delaware (Appendices A and B). Both subjects were provided with written consent forms for the study.

Subject selection was based on presence/absence of asymmetric medial compartment knee joint loading estimated during the stance phase of gait. The gait analysis experiment is described in section 2.2.6. The minimum detectable change threshold (0.30 body weight) was used to verify the presence/absence of asymmetric medial compartment knee joint load [77]. One subject demonstrated inter-limb asymmetry, while the other did not.

4.2.2 Knee kinematic, kinetic and electromyography data analysis

The testing and data analysis procedure is described in section 2.2.6., and the workflow is shown in figure 57 below. The medial compartment joint loads obtained were normalized to body weight (BW), and the inter-limb difference in medial compartment load was calculated for each subject.

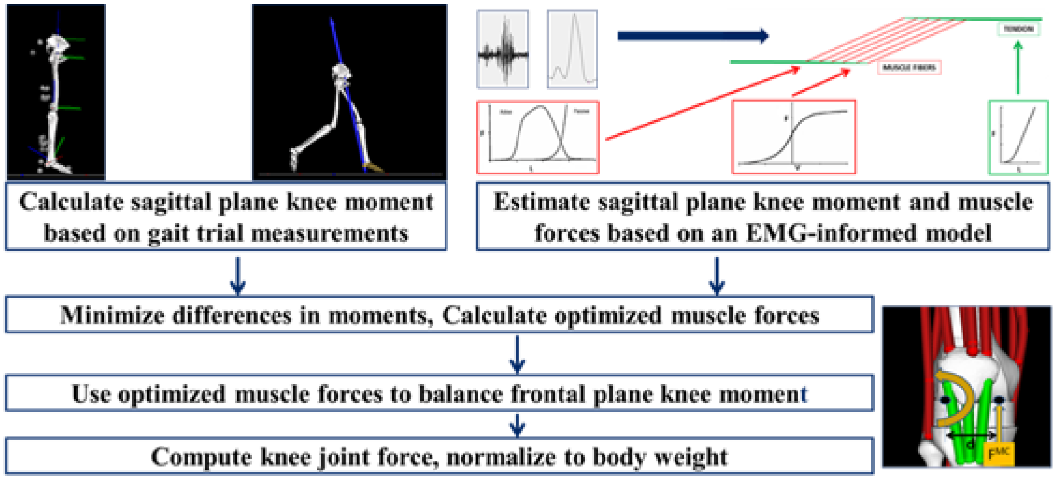

Figure 57. Electromyography (EMG)-informed neuromusculoskeletal modeling flowchart

4.2.3 Quantitative magnetic resonance imaging procedure

For each subject, MRI imaging was performed for the ACLR and the contralateral knee using a clinical 3.0 T MRI unit and a 16-channel knee coil (Philips Healthcare, Amsterdam, Netherlands). The study was approved by the Institutional Review Board at the University of Delaware (Appendices C and D). All subjects were provided with written consent forms for the study. The scan included a 2D sagittal T2-weighted fat-saturated fast spin echo sequence (Repetition time/echo time = 5000/80 ms, slice thickness = 2 mm with no gap, field of view = 14 cm, matrix = 448 x 448) and a proton density weighted sequence (Repetition time/echo time = 5100/30 ms, slice thickness = 2 mm with no gap, field of view = 14 cm, matrix = 800 x 800) These scans were used for morphometric analysis and image registration. A T2 mapping sagittal sequence (Repetition time = 3000 ms, Echo time = 5 echo samples ranging from 15 to 75 ms, slice thickness = 2 mm with no gap, field of view = 14 cm, matrix = 432 x 432) was also included to allow for quantification of T2 relaxation times [173,174].

$$\textit{Signal Intensity} \propto \left(1 - e^{\frac{-TR}{T1}}\right) . e^{\frac{-TE}{T2}}$$

In the equation above, TR represents the repetition time (i.e. time indicating how often radio frequency pulses are applied), which is set to a high value (3000 ms). This minimizes the impact of T1 (tissue-specific longitudinal magnetization recovery time constant) and drives the entire term in brackets on the right hand side to 1. Hence, the signal intensity primarily depends on TE, which represents the echo time (i.e. time when signal is captured) and T2 (tissue-specific transverse magnetization decay time constant). With known values of TE (5 echo samples ranging from 15 to 75 ms) and known (measured) signal intensities, a T2 map was constructed by using the mono-exponential decay relationship implemented by MRI analysis calculator in ImageJ (NIH, Maryland US). Figure 58 below shows the false color T2 map of knee cartilage (sagittal view).

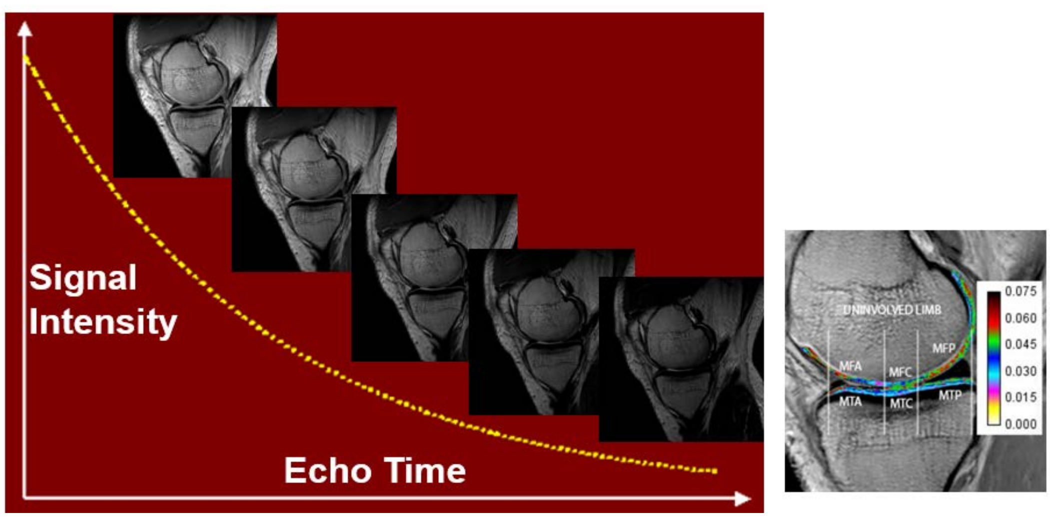

Figure 58. T2 map for knee cartilage established using mono-exponential decay

The cartilage was spatially resolved into four compartments including lateral/medial femoral condyle compartments and lateral/medial tibia compartments. The femoral and tibial compartments were further divided into sub-compartments with regard to the meniscus (Figure 59). In addition to full thickness of cartilage, T2 values were quantified for two equally spaced superficial and deep layers.

4.3 Results

4.3.1 Cartilage thickness of the contralateral versus ACLR knee for a subject with inter-limb asymmetry one year after anterior cruciate ligament reconstruction

The cartilage thickness of the involved (ACLR) knee was slightly greater than the uninvolved (contralateral) knee, for both the femur and the tibia (Table 4).

Table 4. Cartilage thickness of the ACLR versus contralateral knee for a subject with inter-limb asymmetry during gait

CARTILAGE THICKNESS (mm)	CONTRALATERAL	ACLR
Medial Femur	2.25	2.35
Medial Tibia	2.41	2.45

(ACLR = anterior cruciate ligament reconstruction)

4.3.2 T2 cartilage map of the contralateral versus ACLR knee for a subject with inter-limb asymmetry one year after anterior cruciate ligament reconstruction

Figures 59 and 60 show the cartilage T2 maps for the contralateral (uninvolved) and ACLR (involved) knee respectively. The time scale is seconds. Comparing the two images, the ACLR (involved) knee shows greater T2 times in the load-bearing region of the cartilage, compared to the contralateral (uninvolved) knee.

MFA = Medial Femur, Anterior	MFC = Medial Femur, Central	MFP = Medial Femur, Posterior
MTA = Medial Tibia, Anterior	MTC = Medial Tibia, Central	MTP = Medial Tibia, Posterior

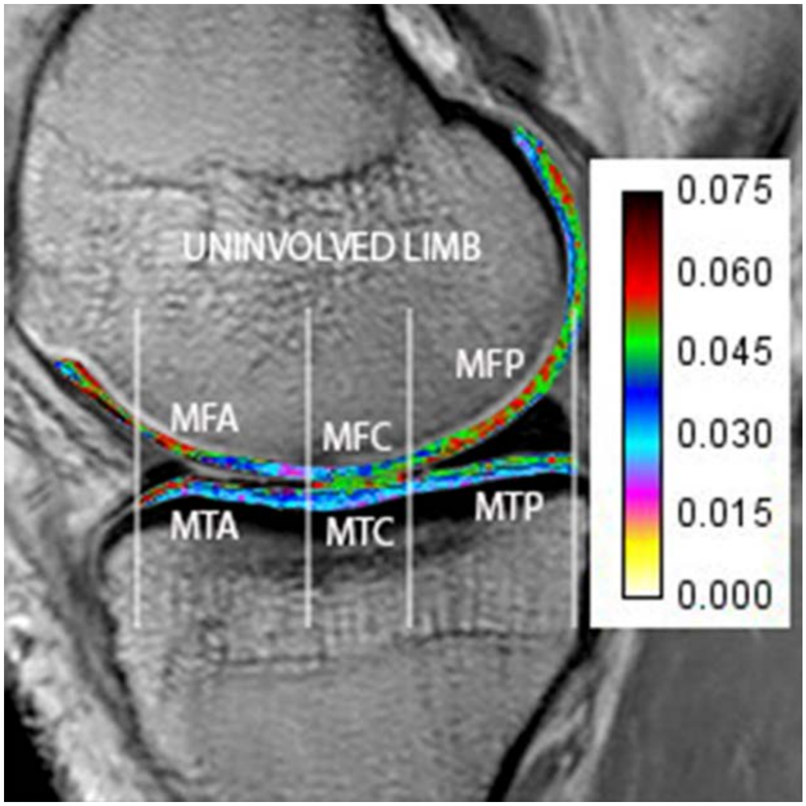

Figure 59. T2 map (seconds) of the contralateral (uninvolved) knee cartilage for a subject with inter-limb asymmetry one year after ACLR

(ACLR = Anterior cruciate ligament reconstruction)

MFA = Medial Femur, Anterior	MFC = Medial Femur, Central	MFP = Medial Femur, Posterior
MTA = Medial Tibia, Anterior	MTC = Medial Tibia, Central	MTP = Medial Tibia, Posterior

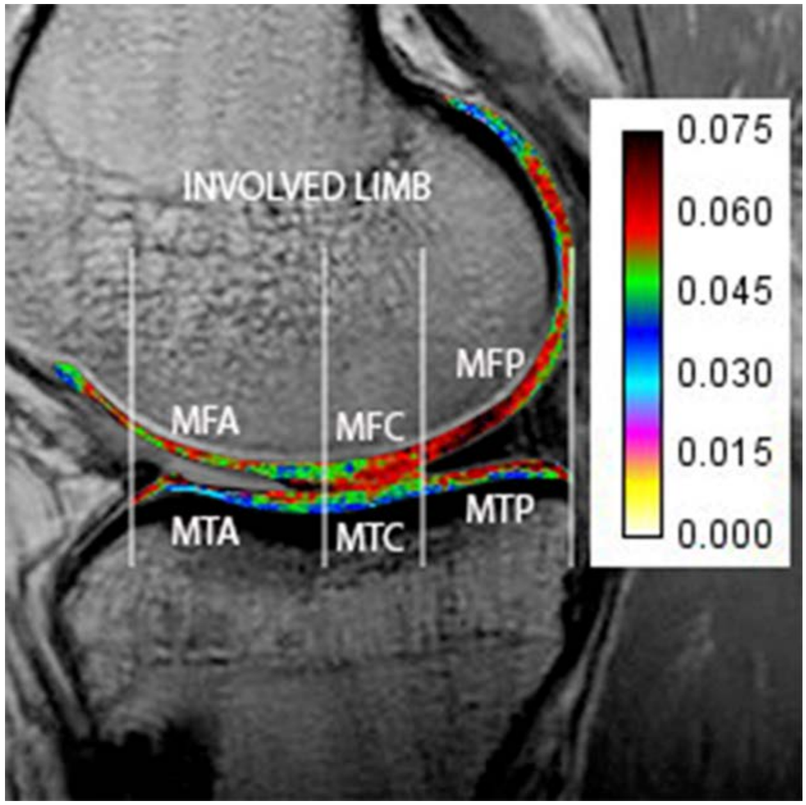

Figure 60. T2 map (seconds) of the ACLR (involved) knee cartilage for a subject with inter-limb asymmetry one year after ACLR

(ACLR = anterior cruciate ligament reconstruction)

4.3.3 T2 values in deep and superficial layers of the medial central knee cartilage for a subject with inter-limb asymmetry one year after anterior cruciate ligament reconstruction

For each region of the medial central knee cartilage (regions identified in figures 59 and 60 above), the ACLR knee demonstrated a higher T2 value, compared to the contralateral knee (figure 61).

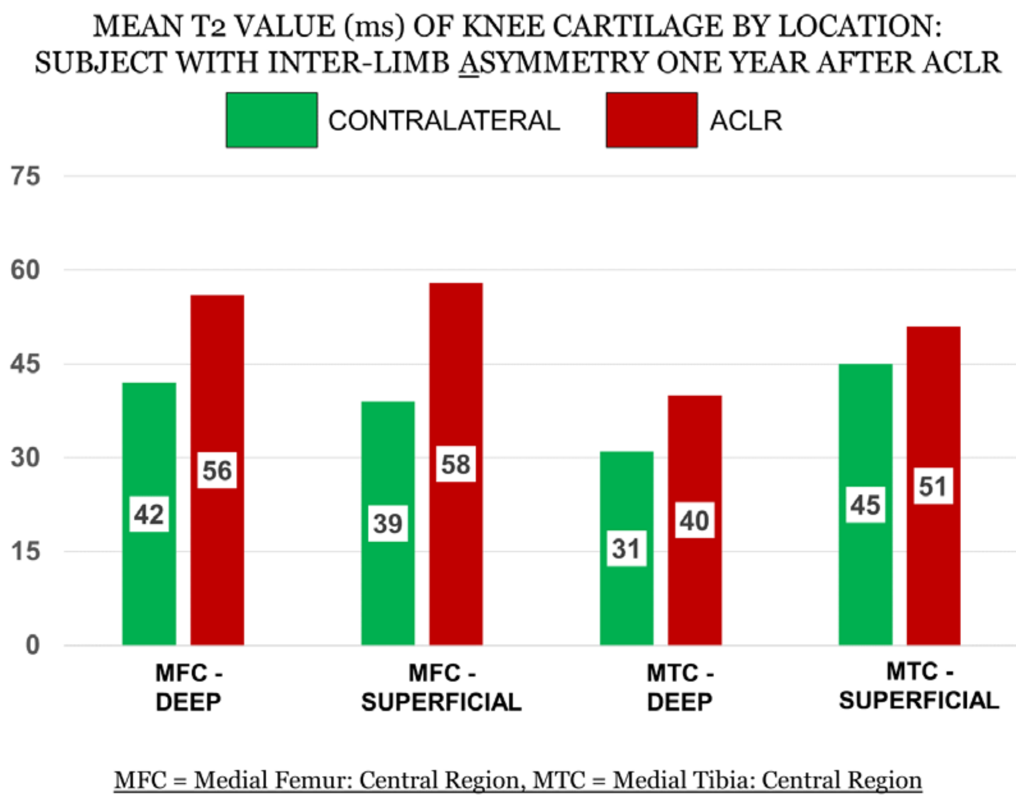

Figure 61. Mean T2 values (ms) of the contralateral versus ACLR knee for a subject with inter-limb asymmetry one year after ACLR

(ACLR = anterior cruciate ligament reconstruction)

4.3.4 Inter-limb difference in T2 values for subjects with/without inter-limb asymmetry one year after anterior cruciate ligament reconstruction

The subject with inter-limb asymmetry in medial compartment load also demonstrated greater inter-limb asymmetry in mean T2 values, in all regions of the medial central knee cartilage (figure 62).

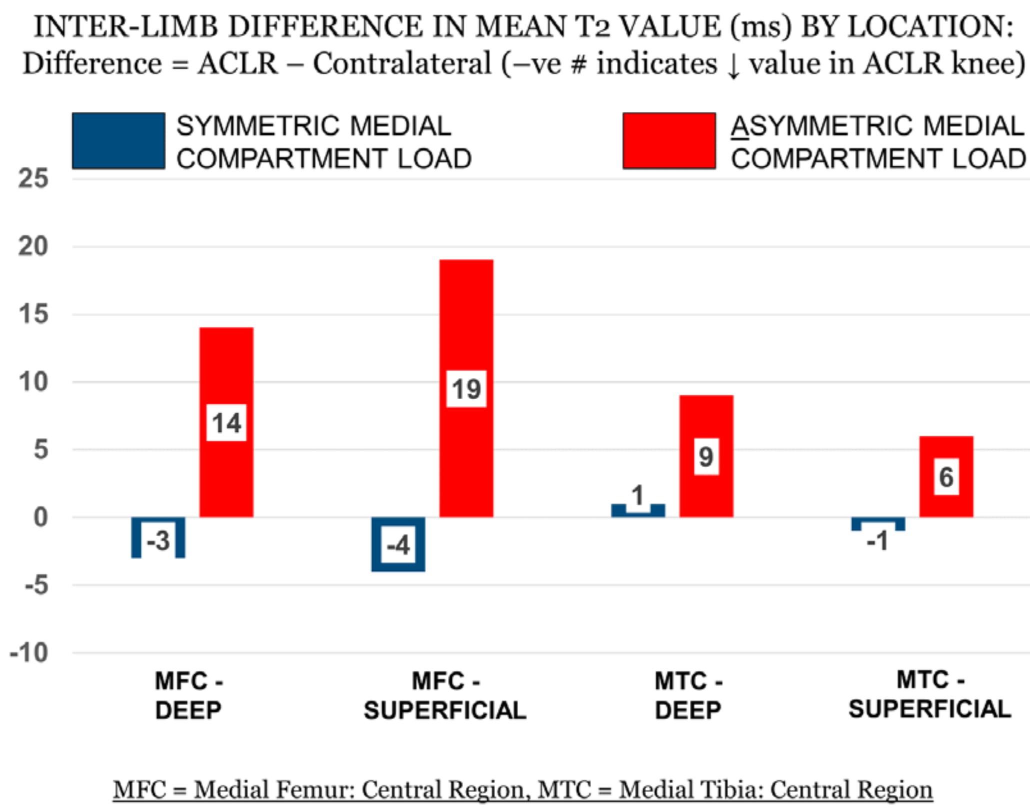

Figure 62. Inter-limb difference in T2 values for subjects with/without inter-limb asymmetry one year after ACLR

(ACLR = anterior cruciate ligament reconstruction)

4.4 Discussion

The exploratory aim included preliminary data from two subjects at six months to one year after ACLR. Based on the limited sample size, it is not possible to validate or reject the proposed hypothesis. However, the data provided preliminary evidence related to greater differences in cartilage T2 values, for the subject demonstrating greater inter-limb loading differences. These differences were observed for superficial as well as deep layers of tibial and femoral knee cartilage. Further evaluation with additional subjects is warranted.

Early signs of cartilage OA at the tissue level include decreased collagen matrix organization, decreased PGs and increased water content, ultimately resulting in loss of normal function and cartilage degeneration [147,148]. Also, early detection of signs of knee OA is crucial in order to implement rehabilitation or treatment, to delay the progression of the disease. An inverse correlation of T1ρ with PG/GAG cartilage content has been validated using in vitro and ex vivo experiments [156,157], while a longer T2 relaxation time compared to healthy tissue is indicative of collagen matrix degradation. These measures have been proven to be useful in many clinical studies [163,164], including studies involving anterior cruciate ligament (ACL) injury/ACLR [103,165,166] and OA [167–169]. Another group has evaluated an ACL injury population six months after surgery [165]. Their results show that even though no morphometric (cartilage volume and thickness) differences existed, prolongation of T2 relaxation times in the cartilage at six months was evident. Animal studies have confirmed that chronic unloading of cartilage via immobilization results in degenerative OA changes [14]. More recently, this phenomenon was demonstrated in human studies using T2 mapping [170,171], and these studies indicate that a lack of mechanical stimulation can potentially be detrimental to cartilage health [172]. More importantly, the human study demonstrated substantial tissue level changes in response to loading and unloading. Unloading in a majority of these studies was achieved by using splints or crutches. During day-to-day gait activities, ACL subjects after surgery do not experience the large amount of unloading that is introduced by crutches, but it is possible that a relatively smaller amount of unloading over a larger amount of time can cause similar detrimental effects in the knee cartilage.

Given the potential applicability of T1ρ and T2 quantitative MRI methods for early detection of knee OA after ACLR, a longitudinal study that includes scans at multiple post-surgery time points (three months, six months and two years) may be useful to verify progression of disease can be captured by these methods. Moreover, comparing quantitative MRI values to discrepancies in early inter-limb joint loading differences due to altered gait may provide further insight that cannot be captured by neuromusculoskeletal (NMS) and finite element (FE) simulations alone. To be able to correlate differences in qMRI measures to differences in cartilage material properties , cadaveric studies, which can correlate the two measures, are required [160]. Incorporating qMRI measure is paramount to ensure that the depth-wise variation of cartilage material properties, as well as the variation of these properties over time, are reflected in mathematical simulation techniques. This would ensure that future biomechanical simulations are truly reflective of changes that occur over time, and not merely necromechanical [143], thereby increasing the validity of these mathematical techniques.

Chapter 5

CONCLUSIONS AND FUTURE WORK

5.1 Conclusions for aim 1

Tables 5 and 6 below include a summary of hypotheses validated/rejected for knee gait parameters evaluated at the first peak of vGRF. For the ACLR knee, the OA (versus non-OA) group demonstrated a significantly lower knee flexion angle and moment, five years after ACLR. The medial compartment and total joint loads were similar for both groups, five years after ACLR. While the differences noted above were observed for the ACLR knee between the two groups, inter-limb asymmetries during gait were resolved over time, for both groups. Hence, rather than evaluating just the inter-limb symmetry, it may be necessary to differentiate between good versus bad inter-limb symmetry, when evaluating knee gait parameters. Finally, it is not clear how knee cartilage stresses are affected in non-OA versus OA groups, as a result of the differences observed in knee gait parameters. Evaluating the resultant effect on knee cartilage stresses may provide more direct insight pertaining to knee OA and altered knee gait mechanics.

Table 5. Summary of hypotheses and results for Aim 1: OA versus non-OA group differences for the ACLR knee, at the first peak of vertical ground reaction force

OA VERSUS NON-OA group differences, for the ACLR knee:	BEFORE SURGERY	6 MONTHS AFTER SURGERY	1 YEAR AFTER SURGERY	5 YEARS AFTER SURGERY
Hypothesis 1.1 Knee Flexion Angle	☒	☒	✓↓	☑↓
Hypothesis 1.2 Knee Flexion Moment	☒	✓↓	☒	☑↓
Hypothesis 1.3 Knee Adduction Moment	✓↓	☒	☒	✓↑
Hypothesis 1.4 Medial Compartment Load	☒	✓↓	☒	☑=
Hypothesis 1.5 Total Joint Load	☒	✓↓	✓↓	☑=

☒ NOT VALIDATED, ☑ VALIDATED, ✓ APPROACHED SIGNIFICANCE (LARGE EFFECT SIZE)

↓ LOWER IN OA (VERSUS NON-OA) GROUP

(OA = osteoarthritis, ACLR = anterior cruciate ligament reconstruction)

Table 6. Summary of hypotheses and results for Aim 1: Inter-limb (ACLR – contralateral) asymmetry for the OA group, at the first peak of vertical ground reaction force

INTER-LIMB ASYMMETRY (ACLR versus contralateral) in subjects with OA:	BEFORE SURGERY	6 MONTHS AFTER SURGERY	1 YEAR AFTER SURGERY	5 YEARS AFTER SURGERY
Hypothesis 1.6 Knee Flexion Angle	☒	☑ ↓	☒	☒
Hypothesis 1.6 Knee Flexion Moment	☑ ↓	☑ ↓	☒	☒
Hypothesis 1.6 Knee Adduction Moment	☑ ↓	☑ ↓	☒	☒
Hypothesis 1.6 Medial Compartment Load	☑ ↓	☑ ↓	☒	☒
Hypothesis 1.6 Total Joint Load	☑ ↓	☑ ↓	☒	☒

☒ NOT VALIDATED, ☑ VALIDATED

↓ LOWER IN ACLR (VERSUS CONTRALATERAL) KNEE

(OA = osteoarthritis, ACLR = anterior cruciate ligament reconstruction)

5.2 Conclusions for aim 2

Table 7 below includes a summary of hypotheses validated/rejected for peak effective von Mises stress near the medial margin of the medial tibial cartilage, evaluated at the first peak of vGRF. For the ACLR knee, the OA (versus non-OA) group demonstrated a significantly higher value of peak effective von Mises stress near the medial margin of the medial tibial cartilage, five years after ACLR.

To our knowledge, this is the first simulation study to show evidence of higher medial tibial cartilage stresses near the medial joint margin (for the OA versus non-OA group), due to altered knee gait mechanics after ACLR. This is the location where osteophytes are observed radiographically five years after ACLR, in subjects who get medial compartment knee OA. Further work is required to incorporate truly subject-specific knee structure material properties, cartilage morphometry and the variation of these parameters over time [141–143]. Incorporation of these parameters in FE simulations, potentially by utilizing quantitative magnetic resonance imaging (qMRI) techniques [103,144,145], can aid in early detection, prediction and treatment of knee OA.

Table 7. Summary of hypotheses and results for Aim 2: OA versus non-OA group differences for the ACLR knee, at the first peak of vertical ground reaction force

OA VERSUS NON-OA group differences, for the ACLR knee:	6 MONTHS AFTER SURGERY	1 YEAR AFTER SURGERY	5 YEARS AFTER SURGERY
Hypothesis 2. Peak stress near medial joint margin	☒	☒	☑ ↑

☒ NOT VALIDATED, ☑ VALIDATED, ✓ APPROACHED SIGNIFICANCE (LARGE EFFECT SIZE)

↑ HIGHER IN OA (VERSUS NON-OA) GROUP

(OA = osteoarthritis, ACLR = anterior cruciate ligament reconstruction)

5.3 Conclusions for exploratory aim 3

The exploratory aim included preliminary data from two subjects at six months to one year after ACLR. Based on the limited sample size, it is not possible to validate or reject the proposed hypothesis. However, the data provided preliminary evidence related to greater differences in cartilage T2 values, for the subject demonstrating greater inter-limb loading differences. These differences were observed for superficial as well as deep layers of tibial and femoral knee cartilage. Further evaluation with additional subjects is warranted.

5.4 Overall summary

Aim 1 established the usefulness of neuromusculoskeletal (NMS) modeling techniques to evaluate differences in knee gait mechanics for subjects with/without medial compartment knee OA after ACLR. Inter-limb differences in knee gait parameters were observed at early time points, while statistically significant differences between (OA versus non-OA) groups were observed five years after surgery, for the ACLR knee. In Aim 2, using the parameters obtained by NMS modeling techniques as input for a finite element (FE) model of the knee, it was shown that stresses in the medial tibial cartilage, near the medial joint margin, were higher for subjects with medial compartment knee OA (versus non-OA) five years after ACLR. It is in this region where radiographic osteophytes are observed in subjects who get medial compartment knee OA after ACLR. However, differences in peak stress values could not be observed at earlier time points, potentially due to lack of truly subject-specific geometry from MRI. The earlier the signs of knee OA can be detected, the greater the possibility of intervention and treatment to delay the progression of the disease. The limitations of the current study can be addressed by incorporating subject-specific MRI scans and qMRI measures in the study workflow. qMRI measures were explored in Aim 3, and warrant further investigation to evaluate the impact of inter-limb knee loading differences that are observed at early time points after ACLR.

A combination of NMS modeling, FE modeling and qMRI may be useful in early detection and prediction of knee OA after ACLR.

5.5 Future Directions

5.5.1 Inclusion of patellofemoral structure in subject-specific finite element knee model

The FE knee model used for the current study did not include the patellofemoral structure, since the focus of the study was medial compartment knee OA and not patellofemoral OA. However, overall knee joint mechanics are influenced by the patellofemoral structure. Moreover, recent magnetic resonance imaging (MRI) studies conducted one year after ACLR have shown the patellofemoral compartment is at increased risk for OA after surgery, especially in men [94]. To that end, subject-specific finite element models that include the patellofemoral structure using MRI scans would provide a more complete picture of stress distribution within all knee joint structures. When used in conjunction with NMS modeling techniques, these methods could help evaluate the risk of patellofemoral knee OA due to changes in knee gait mechanics.

5.5.2 Inclusion of posterior capsule representation in finite element model

The FE knee model used for the current study did not include the representations for the posterior capsule. The capsular structure is commonly represented by uniaxial non-linear elastic components in FE models [37], and plays a significant role as the knee flexion increases from the near neutral position. The impact of the absence of the posterior capsule structures in the current study was evident in the simulation for transverse plane knee kinematics. Inclusion of these structures would help further validate the FE model for all loading modalities through the entire gait cycle.

5.5.3 Inclusion of ACL graft orientation and volume in subject-specific finite element knee representations

For an ACL injury, (small) notch width and (large posterior lateral) tibial plateau slope have been identified as risk factors, based on a systematic meta-analysis and review [175]. Also, ACL volume has been correlated to notch width [176], while ACL force has been shown to increase with an increasing tibial plateau slope [177]. For ACLR, it has been established through multiple studies that the ACL graft orientation influences knee joint mechanics [132,178,179]. Given that ACLR modifies both ACL orientation and ACL volume, the combined effect of these parameters (notch width, tibial slope, ACL graft orientation and ACL graft volume) after ACLR warrants further investigation, in relation to incidence of knee OA. Specifically, the impact of these parameters on cartilage stress distribution (tibiofemoral as well as patellofemoral) needs to be evaluated. To accommodate each of these parameters in a FE simulation, subject-specific NMS modeling experiments and subject-specific MRI scans can be conducted. A combination of subject-specific NMS modeling gait experiments, subject-specific MRI scans and subject-specific FE simulations would help evaluate the risk of knee OA due to each of the anatomical and surgical factors, after ACLR.

5.5.4 Comparing inter-limb differences in gait parameters observed at early time points (three months, six months and two years) after ACLR to differences in T1ρ and T2 time constants of knee cartilage estimated using qMRI

In subjects who get medial compartment knee OA five years after ACLR, the current study demonstrated evidence of inter-limb differences in knee gait parameters at early time points (six months) after surgery. Early OA related changes in knee cartilage involve PG depletion and collagen matrix degradation. qMRI is a non-invasive and indirect method to estimate PG content (T1ρ) and collagen matrix organization (T2) [24]. The current study also provided preliminary evidence related to cartilage tissue level changes (using T2 mapping), in a subject with inter-limb differences in knee joint loading after ACLR. Given the potential applicability of T1ρ and T2 quantitative MRI methods for early detection of knee OA after ACLR, a longitudinal study that includes scans at multiple post-surgery time points (three months, six months and two years) may be useful to verify whether progression of disease can be captured by these methods. Moreover, comparing quantitative MRI values to discrepancies in early inter-limb joint loading differences due to altered gait may provide further insight that cannot be captured by neuromusculoskeletal (NMS) and finite element (FE) simulations alone. To be able to correlate differences in qMRI measures to differences in cartilage material properties , cadaveric studies, which can correlate the two measures, are required [160]. Incorporating qMRI measure is paramount to ensure that the depth-wise variation of cartilage material properties, as well as the variation of these properties over time, are reflected in mathematical simulation techniques. This would ensure that future biomechanical simulations are truly reflective of changes that occur over time, and not merely necromechanical [143], thereby increasing the validity of these mathematical simulations. A combination of NMS modeling, FE modeling and qMRI may be useful in early detection and prediction of knee OA after ACLR.

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Appendix A

APPENDIX A - MOTION AND ELECTROMYOGRAPHY TESTING: INSTITUTIONAL REVIEW BOARD (IRB) APPROVAL LETTER

RESEARCH OFFICE

210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE:	February 17, 2016
TO:	Lynn Snyder-Mackler, PT, ScD, FAPTA
FROM:	University of Delaware IRB
STUDY TITLE:	[225014-14] Can Neuromuscular Training Alter Movement Patterns? (Renewal Period)
SUBMISSION TYPE:	Continuing Review/Progress Report
ACTION:	APPROVED
APPROVAL DATE:	February 17, 2016
EXPIRATION DATE:	March 14, 2017
REVIEW TYPE:	Full Committee Review

Thank you for your submission of Continuing Review/Progress Report materials for this research study. The University of Delaware IRB has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

This submission has received Full Committee Review based on the applicable federal regulation.

Please remember that informed consent is a process beginning with a description of the study and insurance of participant understanding followed by a signed consent form. Informed consent must continue throughout the study via a dialogue between the researcher and research participant. Federal regulations require each participant receive a copy of the signed consent document.

Please note that any revision to previously approved materials must be approved by this office prior to initiation. Please use the appropriate revision forms for this procedure.

All SERIOUS and UNEXPECTED adverse events must be reported to this office. Please use the appropriate adverse event forms for this procedure. All sponsor reporting requirements should also be followed.

Please report all NON-COMPLIANCE issues or COMPLAINTS regarding this study to this office.

Please note that all research records must be retained for a minimum of three years.

Based on the risks, this project requires Continuing Review by this office on an annual basis. Please use the appropriate renewal forms for this procedure.

If you have any questions, please contact Nicole Farnese-McFarlane at (302) 831-1119 or nicolefm@udel.edu. Please include your study title and reference number in all correspondence with this office.

Appendix B

APPENDIX B - MOTION AND ELECTROMYOGRAPHY TESTING: INSTITUTIONAL REVIEW BOARD (IRB) INFORMED CONSENT

UNIVERSITY OF DELAWARE
DEPARTMENT OF PHYSICAL THERAPY
INFORMED CONSENT FORM

Study Title: Can Neuromuscular Training Alter Movement Patterns? (Renewal Period), Experiment 1, Aim 2 (ongoing collection from current observational study).

Principal Investigator: Lynn Snyder-Mackler, PT, ScD

Co-investigators: Thomas Buchanan, PhD, Kurt Manal, PhD, Gregory Hicks, PT, PhD, David Logerstedt, PT, MPT, Michael J. Axe, MD, Emily Gardinier, PhD, Kathleen White, PT, DPT, Zakariya Nawasreh, BS, MS, Matthew Failla, PT, MSPT, Elizabeth Wellsandt, PT, DPT, Amelia Arundale, PT, DPT, Ryan Zarzycki, PT, DPT, Jacob Capin, PT, DPT, MS,

PURPOSE AND BACKGROUND

You are being asked to participate in a study that will investigate the movement patterns and functional abilities of individuals who have had an ACL injury and undergone reconstruction (ACLR). You have been referred to this study because you have had an ACL injury and undergone either non-operative management or ACL reconstruction and you were a participant in a previous project evaluating the effects of perturbation training on people with ACL injuries.

Participation in this research study is voluntary. This program will include testing protocols we currently use in our clinic to assess patients with ACL injury. Your surgeon and physical therapist have agreed that all of the testing procedures included in the study are acceptable.

The study includes strength and functional testing and analysis of your knee movement during walking. There will be a total of one to two (1-2) testing sessions: two (2) testing sessions 2 and 5 years after your ACL reconstruction or one to two (1-2) testing sessions between 3-7 years following your ACL injury if non-operative management was completed. This research study will involve approximately fifty (50) subjects with ACL injury and reconstruction and twentyfive (25) subjects with ACL injury who underwent non-operative management between the ages of 13-55 years. Persons of all sexes, races, and ethnic origins may serve as subjects for this study.

A description of each procedure and the approximate time it takes for each test and the study procedure are outlined below.

Subject's Initials_______

PROCEDURES

ACL Functional Test

Functional testing will take place in the Physical Therapy Clinic at the University of Delaware, 540 South College Avenue, Newark, DE 19713 and will last approximately 1 hour. Testing will be performed 2 and 5 years after your ACL reconstruction or between 3-7 years following your ACL injury if non-operative management was completed. This test is commonly performed at the University of Delaware Physical Therapy Clinic as part of our ACL rehabilitation protocol.

Strength Testing

The test will measure the strength of the quadriceps muscle on the front of your thigh. You will be seated in a dynamometer, a device that resists your kicking motion, and measures how much force your muscle can exert. Self adhesive electrodes will be attached to the front of your thigh, and you will be asked to kick as hard as you can against the arm of the dynamometer. An electrical stimulus will be activated while you are kicking, to fully contract your muscle. During the electrical stimulus you may feel a cramp in your muscles, like a "Charlie Horse", lasting less than a second. Each test will require a series of practice and recorded contractions. Trials will be repeated (up to a maximum of 4 trials) until a maximum contraction is achieved for both legs.

Hop Testing

A series of four (4) single leg hop tests (Diagram 1) will be performed once the swelling in your knee has resolved and you demonstrate good thigh muscle strength. The tests are performed in the order seen in Diagram 1. You are required to wear a standard off-the-shelf knee brace on your injured knee during this portion of the testing.

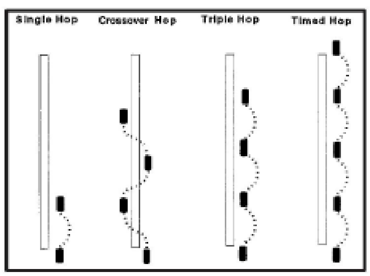

Diagram 1. Four (4) hop tests as part of the functional test protocol.

Two practice trials will precede each of the hop tests before the recorded testing begins. You can put your other leg down at any time to prevent yourself from losing your balance. However, only the two trials in which you are able to 'stick the landing' on one foot will be counted towards your scores. This series of hop tests will be performed on both legs.

Subject's Initials_______

Motion Analysis Testing

All subjects will be asked to perform motion analysis testing, which will take place in the Motion Analysis Laboratory at the University of Delaware, Department of Physical Therapy, 540 South College Avenue, Newark, DE 19713. Motion analysis testing will take place will be performed 2 and 5 years after your ACL reconstruction or between 3-7 years following your ACL injury if nonoperative management was completed.

Motion Analysis

Markers will be affixed 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.

Muscle Activity

Electrodes, taped to your skin, will be used to record the electrical activity of your muscles. After all electrodes have been placed, you will perform a maximum contraction of each muscle, 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 the motion analysis testing. The electrodes will be removed at the conclusion of the testing session.

Walking Trials

Immediately following the initial muscle activity testing, 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. While you are walking, a computer records the 3 dimensional motions of your hips, knees, and ankles. The entire motion analysis session will last approximately two (2) hours.

Risks/Discomfort

You may experience discomfort from the removal of tape holding markers and EMG electrodes in place. Subjects with ACL injury could experience a loss of balance during testing, however your other leg is free to touch down to provide support and prevent loss of balance. The strength testing can be associated with local muscle soreness and fatigue. Following the testing, your muscles may feel as if you have exercised vigorously.

Benefits

The benefits include comprehensive testing sessions that will document your progress following surgery. The results of this study may help us improve the way we treat patients with ACL injury.

Compensation

You will be paid an honorarium of $100 for the motion analysis testing and $100 for the functional testing to compensate you for travel expenses and the time involved.

Confidentiality and records

Only the investigators, you and your physician will have access to the data. All of your data will be de-identified for the purposes of data management and processing. Neither your name nor any identifying information will be used in publication or presentation resulting from this study. A statistical report, which may include slides or photographs which will not identify you, may be disclosed in a scientific paper. Data will be archived indefinitely and may be used for secondary analysis of scientific and clinical questions that arise from this research.

Study Title: Can Neuromuscular Training Alter Movement Patterns? (Renewal Period), Experiment 1, Aim 2 (ongoing collection from current observational study).

Principal Investigator: Lynn Snyder-Mackler, PT, ScD
Co-investigators: Thomas Buchanan, PhD, Kurt Manal, PhD, Gregory Hicks, PT, PhD, David Logerstedt, PT, MPT, Michael J. Axe, MD, Emily Gardinier, PhD, Kathleen White, PT, DPT, Zakariya Nawasreh, BS, MS, Matthew Failla, PT, MSPT, Elizabeth Wellsandt, PT, DPT, Amelia Arundale, PT, DPT, Ryan Zarzycki, PT, DPT

Subject's Statement:

I have read this consent/assent form and have discussed the procedure described above with a principal investigator. I have been given the opportunity to ask questions regarding this study, and they have been answered to my satisfaction.

If you are injured during research procedures, you will be offered first aid at no cost to you. If you need additional medical treatment, 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. I have been fully informed of the above described procedures, with its possible risks and benefits, and I hereby consent/assent (for those under 18 years of age) to the procedures set forth above.

If I am under 18 years of age, I understand that parental or guardian consent is required. My parent or guardian has printed and signed his/her name below.

Subject's Name	Subject's Signature	Date
Parent/Guardian's Name	Parent/Guardian's Signature	Date
Investigator		Date

If you have any questions concerning the rights of individuals who agree to participate in research, you may contact the Institutional Review Board (302-8312137). The Institutional Review Board is created for the protection of human subjects involved in research conducted at the University of Delaware.

Further questions regarding this study may be addressed to:
Lynn Snyder-Mackler, ScD, PT
Physical Therapy Department, (302) 831-3613

Appendix C

APPENDIX C - MAGNETIC RESONANCE IMAGING: INSTITUTIONAL REVIEW BOARD (IRB) APPROVAL LETTER

RESEARCH OFFICE

210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE:	July 23, 2015
TO:	Thomas Buchanan, PhD
FROM:	University of Delaware IRB
STUDY TITLE:	[624833-2] Non-invasive estimation of material properties of knee cartilage using Magnetic Resonance Imaging (MRI) before and after Anterior Cruciate Ligament (ACL) surgery
SUBMISSION TYPE:	Continuing Review/Progress Report
ACTION:	APPROVED
APPROVAL DATE:	July 23, 2015
EXPIRATION DATE:	July 24, 2016
REVIEW TYPE:	Expedited Review
REVIEW CATEGORY:	Expedited review category # *(4)*

Thank you for your submission of Continuing Review/Progress Report materials for this research study. The University of Delaware IRB has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

This submission has received Expedited Review based on the applicable federal regulation.

Please remember that informed consent is a process beginning with a description of the study and insurance of participant understanding followed by a signed consent form. Informed consent must continue throughout the study via a dialogue between the researcher and research participant. Federal regulations require each participant receive a copy of the signed consent document.

Please note that any revision to previously approved materials must be approved by this office prior to initiation. Please use the appropriate revision forms for this procedure.

All SERIOUS and UNEXPECTED adverse events must be reported to this office. Please use the appropriate adverse event forms for this procedure. All sponsor reporting requirements should also be followed.

Please report all NON-COMPLIANCE issues or COMPLAINTS regarding this study to this office.

Please note that all research records must be retained for a minimum of three years.

Based on the risks, this project requires Continuing Review by this office on an annual basis. Please use the appropriate renewal forms for this procedure.

If you have any questions, please contact Nicole Farnese-McFarlane at (302) 831-1119 or nicolefm@udel.edu. Please include your study title and reference number in all correspondence with this office.

Appendix D

APPENDIX D - MAGNETIC RESONANCE IMAGING: INSTITUTIONAL REVIEW BOARD (IRB) INFORMED CONSENT

INFORMED CONSENT TO PARTICIPATE IN RESEARCH

Title of Project: Non-invasive estimation of material properties of knee cartilage using Magnetic Resonance Imaging (MRI) before and after Anterior Cruciate Ligament (ACL) surgery

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

You 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.

Your participation is voluntary 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 study is to gain insight into the rate of progression of knee OsteoArthritis (OA) after Anterior Cruciate Ligament (ACL) surgery.

Even though ACL surgery restores knee stability after injury, it does not fully address abnormal movement and loading patterns, which are believed to be a mechanism leading to knee OA. Knee OA is a condition wherein the load bearing region of the knee, the cartilage, undergoes degradation. In addition to abnormal movement and loading patterns, differences in material properties of knee cartilage are also believed to affect the rate of progression of OA.

Quantitative Magnetic Resonance Imaging (MRI), which is being increasingly used over the past two decades, allows for non-invasive estimation of material properties of knee cartilage. However, estimates of material properties of knee cartilage, specific to an ACL injury/surgery population at different post-operative time points, are not yet readily available in literature.

With that background, the purpose of this research project is to use quantitative MRI to estimate knee cartilage material properties before and after unilateral ACL surgery. Cartilage material properties in the injured/reconstructed knee and the uninjured/normal knee will be determined from the following, mutually exclusive, subject groups:

- 20 ACL injury subjects who have not yet undergone surgery
- 20 ACL surgery subjects who are at a two year post-operative time point
- 20 ACL surgery subjects who are at a five year post-operative time point

Participant's Initials _________

WHY ARE YOU BEING ASKED TO PARTICIPATE?

You are being asked to take part in this study because you have sustained a unilateral ACL injury or have undergone a unilateral ACL surgery approximately two/five years ago.

Standard MRI scans will also be used to construct a geometric, mathematical model of the knee. The ultimate goal of this research project is to use a mathematical simulation approach that allows for a systematic, parametric variation of all three quantities that can affect progression of OA after ACL surgery, i.e. movement patterns, loading patterns and material properties of knee cartilage. Such a parametric, mathematical simulation approach can reveal combinations of the three quantities that negatively impact the knee cartilage after ACL surgery. We also hope that an improved understanding of the effect of these parameters will eventually contribute to the design of better therapeutic protocols.

You could be excluded from volunteering for the study if you have sustained major lower extremity injury or have undergone major lower extremity surgery that requires serious medical management (i.e. fracture or re-injury). You could also be excluded if you have any condition that prevents you from walking, or laying still on your back.

Additionally, the following conditions, if met, will be grounds for exclusion:

- Pregnancy
- Joint replacement with metallic parts
- Lower extremity surgical procedure that includes metallic components
- Extreme claustrophobia
- Pacemaker
- Metal in the body (implants, screws, plates, shrapnel, etc.)
- Aneurysm clips
- Ear or Eye Implants

WHAT WILL YOU BE ASKED TO DO?

The testing session will occur at Diagnostic Imaging Associates, located at L-6 Omega Dr, Newark DE 19713.

During the test, you will be asked to remove all metal accessories, and lay on your back, on an MRI table. During the MRI scan, your legs will be inside a circular, tunnel-like scanner, and your head will always remain outside the scanner.

Participant's Initials _________

The first scan will take approximately 20 minutes, and this scan will capture imaging data that will help us estimate the material properties of the knee cartilage. The second scan will feel exactly similar to the first scan, and it will give us information regarding the geometrical properties of the knee. The second scan will also take approximately 20 minutes. You will be allowed to take a 5 minute break between the two scans.

The total testing duration will be less than or equal to 45 minutes.

While the determination of material and geometrical properties of knee cartilage using MRI scans is experimental in nature, MRI itself is a safe, non-invasive procedure without exposure to any harmful radiation.

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

The testing session involves standard imaging practices and comfortable scan durations. MRI is a safe, non-invasive procedure that does not involve exposure to radiation. Some people, who are afraid of being in small, closed spaces, often experience discomfort while inside the MRI scanner. However, this happens mainly when the upper body and the head are being scanned. For the current study, only the lower legs will be inside the scanner, hence, you should not experience any discomfort. The MRI scanner can sometimes be loud. To avoid discomfort, you will be provided with headphones or earplugs to drown out the sound.

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

If you are injured during research procedures, you will be offered first aid at no cost to you. If you need additional medical treatment, 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.

WHAT ARE THE POTENTIAL BENEFITS?

The proposed study of MRI imaging only aims to characterize material properties of the knee cartilage. Material property characterization, by itself, has not yet been validated as indicative, or predictive, of OA. These material properties will be used in a parametric mathematical model to further elucidate the combination of varying joint loads, varying movement patterns and varying material properties to propose a mechanism for the progression of OA after ACL surgery. Hence, the proposed study of MRI imaging, by itself, cannot identify OA, and as such, no direct benefit to you, as a participating subject, is expected.

However, we do hope that an improved understanding of the effect of these parameters on knee cartilage will provide insight pertaining to the rate of progression of knee OA in an ACL surgery population, and contribute to the design of better therapeutic protocols in the future.

Participant's Initials _________

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 THAT YOU PARTICIPATED IN THIS RESEARCH?

The confidentiality of your records will be protected to the extent permitted by law. Your research records may be viewed by the University of Delaware Institutional Review Board, which is a committee formally designated to approve, monitor, and review biomedical and behavioral research involving humans. Records relating to this research will be kept for at least three years after the research study has been completed.

The research team will make every effort to keep all research records that identify you confidential. The findings of this research may be presented or published. If this happens, no information that gives your name or other details will be shared.

Identities will be kept confidential by coding them with a subject identification number stored on a password protected computer. Only the principal investigator will have access to that password protected computer, which will be backed up regularly on a university server.

Data will be electronically encrypted and archived 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 material properties, knee loading patterns and knee movement patterns reported via peer-reviewed academic journals, national and international conferences that emphasize clinical and biomechanical outcomes after knee.

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

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?

There is no compensation associated with participating in the study.

DO YOU HAVE TO TAKE PART IN THIS STUDY?

Taking part in this research study is entirely voluntary. You do not have to participate in this research. If you choose to take part, you have the right to stop at any time. If you decide not to participate or if you decide to stop taking part in the research at a later date, there will be no penalty or loss of benefits to which

Participant's Initials _________

you are otherwise entitled. Your refusal will not influence current or future relationships with the University of Delaware or Diagnostic Imaging Associates.

Your participation may be terminated if any lower extremity injury that requires serious medical management (i.e. fracture or re-injury) occurs before the MRI scan. If, at any time, you decide to end your participation on this research study, please inform our research team by telling the investigators.

For student volunteers: As a student, if you decide not to take part in this research, your choice will have no effect on your academic status or your grade in the class.

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 (302) 831-2410 or buchanan@udel.edu.

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.

Your signature on this form 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
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 E

APPENDIX E – REPRINT PERMISSION LETTER

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