THE FADING ATHLETE WITH AN OLD KNEE:

INVESTIGATION OF FACTORS AND OUTCOMES

AFTER ANTERIOR CRUCIATE LIGAMENT INJURY

RELATED TO THE DEVELOPMENT OF KNEE OSTEOARTHRITIS

by

Elizabeth Wellsandt

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 Biomechanics and Movement Science

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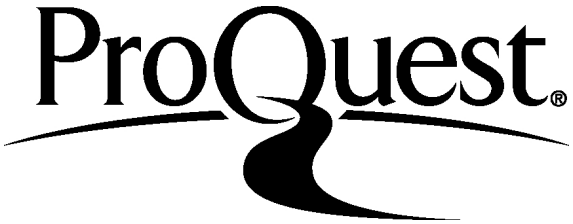

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ABSTRACT

Anterior cruciate ligament (ACL) injury can substantially alter the life of healthy, active individuals and lead to deleterious long-term consequences. Patients often harbor unrealistic expectations of future knee function and risk of knee osteoarthritis after ACL reconstruction. Reconstruction does not guarantee restoration of prior knee function or avoidance of post-traumatic osteoarthritis. Most individuals will experience symptomatic knee osteoarthritis within 10-20 years of ACL injury regardless of surgical or conservative management.

The overall goals of this work were 1) to identify factors early after ACL injury associated with the development of post-traumatic knee osteoarthritis 5 years later and 2) to compare long-term outcomes between operative and non-operative management of ACL injury. The central hypotheses were 1) that modifiable factors present early after ACL injury would differ between individuals who do and do not develop post-traumatic osteoarthritis and 2) that outcomes would not differ between patients treated with operative compared to non-operative management of ACL injury.

Patients with ACL injury who were managed operatively (ACL reconstruction and rehabilitation) or non-operatively (rehabilitation alone) served as subjects for this study. Patients completed biomechanical gait analysis, clinical assessment of knee function, and patient-reported outcomes before and after an extended period of pre-operative or non-operative rehabilitation, and 6 months, 1 year, 2 years, and 5 years after ACL reconstruction or non-operative rehabilitation. Radiographic assessment was completed at 5 years.

Lower knee joint loading and poor knee function were associated with post-traumatic knee osteoarthritis. By identifying modifiable factors early after ACL injury

associated with early osteoarthritis development we have provided rationale to include long-term knee joint health as an important goal early after ACL injury. Patients managed both operatively and non-operatively demonstrated favorable outcomes 5 years after ACL injury. By providing clear evidence of expected long-term outcomes after operative and non-operative management of ACL injury we have opened the door to improved patient education and decision-making regarding surgical management of injury. The findings of this work provide a foundation for future research to optimize treatment strategies to decrease risk for post-traumatic osteoarthritis and prospectively identify the best candidates for surgical compared to conservative care after ACL injury.

Chapter 1

BACKGROUND AND SIGNIFICANCE

1.1 Development of Osteoarthritis After ACL Injury

Anterior cruciate ligament (ACL) rupture is a musculoskeletal injury that can substantially alter the life of healthy, active individuals due to potential inability to return to prior level of function and risk for deleterious long-term consequences. The ACL is the most frequently injured structure of the knee with an estimated 250,000 ACL injuries occurring annually within the United States.[68,121] The high prevalence of such injuries results in an enormous acute impact of ACL injuries on society. However, the decline in function and reduced societal participation experienced by many due to the development of post-traumatic osteoarthritis (OA) will likely cause the greatest long-term socioeconomic impact of ACL injuries.

ACL injuries frequently occur in young individuals participating in sports activities.[68,169] One to two percent of cutting and pivoting athletes will tear an ACL, and the risk of a second ACL injury increases up to 15-fold following an initial ACL injury.[134] The high incidence of graft rupture or contralateral ACL injury is the impetus for using additional ACL injury as a measure of rehabilitative and surgical success. Other common outcomes used to define success after ACL injury include quadriceps strength, patient-reported outcomes, and the ability to return to sport within 1-2 years of injury.[119] However, short and medium-term outcomes ignore the undeniable risk of post-traumatic knee joint OA, suggesting that longer time periods are needed to accurately determine success of ACL management strategies.

Only 2% of patients with an ACL injury expect their risk of OA to be significantly increased, but over 50% will develop radiographic signs of this disease within 10-15 years.[3,47,116] Osteoarthritis is typically believed to be a progressive disease associated with older populations, with knee joint arthroplasty used as the most common surgical operation in its later stages. However, the risk for development of post-traumatic knee OA after ACL injury in young, otherwise healthy individuals is high, contributing to the expected demand for total knee joint arthroplasties to increase 673% from 2005 to 2030.[103] The use of total knee arthroplasty in younger populations possesses an increased risk of need for revision procedures,[141,179] contributing to an increase of 601% for expected revision procedures between 2005 and 2030.[103] An enhanced understanding of post-traumatic OA is needed to provide realistic patient and clinician expectations of long-term knee joint health after ACL injury. In addition further knowledge regarding mechanisms of post-traumatic knee OA will provide insight to develop a new era of secondary prevention strategies aimed to reduce the number of individuals suffering these devastating consequences of post-traumatic knee OA.

Greater than half of patients with ACL injuries will demonstrate symptomatic, radiographic knee OA within 10-20 years after injury.[14,94,116,117,154] The development of OA is not used as a measure of success by experts treating ACL injuries despite its alarming prevalence after ACL injury.[119] Inadequately addressing the risk of OA early after ACL injury is problematic because the pathogenesis of joint degeneration is likely initiated early after injury during rehabilitation and surgical time periods.[116] Thinning of the tibial cartilage is evident on MRI as early as 4 months after isolated ACL injury[177] and these changes persist despite ACL reconstruction.[86] Failure to

include long-term knee joint health as a goal following ACL injury and reconstruction may be an enormous disservice to patients due to the considerable negative consequences resulting from OA development. Because the majority of patients who tear an ACL are of a young age, those who develop post-traumatic OA will be 15-20 years younger than their uninjured counterparts who develop idiopathic OA resulting in the possibility for long-term pain, decreased physical function and activity, socioeconomic burden, and the potential need for total knee replacement.[147]

ACL reconstruction was previously believed to serve chondroprotective purposes by restoring passive knee joint stability.[17,48] ACL reconstruction, however, does not protect the knee from the development of OA. The incidence of knee OA after ACL injury is similar between patients managed operatively and non-operatively.[58,98,117,126,130,140,157] Identifying modifiable factors influencing the development and progression of OA is needed to guide secondary prevention components of rehabilitation programs aimed at decreasing the number of patients who will suffer its effects. Longitudinal assessment of early biomechanical and clinical measures related to subsequent radiographic signs of knee OA after ACL injury is needed to formulate meaningful and predictable relationships between these measures. In addition, a comprehensive comparison of long-term outcomes, including the development of post-traumatic OA, between patients treated with operative compared to non-operative management of ACL injury will help guide informed decision-making whether or not to undergo surgery for young, otherwise healthy individuals.

1.2 Joint Loading Factors in Osteoarthritis

Altered joint biomechanics is likely a key mechanism in the development of post-traumatic knee OA following ACL injury.[116] Articular cartilage relies on dynamic mechanical loading to maintain tissue health. Animal research suggests immobilization and unloading periods can lead to atrophic changes of articular cartilage while progressive loading may improve its mechanical properties.[12,22,175] However, the relationship between mechanical loading and subsequent articular cartilage degeneration following ACL injury and reconstruction in the human knee is not well-understood.

Cartilage in the knee is thought to become conditioned to the repetitive loading it experiences during activities such as walking.[6] The thickness of healthy articular cartilage is correlated with knee joint moments during walking[100] and preliminary data has demonstrated an association between joint unloading and regional cartilage thinning after ACL injury (Koo et al., unpublished data, 2007). Altered joint kinematics, kinetics, and contact forces after ACL injury may be a stimulus in initiating degenerative processes if either a) new regions of articular cartilage are loaded but not equipped to handle the loading it experiences or b) typically loaded regions of articular cartilage undergo a decrease in loading preventing the maintenance of healthy cartilage.[6,8,24]

Evidence of aberrant movement patterns after ACL injury support hypotheses suggesting articular cartilage degradation may relate to insufficient mechanical loading. Sagittal plane knee joint angles, excursions, and moments are asymmetrically lower on the involved limb after ACL rupture[27,62,149,150] and these abnormal sagittal plane movement patterns continue after reconstruction.[23,84,137,144,176,181,184,192] Frontal plane knee joint biomechanics after ACL injury are not as clearly understood. Whether

changes in the knee adduction moment occur initially after injury is not clear,[60] and conflicting reports of frontal plane moments greater than, equal to, and less than the contralateral knee and healthy controls have been described after ACL reconstruction.[23,65,137,181,182,184,192]

A patient-specific electromyographic (EMG)-driven musculoskeletal model is a tool more robust than kinematic and kinetic measures to describe the knee's loading environment. EMG-driven musculoskeletal models calculate muscle forces using EMG data to estimate levels of muscle co-contraction. The contribution of muscle co-contraction is then incorporated into estimations of joint contact forces within the knee.[21,189] Joint contact force is a measure of the compressive force experienced by articular cartilage. Previous work by our group has shown that muscle forces derived from an EMG-driven musculoskeletal model are asymmetrically lower in the knee joint flexors and extensors early after ACL injury corresponding to the lower joint contact forces exhibited during walking.[60,62] Although pre-operative rehabilitation including neuromuscular training is effective in normalizing movement patterns prior to surgery[165] asymmetric joint contact forces are again present in some patients 6 months after ACL reconstruction.[61] Whether altered contact forces are associated with the later development of post-traumatic OA is unknown.

Evidence of aberrant joint biomechanics and movement patterns after ACL injury and reconstruction highlights the necessity for longitudinal testing of ACL cohorts to establish clear associations between these early measures of joint loading and emerging radiographic OA. These relationships are crucial to develop more effective rehabilitation approaches aimed at interrupting the pathogenesis of post-traumatic OA after ACL injury.

1.3 Clinical Factors in Osteoarthritis

Although biomechanical mechanisms likely contribute to the development of post-traumatic knee OA, they can be difficult to identify without expensive gait analysis equipment. Altered muscle activation patterns and joint kinetics, kinematics, and contact forces are present despite resolution of gait impairments detected by clinical observation.[60,165] Moreover, typical osteoarthritic symptoms including pain, stiffness, and decreased function are often absent when initial radiographic signs of knee OA are detectable.[83,139,140] Unfortunately, methods to clinically and prospectively identify patients at greatest risk for post-traumatic OA development or identify those already possessing signs of joint degeneration as detected by imaging modalities have not been developed.

Known risk factors for primary OA include age, a positive family history, joint trauma, work or leisure activities, muscle weakness, obesity, joint instability and lower extremity malalignment.[116] Modifiable risk factors specific to post-traumatic OA are largely unknown because few studies have longitudinally tested patients at specific time points in rehabilitation and then later performed radiographic screening for OA. Age, BMI, manual labor at time of injury, meniscus injury, meniscus resection, and chondral lesions may be risk factors for early-onset OA after ACL injury.[14,112] While these risk factors provide helpful information to flag patients at greater risk for early knee OA, most are unmodifiable and thus possess limited potential to be influenced by rehabilitation interventions. The identification of modifiable factors in the development of post-traumatic OA will provide avenues for physical therapists to influence the enormous risk for joint destruction regardless of underlying, unmodifiable patient risk factors.

The current inability of clinicians to prospectively screen patients at high risk of post-traumatic knee OA risk after ACL injury necessitates further evaluation of clinical measures early after injury and/or surgery in combination with later radiographic evidence of articular cartilage destruction. Identified clinical factors may be manifestations of underlying biomechanical alterations potentially causing the degeneration of articular cartilage or be associated with the development of knee OA independent of any relationship with existing movement patterns. Whatever the mechanism, the ability to alert clinicians of individuals at highest risk for developing post-traumatic OA will provide the initial steps in developing strategies to lower the risk of developing this devastating disease after ACL injury.

1.4 Outcomes After Operative and Non-Operative Management of ACL Injury

Most patients in the United States who tear an ACL undergo ACL reconstruction with the expectation that prior knee function will be restored, prior activity levels will be attained, and further injury will be avoided.[47,106,127] These patient expectations are consistent with measures of success used by experts treating those with ACL injuries.[119] Unfortunately, these goals and measures of success are often not achieved following ACL reconstruction. Mounting evidence suggests non-operative management in comparison to ACL reconstruction may provide equal to or better outcomes for many individuals.

Additional ACL injury is common after reconstruction as nearly one-third of young athletes will endure either a graft rupture or contralateral ACL injury.[135] Fewer than 10% of patients managed non-operatively experience further knee injuries during the first two years after injury, much lower than re-injury rates of their ACL reconstructed counterparts during this time period.[69,135] Although a longer duration

from ACL injury to reconstruction has been linked to higher incidence of secondary knee pathology,[28,67,97] Frobell and colleagues reported no differences in meniscal surgical procedures between patients treated with early ACL reconstruction, delayed ACL reconstruction, or rehabilitation alone in a completed randomized control trial.[58]

Despite current evidence refuting an increased risk of secondary knee injury with non-operative ACL management, some still attempt to use the argument for further knee injury without surgical restoration of passive knee laxity as rationale for early ACL reconstruction.[19,38] However, additional knee joint injury sustained after original ACL injury rarely drives the decision for ACL reconstruction after an initial period of non-operative rehabilitation. Instead, factors including recurrent episodes of knee instability and poor knee function typically result in the decision to undergo later ACL reconstruction.[58,69,170]

Return to sport rates after ACL reconstruction compared to non-operative management show similar trends to those present regarding additional knee joint injury. The ability to return to cutting and pivoting sports after ACL injury undoubtedly requires a stable knee joint. ACL reconstruction is superior to non-operative management of ACL injury in reducing knee joint laxity.[57,58,70,126,157] However, neuromuscular control mechanisms can overcome joint laxity and provide the necessary dynamic knee stability required for high level activities,[51] allowing many patients who complete non-operative management of ACL injury to return to high levels of activity following injury.[49]

Athletes who wish to return to pivoting sports are typically counseled to undergo ACL reconstruction.[31,69] However, approximately one-third of individuals do not return to pre-injury activity levels after ACL reconstruction, and nearly half fail to

return to the same level of competition.[10] A comparison of athletes matched for age, sex, and cutting and pivoting activity level[35,81] prior to injury revealed equal return to sport rates at one and two years following injury regardless of operative or non-operative management.[69,70] High levels of cutting and pivoting activities can be maintained several years after injury utilizing non-operative intervention strategies.[58,98,130] Patient intent to return to sport should not drive early surgical decision-making after ACL injury. Additional evidence is needed to provide evidence-based education for patients and clinicians regarding the clinical course and expected outcomes following both operative and non-operative treatment of ACL injury to guide appropriate surgical decision-making.

Measures of success after ACL injury beyond re-injury and ability to return to sport include functional and patient-reported outcomes.[119] Patients completing non-operative treatment may demonstrate superior performance-based functional outcomes and subjective knee function during the first year after injury than their counterparts who undergo ACL reconstruction.[73,157] Poorer short-term outcomes following ACL reconstruction may be attributed to operative complications such as arthrofibrosis, infection, donor site morbidity and pain associated with surgery.[157] Although outcomes initially differ, strength and subjective knee function are similar between treatment strategies after the first year.[58,157]

Long-term gait biomechanics after completion of operative and non-operative rehabilitation are not well documented. Consideration of long-term movement patterns are important due to their link to risk of second ACL injury, ability to return to sport after ACL injury, and the development of post-traumatic OA.[8,80,136,164] Sagittal plane knee kinematics, kinetics and joint contact forces are altered early after ACL

injury,[27,60,62,149,150] presumably resulting in compensations seen at the hip and ankle joints.[90] Rehabilitation after ACL injury including specialized neuromuscular training, called perturbation training,[50] results in biomechanics more closely resembling uninjured individuals;[25,78,165] however, some biomechanical asymmetries re-emerge following ACL reconstruction and do not fully resolve by two years after surgery.[61,144]

Evidence pertaining to frontal plane kinetics is less clear. Limited evidence suggests the external knee adduction moment is not different between limbs early after ACL injury.[60] Following ACL reconstruction varying frontal plane relationships have been illustrated, but an overriding theme emerges in which lower frontal plane moments in the involved limb are present early after ACL reconstruction with symmetric or higher moments emerging several years after surgery.[23,137,176,181,183,184,192] Movement patterns likely change longitudinally following ACL injury. However, long-term evidence is lacking to comprehensively determine 1) whether joint biomechanics continue to improve after two years following ACL reconstruction and 2) whether symmetric long-term biomechanical strategies exist after a non-operative rehabilitation strategy which incorporated progressive strength and neuromuscular training. Detailed descriptions of long-term movement patterns will highlight long-term outcomes that rehabilitation programs insufficiently address in their current design.

Perhaps the most extensive evidence regarding long-term outcomes comparing operative and non-operative treatment of ACL injury pertains to radiographic signs of OA. No differences exist in rates of post-traumatic OA development between 5 and 20 years after ACL injury between the two treatment strategies.[58,98,117,126,130,140,157] However, as previously described, current evidence regarding differences in other

long-term outcomes is incomplete and inadequate. A comprehensive analysis of long-term functional, patient-reported, and biomechanical outcomes incorporating baseline, additional injury, and radiographic data following operative compared to non-operative management of ACL injury is needed to provide clear evidence of expected outcomes to guide early decision-making for optimal treatment strategy following ACL injury.

1.5 Conclusions

In conclusion, the proposed work will support the inclusion of long-term knee joint health as an important goal early after ACL injury and reconstruction by identifying factors during the rehabilitation period associated with the later development of knee OA. Further, we will provide clear evidence of expected long-term functional, patient-reported, biomechanical and radiographic outcomes after operative compared to non-operative management of ACL injury to assist in early decision-making for optimal treatment strategy of injury. This information will help shape and progress current rehabilitation strategies to provide patients with ACL injury the opportunity to achieve a lifetime of continued physical activity and a rich quality of life.

1.6 Specific Aims

The overall goal of this work is to identify factors early after injury and/or reconstruction associated with the development of post-traumatic knee OA 5 years after ACL injury and to compare long-term outcomes between operative and non-operative management of ACL injury. The central hypotheses are that modifiable factors present early after ACL injury and reconstruction will differ between

individuals who do and do not develop post-traumatic knee OA and that outcomes will not differ between patients treated with operative compared to non-operative management of ACL injury.

The specific aims of this project are to:

1. Determine the relationship between joint biomechanics and loading early after ACL injury with the presence of knee joint osteoarthritis 5 years after ACL reconstruction

    Hypothesis 1.1: Altered knee kinematics and kinetics prior to and early after ACL reconstruction and knee alignment will be associated with radiographic knee osteoarthritis 5 years after ACL reconstruction

    Hypothesis 1.2: Altered hip kinematics and kinetics prior to and early after ACL reconstruction will be associated with radiographic knee osteoarthritis 5 years after ACL reconstruction

    Hypothesis 1.3: Altered knee joint contact forces prior to and early after ACL reconstruction will be associated with radiographic knee osteoarthritis 5 years after ACL reconstruction

2. Determine the relationship between baseline and functional outcomes early after ACL injury with the presence of knee joint osteoarthritis 5 years after injury

    Hypothesis 2.1: Baseline characteristics and functional outcomes early after ACL injury and/or ACL reconstruction will differ between those with and without radiographic signs of knee osteoarthritis 5 years after ACL reconstruction or non-operative rehabilitation

3. Determine the functional, biomechanical, and radiographic differences between patients completing operative compared to non-operative management of ACL injury 5 years after injury

    Hypothesis 3.1: Baseline characteristics will not differ between patients completing operative compared to non-operative management of ACL injury 5 years after injury

    Hypothesis 3.2: Quadriceps strength, single-legged hop scores and knee joint effusion will not differ between patients completing operative compared to non-operative management of ACL injury 5 years after injury

    Hypothesis 3.3: Patient-reported outcomes will not differ between patients completing operative compared to non-operative management of ACL injury 5 years after injury

    Hypothesis 3.4: Involved limb and interlimb differences in hip and knee joint biomechanics will not differ between patients completing operative compared to non-operative management of ACL injury 5 years after injury

    Hypothesis 3.5: Radiographic outcomes will not differ between patients completing operative compared to non-operative management of ACL injury 5 years after injury

Chapter 2

LOWER KNEE JOINT LOADING ASSOCIATED WITH EARLY KNEE OSTEOARTHRITIS AFTER ANTERIOR CRUCIATE LIGAMENT INJURY

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2.1 Abstract

Anterior cruciate ligament injury predisposes individuals for early onset knee joint osteoarthritis. Abnormal joint loading is apparent following anterior cruciate ligament injury and reconstruction. The relationship between altered joint biomechanics and development of knee osteoarthritis is unknown. Therefore, the purpose of this study was to determine whether altered knee joint kinetics and medial compartment contact forces initially after injury and reconstruction are associated with radiographic knee osteoarthritis 5 years after reconstruction.

Individuals with acute, unilateral anterior cruciate ligament injury completed gait analysis before (baseline) and after (post-training) pre-operative rehabilitation and 6 months, 1 year, and 2 years after reconstruction. Surface electromyography and knee biomechanics were input to an electromyographic-driven musculoskeletal model to estimate knee joint contact forces. Patients completed radiographic testing 5 years after reconstruction. Differences in knee joint kinetics and contact forces were compared between those with and without radiographic knee osteoarthritis.

Patients with osteoarthritis walked with greater frontal plane interlimb differences than those without osteoarthritis at baseline (peak knee adduction moment difference: p: 0.014; nonOA: 0.00±0.08 Nm/kg·m; OA: -0.15±0.09 Nm/kg·m; peak knee adduction moment impulse difference: p: 0.042; nonOA: -0.001±0.032

Nm·s/kg·m; OA: -0.048±0.031 Nm·s/kg·m). The involved limb knee adduction moment impulse of the group with osteoarthritis was also lower than the group without osteoarthritis at baseline (p: 0.023; nonOA: 0.087±0.023 Nm·s/kg·m; OA: 0.049±0.018 Nm·s/kg·m). Significant group differences were absent at post-training but reemerged 6 months after reconstruction (peak knee adduction moment difference: p: 0.043; nonOA: 0.02±0.04 Nm/kg·m; OA: -0.06±0.11 Nm/kg·m). In addition the group with osteoarthritis walked with lower involved limb peak medial compartment contact forces than the group without osteoarthritis at 6 months (p: 0.036; nonOA: 2.89±0.52 BW; OA: 2.10±0.69 BW).

Patients with radiographic knee osteoarthritis 5 years after anterior cruciate ligament reconstruction walked with lower knee adduction moments and medial compartment joint contact forces than those without osteoarthritis early after injury and reconstruction. Early gait patterns exhibited by those with osteoarthritis represent a knee joint unloading strategy. Changes in rehabilitation programs may be needed to facilitate normal joint loading after anterior cruciate ligament injury.

2.2 Introduction

The risk of knee osteoarthritis (OA) dramatically increases following anterior cruciate ligament (ACL) reconstruction.[14,58,94] Patients with ACL injury experience higher rates of knee OA at much younger ages compared to healthy individuals.[138] The hallmark osteoarthritic symptom of pain may be absent at the onset of knee OA,[83,139] while the presence of chronic knee pain in younger individuals is not well associated with radiographic OA.[76,138] Patient-reported outcomes of knee function are also poor discriminators for the presence of knee OA following ACL injury and ACL reconstruction.[83,139] Thus, the initial development and progression of OA after ACL

injury can be difficult to predict and detect without the use of routine imaging. Evidence of altered biomechanics has been demonstrated early after ACL injury and ACL reconstruction,[150,192] and abnormal joint loading is one key mechanism that may contribute to the early development of OA. Identifying a link between joint loading and OA is a critical step in better understanding and possibly preventing early onset knee joint OA.

Common surrogate measures of knee joint loading are frontal and sagittal plane knee moments. Higher external knee moments have been associated with the presence and severity of idiopathic knee OA in older populations.[52,107,110,129] However, external knee adduction and flexion moments have been reported to be lower in the limb at risk for OA following ACL reconstruction.[182,185,192] Although it is clear that knee kinetics are altered after ACL injury and ACL reconstruction, there is a lack of information on the impact of abnormal biomechanics to the later development of OA.

The external knee adduction moment is widely used as an indicator of knee joint loading of the medial tibiofemoral compartment.[37,52,107,110,129,194] The knee adduction moment prior to ACL reconstruction has not been well-characterized, while values higher, equal to and lower than the contralateral knee and healthy controls have been reported at varying points in time after ACL reconstruction.[23,137,176,181,183,184,192] Conflicting reports of the knee adduction moment after surgery may be due to longitudinal changes in frontal plane kinetics after ACL reconstruction.[181]

Patients initially walk with decreased external knee flexion moments after ACL injury.[62,90,149,150,185] However, it unclear how long these alterations persist after ACL reconstruction.[84,144,181,184] As with the knee adduction moment, it is not well

understood whether unresolved alterations in the knee flexion moment after ACL injury and ACL reconstruction are detrimental to long-term knee joint health.

Knee joint contact forces estimated using musculoskeletal models are another method to quantify knee joint loading. Models incorporating electromyographic (EMG) data may provide a more comprehensive understanding of the knee's loading environment after ACL injury than joint moments alone by incorporating the contribution of muscular co-contraction in the estimation of joint contact forces.[21,189] Patients walk with asymmetric knee joint contact forces after ACL injury[60] and some demonstrate persistent asymmetries 6 months after ACL reconstruction.[61] However it is unknown if these abnormal loading patterns precede early onset knee OA.

The purpose of this study was to determine whether knee joint moments and contact forces early after injury and ACL reconstruction were associated with radiographic knee OA 5 years after surgery. Based on previous work demonstrating lower knee joint kinetics,[62,90,149,150,185,192] muscle forces,[62] and joint contact forces[60] after ACL injury, we hypothesized that altered knee frontal and sagittal plane kinetics and medial compartment contact forces initially after injury and ACL reconstruction would be associated with medial compartment knee OA 5 years after ACL reconstruction.

2.3 Methods

2.3.1 Subjects

Twenty-two subjects between the ages of 14-47 with complete, unilateral ACL injury within the previous 7 months were included in this study as part of a larger randomized control trial of 55 patients.[79] All patients were regular participants in level

I-II cutting and pivoting activities[35,81] prior to injury and demonstrated dynamic knee instability after injury (noncopers).[49] Exclusion criteria included concomitant repairable meniscus injuries, grade III injury to other knee ligaments, and full-thickness articular cartilage lesion >1 cm^2 diagnosed prior to ACL reconstruction or contralateral ACL injury after initial ACL reconstruction.

Patients were enrolled in this study after effusion, range of motion (ROM), pain, and obvious gait impairments were resolved utilizing the physical therapy protocol described by Hurd et al.[88] Study approval was granted by the Institutional Review Board at the University of Delaware and all patients provided written informed consent. Following study enrollment, patients received additional pre-operative rehabilitation to further restore lower extremity strength and neuromuscular control.[79] All patients underwent ACL reconstruction by a single, board-certified orthopedic surgeon using either a four-bundle semitendinosus-gracilis autograft or soft tissue allograft with a medial and lateral portal and medial parapatellar tendon incision. No surgical procedures were performed to any additional ligamentous knee structures. Patients completed progressive, criterion-based post-operative rehabilitation early after surgery.[1]

2.3.2 Testing

Testing consisted of gait analysis with EMG at 5 time points: pre-operatively after effusion, ROM, pain, and obvious gait impairments were resolved (baseline), immediately following 10 sessions of additional pre-operative rehabilitation (post-training), 6 months after ACL reconstruction following criterion-based rehabilitation (6 months), 1 year after ACL reconstruction (1 year) and 2 years after ACL reconstruction (2 years).

Gait analysis was completed using an 8-camera system (VICON, Oxford Metrics Ltd., London, UK) sampled at 120 Hz and 1 force platform (Bertec Corporation, Worthington, OH) sampled at 1,080 Hz. Retroreflective markers were placed on bony landmarks at each lower extremity with rigid shells containing markers placed at the pelvis, thighs, and shanks.[62] Patients walked at self-selected speed which was maintained (±5%) throughout the testing session and subsequent testing sessions. Stance phase joint angles and moments were calculated using inverse dynamics within commercial software (Visual 3D, C-Motion, Germantown, MD). Moments were normalized to mass (kg) and height (m). Variables of interest included the peak external knee adduction moment, external knee adduction moment impulse during stance phase, and peak external knee flexion moment. Differences between limbs were calculated for each kinetic measure (involved-uninvolved).

Surface EMG was collected at 1,080 Hz (MA-300 EMG System, Motion Lab Systems, Baton Rouge, LA) for seven muscles on each limb (rectus femoris, medial and lateral vasti, semitendinosus, long head of biceps femoris, medial and lateral gastrocnemii). Patients completed maximal voluntary isometric contractions for each muscle group to normalize EMG amplitude during subsequent walking trials. Raw EMG data was high-pass filtered (2nd order Butterworth, 30 Hz), rectified, and then low-pass filtered (2nd order Butterworth, 6 Hz) creating a linear envelope for maximal voluntary isometric contractions and walking trials.

2.3.3 EMG-Driven Modeling

Gait analysis and surface EMG data served as inputs to a musculoskeletal model[62,122] for the estimation of joint contact forces. This model has demonstrated good repeatability[60] and high accuracy when validated using in vivo contact force data

recorded from an instrumented knee prosthesis.[122] In addition, sensitivity analyses conducted on varying experimental inputs to the model have demonstrated that interlimb differences in peak contact forces found within this study are much larger than estimated potential error.[13] Contact forces for 10 of these patients were included in the primary analyses of knee joint contact forces after acute ACL injury ("baseline" time point (Gardinier et al. 2012)) and after ACL reconstruction ("6 months" time point (Gardinier et al. 2014)).

The EMG-driven model of the knee included an anatomical model which characterizes the musculoskeletal geometry,[36] an activation dynamics model which characterizes the transformation of EMG (the neural signal) to muscle activation, and a contraction dynamics model which contains a Hill-type muscle model and characterizes the transformation of muscle activation to muscle force. The anatomical model contained pelvis, femur, tibia and foot segments which were actuated by 10 muscle-tendon units and scaled according to subject anthropometry. The activation dynamics and contraction dynamics models contained adjustable muscle parameters (see Gardinier et al. 2012 MSSE) that are difficult to accurately measure *in vivo*, including optimal muscle fiber length and tendon slack length. These parameters were adjusted during a subject-specific model calibration and were allowed to vary within physiological bounds as described previously (see Gardinier 2012 MSSE for limits used). After calibrating the model, muscle forces were predicted for the stance phase of 3 novel overground walking trials.

Medial compartment contact force was calculated by balancing the external knee adduction moment (expressed about the lateral compartment contact point which was fixed at a distance of 25% of tibial plateau width from the knee joint center) with

the internal adduction moments due to the muscle forces and the contact force in the medial compartment.[189] The peak medial compartment contact force occurring in the first half of stance was the discrete variable of interest for this study, and the average of 3 trials was used for analysis.

2.3.4 Radiographs

Weight-bearing posterior-anterior (PA) bent knee (30 degree) radiographs were completed 5 years after ACL reconstruction and graded using the Kellgren-Lawrence (KL) system.[96] The presence of OA was defined as a KL grade ≥ 2 in the medial compartment (graded by EW; between-day kappa statistic: 0.904, p:<0.001; all KL grades verified by board-certified orthopedic surgeon). Initial radiographs after ACL injury were not obtained; however, articular cartilage pathology was assessed during arthroscopic evaluation at the time of ACL reconstruction. Two patients demonstrated chronic articular cartilage changes at the medial femoral condyle during arthroscopic evaluation during ACL reconstruction. One of these two patients had OA in the medial compartment at 5 years, one did not.

2.3.5 Statistical Analysis

Statistical analyses were completed using PASSW 21.0 software (SPSS Inc., Chicago, IL). Independent *t*-tests and Fisher's exact tests were performed to test differences in demographics, baseline characteristics, and concomitant injuries between those with and without radiographic knee OA in the medial compartment (nonOA, OA) 5 years after ACL reconstruction. Independent *t*-tests were also used to test differences in loading measures for the involved limb between the nonOA and OA groups (peak knee adduction moment, knee adduction moment impulse, peak knee

flexion moment, peak medial compartment contact force) and interlimb differences between groups at each time point for each of these measures. Effect sizes were calculated for group differences in loading measures.[29] Previously reported minimally detectable changes were used to determine meaningful asymmetry between limbs for peak knee adduction moment (0.06 Nm/kg·m), peak knee flexion moment (0.09 Nm/kg·m), and peak medial compartment contact force (0.30 BW).[63] Statistical significance was set at ≤ 0.05.

2.4 Results

In total, 22 subjects were brought back in for radiographic testing 5 years after ACL reconstruction (15 nonOA, 7 OA) (Figure 2.1). Of these 22 subjects, the number completing testing at each of the 5 earlier time points is described in Table 2.1. A greater proportion of subjects who completed testing at 2 years with OA at 5 years were female (p: 0.036; nonOA: 9 males, 2 females; OA: 1 male, 4 females). No further group differences existed for sex at other time points (Table 2.1). No differences in age, mass, body mass index (BMI), pre-injury activity level, time from injury to baseline, time from injury to ACL reconstruction, or graft type were present between groups (Table 2.1). The OA group walked slower than the nonOA group at 1 year (p: 0.035; nonOA: 1.64±0.12 m/s; OA: 1.49±0.04 m/s) but not at any other testing sessions (Table 2.1). Presence of concomitant meniscus or articular cartilage injuries identified arthroscopically during ACL reconstruction did not differ between groups at any time point for all compartments of the involved knee or specifically the medial tibiofemoral compartment (Table 2.1). No differences existed in additional knee injuries or surgeries sustained between time of initial ACL injury and 5 year

radiographic testing (nonOA: 1 ipsilateral re-tear, 1 ipsilateral partial PCL tear and meniscus tear; OA: 1 ipsilateral re-tear) (Table 2.1).

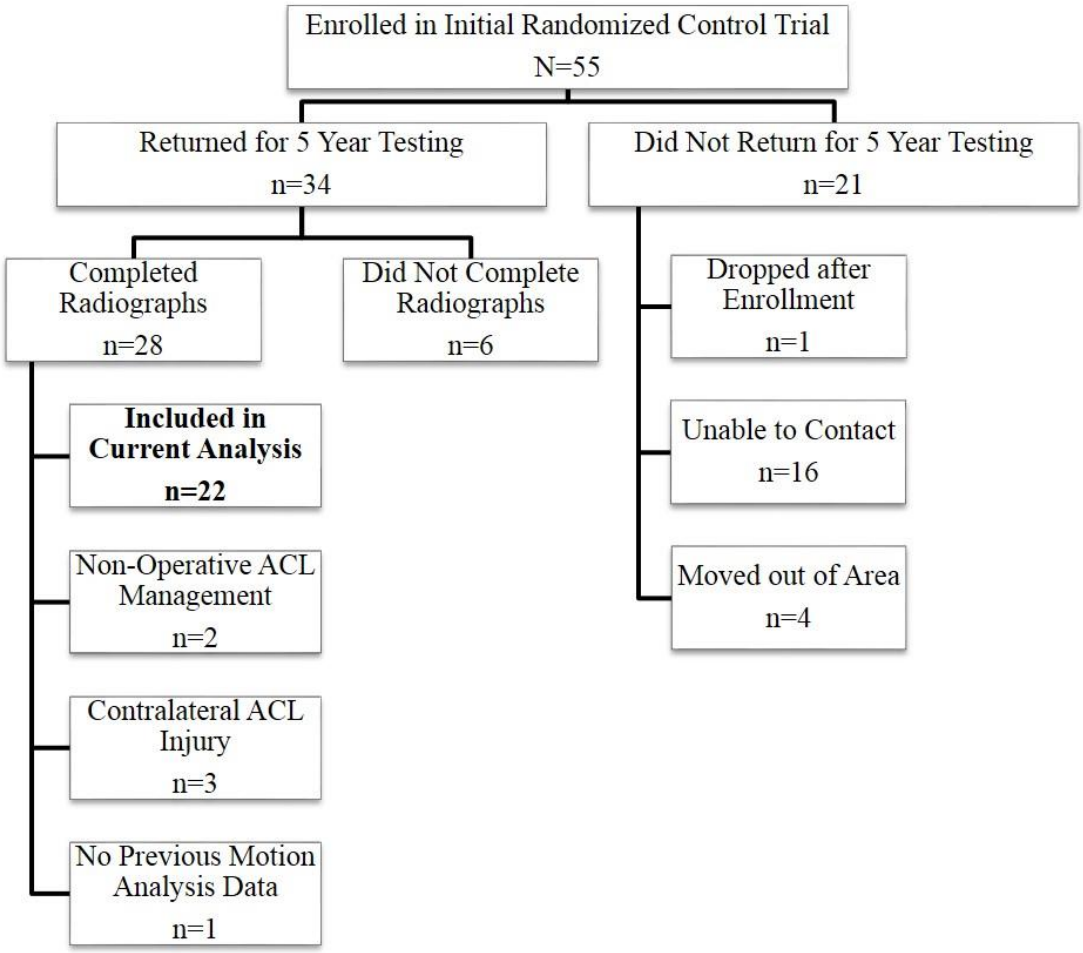

Figure 2.1: Flow diagram of study cohort.

Table 2.1: Demographic, baseline, and concomitant injury characteristics between those with and without radiographic medial compartment knee OA 5 years after ACL reconstruction. Boldface numbers indicate statistically significant group differences. Abbreviations: SD, standard deviation; yrs, years; kg, kilograms; m, meter; wks, weeks; ACLR, ACL reconstruction; s, second; M, male; F, female; Allo, allograft; Auto, autograft.

	Group	Baseline		Post-Training		6 Months		1 Year		2 Years	
		Mean (SD)	p	Mean (SD)	p	Mean (SD)	p	Mean (SD)	p	Mean (SD)	p
Age at baseline, yrs	nonOA	33.4 (10.9)	0.868	33.8 (10.4)	0.983	32.5 (11.2)	0.062	32.9 (11.6)	0.309	35.2 (10.1)	0.463
	OA	34.7 (14.3)		33.7 (13.7)		44.8 (5.6)		26.0 (8.8)		39.6 (12.5)	
Mass, kg	nonOA	86.6 (19.1)	0.351	86.1 (20.7)	0.936	86.8 (15.3)	0.238	89.4 (14.5)	0.727	87.7 (13.8)	0.338
	OA	75.0 (14.5)		85.2 (17.1)		76.3 (11.0)		86.2 (18.0)		80.3 (14.3)	
Body Mass Index, kg/m^2	nonOA	28.1 (3.7)	0.313	28.0 (3.9)	0.591	28.1 (2.9)	0.104	28.7 (4.2)	0.853	28.8 (3.0)	0.217
	OA	25.6 (4.3)		29.1 (4.2)		25.2 (2.4)		28.2 (5.1)		26.5 (3.8)	
Injury to basline, wks	nonOA	9.8 (8.3)	0.444	9.7 (9.2)	0.687	9.8 (7.2)	0.873	8.1 (7.1)	0.542	8.5 (7.3)	0.692
	OA	5.8 (2.3)		11.6 (8.3)		10.5 (7.4)		10.9 (9.0)		10.0 (6.5)	
Injury to ACLR, wks	nonOA	18.8 (11.0)	0.189	18.9 (12.3)	0.916	15.2 (8.4)	0.422	19.3 (22.6)	0.709	19.8 (21.5)	0.941
	OA	9.7 (2.3)		19.7 (15.7)		21.0 (18.6)		14.8 (9.2)		19.0 (16.6)	
Gait velocity, m/s	nonOA	1.6 (0.1)	0.592	1.6 (0.1)	0.418	1.6 (0.1)	0.320	1.6 (0.1)	**0.035**	1.6 (0.1)	0.226
	OA	1.5 (0.1)		1.6 (0.1)		1.5 (0.1)		1.5 (0.0)		1.5 (0.1)	
Sex, M:F	nonOA	8:4	0.077	7:3	0.302	8:2	0.095	8:2	0.520	9:2	**0.036**
	OA	0:3		2:4		1:3		2:2		1:4	
Pre-Injury Activity Level, 1:2	nonOA	6:6	<1.00	6:4	0.608	6:4	0.085	7:3	0.580	8:3	0.106
	OA	1:2		2:4		0:4		2:2		1:4	
Graft type, Allo:Auto	nonOA	9:3	<1.00	8:2	0.299	8:2	0.520	8:2	0.520	10:1	0.214
	OA	2:1		3:3		2:2		2:2		3:2	
Meniscus or articular carti-	nonOA	5:7	0.200	5:5	0.633	4:6	0.559	3:7	0.580	4:7	0.282
lage injury,No:Yes	OA	3:0		4:2		3:1		2:2		4:1	

Table 2.1: continued

	Group	Baseline		Post-Training		6 Months		1 Year		2 Years	
		Mean (SD)	p	Mean (SD)	p	Mean (SD)	p	Mean (SD)	p	Mean (SD)	p
Medial tibiofemoral compartment injury, No:Yes	nonOA	8:4	0.516	7:3	<1.00	7:3	<1.00	7:3	<1.00	7:4	<1.00
	OA	3:0		5:1		3:1		3:1		4:1	
Additional knee injury after initial ACL injury, No:Yes	nonOA	10:2	0.516	9:1	0.625	9:1	0.714	9:1	0.505	11:0	0.313
	OA	2:1		5:1		4:0		3:1		4:1	

The OA group walked with lower peak knee adduction moment than the nonOA group with significant interlimb differences and large effect sizes present at baseline (p: 0.014; peak knee adduction moment difference: nonOA: 0.00±0.08 Nm/kg·m; OA: -0.15±0.09 Nm/kg·m) (Figure 2.2A and 2.2B, Table 2.2). Asymmetric peak frontal plane moments improved in the OA group after rehabilitation prior to ACL reconstruction but significant group differences were again present 6 months after ACL reconstruction (p: 0.043; peak knee adduction moment difference: nonOA: 0.02±0.04 Nm/kg·m; OA: -0.06±0.11 Nm/kg·m) (Figure 2.2B). Both groups demonstrated symmetry in peak knee adduction moment 1 and 2 years after surgery (Figure 2.2B). Large group differences for the involved limb peak knee adduction moment were present at baseline but no further time points (Figure 2.2A).

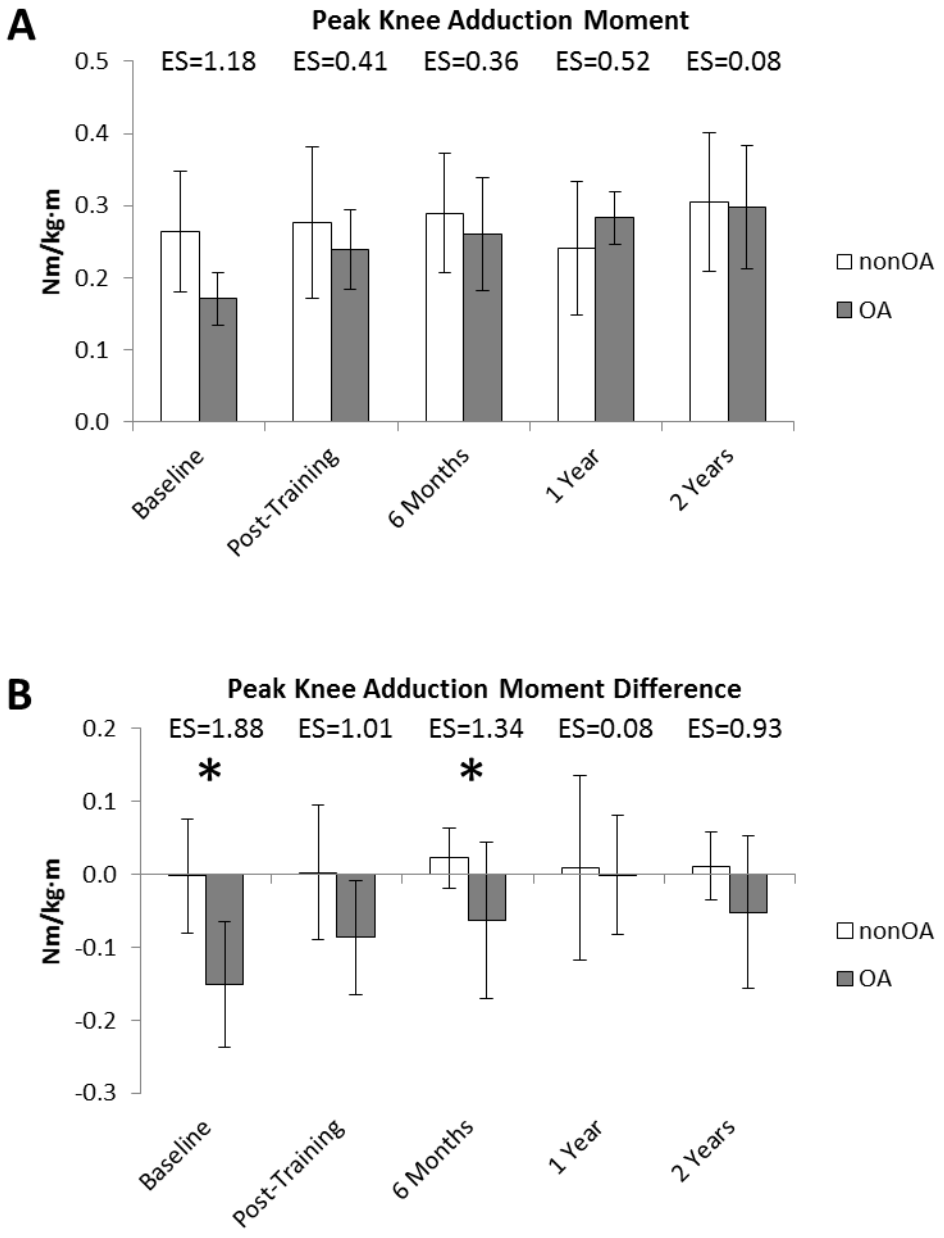

Figure 2.2: Mean values for involved limb (A) and interlimb differences (B) in the peak knee adduction moment between those with and without radiographic medial compartment knee OA 5 years after ACL reconstruction. Effect sizes (ES) provided. Asterisk represents $p \leq 0.05$. Whiskers represent ±1 standard deviation.

Additional frontal plane group differences were present in the knee adduction moment impulse (Table 2.2). At baseline the OA group had lower knee adduction moment impulse at the involved limb than the nonOA group (p: 0.023; nonOA: 0.087±0.023 Nm·s/kg·m; OA: 0.049±0.018 Nm·s/kg·m) (Figure 2.3A) and asymmetrically underloaded compared to the contralateral limb (p: 0.042; knee adduction moment impulse difference: nonOA: -0.001±0.032 Nm·s/kg·m; OA: -0.048±0.031 Nm·s/kg·m) with large effect sizes exhibited (Figure 2.3B). Group differences in knee adduction moment impulse were absent following rehabilitation prior to ACL reconstruction and continued through 1 year after surgery. At 2 years no differences at the involved limbs existed between groups in the knee adduction moment impulse but the OA group had a significantly lower interlimb difference (lower knee adduction moment impulse on the involved limb, represented by a negative knee adduction moment impulse difference) than the nonOA group (p: 0.027; knee adduction moment impulse difference: nonOA: 0.010±0.018 Nm·s/kg·m; OA: -0.021±0.032 Nm·s/kg·m) (Figure 2.3A and 2.3B).

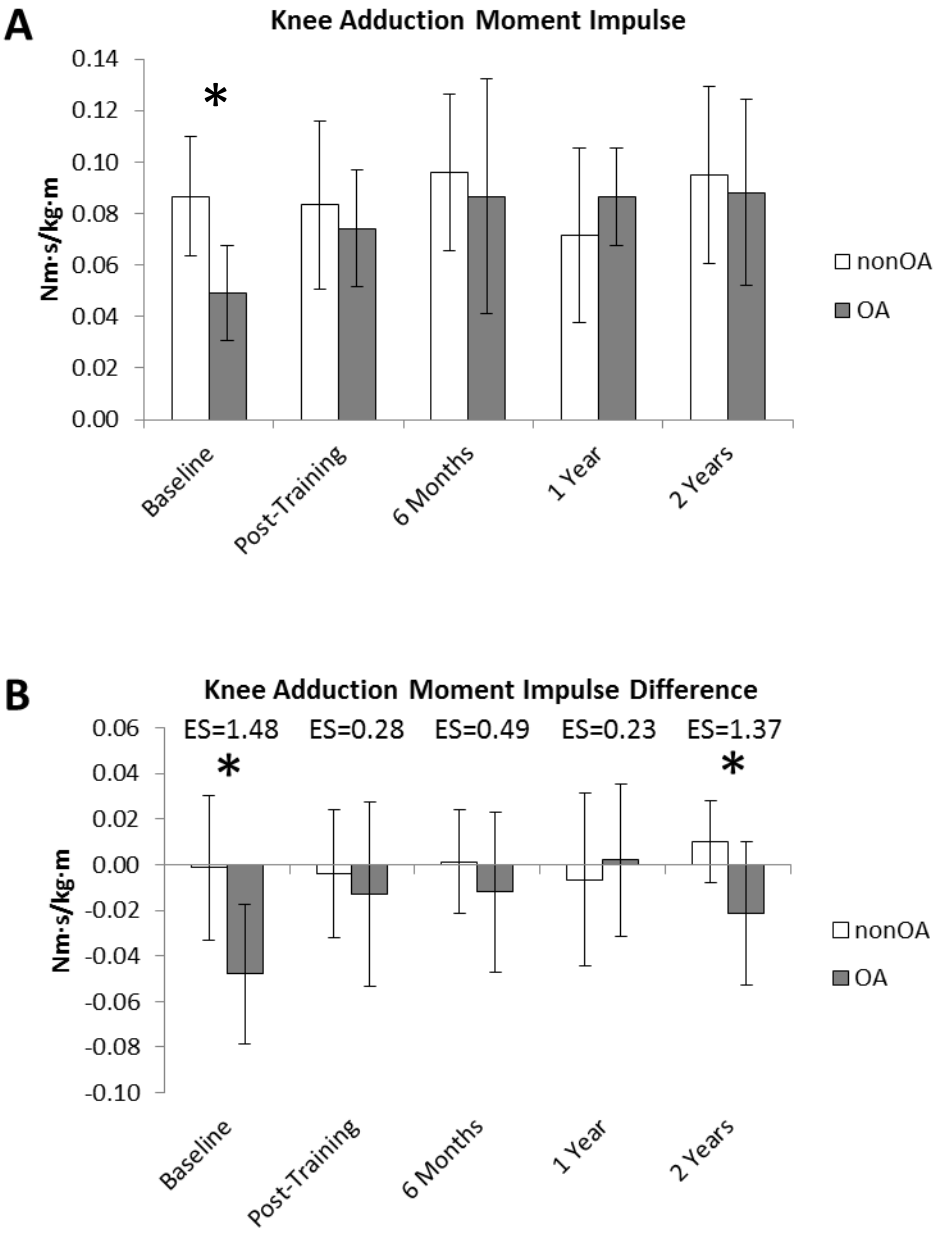

Figure 2.3: Mean values for involved limb (A) and interlimb differences (B) in the peak knee adduction moment impulse between those with and without radiographic medial compartment knee OA 5 years after ACL reconstruction. Effect sizes (ES) provided. Asterisk represents $p \leq 0.05$. Whiskers represent ±1 standard deviation.

There were large differences between limbs in peak knee flexion moment for both the OA and nonOA groups at baseline with both groups demonstrating lower sagittal plane moments on their involved knee (Figure 2.4A and 2.4B, Table 2.2). Large interlimb differences continued in the OA group at 6 months. However, these differences did not reach statistical significance between groups at either time point.

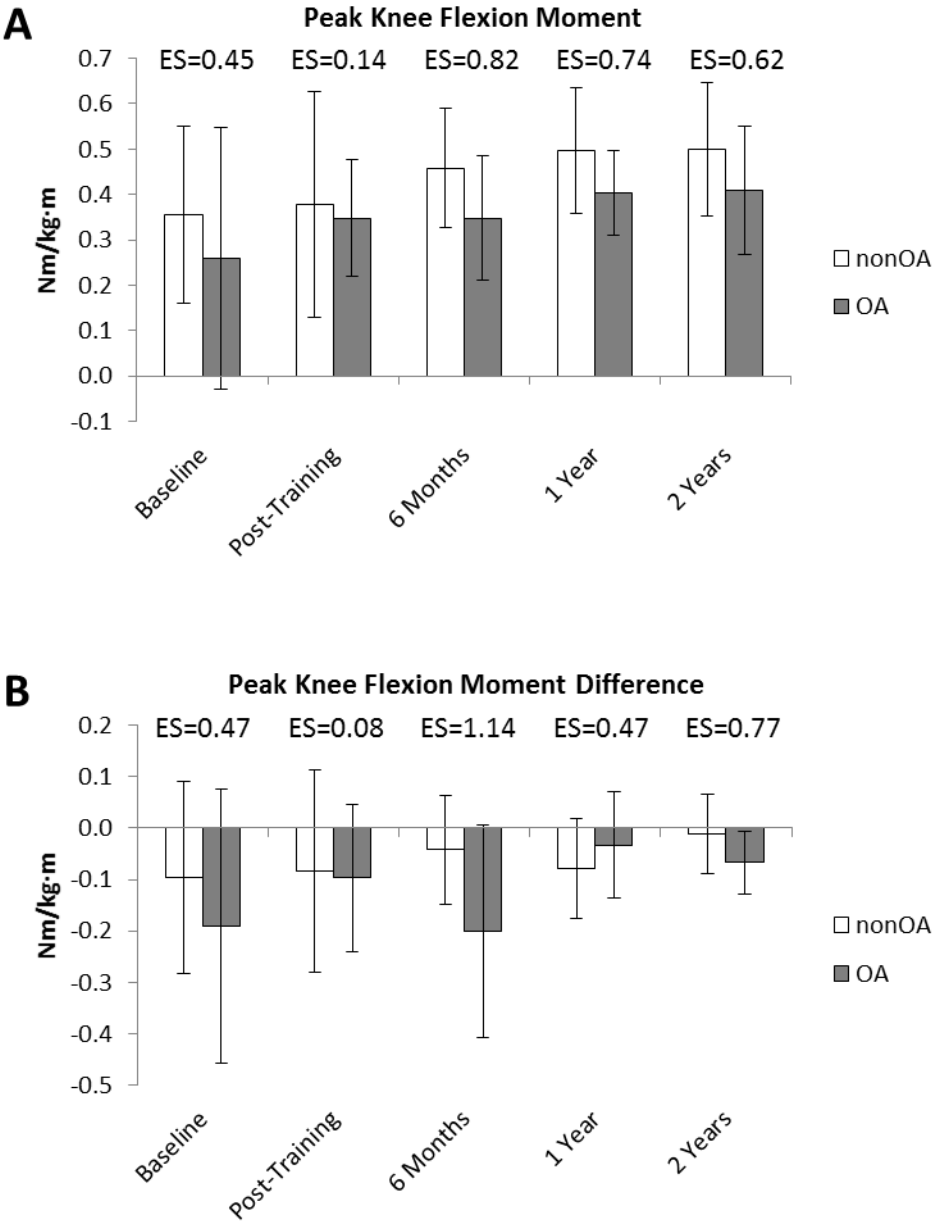

Figure 2.4: Mean values for involved limb (A) and interlimb differences (B) in the peak knee flexion moment between those with and without radiographic medial compartment knee OA 5 years after ACL reconstruction. Effect sizes (ES) provided. Asterisk represents $p \leq 0.05$. Whiskers represent ±1 standard deviation.

Large group differences in peak medial compartment contact forces of involved limbs were seen at baseline, 6 months and 1 year reaching statistical significance at 6 months (p: 0.036; peak medial compartment contact force: nonOA: 2.89±0.52 BW; OA: 2.10±0.69 BW) (Figure 2.5A, Table 2.2). Large interlimb differences were also present between groups at baseline and 6 months (Figure 2.5B). Neither involved limb peak medial compartment contact force nor interlimb differences in peak medial compartment contact force were different between groups following pre-operative rehabilitation.

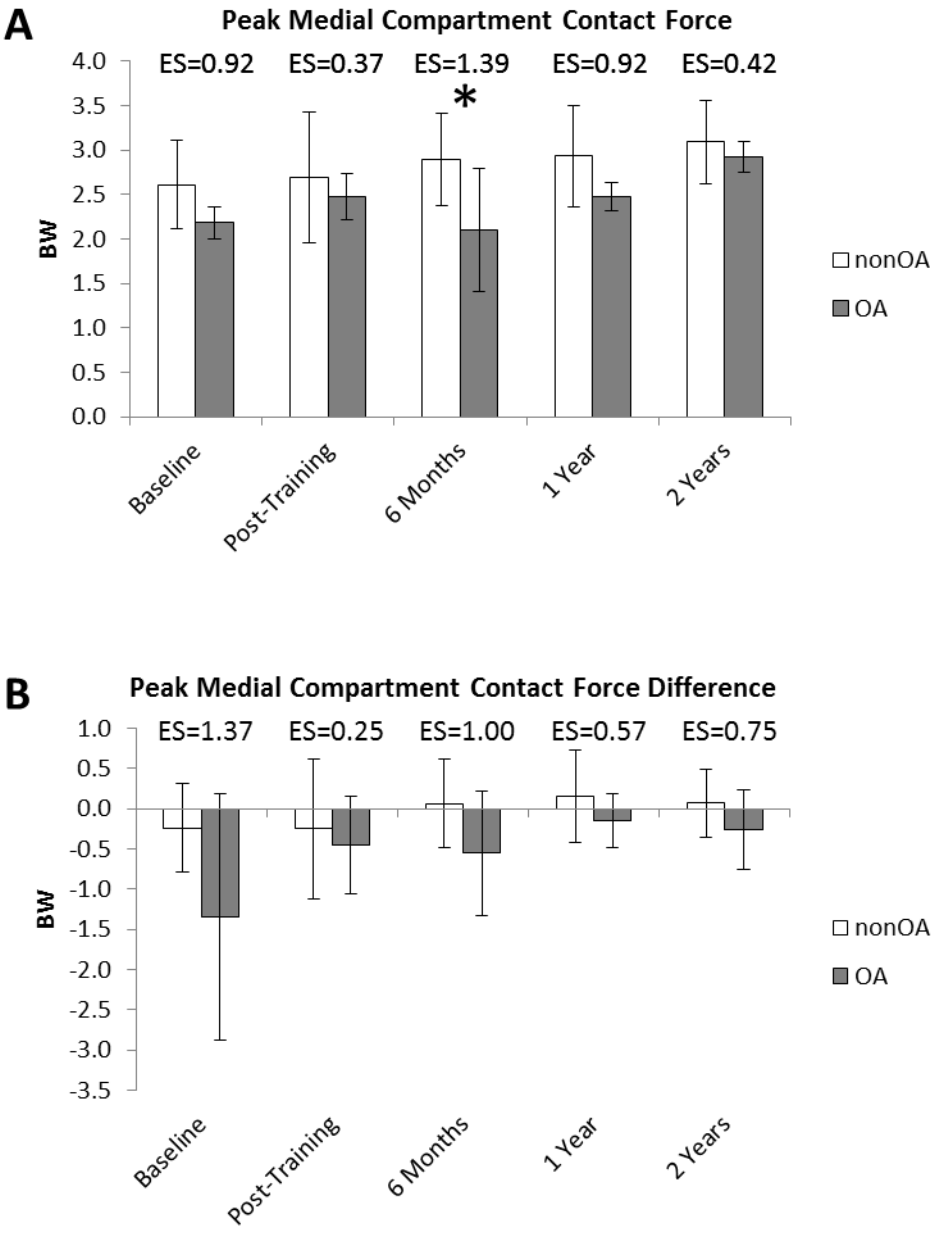

Figure 2.5: Mean values for involved limb (A) and interlimb differences (B) in the peak medial compartment contact force between those with and without radiographic medial compartment knee OA 5 years after ACL reconstruction. Effect sizes (ES) provided. Asterisk represents $p \leq 0.05$. Whiskers represent ±1 standard deviation.

Table 2.2: Involved limb and interlimb differences in sagittal and frontal plane knee kinetics and medial compartment contact forces during walking between those with and without radiographic medial compartment knee OA 5 years after ACL reconstruction. Abbreviations: SD, standard deviation; N, newton; m, meter; kg, kilogram; BW, body weight.

	Group	Baseline	Post-Training	6 Months	1 Year	2 Years
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Peak Knee Adduction Moment (Nm/kg·m)	nonOA	0.26 (0.08)	0.28 (0.11)	0.29 (0.08)	0.24 (0.09)	0.31 (0.10)
	OA	0.17 (0.04)	0.24 (0.06)	0.26 (0.08)	0.28 (0.04)	0.30 (0.09)
Interlimb Difference (Nm/kg·m)	nonOA	0.00 (0.08)	0.00 (0.09)	0.02 (0.04)	0.01 (0.13)	0.01 (0.05)
	OA	-0.15 (0.09)	-0.09 (0.08)	-0.06 (0.11)	0.00 (0.08)	-0.05 (0.10)
Knee Adduction Moment Impulse (Nm·s/kg·m)	nonOA	0.087 (0.023)	0.083 (0.032)	0.096 (0.030)	0.072 (0.034)	0.095 (0.035)
	OA	0.049 (0.018)	0.074 (0.023)	0.087 (0.046)	0.086 (0.019)	0.088 (0.036)
Interlimb Difference (Nm·s/kg·m)	nonOA	-0.001 (0.032)	-0.004 (0.028)	0.001 (0.023)	-0.007 (0.038)	0.010 (0.018)
	OA	-0.048 (0.031)	-0.013 (0.040)	-0.012 (0.035)	0.002 (0.033)	-0.021 (0.032)
Peak Knee Flexion Moment (Nm/kg·m)	nonOA	0.36 (0.19)	0.38 (0.25)	0.46 (0.13)	0.50 (0.14)	0.50 (0.15)
	OA	0.26 (0.29)	0.35 (0.13)	0.35 (0.14)	0.40 (0.09)	0.41 (0.14)
Interlimb Difference (Nm/kg·m)	nonOA	-0.10 (0.19)	-0.08 (0.20)	-0.04 (0.11)	-0.08 (0.10)	-0.01 (0.08)
	OA	-0.19 (0.27)	-0.10 (0.14)	-0.20 (0.21)	-0.03 (0.10)	-0.07 (0.06)
Peak Medial Compartment Contact Force (BW)	nonOA	2.61 (0.50)	2.70 (0.73)	2.89 (0.52)	2.93 (0.57)	3.09 (0.47)
	OA	2.18 (0.18)	2.47 (0.26)	2.10 (0.69)	2.47 (0.16)	2.92 (0.17)
Interlimb Difference (BW)	nonOA	-0.24 (0.56)	-0.25 (0.87)	0.06 (0.56)	0.15 (0.57)	0.07 (0.42)
	OA	-1.34 (1.54)	-0.45 (0.61)	-0.55 (0.77)	-0.14 (0.34)	-0.26 (0.49)

2.5 Discussion

The purpose of this study was to determine if loading measures before and after ACL reconstruction were associated with knee OA 5 years after surgery. Results indicate that those who go on to develop radiographic OA walk with lower moments and contact forces at the involved limb and greater interlimb differences early after injury and ACL reconstruction compared to those without radiographic OA 5 years after surgery. Differences were largest and statistically significant prior to pre-operative rehabilitation and 6 months after ACL reconstruction.

The current findings are consistent with a growing body of evidence suggesting joint unloading, not overloading, may be associated with the cascade of early degenerative changes at the knee after ACL injury.[6,192] Koo and colleagues have suggested that healthy cartilage increases in thickness in response to higher repetitive loading during walking[100] while after ACL injury joint unloading is associated with regional cartilage thinning (Koo et al., unpublished data, 2007). The lower joint moments and joint contact forces seen in our subjects early after injury and ACL reconstruction who went on to develop OA may be markers for underlying structural alterations to otherwise healthy articular cartilage prior to ACL injury. In our study joint loading variables increased on the involved limb to levels similar to the nonOA group by 1 year after ACL reconstruction. Although it is unclear when early degenerative changes first begin, the increase in loading at 2 years may not be tolerated if cartilage structures are already deconditioned or deteriorating. Further work is needed to determine if the more symmetric loading present at 2 years will eventually lead to joint overloading as the degeneration progresses.

Seven of 22 patients demonstrated radiographic knee OA 5 years after ACL reconstruction. A recent systematic review indicates cartilage degeneration detected by MRI occurs prior to radiographic evidence.[65] Tibial cartilage thinning is evident on MRI as early as four months after isolated ACL injury[177] and these changes persist despite ACL reconstruction.[86] The occurrence of pre-operative articular cartilage changes highlights the importance of sufficient and purposeful rehabilitation prior to surgery. Despite resolution of knee joint effusion, ROM, pain, and obvious gait impairments, significant differences in frontal plane moments but also notable differences in medial compartment joint contact forces were present at baseline between subjects who later developed radiographic OA in the present study. All of these group differences were considerably smaller after an additional ten rehabilitation sessions targeting further strength and neuromuscular improvements prior to surgery. It is likely that more subjects than the seven in our study with radiographic OA exhibited early signs of cartilage degeneration. Weninger et al. reported that nearly 70% of patients demonstrated cartilage degeneration on MRI 2.8 years after ACL reconstruction but only 11% had radiographic knee OA.[187] Early rehabilitation programs both prior to and after ACL reconstruction may be a primary modifiable component to restore knee biomechanics and modify the course of early onset knee OA.

The knee adduction moment was lower in the OA group when compared to both the contralateral limb as well as the involved limb of the nonOA group early after injury and surgery. Previous conflicting evidence regarding whether the knee adduction moment is increased or decreased after ACL reconstruction may be a result of failing to dichotomize ACL-injured subjects by the presence of later knee OA and

to consider longitudinal changes in frontal plane loading after ACL injury. Webster and colleagues have reported a lower knee adduction moment at 10 months after ACL reconstruction compared to both the contralateral limb and healthy controls which improved at 3 years consistent with current findings within the OA group in the present study.[181,183] However, they reported the absence of interlimb differences in the knee adduction moment at 20 months[184] while our 2 year results in the OA group show large between limb differences for both the peak knee adduction moment and knee adduction moment impulse consistent with 26 month findings by Zabala et al.[192] Previous research has reported knee adduction moment values greater than, equal to and less than healthy controls between 3.5 to 5.3 years after ACL reconstruction.[23,137,176] Further analysis is required within our cohort to determine if this period represents a critical time where a shift to overloading patterns becomes evident.

Significant differences in peak knee adduction moment and knee adduction moment impulse between the nonOA and OA group were present at baseline but not following pre-operative rehabilitation. Those with OA demonstrated larger asymmetries between limbs in peak knee adduction moment and knee adduction moment impulse and lower knee adduction moment impulse on the involved limb at baseline which normalized following rehabilitation. Meanwhile the nonOA group walked with symmetric frontal plane moments at both points in time. Early identification of individuals at high risk of early onset knee OA and determination of sufficient pre-operative rehabilitation dosages may play a key role in curbing the unloading tendencies of certain individuals and potential pathway of irreversible knee joint OA.

Sagittal plane moments undoubtedly play a role in describing the loading environment of the knee's medial compartment.[178] Previous work has established that the peak knee flexion moment is lower both before and after ACL reconstruction.[62,84,90,144,149,150,185,192] The negative interlimb differences in the peak knee flexion moment found for both the nonOA and OA groups at each time point further support this involved limb unloading trend. Although only 7 of 22 subjects had radiographic knee OA at 5 years, the majority will likely develop radiographic knee OA within 15 years of surgery.[14] It is possible that sagittal plane moments may be associated with overall long-term risk of knee OA while frontal plane moments may better differentiate subjects at risk of earlier radiographic knee OA present within 5 years of ACL reconstruction.

Six months after ACL reconstruction, differences between groups for both involved limb peak knee flexion moment and interlimb difference in peak knee flexion moment were not statistically significant as others have shown.[84,144] The limited sample size in our current study may be restricting achievement of significant findings. However, large effect sizes were present for both measures suggesting sagittal plane kinetics may also play a role in the early onset of knee OA.

Medial compartment joint contact forces estimated using an EMG-driven musculoskeletal model differed between those who did and did not develop radiographic knee OA at 5 years. An inherent strength of using this approach to describe the knee's loading environment is that it incorporates individual muscle activation patterns, which are known to be altered after ACL injury[90,149,150] in addition to joint biomechanics. The OA group walked with lower involved limb medial compartment contact forces and large interlimb differences at baseline and 6 months

after ACL reconstruction when compared to those without radiographic knee OA. Large differences between groups for the involved limb contact forces also persisted at 1 year. Previous work within this cohort found that medial compartment contact forces were significantly less than the contralateral limb prior to ACL reconstruction.[60] When separating these subjects by the presence of knee OA at 5 years, the OA group loaded the involved medial compartment nearly a half bodyweight less than the involved limb of the nonOA group at baseline. The OA group also had nearly an entire bodyweight greater loading difference relative to the contralateral limb compared to the nonOA group at baseline. Again, these group differences were eliminated following additional pre-operative rehabilitation. This relative unloading present in the OA group prior to and after surgery further highlights the key contributions that not only joint biomechanics but also muscle activation patterns may provide to the development of early knee OA. The more comprehensive approach undertaken by the musculoskeletal model to estimate joint loading, including the use of frontal and sagittal plane kinetics with co-contraction estimates via EMG input, may provide enhanced insight into the development of OA as compared to kinetic measures alone. Further work is needed to determine if relative contributions of muscle activation and joint biomechanics to joint contact forces differ between OA groups.

Concomitant meniscus and articular cartilage injuries increase the risk of degenerative changes in the knee after ACL injury.[14,65,82,94,112] However, no subjects within either group possessed acute cartilage injury at the time of ACL reconstruction, and the proportion of meniscus injuries did not differ between subjects who did or did not go on to develop radiographic OA by 5 years. There were also no differences in the occurrence of additional knee injuries or surgery during the time from initial ACL

injury to 5 year radiographic testing between those with and without OA at 5 years. Current findings do not substantiate refutation of previous findings regarding the increased OA risk associated with concomitant injuries. They do, however, allow attribution of the strong association between biomechanical alterations and future knee joint degeneration to ACL rupture independent of additional knee joint damage.

Female sex increases the risk for development of primary knee OA[133,161] and it has been suggested this risk factor may play a role in the risk for OA after ACL injury.[116] However, more recent studies have shown no risk factor of sex[14] and further that males are at higher risk of knee OA following ACL injury.[112] Of the patients completing testing at 2 years a larger proportion whom went on to demonstrate OA at 5 years were female (4 females, 1 male) compared to the nonOA group (2 females, 9 males). Women are more likely than men to demonstrate dynamic knee instability after sustaining an ACL injury,[89] and within those with poor dynamic stability, women demonstrate greater biomechanical asymmetries than men[165]. The altered biomechanics in individuals with poor dynamic knee stability[78,90] may place women at higher risk of early development of OA after ACL injury.

Age, obesity, and manual labor at the time of injury are additional factors which increase the risk of developing knee OA after ACL injury but are difficult to modify.[14,112] Clinical signs such has muscle weakness have been linked to the development of primary knee OA, but modifiable risk factors related to knee OA after ACL injury are largely unknown.[116] The identification of clinical tests and measures which relate to either underlying altered joint biomechanics or directly to the development of knee OA after ACL injury are needed to effectively screen patients at

greatest risk for post-traumatic OA in which targeted prevention strategies will be most effective.

Limitations do exist within the present study. Sample sizes are limited at each time point. Small sample size is likely resulting in group differences demonstrating large effect sizes but lacking statistical significance. Caution must be demonstrated in drawing firm conclusions from effect sizes where statistically significant group differences are not present, which warrants future study with the use of a larger sample. Further, not all subjects at each time point are the same limiting further longitudinal analysis and chronological conclusions regarding loading patterns to be made. Despite these limitations, it is important to note that this study is the first of its kind to not merely speculate but rather demonstrate a link between altered movement patterns and radiographic evidence of knee OA after ACL injury. Further work is necessary to determine whether the presence of knee OA and altered knee joint biomechanics after ACL injury is also related to altered mechanics at the hip and ankle.

2.6 Conclusion

Patients with radiographic knee OA 5 years after anterior cruciate ligament reconstruction walked with lower involved limb knee adduction moments and medial compartment joint contact forces than those without OA early after injury and reconstruction. Knee joint loading becoming more similar between groups 1 year after ACL reconstruction. The time frame between injury and 2 years after ACL reconstruction may represent a critical period during which articular cartilage health is highly sensitive to joint unloading and cartilage deconditioning. Further work is needed to determine effective rehabilitation strategies to both identify and amend these

altered loading patterns associated with early onset knee OA in addition to evaluating whether loading strategies differ after 2 years following ACL reconstruction between those who do and do not go on to develop radiographic knee OA.

2.7 Acknowledgements

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Chapter 3

POST-TRAUMATIC KNEE OSTEOARTHRITIS ASSOCIATED WITH ALTERED HIP JOINT BIOMECHANICS AFTER ANTERIOR CRUCIATE LIGAMENT INJURY

3.1 Abstract

Anterior cruciate ligament injury predisposes individuals to a high risk for the development of osteoarthritis. Patients with anterior cruciate ligament injury demonstrate alterations in movement patterns at both the knee and hip joints. Abnormal joint angles and moments in the knee likely contribute to the development of post-traumatic knee osteoarthritis, but aberrant hip biomechanics may also contribute to non-traumatic forms of osteoarthritis in the hip. Further, a history of osteoarthritis is a risk factor for the development of osteoarthritis in an additional joint. Therefore, the purpose of this study was to determine if hip joint biomechanics early after ACL injury and reconstruction were different between those who did and did not develop knee osteoarthritis by 5 years after anterior cruciate ligament reconstruction.

Nineteen athletes with unilateral anterior cruciate ligament injury completed standard gait analysis before (baseline) and after (post-training) extended pre-operative rehabilitation and again at 6 months, 1 year, and 2 years after anterior cruciate ligament reconstruction. Weightbearing knee radiographs were completed 5 years after reconstruction to identify the presence of osteoarthritis in the medial compartment of the involved knee. Peak hip joint angles and external moments in the sagittal and frontal planes early after anterior cruciate ligament injury and reconstruction were compared between those with and without radiographic knee osteoarthritis 5 years after surgery.

Five of the 19 patients had radiographic knee osteoarthritis at 5 years. Patients with knee osteoarthritis walked with a smaller peak hip flexion angle in the involved limb resulting in a main effect of group (p: 0.043; nonOA: 31.3±1.4°; OA: 25.3±2.4°; ES: 0.88). A main effect of group also existed in the interlimb difference for peak hip adduction moment with asymmetrically lower moments in the involved limb of patients with osteoarthritis (negative interlimb difference) compared to asymmetrically higher moments in those without knee osteoarthritis (positive interlimb difference) (p: 0.042; nonOA: 0.09±0.13 Nm/kg·m; OA: -0.05±0.17 Nm/kg·m; ES: 0.95). In addition, patients with knee osteoarthritis walked with an asymmetrically lower peak hip flexion moment at 1 and 2 years after reconstruction compared to symmetrical moments in those without knee osteoarthritis (1 year: nonOA: 0.01 Nm/kg·m, OA: -0.18 Nm/kg·m; 2 years: nonOA: -0.01 Nm/kg·m, OA: -0.13 Nm/kg·m).

Patients with radiographic knee osteoarthritis 5 years after anterior cruciate ligament reconstruction demonstrate smaller sagittal plane hip angles and asymmetrically lower sagittal and frontal plane hip moments in the anterior cruciate ligament-injured limb compared to those without osteoarthritis at 5 years. Alterations in hip joint motion and mechanics may increase susceptibility of individuals with post-traumatic knee osteoarthritis for additional articular cartilage degeneration in the hip joint.

3.2 Introduction

Anterior cruciate ligament (ACL) injury is a musculoskeletal pathology which predisposes individuals to the development of post-traumatic knee joint osteoarthritis (OA). It is estimated that over 50% of those with an ACL injury will demonstrate symptomatic knee OA within 10 to 20 years of injury.[116] Changes in joint kinematics

and kinetics after ACL injury have been postulated to initiate subsequent joint degeneration by altering the location and magnitude of load bearing regions of the articular cartilage.[7] Altered movement patterns are common after ACL injury,[27,62,149,150] and persist despite surgical reconstruction and rehabilitation.[23,84,137,144,176,181,184,192] Direct links between knee joint biomechanics and OA emergence are limited. However, recent evidence suggests that decrease knee joint loading early after ACL injury and reconstruction is associated with the development of radiographic knee OA 5 years after injury.[186]

Movement patterns in the hip joint of the injured limb are also altered after ACL injury.[46,75,77,90,131,136,164,166] Ferber et al. hypothesized that changes in movement patterns at the hip may be a compensatory effort by ACL-deficient individuals to reduce anterior tibial translation.[46] Biomechanical hip strategies appear to be dependent on the extent of aberrant joint motion at the knee. Patients with poor dynamic knee stability (noncopers) display smaller hip extensor moments and sagittal plane hip joint excursions and angles.[4,162,165] Meanwhile those with more normal gait patterns after ACL injury (copers) use a hip strategy utilizing increased hip extension moments.[4,172] Because individuals who develop early knee OA demonstrate greater biomechanical knee asymmetry early after ACL injury and reconstruction compared to those who do not,[186] aberrant movement patterns may also be present at the hip.

The pathogenesis of hip joint degeneration is thought to be affected by biomechanics experienced by the joint in a similar fashion to the knee.[18] Altered hip joint movement patterns are associated with the presence and severity of hip joint OA.[41,102] Patients with hip OA walk with smaller sagittal plane angles and joint excursions, smaller sagittal plane moments, and smaller frontal plane moments in the

hip.[55,56,193] Further, individuals with OA in a single hip or knee joint demonstrate a nonrandom progression of OA to other hip and knee joints,[155,156] which is thought to be influenced by global lower extremity changes in biomechanics.[155] The nonrandom progression of lower extremity OA may predispose individuals with post-traumatic knee OA after ACL injury to also possess increased risk of OA in other lower extremity joints. Therefore, the purpose of this study was to determine if hip joint biomechanics early after ACL injury and reconstruction were different between those who did and did not develop knee OA by 5 years after ACL reconstruction.

Given the association of reduced hip joint motion and joint mechanics in patients who demonstrate dynamic knee instability after ACL injury and in patients with hip OA, we hypothesized that those with radiographic knee OA at 5 years after reconstruction would demonstrate greater asymmetry in hip joint kinematics and kinetics early after injury and reconstruction compared to more symmetric patterns by those without radiographic knee OA at 5 years.

3.3 Methods

3.3.1 Subjects

Nineteen patients were included. All had been part of a larger, randomized control trial of 55 patients determining the effects of augmenting pre-operative rehabilitation with specialized neuromuscular training called perturbation training.[79] All patients had a complete, unilateral ACL injury (confirmed by a positive Lachman test and 3-mm or greater difference in anterior tibial excursion with instrumented arthrometry[35] (KT1000; MEDmetric Corporation, San Diego, CO) within the previous 7 months and were between the ages of 14-51. Patients were regular participants in

level I (e.g. soccer, basketball) or II (e.g. tennis, downhill skiing) cutting and pivoting activities[35,81] prior to injury and demonstrated dynamic knee instability after injury (classified as noncopers pre-operatively[49]). Exclusion criteria included a repairable meniscus, symptomatic grade III injury to other knee ligaments, and full-thickness articular cartilage lesions greater than 1 cm^2.

Patients were enrolled in this study after effusion, range of motion, pain, and obvious gait impairments were resolved and quadriceps strength was at least 70% of the uninvolved limb through utilization of a physical therapy protocol described by Hurd et al.[88] Following study enrollment, patients received an additional 10 pre-operative rehabilitation sessions to further restore lower extremity strength and neuromuscular control.[79] All patients underwent ACL reconstruction by a single, board-certified orthopedic surgeon using either a four-bundle semitendinosus-gracilis autograft or soft tissue allograft. Progressive, criterion-based post-operative rehabilitation was completed by all patients early after surgery.[1]

3.3.2 Gait Analysis

Kinematic and kinetic data was collected during gait analysis at 5 time points: pre-operatively after initial impairment resolution (baseline), immediately following 10 sessions of additional pre-operative rehabilitation (post-training), 6 months after ACL reconstruction (6 months), 1 year after ACL reconstruction (1 year), and 2 years after ACL reconstruction (2 years). Eight infrared cameras (VICON, Oxford Metrics Ltd., London, UK) sampled at 120 Hz were used to detect the position of sixteen-millimeter spherical retro-reflective markers placed at each iliac crest, greater trochanter, medial and lateral femoral epicondyle, medial and lateral malleoli, superior and inferior heel, base of the first metatarsal, and base of the fifth metatarsal (Figure

3.1). This marker set has previously been shown to have excellent intersession reliability.[163] Rigid, thermoplastic shells each with four markers were secured laterally at each thigh and shank and a pelvic shell with three markers was secured midway between the posterior superior iliac spines to track segment motion during gait. A standing calibration was used to identify joint centers and create local coordinate systems for each segment.

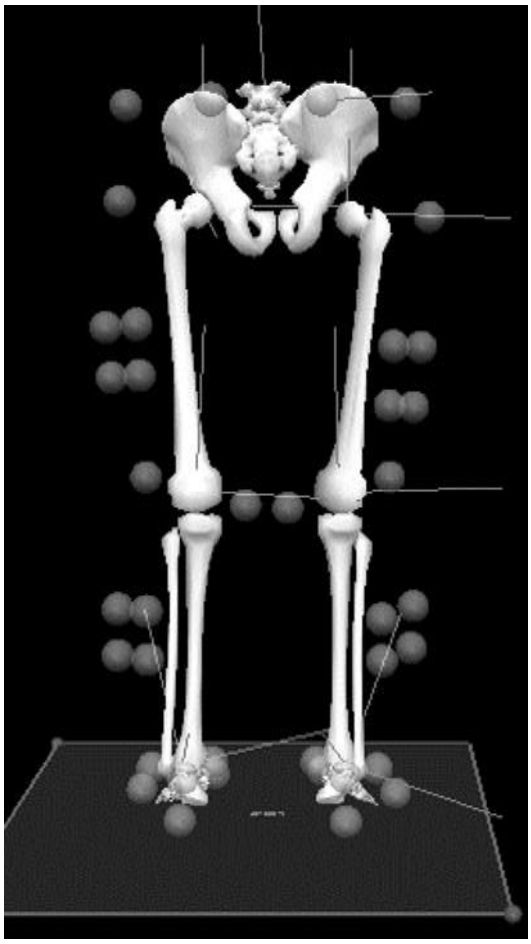

Figure 3.1: Subject with the marker set applied to the lower extremity and used within this study. Image produced from Visual 3D (C-Motion, Germantown, MD).

Patients walked at a self-selected speed along a 6-meter walkway with an embedded force plate sampled at 1,080 Hz (Bertec Corporation, Worthington, OH). Walking speed was established during the baseline testing session and maintained (±5%) at each follow-up session using a timing system. Stance phase joint angles and moments were processed using inverse dynamics within custom software (Visual 3D, C-Motion, Germantown, MD) as the average of 5 walking trials. Kinematic and

kinetic data were low pass filtered at 6 Hz and 40 Hz, respectively. Initial contact and end of stance were identified using a 50-N threshold. All trials were normalized to 100% of stance. Moments were normalized to mass (kg) and height (m). Variables of interest were peak hip joint angles and external moments during any part of stance phase in the sagittal plane and during the first 50% of stance phase in the frontal plane. Hip joint excursion was equal to the difference between the peak hip flexion angle and peak hip extension angle during stance. Interlimb kinematic and kinetic differences were also calculated for each variable (involved limb minus uninvolved limb).

3.3.3 Radiographs

Patients completed bilateral weightbearing posterior-anterior (PA) bent knee (30°) radiographs 5 years after ACL reconstruction. SigmaView software (Agfa HealthCare Corporation, Greenville, SC) was used to view radiographs. The Kellgren-Lawrence (KL) system was used to grade levels of OA in the medial tibiofemoral compartment.[96] Excellent between day, intrarater reliability for radiographic measures of interest has been demonstrated using 20 radiographs included in a larger project of patients at 5 years after ACL injury (graded by EW; Cohen's kappa (κ): 0.904, p: <0.001). All Kellgren-Lawrence grades were verified by a board-certified orthopedic surgeon. The presence of OA in the medial tibiofemoral compartment was operationally defined as a Kellgren-Lawrence grade greater than or equal to 2.

3.3.4 Statistical Analysis

Statistical analyses were completed using PASSW 23.0 software (SPSS Inc., Chicago, IL). Independent *t*-tests and Fisher's exact tests were used to test differences in baseline characteristics and concomitant injuries between those with and without

radiographic knee OA (OA, nonOA) 5 years after ACL reconstruction. Two-way mixed design analyses of variance (ANOVA) were used to test differences in hip kinematics and kinetics in the involved limb and interlimb differences in each these variables with a between subjects factor of OA and within subjects factor of time. Post-hoc testing was completed using Bonferroni corrections. Minimal detectable change (MDC) values for interlimb differences in hip kinematics and kinetics were established from 15 healthy, active subjects (Table 3.1) tested within our lab at self-selected gait speed. Minimal detectable changes and effect sizes (ES)[29] were used qualitatively to determine if meaningful asymmetry existed between limbs. *A priori* statistical significance was set at $\alpha \leq 0.05$.

Table 3.1: Minimal detectable change (MDC) values at a 95% confidence interval for interlimb differences in sagittal and frontal plane hip kinematics and kinetics during gait.

Gait Variable during Stance	MDC_{95}
Peak Hip Flexion Angle	3°
Peak Hip Extension Angle	2°
Hip Excursion Angle	4°
Peak Hip Adduction Angle	3°
Peak Hip Flexion Moment	0.08 Nm/kg·m
Peak Hip Extension Moment	0.04 Nm/kg·m
Peak Hip Adduction Moment	0.06 Nm/kg·m

3.4 Results

In total, 19 patients completed gait analysis at all 5 time points (baseline, post-testing, 6 months, 1 year, and 2 years) and radiographs 5 years after ACL reconstruction (Figure 3.2). Five patients demonstrated radiographic medial compartment OA in their ACL-injured knee at 5 years while 14 did not. No baseline differences existed in age, mass, body mass index (BMI), sex, pre-injury cutting and pivoting activity level, graft type, or gait speed between those with and without knee OA (Table 3.2). There were also no group differences in the time between ACL injury to baseline testing nor to ACL reconstruction, or from ACL reconstruction to 5 year radiographic testing (Table 3.2). Further, the proportion of patients who had radiographic knee OA in the uninvolved limb or who experienced an additional lower extremity injury by 5 years after ACL reconstruction did not differ between those with and without involved limb medial compartment OA at 5 years (Table 3.2). One patient without OA at 5 years had experienced an ipsilateral partial posterior cruciate ligament (PCL) and meniscus tear, while one patient with OA at 5 years had experienced an ipsilateral second ACL injury in the interim.

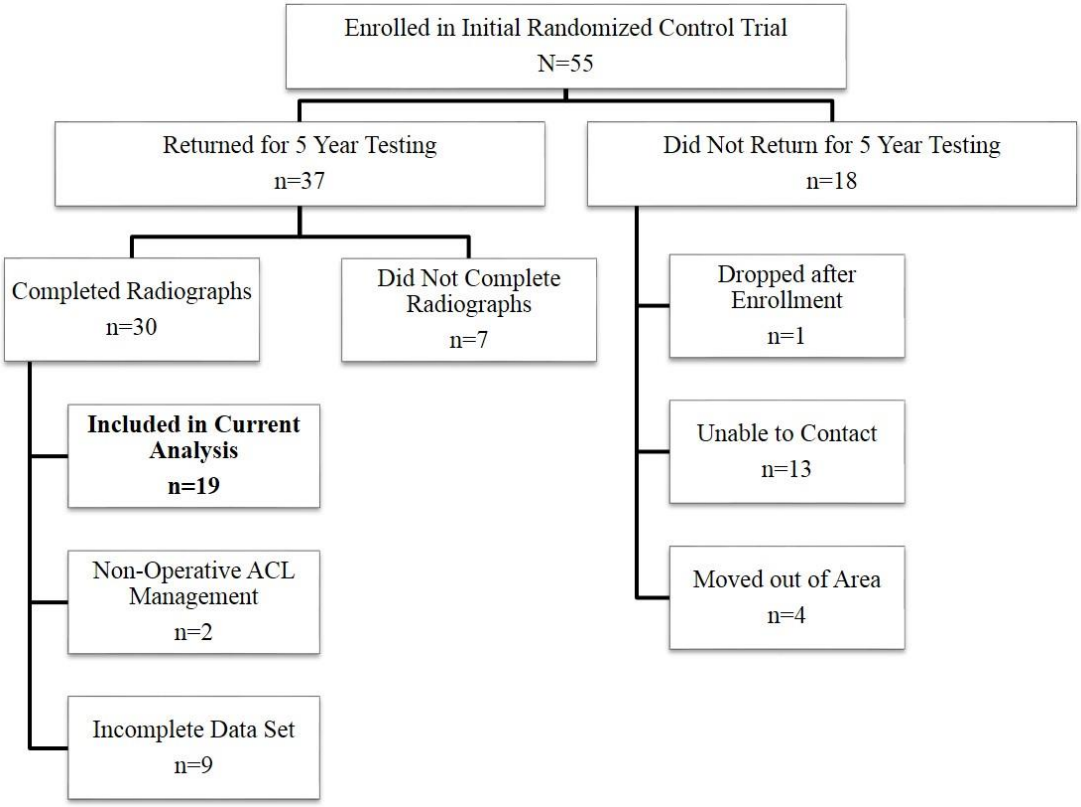

Figure 3.2: Flow diagram of study cohort.

Table 3.2: Baseline and concomitant injury characteristics between those with and without radiographic medial compartment knee OA 5 years after ACL reconstruction. Abbreviations: yrs, years; kg, kilogram; m, meter; wks, weeks; s, second; M, male; F, female; Allo, allograft; Auto, hamstring-gracilis autograft; OA, osteoathritis.

	nonOA (n=14)	OA (n=5)	p-value
Age (baseline) (yrs)	32.1 (11.0)	33.4 (13.1)	0.837
Mass (kg)	87.1 (14.4)	84.0 (17.5)	0.703
Body Mass Index (kg/m^2)	27.8 (3.2)	27.6 (5.2)	0.912
Time from injury to basline (wks)	4.7 (4.5)	5.4 (2.1)	0.718
Time from injury to ACL reconstruction (wks)	20.9 (18.7)	12.0 (4.0)	0.313
Time from ACL reconstruction to radiographic testing (yrs)	5.8 (0.9)	5.6 (0.2)	0.722
Gait velocity (m/s)	1.55 (0.15)	1.48 (0.06)	0.263
Sex (M:F)	11:3	2:3	0.262
Pre-Injury Activity Level (1:2)[35,81]	8:6	1:4	0.303
Graft type (Allo:Auto)	10:4	3:2	>0.999
Additional lower extremity injury after initial ACL injury (No:Yes)	1:13	1:4	0.199
Uninvolved medial compartment OA at 5 years (No:Yes)	1:13	2:3	0.155

A main effect of group was present for peak hip flexion angle in the involved limb as those with knee OA at 5 years walked with a lower hip flexion angle across the 5 time points than those without knee OA (p: 0.043; nonOA: 31.3±1.4°; OA: 25.3±2.4°; ES: 0.88) (Figure 3.3). A significant interaction effect existed between the nonOA and OA groups for interlimb difference (involved limb minus uninvolved limb) in peak hip flexion angle (p: 0.038) with a statistical group difference only present at 1 year (p: 0.040, nonOA: 1.3±0.8°; OA: -2.1±1.3°) (Figure 3.3). However, meaningful interlimb asymmetry exceeding the minimal detectable change of 3° only existed in the nonOA group at 6 months (Table 3.3).

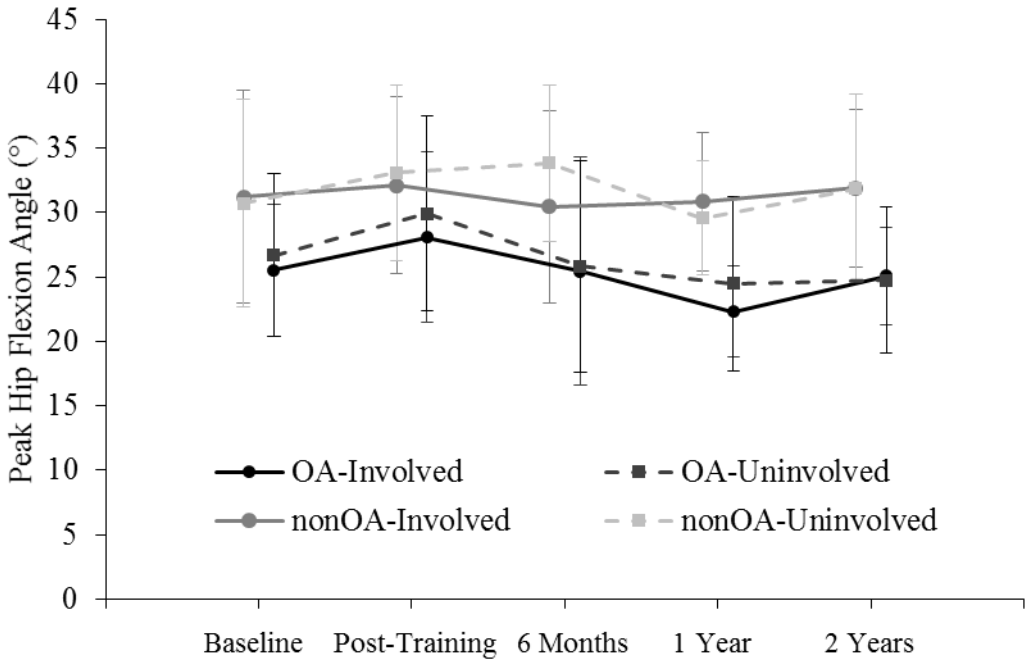

Figure 3.3: Mean values in peak hip flexion angle during stance phase of gait between those with and without radiographic medial compartment knee OA 5 years after ACL reconstruction. Whiskers represent ±1 standard deviation.

Table 3.3: Involved limb and interlimb differences in peak sagittal and frontal plane hip kinematics and kinetics during stance phase of gait for those with and without knee OA 5 years after ACL reconstruction. Boldface numbers indicate statistically significant group differences. Abbreviations: SD, standard deviation; N, newton; m, meter; kg, kilogram.

	Group	Baseline	Post-Training	6 Months	1 Year	2 Years	Interaction Effect	Main Effect (Time)	Main Effect (Group)
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	p	p	p
Hip Flexion Angle (°)	nonOA	31.2 (8.2)	32.1 (6.9)	30.5 (7.4)	30.8 (5.4)	31.9 (6.1)	0.769	0.442	**0.043**
	OA	25.5 (6.3)	28.1 (7.6)	25.5 (8.2)	22.3 (6.7)	25.1 (5.7)			
Interlimb Difference (°)	nonOA	0.5 (3.5)	-1.0 (2.4)	-3.4 (3.7)	1.3 (2.7)	0.0 (3.0)	**0.038**	0.270	0.608
	OA	-1.2 (3.9)	-1.8 (3.8)	-0.4 (2.4)	-2.1 (3.7)	0.3 (3.5)			
Hip Extension Angle (°)	nonOA	19.2 (7.6)	17.6 (6.2)	17.3 (6.7)	19.2 (6.5)	15.4 (6.4)	0.731	0.304	0.337
	OA	21.1 (7.6)	17.8 (6.2)	19.8 (5.4)	22.5 (6.3)	20.4 (5.5)			
Interlimb Difference (°)	nonOA	0.4 (3.9)	-1.3 (4.3)	-1.1 (3.2)	-1.6 (3.4)	-2.7 (2.5)	0.056	0.766	0.545
	OA	-1.6 (3.7)	-2.0 (3.5)	-1.7 (1.9)	0.8 (3.7)	1.5 (2.6)			
Hip Excursion Angle (°)	nonOA	50.4 (5.3)	49.7 (5.7)	47.6 (5.3)	50.0 (4.5)	47.3 (3.8)	0.566	0.239	0.100
	OA	46.6 (2.9)	45.9 (5.0)	45.2 (2.9)	44.8 (0.81)	45.5 (2.5)			
Interlimb Difference (°)	nonOA	1.0 (4.2)	-2.3 (5.1)	-4.5 (4.8)	-0.4 (4.8)	-2.6 (4.8)	0.077	0.209	0.951
	OA	-2.8 (5.5)	-3.9 (5.4)	-2.1 (2.1)	-1.4 (1.5)	1.8 (1.7)			
Hip Adduction Angle (°)	nonOA	9.2 (4.2)	9.4 (3.1)	8.7 (3.1)	7.9 (3.3)	8.0 (3.4)	0.545	0.063	0.928
	OA	10.0 (4.0)	9.4 (3.4)	7.2 (2.3)	7.1 (2.1)	8.9 (3.2)			
Interlimb Difference (°)	nonOA	2.8 (5.4)	3.6 (5.1)	3.5 (4.4)	2.4 (4.7)	1.6 (4.9)	0.463	0.635	0.289
	OA	1.4 (5.9)	1.4 (5.7)	-1.0 (3.9)	-0.5 (4.1)	1.1 (4.0)			

Table 3.3: continued

	Group	Baseline	Post-Training	6 Months	1 Year	2 Years	Interaction Effect	Main Effect (Time)	Main Effect (Group)
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	p	p	p
Hip Flexion Moment (Nm/kg·m)	nonOA	0.77 (0.24)	0.82 (0.26)	0.73 (0.24)	0.70 (0.19)	0.64 (0.16)	0.977	**<0.001**	0.414
	OA	0.72 (0.14)	0.72 (0.14)	0.65 (0.16)	0.62 (0.11)	0.57 (0.09)			
Interlimb Difference (Nm/kg·m)	nonOA	0.02 (0.12)	0.01 (0.13)	0.02 (0.10)	0.01 (0.10)	-0.01 (0.12)	0.091	**0.021**	0.072
	OA	-0.05 (0.21)	-0.06 (0.14)	-0.01 (0.11)	-0.18 (0.08)	-0.13 (0.09)			
Hip Extension Moment (Nm/kg·m)	nonOA	0.64 (0.15)	0.61 (0.22)	0.62 (0.17)	0.69 (0.16)	0.64 (0.11)	0.946	0.919	0.131
	OA	0.73 (0.13)	0.73 (0.08)	0.72 (0.13)	0.73 (0.17)	0.70 (0.12)			
Interlimb Difference (Nm/kg·m)	nonOA	0.00 (0.10)	-0.02 (0.09)	-0.01 (0.08)	-0.02 (0.09)	-0.03 (0.07)	0.495	0.880	0.494
	OA	-0.01 (0.11)	0.01 (0.10)	-0.02 (0.16)	0.03 (0.10)	0.04 (0.10)			
Hip Adduction Moment (Nm/kg·m)	nonOA	0.58 (0.09)	0.61 (0.16)	0.56 (0.13)	0.57 (0.12)	0.61 (0.12)	0.815	0.220	0.781
	OA	0.56 (0.09)	0.56 (0.05)	0.56 (0.06)	0.55 (0.07)	0.63 (0.08)			
Interlimb Difference (Nm/kg·m)	nonOA	0.11 (0.13)	0.07 (0.12)	0.11 (0.10)	0.06 (0.17)	0.08 (0.15)	0.555	0.786	**0.042**
	OA	-0.06 (0.21)	-0.08 (0.21)	-0.06 (0.13)	-0.03 (0.18)	0.00 (0.10)			

A main effect of time was present in peak hip flexion moment in the involved limb (p: <0.001) (Figure 3.4). The peak hip flexion moment for the nonOA and OA groups combined decreased over time from post-training to 2 years. The sagittal plane moment at 2 years (0.60±0.15 Nm/kg·m) was significantly lower than at all previous testing time points (baseline: p: <0.001, 0.75±0.21 Nm/kg·m; post-training: p: 0.002, 0.77±0.23 Nm/kg·m; 6 months: p: 0.020, 0.69±0.22 Nm/kg·m; 1 year: p: 0.017, 0.66±0.17 Nm/kg·m). A main effect of time also existed in the interlimb differences (involved limb minus uninvolved limb) in peak hip flexion moment (p: 0.021) (Figure 3.4). The symmetrical hip flexion moment demonstrated by the combined OA and nonOA groups at 6 months (0.01±0.10 Nm/kg·m) was significantly different from the asymmetrical lower hip flexion moment in the involved limb compared to uninvolved limb at 1 year (p: <0.001; -0.09±0.13 Nm/kg·m) and 2 years (p: 0.031; -0.07±0.13 Nm/kg·m).

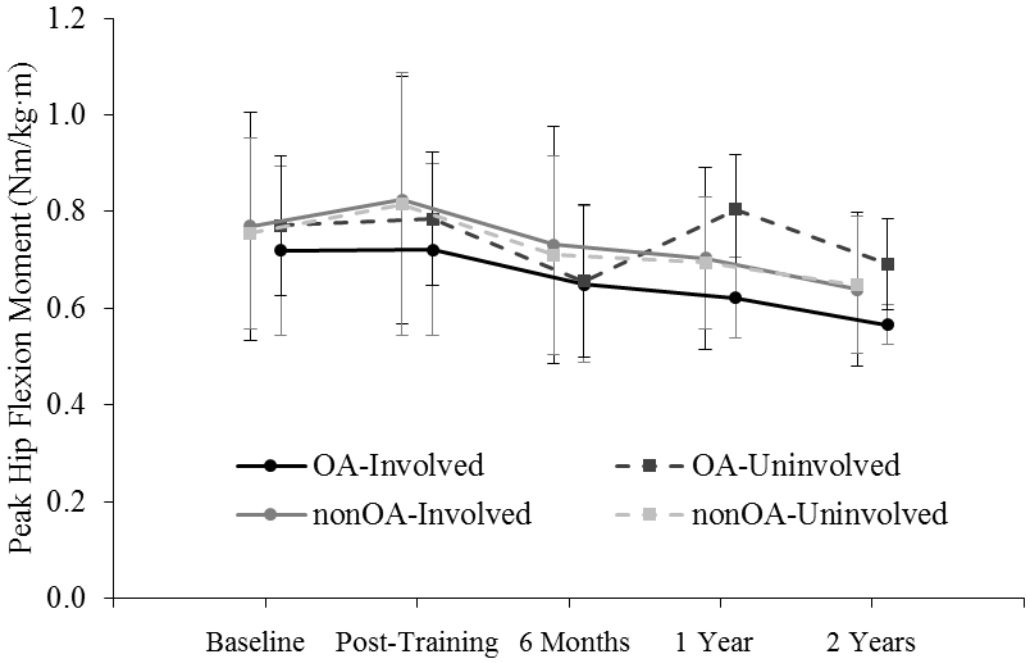

Figure 3.4: Mean values in peak hip flexion moment during stance phase of gait between those with and without radiographic medial compartment knee OA 5 years after ACL reconstruction. Whiskers represent ±1 standard deviation.

Differences between those with and without knee OA at 5 years were also present in the frontal plane. A main effect of group existed in the interlimb difference for peak hip adduction moment. The nonOA group walked with an asymmetrically higher hip adduction moment in the involved limb compared to the uninvolved limb across all 5 times points while the OA group walked with an asymmetrically lower adduction moment (p: 0.042; nonOA: 0.09±0.13 Nm/kg·m; OA: -0.05±0.17 Nm/kg·m; ES: 0.95) (Figure 3.5). No further biomechanical differences existed between the nonOA and OA groups (Table 3.3).

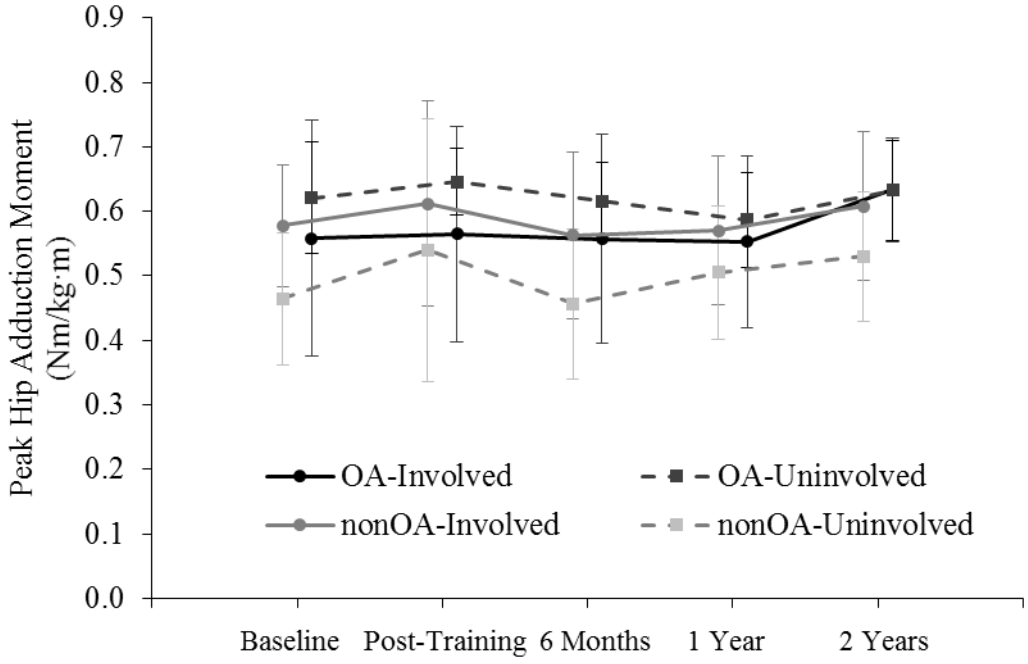

Figure 3.5: Mean values in peak hip adduction moment during the first 50% of stance phase of gait between those with and without radiographic medial compartment knee OA 5 years after ACL reconstruction. Whiskers represent ±1 standard deviation.

3.5 Discussion

The purpose of this study was to determine if hip joint biomechanics early after ACL injury and reconstruction were different between those who did and did not develop radiographic knee OA by 5 years after ACL reconstruction. Our findings indicate that patients who develop medial compartment knee OA within 5 years of ACL reconstruction walk with less hip flexion motion and asymmetrically lower external hip adduction moments both before and after surgery compared to their counterparts without knee OA at 5 years. In addition and irrespective of the presence of knee OA at 5 years, all subjects demonstrated higher magnitudes of peak external hip flexion moment in the involved limb prior to ACL reconstruction which decreased over post-operative time points up to 2 years after surgery.

The presence of altered hip joint motion and loading after ACL injury is not surprising. Alterations in movement after ACL rupture are known to not only include changes in joint angles and moments in the knee but also proximally in the hip.[4,46,75,131,162,165,172] Of greater interest is the finding that patients who already possessed radiographic signs of OA in the medial compartment of their ACL-injured knee at a very early time point of 5 years after reconstruction exhibited greater asymmetries in hip joint measures of loading and smaller sagittal plane angles initially after ACL injury and reconstruction compared to those who had not developed knee OA by 5 years. Osteoarthritis in one lower extremity joint is a known risk factor for the progression of OA to other lower extremity joints,[64,155,156] and altered hip biomechanics are associated with the progression and severity of hip OA.[18,41,55,193] Therefore, patients who possess the lifelong burden of post-traumatic knee OA along with abnormal movement patterns at the hip may also be more susceptible for hip joint degeneration. Secondary prevention approaches aimed at maintaining articular

cartilage health after ACL injury may need to integrate strategies for both the hip and the knee joint to eliminate the long-term burden of such injuries.

Movement deviations in both the sagittal and frontal plane can discriminate patients with hip OA from their healthy counterparts.[125] Patients with hip OA frequently walk with reduced hip joint excursion and moments in the sagittal plane and reduced joint moments in the frontal plane.[42,193] In addition, patients who walk with the smallest hip flexion angles, sagittal plane moments, and frontal plane moments are most likely to later undergo total hip arthroplasty. In our study, patients with knee OA 5 years after ACL reconstruction demonstrated many of these aberrant gait patterns both prior to surgery and up to 2 years after surgery. Lower peak hip flexion angles in both limbs were found in those with medial compartment knee OA at 5 years compared to those without knee OA. Further, the OA group demonstrated meaningful asymmetries which exceeded minimal detectable change values in peak hip flexion moments at 1 and 2 years after ACL reconstruction and also in peak hip adduction moments both prior to and 6 months after surgery. The asymmetries in hip joint moments demonstrated by patients with knee OA were consistently in the direction of lower joint loads in the involved limb and greater joint loads in the uninvolved limb. In contrast, the nonOA group walked with symmetric hip flexion moments and asymmetrically higher hip adduction moments in the involved compared to uninvolved limb across time points.

Although early evidence suggests that lower joint loading after ACL injury may be a precursor to post-traumatic OA development in the knee,[186] whether lower joint loading is detrimental or protective to the articular cartilage of the hip is unknown. A review of over 230,000 lower extremity total joint arthroplasties from the

Australian Orthopaedic Association National Joint Replacement Registry and the Norwegian Arthroplasty Register found that contralateral non-cognate joints are at a higher risk for future total joint arthroplasty than joints on the ipsilateral limb.[64] If to occur, OA development in the hip after ACL may follow different pathomechanics than at the knee, where acute joint trauma was encountered. Therefore, the possibility that the asymmetrically higher joint moments demonstrated by the OA group in the contralateral hip could induce the initiation of cartilage degeneration cannot be dismissed. Further long-term study is warranted to determine if ACL-injured patients with post-traumatic knee OA are also subject to a greater risk of non-traumatic OA development in both the ipsilateral and contralateral hip joint.

The current analysis investigated differences in hip biomechanics between those with and without post-traumatic medial compartment knee OA after ACL injury. Hart et al. reported biomechanical hip findings of patients with lateral compartment knee OA at an average 12 years after ACL reconstruction.[77] Patients after ACL reconstruction had larger peak hip flexion angles compared to healthy control subjects. No further kinematic or kinetic differences in the hip existed in this previous study. The larger hip flexion angles reported by Hart and colleagues are in contrast to the smaller hip flexion motion exhibited by those with medial compartment knee OA in the current study. Several methodological differences exist between the two studies preventing direct comparison. The current study examined hip angles and moments early after ACL injury and reconstruction in patients with knee OA at 5 years and compared variables to the contralateral limb and to patients without radiographic signs of knee OA. Hart et al. examined hip biomechanics at a more long-term time point (i.e. 12 years) and referenced healthy controls for comparison; uninvolved limb

measures were not reported. Despite these differences, it is important to highlight that any change in hip kinematics during gait may influence the location of joint contact within the hip joint and alter the forces experienced by various portions of articular cartilage. A change in the load-bearing region of articular cartilage may be a precipitating stimulus for articular cartilage degeneration to occur.[7]

Changes in proximal and distal joints within the kinetic chain exist presumably to compensate for altered knee joint motion after ACL injury.[90] The decreasing peak hip extension moment in the involved limb from pre-operative time points up to 2 years after reconstruction demonstrated by all patients is not surprising as moments in the knee increase over this same time period.[144] Rutherford et al. reported mitigated knee joint excursions in patients with moderate hip OA compared to asymptomatic controls without hip OA and concluded the need for bilateral knee examination when treating patients with hip OA.[151] Inclusion of hip joint analysis and intervention may similarly be warranted in patients with post-traumatic knee OA to prevent the progression of articular cartilage degeneration to additional lower extremity joints.

Assessment of movement patterns in the hip after ACL injury and reconstruction are important in screening for outcomes outside of risk for OA development. Patients who fail objective return to sport criteria after ACL reconstruction demonstrate lower sagittal plane hip angles compared to those who pass.[164] Further, hip moments after ACL reconstruction are predictive of second ACL injury early after returning to sport.[136] Identification of faulty hip biomechanics may assist clinicians in preventing poor outcomes in arguably the three most impactful aspects after ACL injury (i.e. return to sport, second ACL injury, post-traumatic knee OA).

The association between altered hip biomechanics and development of non-traumatic hip OA cannot be concluded from the current study. Diagnostic imaging of the hip joint was not completed 5 years after ACL reconstruction when radiographic knee testing was done. Further, although no subjects experienced additional hip joint pathology diagnosed by a physician or physical therapist during the time between ACL injury and 5 year testing, subjective reporting of hip symptoms that may represent underlying hip pathology was not completed. It is also acknowledged that multiple comparisons in hip biomechanics were made between those with and without knee OA without use of a correction factor presenting risk for type I errors. However, group differences exceeded minimal detectable change values established for biomechanical variables used in this study mitigating this risk. Further study is needed to confirm whether the risk of hip OA is increased after ACL injury and the role of hip joint biomechanics in its development.

3.6 Conclusion

Patients with radiographic knee OA 5 years after ACL reconstruction demonstrate smaller sagittal plane hip angles and asymmetrically lower sagittal and frontal plane hip moments in the ACL-injured limb compared to those without knee OA at 5 years. Alterations in hip joint motion and mechanics may increase susceptibility of individuals with post-traumatic knee OA for additional articular cartilage degeneration in the hip joint.

3.7 Acknowledgements

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Chapter 4

CLINICAL MEASURES OF KNEE FUNCTION PREDICT DEVELOPMENT OF POST-TRAUMATIC KNEE OSTEOARTHRITIS AFTER ANTERIOR CRUCIATE LIGAMENT INJURY

4.1 Abstract

The risk for early knee osteoarthritis is substantially increased after anterior cruciate ligament injury and leads to deleterious and lifelong health consequences. Tools to identify characteristics of patients early after anterior cruciate ligament injury who are at greatest risk for post-traumatic osteoarthritis are needed. The purpose of this study was to determine if clinical measures of knee function after anterior cruciate ligament injury were associated with the development of radiographic knee osteoarthritis 5 years after anterior cruciate ligament injury.

Eighty-four athletes with an isolated anterior cruciate ligament injury were included in this study after initial impairment resolution early after injury. Quadriceps strength testing, single-legged hop testing, joint effusion testing, and subjective reports of knee function were completed after initial impairment resolution (baseline), after an additional 10 pre-operative or non-operative rehabilitation sessions (post-training), and 6 months, 1 year, and 2 years after anterior cruciate ligament reconstruction or non-operative rehabilitation. Weightbearing posterior-anterior bent knee radiographs were completed at 5 years. Knee osteoarthritis was operationally defined by a Kellgren-Lawrence grade of 2 or more in the involved medial compartment.

Twelve patients had knee osteoarthritis at 5 years, 72 did not. The single hop, 6-meter timed hop, Knee Outcome Survey Activities of Daily Living Scale, and Global Rating of Perceived Knee Function Scale explained the greatest amount of variance in post-traumatic osteoarthritis development at post-training (39.4%)

compared to other statistically significant time points (baseline: 28.0%; 2 years: 36.7%). At post-training patients who developed osteoarthritis by 5 years had worse scores on the single hop (p: 0.001, nonOA: 95.9±9.5%, OA: 80.0±20.9%), 6-meter timed hop (p: <0.001, nonOA: 97.2±5.9%, OA: 84.9±14.1%), Knee Outcome Survey Activities of Daily Living Scale (p: 0.001, nonOA: 93.0±7.8%, OA: 84.2±10.5%), and Global Rating of Perceived Knee Function Scale (p: 0.039, nonOA: 82.9±13.9%, OA: 73.8±14.5%) compared to those without osteoarthritis at 5 years. Similar significant group differences in hop scores and subjective reports of knee function were present at baseline and 2 years.

Poor performance in single-legged hop tests and lower subjective knee function are associated with the early development of post-traumatic knee osteoarthritis after anterior cruciate ligament injury. Clinical measures of knee function were most predictive of subsequent osteoarthritis development following an extended period of rehabilitation early after anterior cruciate ligament injury to restore muscle strength and neuromuscular control.

4.2 Introduction

Anterior cruciate ligament (ACL) injury is a musculoskeletal pathology which results in negative sequelae beyond the short-term limitations in function and physical activity, including a predisposition for the development of knee osteoarthritis (OA). Although the precise mechanisms causing long-term joint degeneration are unknown, greater than half of patients will demonstrate radiographic and symptomatic knee OA within 10-20 years of ACL injury.[14,94,116,117,154] Initial phases of articular cartilage degradation likely occur early after ACL injury. Tibial cartilage thinning is evident on magnetic resonance imaging (MRI) as early as 4 months after isolated ACL injury[177]

and these undesirable changes persist despite ACL reconstruction.[86] The identification of individuals possessing post-traumatic knee OA is difficult without routine imaging because typical osteoarthritic symptoms such as pain, stiffness, and decreased function are often absent when initial signs of joint damage are detectable.[83,139,140] Establishment of clinically measureable patient characteristics and outcomes is needed to allow prospective identification of patients at greatest risk for early development of knee OA after ACL injury.

Factors which increase the risk of developing knee OA after ACL injury include age, body mass index, manual labor at time of injury, and concomitant meniscus and chondral injury.[14,112] Although these factors provide information regarding patient risk for post-traumatic knee OA development, they are largely unmodifiable by rehabilitative interventions. One modifiable risk factor of OA after ACL injury is knee joint mechanics. Altered knee joint moments and contact forces demonstrated during walking early after injury and reconstruction have been linked to the development of radiographic knee OA within 5 years of ACL injury.[186] Unfortunately, biomechanical gait asymmetries can exist despite the absence of observational gait impairments.[60,62,78,90,144,166] The current inability of clinicians to prospectively screen patients for risk of post-traumatic knee OA after ACL injury necessitates further evaluation of clinical measures early after injury with comparison to subsequent radiographic evidence of articular cartilage destruction.

Post-traumatic OA accounts for approximately $3 billion of healthcare costs spent within the United States annually.[20] The negative consequences which ensue following its development include pain, impaired knee function, reduced physical activity, and poor quality of life.[116] To minimize the socioeconomic impact and considerable health

concerns imparted by post-traumatic OA after ACL injury, the development of targeted rehabilitation programs to decrease it risk is needed. However, effective testing of such rehabilitation strategies requires identification of patients with ACL injury who are most likely to develop post-traumatic OA and benefit from such interventions. No clinical tools currently exist to identify patients early after ACL injury who are at greatest risk for subsequent post-traumatic OA. Therefore, the primary purpose of this study was to determine if clinical measures of knee function after ACL injury were associated with the later development of radiographic knee OA 5 years after ACL injury. We hypothesized that patients who developed post-traumatic knee OA would demonstrate poorer knee function early after ACL injury compared to those who did not develop OA.

4.3 Methods

4.3.1 Subjects

Eighty-four athletes between the ages of 14-55 with an acute, unilateral ACL injury (confirmed by a positive Lachman test and 3-mm or greater difference in anterior tibial excursion with instrumented arthrometry)[35] (KT1000; MEDmetric Corporation, San Diego, CO) who participated in level 1 (e.g. soccer, basketball) or level 2 (e.g. tennis, downhill skiing) cutting and pivoting activities[35,81] prior to injury were included. Patients were enrolled in this study following physical therapy treatment to resolve initial impairments (i.e. pain, effusion, knee range of motion, obvious gait impairments, and quadriceps strength deficits (70% of uninvolved limb required) using a protocol previously described.[88] Exclusion criteria included a repairable meniscus, symptomatic grade III injury to other knee ligaments, or articular

cartilage lesions greater than 1 cm^2 at the time of study enrollment. This study was approved by the Institutional Review Board at the University of Delaware and all participants provided written informed consent.

After study enrollment all patients completed an additional 10 physical therapy sessions to further restore lower extremity strength and neuromuscular deficits.[79] Nineteen patients completed non-operative management of injury and 65 underwent ACL reconstruction. Patients managed non-operatively were discharged to a home exercise program to maintain strength and neuromuscular control after the additional 10 physical therapy sessions described above. Patients managed operatively underwent reconstruction by a single, board-certified orthopedic surgeon using either a four-bundle semitendinosus-gracilis autograft or soft tissue allograft. After ACL reconstruction patients completed criterion-based post-operative rehabilitation early after surgery.[1] Clinical testing was completed by patients managed operatively and non-operatively at 5 time points: at study enrollment after initial impairment resolution (baseline), immediately following the 10 additional physical therapy sessions (post-training), and 6 months, 1 year, and 2 years after completion of non-operative rehabilitation or ACL reconstruction. Due to the prospective, clinical nature of this study not all subjects completed all parts of testing at all time points.

4.3.2 Clinical Measures of Knee Function

Clinical testing consisted of quadriceps strength testing, single-legged hop testing, knee joint effusion assessment, and completion of patient-reported outcomes at each time point. Patient-reported outcomes included the Knee Outcome Survey-Activities of Daily Living Scale (KOS-ADLS), Global Rating of Perceived Function

Scale (GRS), International Knee Documentation Committee Subjective Knee Form 2000 (IKDC), and Marx Activity Rating Scale (Marx).

Quadriceps strength was tested using the burst superimposition technique during maximal voluntary isometric contraction (MVIC) using an electromechanical dynamometer (Kin-Com; DJO Global, Vista, CA) with patients seated in 90° of hip and knee flexion (Appendix Figure A1).[158] Stabilization straps secured the pelvis and thighs with the force transducer placed just proximal to the talocrural joint. Two 3 x 5-inch self-adhesive electrodes were placed proximally over the vastus lateralis and distally over the vastus medialis. Submaximal (50%, 75% of perceived maximum) and maximal (100% of perceived maximum) isometric knee extension contractions were completed to provide familiarization to the task and ensure absence of knee pain. Patients then completed a MVIC with an imposed supramaximal 10-pulse (600 microseconds, 135 V), 100-pulse-per-second train of electrical stimulation. Quadriceps activation was defined by the MVIC divided by the maximal force output during the superimposed electrical stimulation multiplied by 100. Up to 3 trials were completed on each limb (uninvolved first, followed by involved) until 95% quadriceps activation was achieved, activation levels plateaued, or the patient fatigued. Quadriceps index was the strength variable of interest in this study, calculated as the quotient of the involved limb MVIC to the uninvolved limb MVIC multiplied by 100.

Four single-legged hop tests (single, crossover, triple hop for distance; 6-meter timed hop) were completed on each limb using a 6-meter strip 15 cm wide (Appendix Figure A2).[13,34,132] The uninvolved limb was tested first followed by the involved limb for each hop test. Two practice trials provided familiarization to the task and the next 2 usable trials on each limb were recorded (controlled landing on unilateral limb

required). The average of 2 trials for each limb was used to calculate the quotient of the involved limb to the uninvolved limb multiplied by 100 for the single, crossover, and triple hops and the quotient of the uninvolved limb to the involved limb multiplied by 100 for the 6-meter timed hop. Single-legged hop tests were not completed if the quadriceps index was less than 70% in patients after non-operative rehabilitation or less than 80% in patients after ACL reconstruction.

Knee joint effusion was measured using the modified stroke test.[168] The modified stroke test is reliable in a clinical setting and is scored on a 5-point scale (Appendix Table A1). The presence of knee joint effusion was operationally defined by a grade of trace or greater.

The KOS-ADLS is a valid and reliable measure of impairment and functional limitation experienced during activities of daily living secondary to knee pathology.[93] Fourteen items are scored using a 6-point ordinal scale, with a total score out of a possible 70 points represented as a percentage. A score of 100% represents the absence of knee impairment and functional limitation during activities of daily living.

The GRS consists of a single, reliable question asking the patient to rate their current perceived level of knee function compared to their perceived knee function prior to injury on a scale from 0 to 100.[85,115] Zero represents the inability to perform any activity and 100 indicates the level of activity prior to injury.

The IKDC is a measure of knee specific symptoms, function and sports activities valid and reliable for a variety of knee conditions including ACL injury.[9,91] It is calculated from 18 items and scored on a scale from 0 to 100, with higher scores indicating higher self-reported levels of knee function.

The Marx Activity Rating Scale (Marx) is a reliable scale which assesses the frequency of activities including running, cutting, decelerating and pivoting for patients with knee pathology.[124] It is useful within ACL populations to assess the frequency to which patients have returned to pre-injury activities. Four items are scored on a 4-point scale resulting in a score from 0 to 16, with 0 indicating completion of the four activity items less than one time per month and 16 indicating completion of the four activity items at least four times per week.

Additionally, patients reported return to sport outcomes at each time point. Patients reported "yes" or "no" to the following questions: "Have you returned to sports or recreational activities?" and "Have you returned to the same level of sports or recreational activities as before your injury?"

4.3.3 Radiographs

Patients completed weightbearing posterior-anterior (PA) bent knee (30°) radiographs 5 years after ACL reconstruction or completion of non-operative rehabilitation. SigmaView software (Agfa HealthCare Corporation, Greenville, SC) was used to view radiographs. Osteoarthritis in the medial tibiofemoral compartment of each limb was graded using the Kellgren-Lawrence (KL) system.[96] Excellent between day, intrarater reliability for KL grading has previously been demonstrated using 20 radiographs of patients 5 years after ACL injury (graded by EW; Cohen's kappa (κ): 0.904, p: <0.001; all KL grades verified by board-certified orthopedic surgeon). The presence of OA was defined as a KL grade greater than or equal to 2. Additionally, anatomical alignment was measured from the PA bent knee radiographs using previously described methods.[101] Offsets (2° for women, 4° for men) were added to anatomical alignment measures to estimate the mechanical alignment of the knee.

The offsets used have been shown to be reliable in calculating mechanical alignment from full limb films.[45] Mechanical alignment was categorized into varus alignment (< -2°), neutral alignment (between -2° and +2°), and valgus alignment (> +2°).[45]

4.3.4 Statistical Analysis

Statistical analyses were completed using PASSW 23.0 software (SPSS Inc., Chicago, IL). Independent *t*-tests, Fisher's exact tests, and Chi-square tests were used to test differences in baseline characteristics, concomitant injuries, second ACL injuries, mechanical alignment, and the presence of OA in the involved lateral compartment and contralateral medial and lateral compartment between those with medial compartment OA at 5 years and those without. Independent *t*-tests and Fisher's exact tests were also used to test group differences in clinical measures at each of the 5 time points (baseline, post-training, 6 months, 1 year, 2 years). The Marx was only completed by patients at 1 and 2 years. In addition, return to sport outcomes were only analyzed at 6 months, 1 year, and 2 years. Minimal detectable changes (MDC) (Table 4.1) and effect sizes (ES)[29] were used qualitatively to determine if meaningful differences existed in clinical measures between those with and without OA. Logistic regression was used to determine the ability of clinical measures at each of the 5 time points to predict the later development of medial compartment knee OA at 5 years. Clinical variables included in logistic regression analyses were chosen based on frequency of statistically significant differences and effect size between those with and without OA. *A priori* statistical significance was set at $\alpha \leq 0.05$.

Table 4.1: Minimal detectable change (MDC) values for single-legged hop tests,[142,148] Knee Outcome Survey Activities of Daily Living Scale (KOS-ADLS),[30] Global Rating Scale of Perceived Function (GRS),[85] and International Knee Documentation Committee Subjective Knee Form 2000 (IKDC).[91]

Clinical Measure	MDC (%)
Single hop	8.1
Crossover hop	12.3
Triple hop	10.0
6-meter timed hop	13.0
KOS-ADLS	7.1
GRS	6.5
IKDC	11.5

4.4 Results

Eighty-four patients returned for radiographic testing 5 years after ACL reconstruction or completion of non-operative management (Figure 4.1). Twelve of the 84 patients had medial compartment OA at 5 years, 72 did not. No differences in age, body mass index, sex, pre-injury activity level, or surgical management of ACL injury (ACL reconstruction, non-operative management) were present between those with and without knee OA (Table 4.2). The time from ACL injury to initial physical therapy evaluation did not differ between groups, but those with OA at 5 years took 2 weeks longer to reach baseline testing through resolution of initial impairments (pain, effusion, knee range of motion, obvious gait impairments, and quadriceps strength deficits) than those who did not develop OA (Injury to initial physical therapy evaluation: p: 0.181, nonOA: 5.6±6.6 wks, OA: 8.5±8.7 wks; Injury to baseline: p: 0.040, nonOA: 7.8±7.2 wks, OA: 12.7±9.4 wks). Eight-three percent of patients with OA at 5 years were categorized as a noncoper[49] at baseline compared to only 49% of

patients without OA (p: 0.031; nonOA: 35 noncopers, 37 potential copers; OA: 10 noncopers, 2 potential copers). This relationship is further detailed below in the analysis of single-legged hop tests, KOS-ADLS, and GRS. No group differences existed in the presence of concomitant meniscal, articular cartilage, or bone bruise lesions in the medial compartment at the time of ACL injury or in the rate of additional ACL injuries (Table 4.2).

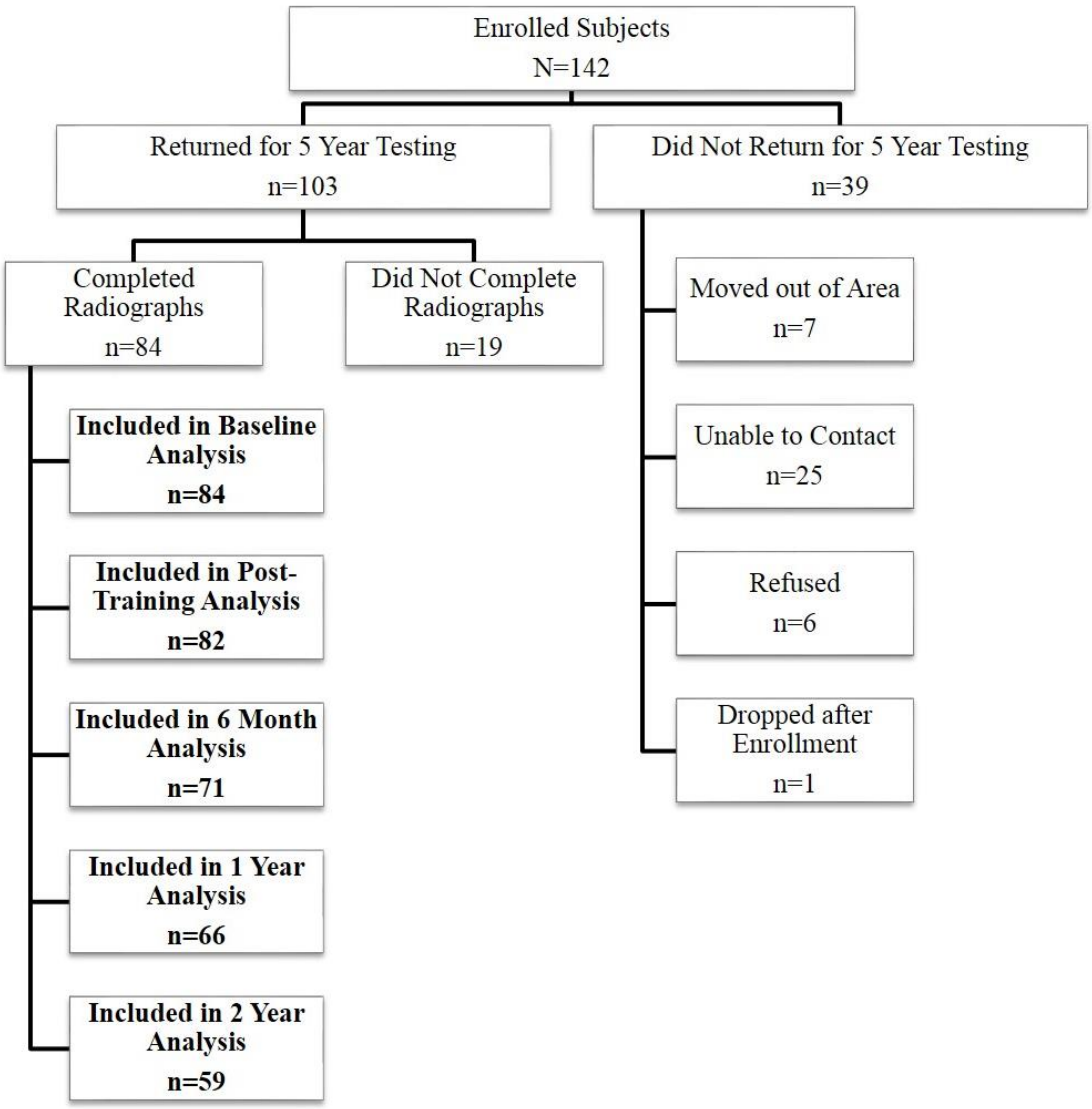

Figure 4.1: Flow diagram of study cohort.

Table 4.2: Baseline, concomitant, mechanical alignment, and additional knee injury characteristics between those with and without radiographic medial compartment knee OA 5 years after ACL reconstruction or completion of non-operative rehabilitation. Boldface numbers indicate statistically significant group differences. *Bone bruise data includes 72/84 patients. †Mechanical alignment data includes 83/84 patients. Abbreviations: SD, standard deviation; yrs, years; kg, kilogram; m, meter; wks, weeks; M, male; F, female.

	nonOA (SD)	OA (SD)	p
Age (baseline) (yrs)	28.6 (11.1)	34.1 (14.4)	0.131
Body Mass Index (kg/m^2)	25.5 (3.8)	26.4 (4.7)	0.475
Time from injury to initial evaluation (wks)	5.6 (6.6)	8.5 (8.7)	0.181
Time from injury to baseline (wks)	7.8 (7.2)	12.7 (9.4)	**0.040**
Sex (M:F)	46:26	6:6	0.522
Pre-Injury Activity Level (1:2)[35,81]	49:23	6:6	0.325
Noncoper:Potential Coper[49]	35:37	10:2	**0.031**
ACL Reconstruction: Non-Operative Rehabilitation	54:18	11:1	0.282
Concomitant meniscus tear (medial compartment) (Yes:No)	22:50	6:6	0.202
Concomitant chondral injury (medial compartment) (Yes:No)	1:71	1:11	0.267
Concomitant bone bruise (medial compartment) (Yes:No)*	28:33	6:5	0.746
Second ACL injury after initial ACL injury (Yes:No)	8:64	2:10	0.630
Ipsilateral second ACL injury after initial ACL injury (Yes:No)	5:67	2:10	0.261
Mechanical alignment (Varus:Neutral:Valgus)†	15:41:15	3:7:2	0.918
Involved lateral compartment OA at 5 years (Yes:No)	5:67	4:8	**0.021**
Uninvolved medial/lateral compartment OA at 5 years (Yes:No)	4:68	3:9	0.057

The mechanical alignment calculated from radiographic analysis at 5 years approached 0º for patients both with and without medial compartment knee OA (nonOA: 0.1±2.5º valgum, OA: 0.5±3.3º varum), and the proportion of patients in each group with involved knee valgum compared to varum compared to neutral alignment did not differ (Table 4.2). More patients with medial compartment OA at 5

years also demonstrated lateral compartment OA in the involved knee (p: 0.021; nonOA: 5 with lateral OA, 67 without lateral OA; OA: 4 with lateral OA, 8 without lateral OA) but the rate of OA in the uninvolved knee did not differ between groups (Table 4.2).

Patients with OA at 5 years performed worse on single-legged hop tests during baseline testing (Single Hop: p: 0.005, nonOA: 88.0±13.9%, OA: 72.0±21.2%, ES: 1.08; Triple Hop: p: 0.001, nonOA: 89.0±11.3%, OA: 69.5±11.6%, ES: 0.73; 6-meter Timed Hop: p: 0.003, nonOA: 95.1±9.3%, OA: 81.9±19.3%, ES: 1.24) and also reported lower knee function on the GRS (p: 0.029, nonOA: 75.6±15.7%, OA: 64.6±17.5%, ES: 0.69) compared to those without OA. Group differences in clinical measures were magnified and more numerous at post-training. Patients who later developed OA had worse scores on all 4 single-legged hop tests (Single Hop: p: 0.001, nonOA: 95.9±9.5%, OA: 80.0±20.9%, ES: 1.43; Crossover Hop: p: <0.001, nonOA: 95.7±9.1%, OA: 80.9±11.3%, ES: 1.79; Triple Hop: p: 0.001, nonOA: 95.6±6.9%, OA: 83.0±15.5%, ES: 1.71; 6-meter Timed Hop: p: <0.001, nonOA: 97.2±5.9%, OA: 84.9±14.1%, ES: 1.72), the KOS-ADLS (p: 0.001, nonOA: 93.0±7.8%, OA: 84.2±10.5%, ES: 1.07), the GRS (p: 0.039, nonOA: 82.9±13.9%, OA: 73.8±14.5%, ES: 0.65), and the IKDC (p: 0.011, nonOA: 78.0±14.0%, OA: 65.5±17.1%, ES: 0.86).

Six months after ACL reconstruction or completion of non-operative management there were no differences in any clinical measures between the group with OA and without OA at 5 years (Table 4.3). The only group difference at 1 year was in the crossover hop (p: 0.036, nonOA: 99.5±8.0%, OA: 94.0±6.2%, ES: 0.71) but this difference was not meaningful (MDC: 12.3%). Patients with OA performed statistically worse on the single hop (p: 0.002, nonOA: 100.6±5.8%, OA: 92.6±10.3%,

ES: 1.16) and scored lower on the GRS (p: 0.029, nonOA: 96.3±4.5%, OA: 90.9±14.1%, ES: 0.75) 2 years after ACL reconstruction or non-operative rehabilitation with both differences approaching clinically meaningful differences (MDC: Single Hop: 8.1%, GRS: 6.5%). Patients with OA were not different from those without OA in quadriceps strength, Marx scores, knee joint effusion, or return to sport rates at any time point (Table 4.3).

Table 4.3: Clinical measures between those with and without radiographic medial compartment knee OA 5 years after ACL reconstruction or completion of non-operative rehabilitation. Boldface numbers indicate statistically significant group differences. Abbreviations: SD, standard deviation; KOS-ADLS, Knee Outcome Survey Activities of Daily Living Scale; GRS, Global Rating of Perceived Function Scale; IKDC, International Knee Documentation Committee Subjective Knee Form 2000; Marx, Marx Activity Rating Scale.

	Group	Baseline		Post-Training		6 Months		1 Year		2 Years	
		Mean (SD)	p	Mean (SD)	p	Mean (SD)	p	Mean (SD)	p	Mean (SD)	p
Quadriceps Index (%)	nonOA	89.0 (13.9)	0.522	95.7 (14.6)	0.277	99.7 (13.6)	0.674	99.5 (11.9)	0.771	106.3 (16.0)	0.214
	OA	86.3 (10.9)		90.3 (21.5)		97.8 (11.3)		100.8 (19.0)		99.5 (15.6)	
Single Hop (%)	nonOA	88.0 (13.9)	**0.005**	95.9 (9.5)	**0.001**	94.8 (7.5)	0.142	99.1 (7.2)	0.136	100.6 (5.8)	**0.002**
	OA	72.0 (21.2)		80.0 (20.9)		90.7 (10.2)		95.4 (7.9)		92.6 (10.3)	
Crossover Hop (%)	nonOA	89.6 (17.0)	0.130	97.5 (9.1)	**<0.001**	96.9 (7.4)	0.966	99.5 (8.0)	**0.036**	100.9 (6.6)	0.118
	OA	77.5 (13.6)		80.9 (11.3)		97.0 (8.1)		94.0 (6.2)		97.1 (7.7)	
Triple Hop (%)	nonOA	89.0 (11.3)	**0.001**	96.5 (6.9)	**0.001**	96.1 (5.3)	0.142	99.5 (6.5)	0.075	99.8 (5.1)	0.368
	OA	69.5 (11.6)		83.0 (15.5)		93.4 (4.9)		95.7 (5.2)		97.8 (10.0)	
6-meter Timed Hop (%)	nonOA	95.1 (9.3)	**0.003**	97.2 (5.9)	**<0.001**	98.3 (7.7)	0.083	99.5 (7.3)	0.065	96.2 (22.2)	0.974
	OA	81.9 (19.3)		84.9 (14.1)		93.7 (6.5)		95.2 (4.7)		96.0 (7.0)	
KOS-ADLS	nonOA	84.6 (12.6)	0.233	93.0 (7.8)	**0.001**	97.1 (3.3)	0.308	97.9 (3.2)	0.276	98.1 (2.7)	0.108
	OA	79.9 (12.2)		84.2 (10.5)		96.0 (2.7)		96.7 (5.1)		96.5 (4.1)	
GRS	nonOA	75.6 (15.7)	**0.029**	82.9 (13.9)	**0.039**	91.6 (6.6)	0.471	96.2 (4.3)	0.236	96.3 (4.5)	**0.029**
	OA	64.6 (17.5)		73.8 (14.5)		93.2 (4.5)		94.1 (9.8)		90.9 (14.1)	
IKDC	nonOA	68.8 (14.5)	0.091	78.0 (14.0)	**0.011**	89.5 (8.3)	0.731	93.5 (7.9)	0.355	93.5 (7.3)	0.387
	OA	61.1 (13.9)		65.5 (17.1)		88.5 (8.8)		91.0 (10.9)		91.3 (9.0)	

Table 4.3: continued

	Group	Baseline		Post-Training		6 Months		1 Year		2 Years	
		Mean (SD)	p	Mean (SD)	p	Mean (SD)	p	Mean (SD)	p	Mean (SD)	p
Marx	nonOA							9.9 (4.2)	0.506	10.0 (4.7)	0.749
	OA							10.8 (5.5)		10.5 (4.4)	
		Ratio	p	Ratio	p	Ratio	p	Ratio	p	Ratio	p
Effusion (Yes:No)	nonOA	48:13	0.190	41:23	0.317	32:27	0.331	26:27	0.122	18:26	0.505
	OA	10:0		10:2		8:3		9:3		6:5	
Return to Sport-Any (Yes:No)	nonOA					35:24	>0.999	46:7	>0.999	45:2	>0.999
	OA					6:5		11:1		11:0	
Return to Sport-Same PreInjury Level (Yes:No)	nonOA					17:42	0.723	32:21	0.754	35:12	0.475
	OA					4:7		8:4		7:4	

The single hop, 6-meter timed hop, KOS-ADLS, and GRS at each time point were inputs into a logistic regression model to determine the likelihood that patients would develop medial compartment knee OA at 5 years. Logistic regression models were statistically significant at baseline ($\chi^2(4)$: 9.9, p: 0.042), post-training ($\chi^2(4)$: 14.0, p: 0.007), and 2 years ($\chi^2(4)$: 13.4, p: 0.010) explaining 28.0%, 39.4%, and 36.7% of the variance in knee OA development at 5 years for each time point, respectively. No individual clinical predictor contributed significantly to the model at any time point (Table 4.4).

Table 4.4: Logistic regression analysis of the single hop, 6-meter timed hop, KOS-ADLS and GRS to the development of medial compartment knee OA 5 years after ACL reconstruction or completion of non-operative rehabilitation. Boldface numbers indicate a statistically significant logistic regression model. Abbreviations: KOS-ADLS, Knee Outcome Survey Activities of Daily Living Scale; GRS, Global Rating of Perceived Function Scale.

			Single Hop		6-meter Timed Hop		KOS-ADLS		GRS	
	p (Model)	Nagelkerke R^2	p	β:	p	β:	p	β:	p	β:
Baseline (n=61 nonOA, 7 OA)	**0.042**	0.280	0.174	0.946	0.352	0.957	0.692	0.980	0.662	1.014
Post-Training (n=57 nonOA, 7 OA)	**0.007**	0.394	0.871	0.993	0.069	0.841	0.499	0.939	0.557	1.036
6 Months (n=56 nonOA, 9 OA)	0.522	0.087	0.665	0.971	0.362	0.945	0.301	0.879	0.278	1.103
1 Year (n=51 nonOA, 11 OA)	0.325	0.119	0.842	0.988	0.175	0.920	0.703	0.949	0.944	0.994
2 Years (n=41 nonOA, 10 OA)	**0.010**	0.367	0.092	0.872	0.228	0.895	0.584	0.919	0.462	0.928

4.5 Discussion

The purpose of this study was to determine if clinical measures of knee function after ACL injury were associated with the later development of radiographic knee OA 5 years after ACL injury. Our findings support our hypothesis that poorer knee function after ACL injury would be associated with the development of post-traumatic knee OA. Patients with radiographic medial compartment OA at 5 years demonstrated poorer performance on single-legged hop tests and reported lower subjective knee function early after injury and at 2 years after ACL reconstruction or non-operative rehabilitation compared to those who did no develop OA by 5 years.

Single-legged hop tests have previously demonstrated the ability to predict normal and below normal knee function 1 year after non-operative rehabilitation or ACL reconstruction.[73,113] A more positive subjective assessment of knee function after ACL reconstruction increases the likelihood of returning to pre-injury levels of sport.[11] Further, the incorporation of subjective knee function into an objective test battery can successfully identify patients who can return to cutting and pivoting activities without undergoing ACL reconstruction and also identify patients with persistent abnormal movement patterns after reconstruction.[49,61,164] In the current study patients with medial compartment knee OA by 5 years demonstrated worse hop scores in all 4 tests (single, crossover, triple, 6-meter timed) and lower KOS-ADLS, GRS, and IKDC scores at time points before and after an extended bout of rehabilitation early after injury. The link between self-reported knee function and subsequent knee degeneration emphasizes the importance of implementing patient-reported outcomes in clinical practice, considering that a patient's self-assessment does not always match clinical measures of function.[146] The minimal need for special equipment to assess

single-legged hop performance and subjective knee function provides the possibility for these measures to be powerful and impactful screening tools for post-traumatic OA risk after ACL injury.

Quadriceps strength after ACL injury was not found to be a predictor for the development of post-traumatic knee OA. However, the importance of quadriceps strength after ACL injury is clear. Greater levels of quadriceps strength early after injury result in improved outcomes after reconstruction including higher levels of subjective knee function and the ability to return to sport.[33,43,109,114,152,174,195] The role of quadriceps strength in the development of both non-traumatic (primary) and post-traumatic knee osteoarthritis is not clear. The presence of quadriceps weakness with concurrent evidence of radiographic primary knee OA has been well-established, but its link to the development and progression of the disease is conflicting.[5,15,16,153] Quadriceps weakness may be a negative sequelae rather than a precipitating factor in joint degeneration similar to patterns present in the primary OA population.

Clinical measures of knee function measured early after ACL injury (baseline, post-training) were effective predictors of post-traumatic knee OA development by 5 years after reconstruction or non-operative rehabilitation. In addition, patients with OA at 5 years required an additional 5 weeks to achieve resolution of initial knee pain, range of motion, gait impairments, joint effusion, and strength impairments after ACL injury compared to those who did not develop radiographic OA. The time required to resolve impairments initially after ACL injury can be dependent on early presentation to rehabilitation and patient response to implemented rehabilitation interventions. The interaction of these two variables may critically factor into the risk for later OA development. Knee joint loading and inflammatory pathways are thought to be

avenues for initial articular cartilage destruction.[116,159] Thus, failure to quickly resolve impairments such as range of motion, joint effusion, and abnormal gait patterns may create early risk for cartilage degeneration. In contrast, early and effective rehabilitation after ACL injury may curb the increased risk for post-traumatic OA development in this population.

No individual clinical measure of knee function at any time point after ACL injury was a predictor of subsequent post-traumatic knee OA. The required combination of objective measures including single-legged hop tests (single, 6-meter timed) and patient-reported outcomes (KOS-ADLS, GRS) to effectively predict early OA development points to its likely multifactorial evolution and advocates for the increased use of criterion-based rehabilitation interventions which implement objective measures of patient function. An extended bout of early, criterion-based rehabilitation after ACL injury is known to result in clinically relevant improvements in knee function.[44] The benefits of extended rehabilitation prior to ACL reconstruction or as part of a non-operative management strategy are further demonstrated by the results of this study. The predictive ability of clinical measures of knee function in subsequent OA development was greater at post-training compared to baseline testing, accounting for 39.4% compared to 28.0% of the variance in medial compartment OA at 5 years, respectively. Using objective measures of knee function to screen for post-traumatic OA risk may be most effective following early, extended rehabilitation. However, it is unknown whether additional intervention to avoid the initiation of articular cartilage breakdown will be effective at this time point or if irreversible processes have already begun.

Outcomes in single-legged hop tests and subjective knee function were again predictive of later radiographic medial compartment OA development at 2 years after ACL reconstruction or non-operative rehabilitation, after lacking statistical significance at 6 months and 1 year. Specifically, patients who did develop OA demonstrated lower single hop scores and global knee function on the GRS at 2 years that those who did not develop knee OA. The re-emergence of poorer knee function at 2 years by individuals in whom post-traumatic knee OA arises by 5 years may mark a time in which the disease first becomes symptomatic in contrast to signs of disease initiation. The process of cartilage breakdown may already be occurring by 2 years. Thinning of articular cartilage has been demonstrated within months of ACL injury and the diagnosis of OA can be made using magnetic resonance imaging by 1 year after ACL reconstruction.[32,177] Further work is necessary to identify when early signs of post-traumatic knee OA are first identifiable when additional secondary prevention strategies may be warranted.

Non-traumatic, primary OA is commonly characterized by progressive degenerative changes resulting in part from excessive mechanical loading and overuse.[74] However, in the current study, frequency of running, cutting and pivoting activities as assessed by Marx scores and return to sport outcomes did not influence whether radiographic knee OA was present at 5 years. Improved understanding of mechanisms initiating early OA after ACL injury is needed before healthy levels of mechanical loading during sports and other forms of physical activity can be determined. For example, although the current findings indicate that returning to sport does not differentiate the later development of knee OA, the increase in knee joint

loading associated with sports activities may be detrimental in individuals where degenerative pathways have already begun.

The capability to assess the future risk of post-traumatic knee OA development after ACL injury is critical. Inability to prospectively identify patients at greatest risk for its development will make testing and implementation of targeted rehabilitation strategies to lower the rates of patients developing this irreversible and lifelong disease difficult. The comprehensive battery of clinical measures and long course of follow-up used within this study limited the number of subjects completing the full testing protocol. Therefore, analyses to determine if longitudinal changes in clinical measures of knee function influence early OA development could not be made. Further, patients included in this study were active in sports activities prior to ACL injury and did not have diagnosed repairable menisci or large articular cartilage lesions at the time of injury. It is unknown whether patients with non-athletic backgrounds or with more extensive concomitant injuries would demonstrate similar relationships between clinical measures of knee function and early OA development as presented in this study. However, the findings of this study provide important initial findings to the role clinical tools may have in providing insight into the process of post-traumatic OA after ACL injury.

4.6 Conclusion

Poor performance in single-legged hop tests and lower subjective knee function are associated with the early development of post-traumatic knee OA after ACL injury. Clinical measures of knee function were most predictive of subsequent OA development following an extended period of rehabilitation early after ACL injury to restore muscle strength and neuromuscular control.

4.7 Acknowledgements

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Chapter 5

RADIOGRAPHIC EVIDENCE OF OSTEOARTHRITIS AFTER ANTERIOR CRUCIATE LIGAMENT INJURY

5.1 Abstract

The risk of post-traumatic knee osteoarthritis is significantly increased after anterior cruciate ligament injury. Changes in joint space width are a radiographic feature of osteoarthritis which can occur within years after anterior cruciate ligament injury and reconstruction. The purpose of this study was to describe the joint space width and mechanical alignment of patients 5 years after complete unilateral anterior cruciate ligament rupture managed non-operatively or with reconstruction. We also aimed to determine if Kellgren-Lawrence grades of knee osteoarthritis and mechanical knee alignment were associated with joint space width measurements at 5 years.

Eighty-three athletes with an acute anterior cruciate ligament injury were included. Weightbearing posterior-anterior bent knee radiographs were completed at 5 years and analyzed using measures of joint space width, Kellgren-Lawrence grades, and mechanical alignment.

Twelve of 83 patients had a Kellgren-Lawrence grade of 2 or greater in the medial compartment of the involved knee at 5 years. The medial minimum joint space width in the involved knee of patients with a Kellgren-Lawrence grade of 2 or greater was 0.5 millimeters smaller than the uninvolved knee but 0.1 millimeters larger in patients with a Kellgren-Lawrence grade of 0 or 1 (p: 0.115). Radiographic mechanical alignment at 5 years was not related to concurrent measures of joint space width at 5 years.

Patients with advanced radiographic signs of post-traumatic knee osteoarthritis after anterior cruciate ligament injury (Kellgren-Lawrence grade of 2 or greater)

demonstrated joint space narrowing while joint space width was similar to the contralateral limb in patients without osteoarthritis. Knee malalignment did not correspond to joint space width in the anterior cruciate ligament-injured knee at 5 years; however, its long-term influence on post-traumatic knee osteoarthritis progression is not known.

5.2 Introduction

The risk of post-traumatic knee osteoarthritis (OA) is significantly increased after anterior cruciate ligament (ACL) injury despite many individuals restoring favorable knee function, returning to sports, and reducing anteroposterior knee instability through surgical reconstruction. Lohmander and colleagues estimated that 50% of ACL-injured individuals develop radiographic knee OA with associated symptoms of pain and decreased function with 10-20 years of injury.[116] Grading radiographic knee OA can be accomplished using a multitude of methods. A grade equal to or greater than 2 on the Kellgren-Lawrence (KL) grading system, or a grade comparable to a KL grade of 2, is mostly commonly used as a threshold.[116] However, more liberal definitions requiring only a single radiographic feature of OA to be present (e.g. change in joint space width, osteophytes) result in even more patients classified with post-traumatic knee OA diagnosis[117] and potentially highlight additional individuals demonstrating early stages of joint degeneration after ACL injury.

Changes in joint morphology can occur early after ACL injury and reconstruction.[95,173] Therefore the purpose of this study was to describe the joint space width (JSW) and mechanical alignment of patients 5 years after complete unilateral ACL rupture managed non-operatively or with ACL reconstruction. We also aimed to

determine if KL grades of knee osteoarthritis and mechanical knee alignment were associated with JSW measurements at 5 years. We hypothesized that patients with knee OA as defined by KL grading and varus mechanical alignment would demonstrate narrower JSW than those without knee OA and those with neutral or valgus alignment.

5.3 Methods

5.3.1 Subjects

Eighty-three athletes between the ages of 14-55 with an acute, unilateral ACL injury who participated in level 1 (e.g. soccer, basketball) or level 2 (e.g. tennis, downhill skiing) cutting and pivoting activities[35,81] prior to injury were included. Patients were enrolled in this study following physical therapy treatment to resolve initial impairments using a protocol previously described.[88] Exclusion criteria included a repairable meniscus, symptomatic grade III injury to other knee ligaments, or articular cartilage lesions greater than 1 cm^2 at the time of study enrollment. This study was approved by the Institutional Review Board at the University of Delaware and all participants provided written informed consent.

After study enrollment all patients completed an additional 10 physical therapy sessions to further restore lower extremity strength and neuromuscular deficits.[79] Nineteen patients completed non-operative management of injury and 65 underwent ACL reconstruction (completed by single, board-certified orthopedic surgeon using either a four-bundle semitendinosus-gracilis autograft or soft tissue allograft).

5.3.2 Radiographs

Patients completed weightbearing posterior-anterior (PA) bent knee (30°) radiographs 5 years after ACL reconstruction or completion of non-operative rehabilitation. Minimum JSW measurements were manually measured in the medial tibiofemoral compartment of each limb (Figure 5.1) using SigmaView software (Agfa HealthCare Corporation, Greenville, SC) to view radiographs. JSW was also measured at a fixed location within the medial tibiofemoral joint (25% of distance from medial to lateral edge of femur ($JSW_{.25}$)). This specific location has demonstrated the greatest responsiveness to longitudinal medial compartment JSW changes in the Osteoarthritis Initiative (OAI) cohort.[39] Interlimb JSW differences were calculated for each JSW measure (involved minus uninvolved). Radiographic changes in the medial tibiofemoral compartment was also assessed using the Kellgren-Lawrence (KL) system.[96] The presence of OA as defined by KL grades was set as greater than or equal to 2. Excellent between day, intrarater reliability for radiographic measures of interest has previously been demonstrated using 20 radiographs of patients 5 years after ACL injury (graded by EW; intracorrelation coefficient (ICC) for minimum JSW: 0.981, p: <0.001; Cohen's kappa (κ) for KL grades: 0.904, p: <0.001; all KL grades verified by board-certified orthopedic surgeon). Additionally, anatomical alignment was measured from the PA bent knee radiographs using previously described methods.[101] Offsets (2° for women, 4° for men) were added to anatomical alignment measures to estimate the mechanical alignment of the knee. The offsets used have been shown to be reliable in calculating mechanical alignment from full limb films.[45] Mechanical alignment for each patient was categorized as varus alignment (< -2°), neutral alignment (between -2° and +2°), or valgus alignment (> +2°).[45]

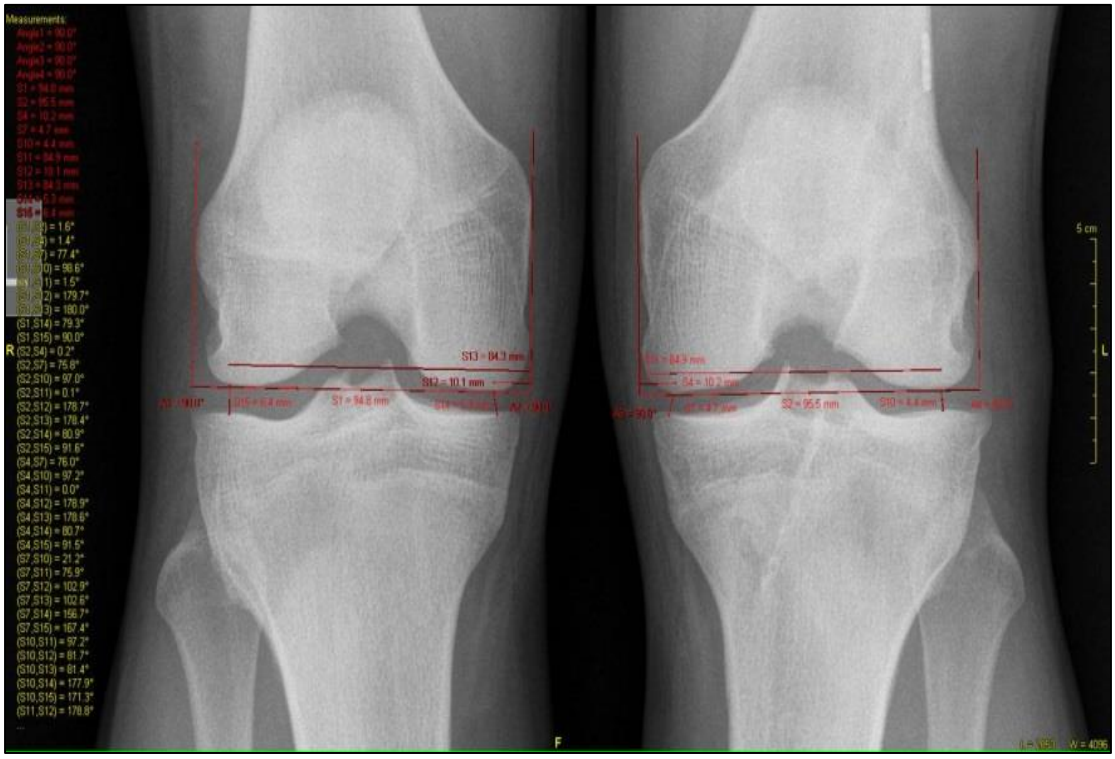

Figure 5.1: Example of minimum joint space width measurements on a posterior-anterior 30° bent knee radiograph in a patient 5 years after ACL injury.

5.3.3 Statistical Analysis

Statistical analyses were completed using PASSW 23.0 software (SPSS Inc., Chicago, IL). An independent *t*-test was used to determine if JSW measurements differed between those with and without medial OA as defined by KL grades. A one-way analyses of variance (ANOVA) was used to determine if mechanical alignment was associated with JSW measurements. *A priori* statistical significance was set at $\alpha \leq 0.05$.

5.4 Results

Thirty-nine percent of the included 83 patients were women, average age at 5 years was 35.0±11.8 years, and 23% were managed non-operatively. Patients completed radiographs an average 5.3±0.7 years after ACL reconstruction or completion of non-operative rehabilitation. The average medial compartment minimum JSW was 4.8±1.2 mm in the involved knee and 4.9±1.0 mm in the contralateral knee. The average $JSW_{.250}$ was 6.4±1.3 mm in the involved knee and 6.3±1.1 mm in the contralateral knee.

Twelve of the 83 patients had OA (as defined by a KL grade of 2 or greater) in the medial compartment of the involved knee. Those with medial knee OA had smaller minimum JSW compared to the contralateral knee but differences were not statistically different from those without OA (p: 0.115, nonOA: 0.1±1.0 mm, OA: -0.5±1.8 mm). Interlimb differences in $JSW_{.250}$ did not differ between those with and without OA (p: 0.611, nonOA: 0.2±0.8 mm, OA: 0.1±1.6 mm). Forty-eight patients demonstrated radiographically neutral alignment at 5 years, 18 demonstrated varus alignment, and 17 demonstrated valgus alignment. Mechanical alignment was not associated with the interlimb difference in minimum JSW (p: 0.511, Varus: -0.2±1.3 mm, Neutral: -0.1±1.2 mm, Valgus: 0.2±1.0 mm) or $JSW_{.250}$ (p: 0.756, Varus: 0.1±0.9 mm, Neutral: 0.2±1.0 mm, Valgus: 0.3±0.9 mm) in the medial compartment.

5.5 Discussion

The purpose of this study was to describe the JSW and mechanical alignment of patients 5 years after complete unilateral ACL rupture managed non-operatively or with ACL reconstruction. We also aimed to determine if KL grades of knee OA and mechanical knee alignment were associated with JSW measurements at 5 years. Our

hypothesis that patients with medial compartment KL grades greater than or equal to 2 would demonstrate narrower JSW than those without knee OA was supported. The medial minimal JSW of patients with a KL grade of 2 or more in the medial compartment was 0.5 mm smaller than the contralateral knee while no interlimb difference was present in those with KL grades of 0 or 1. The difference of 0.5 mm is meaningful considering the smallest detectable difference for minimum JSW is 0.2 mm.[87] Our hypothesis that patients with varus mechanical alignment would demonstrate the smallest medial compartment JSW was not supported as differences were not present between patients with varus, valgus, and neutral alignment.

The smaller JSW measures in the limbs of patients with KL grades of 2 or greater was not surprising. Joint space width is a component directly used in the KL grading system.[96] Further, radiography is not a sensitive measure to early changes in articular cartilage morphology during OA development compared to other imaging modalities.[87] The requirement for at least a KL grade of 2 to operationally define OA indicates considerable disease progression has already occurred. The average loss of 0.5 millimeters exhibited by our patients with KL grades of 2 or more is in line with the expected 0.10 to 0.15 millimeter annual JSW reduction expected by patients with a primary knee OA diagnosis.[87]

Mechanical alignment was not found to be related to JSW changes in our cohort of patients 5 years after ACL reconstruction or non-operative rehabilitation. Lower extremity malalignment is considered a strong independent predictor for progression of radiographic knee OA, but less is known regarding its role in initial disease development.[171] Further longitudinal radiographic follow-up of the current patients may be required to correctly understand the role of mechanical alignment in

post-traumatic knee OA after ACL injury. Recognition of the long-term effects of malalignment on knee joint health may affect surgical decisions to use alignment-modifying procedures such as osteotomies after ACL injury.

Ambiguity exists in interpretation of JSW changes after ACL injury. Patients in the current study, specifically those with a KL grade of 0 or 1, had JSW measures similar to the contralateral knee. Jones and colleagues reported that minimum JSW in the medial compartment of ACL-reconstructed knees was 0.35 millimeters greater than the contralateral knee in a sample of 262 subjects 3 years after reconstruction.[95] Tourville and colleagues also reported increases in joint space width by a small proportion of individuals nearly 4 years after ACL reconstruction.[173] Similarly, Frobell and Eckstein noted increases in cartilage volume of the medial femoral condyle after ACL injury, a finding that was more pronounced in younger compared to older patients.[40,59] The average age of patients in the current study was older than the cohorts used by Jones et al. and Tourville et al.;[95,173] however, interlimb differences in minimum JSW was not correlated to age in our cohort (p: 0.541, r: -0.069). Controversy exists whether increases in joint space width, a surrogate measure for articular cartilage thickness, is representative of the earliest stages of post-traumatic OA development or rather a protective mechanism of the articular cartilage to prevent breakdown after ACL injury.[40,95,173] If cartilage thickening initially occurs during post-traumatic knee OA development, cross-sectional designs using JSW as a marker for OA may be inappropriate due to the inability to identify the stage of disease. Patients in early stages of the disease process could have joint space widening, patients who in more advanced stages of the disease could have joint space narrowing, and patients both in between those stages of OA or without any articular cartilage degeneration

could present with “normal” JSW as compared to the contralateral limb. Longitudinal assessment of JSW may be required to more clearly identify patterns of JSW changes which indicate both early stages and later progression of post-traumatic OA after ACL injury.

Baseline radiographic testing early after ACL injury was not part of the current study protocol. Concurrent JSW measures of the contralateral limb at 5 years served as control measures to compare JSW of the ACL-injured limb. Although baseline testing of JSW early after ACL injury would provide insight into disease progression of the included patients, the use of the contralateral limb as comparison at 5 years is not considered a limitation according to the purpose of this study. The use of the contralateral limb has previously been established as a valid control for comparing JSW after ACL injury. Contralateral JSW measures are stable when measured before ACL reconstruction to 46 months after surgery.[173] Further, some individuals demonstrate JSW widening even before ACL reconstruction making baseline measurements early after injury potential poor estimations of original pre-injury magnitudes of joint space.[173]

5.6 Conclusion

Patients with advanced radiographic signs of post-traumatic knee OA after ACL injury (KL grade of 2 or greater) demonstrated joint space narrowing while JSW was equal to the contralateral limb in patients without OA. Knee malalignment did not correspond to JSW in the ACL-injured knee at 5 years; however, its long-term influence on post-traumatic knee OA progression is not known.

5.7 Acknowledgements

We would like to acknowledge Dr. Kathleen Cummer for her assistance with data collection and the University of Delaware Physical Therapy Clinic for providing the physical therapy treatments for our research participants. We also thank Martha Callahan and the Delaware Rehabilitation Institute's Clinical Research Core (http://www.udel.edu/dri/ResCore.html) for their assistance with patient recruitment, scheduling, and data management. This work was supported by the National Institute of Health (R37 HD037985, R01 AR048212, R01 AR046386, P30 GM103333).

Chapter 6

IS OPERATIVE OR NON-OPERATIVE TREATMENT OF ACL INJURIES BEST?: A COMPARISON OF OUTCOMES 5 YEARS AFTER INJURY

6.1 Abstract

Misconceptions regarding surgical reconstruction after anterior cruciate ligament (ACL) injury are common among patients and healthcare providers. Improved awareness of expected outcomes after operative compared to non-operative management strategies is needed to facilitate open decision-making regarding surgical management after injury. The purpose of this study was to determine if differences exist in long-term functional, biomechanical, and radiographic outcomes between subjects completing operative compared to non-operative management of anterior cruciate ligament injury.

One-hundred five athletes with anterior cruciate ligament injury were included and all completed progressive, criterion-based pre-operative/post-operative rehabilitation or non-operative rehabilitation. Patients returned 5 years after reconstruction or non-operative rehabilitation and completed combinations of functional testing (n=94), patient-reported outcomes (n=104), gait analysis (n=91), and radiographs (n=84).

Quadriceps strength and single-legged hop test scores did not differ between the operative and non-operative groups. Nearly half of patients managed operatively demonstrated knee joint effusion at 5 years compared to only 10% of patients managed non-operatively (p: 0.008). Patients treated operatively reported higher scores on the Global Rating Scale of Perceived Function (p: 0.011; Op: 94.5±6.9%, Non-Op: 87.2±11.9%) and knee-related quality of life subscale of the Knee Injury and Osteoarthritis Outcome Score (p: 0.050; Op: 85.9±17.7%, Non-Op: 77.0±21.7%), and

lower levels of fear on the Tampa Scale for Kinesiophobia (TSK-11) (p: 0.023; Op: 16.2±5.5, Non-Op: 19.2±5.0). There were no group differences in the Knee Outcome Survey Activities of Daily Living Scale (KOS-ADLS), International Knee Documentation Committee Subjective Knee Form 2000 (IKDC), Marx Activity Rating Scale, ACL-Return to Sport after Injury (ACL-RSI), return to sport outcomes, or any of the other 4 subscales of the Knee Injury and Osteoarthritis Outcome Score at 5 years. The non-operative group walked with greater involved limb knee adduction moments and medial compartment contact forces than the patients treated with reconstruction. There were no differences in the presence of radiographic knee osteoarthritis.

Overall outcomes at 5 years were generally favorable for both surgical and non-surgical treatment approaches to anterior cruciate ligament injury where progressive, criterion-based rehabilitation was used. Patients treated operatively and non-operatively did demonstrate differences in joint effusion, some subjective reports of knee function, and measures of knee joint loading but not in quadriceps strength, performance on hop tests, return to sport outcomes, and the development of knee osteoarthritis at 5 years. Further study is needed to identify clinical algorithms for identifying the best candidates for surgical compared to conservative care after anterior cruciate ligament injury.

6.2 Introduction

An estimated 250,000 anterior cruciate ligament (ACL) injuries occur annually within the United States.[68,121] The majority (175,000) of patients in the United States undergo ACL reconstruction[66,160] assuming prior knee function will be restored, prior

activity levels will be attained, and further injury will be avoided.[47,106,127] Unfortunately, these goals are often not achieved following ACL reconstruction.[10,188]

Unrealistic expectations accompany patients who undergo ACL reconstruction. Feucht and colleagues surveyed 133 patients prior to primary ACL reconstruction regarding their beliefs on the overall condition of their knee joint, return to sports, and risk of knee osteoarthritis (OA) after surgery.[47] All patients expected a normal or nearly normal condition of the knee joint after ACL reconstruction. Returning to the same level of sport with no or only slight restrictions was expected by 94% of patients. Only 1% of patients expected their risk of knee OA to be significantly increased. Inflated assumptions regarding ACL reconstruction may influence decision-making regarding optimal management of injury and ultimately lead to inappropriate surgical care and poorer long-term outcomes.

Misconceptions regarding surgical reconstruction after ACL injury are also common among healthcare providers. In a survey of orthopedic surgeons only 15% believed patients can participate in all recreational sports activities without ACL reconstruction and 98% identified high-demand activities a positive factor influencing the decision to perform an ACL reconstruction.[123] Over half of surgeons reported the belief that ACL reconstruction reduces the rate of arthrosis in ACL-deficient knees.[123] Comparative studies of operative compared to non-operative outcomes after ACL injury do not support these beliefs. A comparison of athletes matched for age, sex, and pre-injury cutting and pivoting activity level revealed equal return to sport rates at 1 and 2 years following ACL injury regardless of operative or non-operative management.[69,71] Further, ACL reconstruction does not serve chondroprotective purposes despite restoration of passive knee joint stability. The incidence of knee OA

after ACL injury is similar between ACL-reconstructed and ACL-deficient patients.[157] Patient and clinician expectations, beliefs, and opinions of both surgical and non-surgical treatment approaches for ACL injury do not match current evidence.

The purpose of this study was to determine if differences exist in long-term functional, biomechanical, and radiographic outcomes between subjects completing operative compared to non-operative management of ACL injury when both groups complete a progressive, criterion-based rehabilitation protocol. We hypothesized that no differences in these outcomes would be present between the two groups. The comprehensive analysis of long-term outcomes after both reconstructive and non-operative treatment strategies for ACL deficiency will provide groundwork for improved education and decision-making between patient and clinicians.

6.3 Methods

6.3.1 Subjects

One-hundred five athletes with an acute, unilateral ACL injury (confirmed by a positive Lachman test and 3-mm or greater difference in anterior tibial excursion with instrumented arthrometry)[35] (KT1000; MEDmetric Corporation, San Diego, CO) between the ages of 14-55 at the time of injury were included. All patients participated in level 1 (e.g. soccer, basketball) or level 2 (e.g. tennis, downhill skiing) cutting and pivoting activities[35,81] prior to injury. Exclusion criteria included a repairable meniscus, symptomatic grade III injury to other knee ligaments, or articular cartilage lesions greater than 1 cm^2 diagnosed at the time of ACL injury. This study was approved by the Institutional Review Board at the University of Delaware and all participants provided written informed consent.

All patients completed physical therapy treatment early after ACL injury to resolve initial impairments (i.e. pain, effusion, knee range of motion, obvious gait impairments, and quadriceps strength deficits (70% of uninvolved limb required) and an additional 10 progressive physical therapy sessions to further restore lower extremity strength and neuromuscular control using protocols previously described.[79,88] Eighty-three patients underwent ACL reconstruction and 22 completed non-operative management of injury. No standardized process was used for surgical decision-making. Patients self-selected treatment strategy using recommendations from the orthopaedic surgeon and physical therapy team. Patients managed non-operatively were discharged to a home exercise program to maintain strength and neuromuscular control after the extended bout of rehabilitation described above and achievement of objective return to sport criteria[70,79] if patient goals included return to sports activities. Patients managed operatively underwent reconstruction by a single, board-certified orthopedic surgeon using either a four-bundle semitendinosus-gracilis autograft or soft tissue allograft. Criterion-based post-operative rehabilitation was completed early after surgery.[1]

Testing was completed 5 years after ACL reconstruction or completion of non-operative rehabilitation. Testing consisted of clinical measures of knee function, biomechanical gait analysis, and knee radiographs.

6.3.2 Clinical Measures of Knee Function

Clinical testing consisted of quadriceps strength testing, single-legged hop testing, knee joint effusion assessment, and completion of patient-reported outcomes. Patient-reported outcomes included the Knee Outcome Survey-Activities of Daily Living Scale (KOS-ADLS), Global Rating Scale of Perceived Function (GRS),

International Knee Documentation Committee Subjective Knee Form 2000 (IKDC), Knee Injury and Osteoarthritis Outcome Score (KOOS), Marx Activity Rating Scale (Marx), Tampa Scale for Kinesiophobia (TSK-11), and ACL-Return to Sport after Injury (ACL-RSI).

Quadriceps strength was tested using the burst superimposition technique during maximal voluntary isometric contraction (MVIC) using an electromechanical dynamometer (Kin-Com; DJO Global, Vista, CA) with patients seated in 90° of hip and knee flexion (Appendix Figure A1).[158] Stabilization straps secured the pelvis and thighs with the force transducer placed just proximal to the talocrural joint. Two 3 x 5-inch self-adhesive electrodes were placed proximally over the vastus lateralis and distally over the vastus medialis. Submaximal (50%, 75% of perceived maximum) and maximal (100% of perceived maximum) isometric knee extension contractions were completed to provide familiarization to the task and ensure absence of knee pain. Patients then completed a MVIC with an imposed supramaximal 10-pulse (600 microseconds, 135 V), 100-pulse-per-second train of electrical stimulation. Quadriceps activation was defined by the MVIC divided by the maximal force output during the superimposed electrical stimulation multiplied by 100. Up to 3 trials were completed on each limb (uninvolved first, followed by involved) until 95% quadriceps activation was achieved, activation levels plateaued, or the patient fatigued. Quadriceps index was the strength variable of interest in this study, calculated as the quotient of the involved limb MVIC to the uninvolved limb MVIC multiplied by 100.

Four single-legged hop tests (single, crossover, triple hop for distance; 6-meter timed hop) were completed on each limb using a 6-meter strip 15 cm wide (Appendix Figure A2).[13,34,132] The uninvolved limb was tested first followed by the involved limb

for each hop test. Two practice trials provided familiarization to the task and the next 2 usable trials on each limb were recorded (controlled landing on unilateral limb required). The average of two trials for each limb was used to calculate the quotient of the involved limb to the uninvolved limb multiplied by 100 for the single, crossover, and triple hops and the quotient of the uninvolved limb to the involved limb multiplied by 100 for the 6-meter timed hop. Single-legged hop tests were not completed if the quadriceps index was less than 70% in patients after non-operative rehabilitation or less than 80% in patients after ACL reconstruction.

Knee joint effusion was measured using the modified stroke test.[167] The modified stroke test is reliable in a clinical setting and is scored on a 5-point scale (Appendix Table A1). The presence of knee joint effusion was operationally defined by a grade of trace or greater.

The KOS-ADLS is a valid and reliable measure of impairment and functional limitation experienced during activities of daily living secondary to knee pathology.[93] Fourteen items are scored using a 6-point ordinal scale, with a total score out of a possible 70 points represented as a percentage. A score of 100% represents the absence of knee impairment and functional limitation during activities of daily living.

The GRS consists of a single, reliable question asking the patient to rate their current perceived level of knee function compared to their perceived knee function prior to injury on a scale from 0 to 100.[85,115] Zero represents the inability to perform any activity and 100 indicates the level of activity prior to injury.

The IKDC is a measure of knee specific symptoms, function and sports activities valid and reliable for a variety of knee conditions including ACL injury.[9,91]

Eighteen items are scored on a scale from 0 to 100, with higher scores indicating higher self-reported levels of knee function.

The KOOS is a reliable measure widely used in the ACL population.[2,58,120,191] It consists of 5 subscales assessing patient symptoms, complaints of pain, function in daily life, function during sports and recreational activities, and knee-related quality of life.[145] The score for each subscale ranges from 0 to 100, with higher scores indicating higher subjective knee function within each domain.

The Marx is a reliable scale which assesses the frequency of activities including running, cutting, decelerating and pivoting for patients with knee pathology.[124] Four items are scored on a 4-point scale resulting in a score from 0 to 16, with 0 indicating completion of the four activity items less than one time per month and 16 indicating completion of the four activity items at least four times per week.

The TSK-11 is a modified version of the original Tampa Scale for Kinesiophobia that measures fear of movement and re-injury. It is a reliable and valid measure although not specifically designed for patients with knee pathology.[190] Eleven items can result in a range of scores from 11 to 44, with higher scores indicating higher levels of fear. TSK-11 scores have been shown to be elevated following ACL injury and related to lower self-report of knee function and rates of return to pre-injury activity levels in this population.[26,104,108]

The ACL-RSI is a reliable and valid patient-reported measure of emotions, confidence in performance, and risk appraisal associated with return to sport activities specifically designed for patients with ACL injury.[105,180] Scores range from 0 to 100 calculated from the average of 12 questions, with lower scores indicating more negative psychological responses in regard to returning to sport.

Additionally, patients reported the level of participating cutting and pivoting activities as described by the IKDC 2000 activity scale.[9,35,81] Comparison of the patient's current participation level was made with their reported level prior to ACL injury on the same scale. Patients also reported current pain, worst pain, and best pain over the past week on a visual analog scale from 0 to 10, with 0 indicating no pain and 10 indicating the worst pain imaginable.

6.3.3 Gait Analysis

Kinetic, kinematic, and surface electromyography (EMG) data was collected during gait analysis. Eight infrared cameras (VICON, Oxford Metrics Ltd., London, UK) sampled at 120 Hz tracked the position a retro-reflective marker set placed at the pelvis and bilateral lower extremities which has previously been shown to have excellent intersession reliability.[163] Surface EMG data was collected using a MA-300 EMG system sampled at 1,080 Hz (Motion Lab Systems, Baton Rouge, LA) for the medial and lateral vasti, rectus femoris, biceps femoris, semimembranosus, medial and lateral gastrocnemii, and soleus of each limb. Patients completed maximal voluntary isometric contractions (MVIC's) for each muscle group (quadriceps, hamstrings, gastrocnemii, and soleus) to later normalize EMG amplitude during walking trials.

Patients walked at a self-selected speed along a 6-meter walkway with an embedded force plate sampled at 1,080 Hz (Bertec Corporation, Worthington, OH). Walking speed was maintained (±5%) for all walking trials using a timing system. Stance phase joint angles and moments were processed using inverse dynamics within custom software (Visual 3D, C-Motion, Germantown, MD) as the average of three walking trials. Kinematic and kinetic data were low pass filtered at 6 Hz and 40 Hz, respectively. Initial contact and end of stance were identified using a 50-N threshold.

All trials were normalized to 100% of stance. Moments were normalized to mass (kg) and height (m). Variables of interest included the stance phase peak knee flexion angle, peak knee adduction angle, peak external knee flexion moment, and peak external knee adduction moment (during first 50% of stance).

EMG data were high-pass filtered (2nd order Butterworth, 30 Hz), rectified, and low-pass filtered (2nd order Butterworth, 6 Hz) to creased a linear envelope for MVIC's and walking trials. EMG data during walking trials were normalized to maximal activity for each muscle detected during any of the MVIC or walking trials and used as input for a musculoskeletal model to estimate knee joint contact forces.[21,62] This model has demonstrated good repeatability in patients with ACL injury[60] and has been validated by accurately predicting in vivo joint contact forces in an instrumented knee prosthesis.[122] The EMG-driven model uses an anatomical, activation dynamics, and contraction dynamics model. The anatomic model uses 10 muscle-tendon units to actuate pelvis, femur, tibia and foot segments scaled to subject anthropometry to characterize musculoskeletal geometry. The activation dynamics model transforms the neural EMG signal to a muscle activation signal. The contraction dynamics model uses a Hill-type muscle model to transform muscle activation to muscle force. Muscle parameters including optimal muscle fiber length and tendon slack length are adjusted within each of the latter two models during subject-specific model calibration. These parameters were allowed to vary within physiological bounds previously described.[62] Muscle forces for 3 walking trials were then predicted by the model using a set of EMGs. Medial compartment contact forces for each trial were calculated by balancing the external knee adduction moment (calculated from inverse dynamics) with the internal adduction moment (predicted by muscle forces) and the

contact force in the medial compartment.[189] The external and internal knee adduction moments were expressed about a contact point at the midpoint of the lateral compartment (25% tibial plateau width) with the medial compartment contact force acting at the midpoint of the medial compartment. The variable of interest in this study was the peak medial compartment contact force during the first half of stance presented over 3 walking trials.

6.3.4 Radiographs

Patients completed weightbearing posterior-anterior (PA) bent knee (30°) radiographs 5 years after ACL reconstruction or completion of non-operative rehabilitation. SigmaView software (Agfa HealthCare Corporation, Greenville, SC) was used to view radiographs. Osteoarthritis in the medial and lateral tibiofemoral compartment of each limb was graded using the Kellgren-Lawrence (KL) system.[96] The presence of osteoarthritis was defined as a KL grade greater than or equal to 2. Additionally, minimum joint space width (JSW) measurements were manually measured in each tibiofemoral compartment of each limb. Joint space width was also measured at fixed locations within the tibiofemoral joint (medial compartment: 25% of distance from medial to lateral edge of femur ($JSW_{.25}$); lateral compartment: 70% of distance from medial to lateral edge of femur ($JSW_{.70}$). These specific locations have demonstrated the greatest responsiveness to longitudinal changes within each compartment, respectively, in the Osteoarthritis Initiative (OAI) cohort.[39] Interlimb JSW differences were calculated for each JSW measure (involved minus uninvolved). Excellent between day, intrarater reliability for radiographic measures of interest has previously been demonstrated using 20 radiographs of patients 5 years after ACL injury (graded by EW; Cohen's kappa (κ) for KL grades: 0.904, p: <0.001; all KL

grades verified by board-certified orthopedic surgeon; intracorrelation coefficient (ICC) for minimal JSW: 0.981, p: <0.001).

6.3.5 Statistical Analysis

Statistical analyses were completed using PASSW 23.0 software (SPSS Inc., Chicago, IL). Independent *t*-tests, Fisher's exact tests, and Chi-square tests were used to test differences in baseline characteristics, concomitant injuries, second ACL injuries, clinical measures of knee function, hip and knee joint biomechanics, and radiographic measures between patients who underwent ACL reconstruction compared to non-operative ACL management. Minimal detectable changes (MDC) (Table 6.1-6.3) and effect sizes (ES)[29] were used qualitatively to determine if meaningful differences existed in clinical and biomechanical measures between the patients managed operatively and non-operatively. *A priori* statistical significance was set at $\alpha \leq 0.05$.

Table 6.1: Minimal detectable change (MDC) values for single-legged hop tests,[142,148] Knee Outcome Survey Activities of Daily Living (KOS-ADLS),[30] Global Rating Scale of Perceived Function (GRS),[85,115] International Knee Documentation Committee Subjective Knee Form 2000 (IKDC),[92] Knee Injury and Osteoarthritis Outcome Score (KOOS),[30] Tampa Scale for Kinesiophobia (TSK-11),[26] and ACL-Return to Sport after Injury (ACL-RSI).[105] Abbreviations: ADL, activities of daily living; Rec, recreation; QoL, knee-related quality of life.

Clinical Measure	MDC
Single hop	8.1 %
Crossover hop	12.3 %
Triple hop	10.0 %
6-meter timed hop	13.0 %
KOS-ADLS	11.4 %
GRS	6.5 %
IKDC	12.8%
KOOS-Pain Subscale	6.1%
KOOS-Symptoms Subscale	8.5%
KOOS-ADL Subscale	8.0%
KOOS-Sport/Rec Subscale	12.0%
KOOS-QoL Subscale	7.2%
TSK-11	3.0
ACL-RSI	1.9

Table 6.2: Minimal detectable change (MDC) values for sagittal and frontal plane knee kinematics and kinetics and peak medial compartment contact forces during gait.[63]

Gait Variable during Stance	MDC_{95}
Peak Knee Flexion Angle	2.9 °
Peak Knee Adduction Angle	1.7 °
Peak Knee Flexion Moment	0.09 Nm/kg·m
Peak Knee Adduction Moment	0.06 Nm/kg·m
Peak Medial Compartment Force	0.30 BW

Table 6.3: Minimal detectable changes (MDC) values at a 95% confidence interval for sagittal and frontal plane hip kinematics and kinetics during gait.

Gait Variable during Stance	MDC_{95}
Peak Hip Flexion Angle	3°
Peak Hip Extension Angle	2°
Hip Excursion Angle	4°
Peak Hip Adduction Angle	3°
Peak Hip Flexion Moment	0.08 Nm/kg·m
Peak Hip Extension Moment	0.04 Nm/kg·m
Peak Hip Adduction Moment	0.06 Nm/kg·m

6.4 Results

One-hundred five patients returned for 5-year testing (Figure 6.1). Eighty-three underwent ACL reconstruction and 22 completed non-operative ACL management. The operative and non-operatively managed patients did not differ in age, body mass index, time to 5-year testing (calculated as time since ACL reconstruction or completion of non-operative rehabilitation), sex, concomitant injuries at the time of ACL injury, or classification as a noncoper or potential coper early after injury[49] (Table 6.4). A greater proportion of patients managed operatively were participating in level I cutting and pivoting activities prior to injury compared to a greater proportion of patients managed non-operatively completing level II activities (p: 0.041; Op: Level I: 59, Level II: 24; Non-Op: Level I; 10, Level II: 12). None of the patients managed non-operatively experienced a contralateral ACL injury. Fifteen patients managed operatively experienced a second ACL injury (10 ipsilateral, 5 contralateral), but the rate of contralateral ACL injuries was not statistically different between the patients managed operatively or non-operatively (Table 6.4).

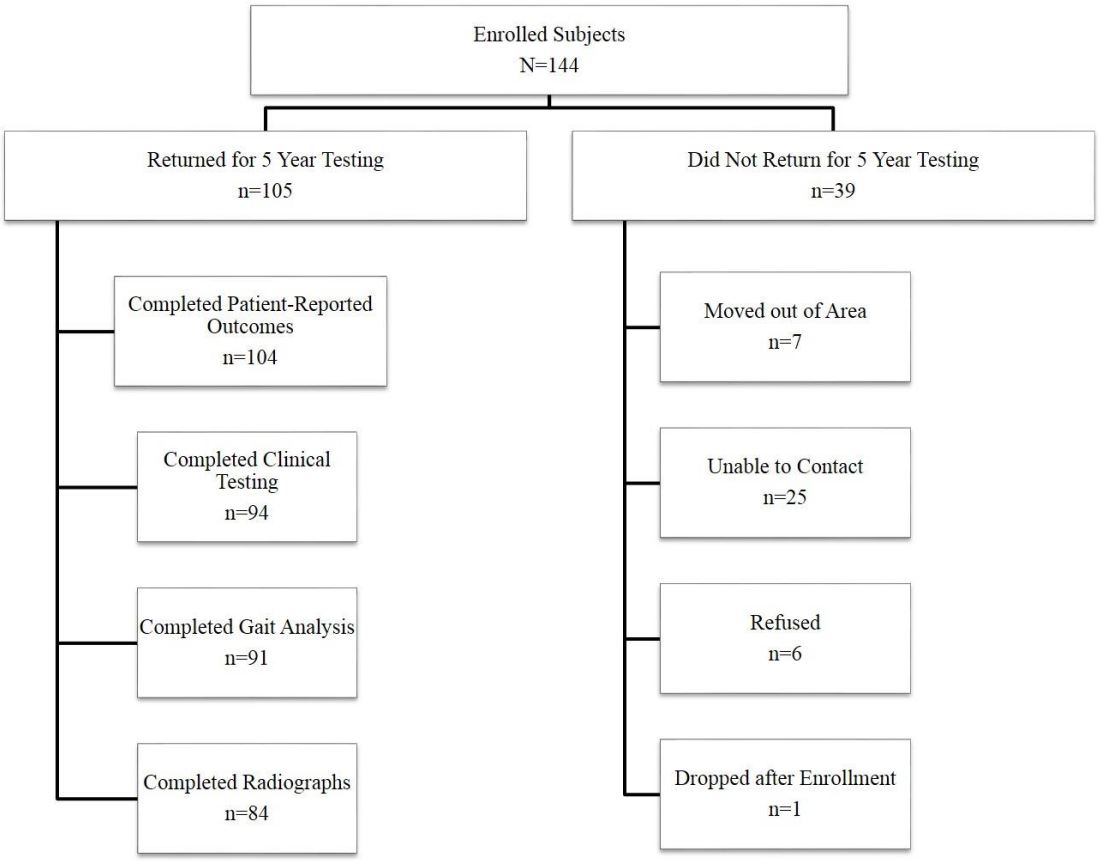

Figure 6.1: Flow diagram of study cohort.

Table 6.4: Baseline, concomitant, and second ACL injury characteristics between patients who underwent ACL reconstruction compared to non-operative management of ACL injury. Boldface numbers indicate statistically significant group differences. *Bone bruise data includes 89/105 patients. Abbreviations: yrs, years; kg, kilogram; m, meter; M, male; F, female.

	Op (n=83)	Non-Op (n=22)	p
Age (at 5 year testing) (yrs)	33.6 (11.0)	36.8 (13.0)	0.248
Body Mass Index (kg/m^2)	26.6 (4.3)	26.5 (4.7)	0.862
Time from ACL reconstruction/non-op rehabilitation to 5 year testing (yrs)	5.4 (0.8)	5.1 (0.6)	0.092
Sex (M:F)	56:27	10:12	0.082
Pre-Injury Activity Level (1:2)[35,81]	59:24	10:12	**0.041**
Noncoper:Potential Coper[49]	47:36	8:14	0.100
Concomitant meniscus tear (Yes:No)	35:48	6:16	0.202
Concomitant chondral injury (Yes:No)	3:80	3:19	0.105
Concomitant bone bruise (Yes:No)*	59:11	15:4	0.730
Second ACL injury after initial ACL injury (Yes:No)	15:68	0:22	**0.037**
Contralateral second ACL injury after initial ACL injury (Yes:No)	5:78	0:22	0.581

Due to the long-term follow-up required by this study, a portion of patients who had moved out of the area completed patient-reported outcomes remotely but did not return for quadriceps strength, single-legged hop, and effusion testing. Ninety-four patients (Op: 75, Non-Op: 19) completed quadriceps strength testing and 90 (Op: 71, Non-Op 19) completed effusion testing. An additional 24 patients who completed quadriceps strength testing did not complete single-legged hop testing for reasons listed in Table 6.5, leaving 69 (Op: 55, Non-Op: 15) available for data analysis. The patients managed operatively compared to non-operatively did not differ in quadriceps strength or any of the 4 single legged hop tests (single, crossover, triple, 6-meter timed) at 5 years (Table 6.6). Nearly half of the patients treated with reconstruction

demonstrated knee joint effusion at 5 years compared to only 10% of patients managed non-operatively (p: 0.008; Op: 31 with effusion, 40 without effusion; Non-Op: 2 with effusion, 17 without effusion).

Table 6.5: Primary reasons single-legged hop testing was not completed during 5 year testing.

Hop Testing Not Completed Due To:	Number of Patients
Knee joint effusion:	2 Op
Quadriceps index <90%	2 Op
Knee joint effusions and quadriceps index <90%	2 Op
Knee pain with hopping	4 Op
Contralateral lower extremity pain with hopping	1 Op
Recent additional lower extremity injury	3 Op
Patient safety	3 Op, 1 Non-Op
Patient refusal	2 Op, 3 Non-Op
Unknown	1 Op

Table 6.6: Clinical measures of knee function between patients who underwent ACL reconstruction compared to non-operative management of ACL injury. Boldface numbers indicate statistically significant group differences. Abbreviations: KOS-ADLS, Knee Outcome Survey Activities of Daily Living Scale; GRS, Global Rating Scale of Perceived Function; IKDC, International Knee Documentation Committee Subjective Knee Form 2000; KOOS, Knee Injury and Osteoarthritis Outcome Score; ADL, activities of daily living; QoL, quality of life; Marx, Marx Activity Rating Scale; TSK-11, Tampa Scale for Kinesiophobia; ACL-RSI, Anterior Cruciate Ligament Return to Sport after Injury.

	Op	Non-Op	p
Quadriceps Index (%)	104.7 (17.9)	103.1 (17.9)	0.734
Single Hop (%)	101.1 (10.8)	101.8 (7.4)	0.812
Crossover Hop (%)	102.2 (10.4)	97.8 (7.8)	0.131
Triple Hop (%)	101.2 (9.4)	100.9 (6.3)	0.930
6-meter Timed Hop (%)	101.2 (8.1)	100.5 (5.5)	0.758
KOS-ADLS (%)	96.7 (4.5)	95.5 (5.5)	0.291
GRS (%)	94.5 (6.9)	87.2 (11.9)	**0.011**
IKDC (%)	92.1 (9.7)	87.8 (11.9)	0.078
KOOS-Pain Subscale (%)	95.8 (6.6)	94.2 (9.3)	0.361
KOOS-Symptoms Subscale (%)	90.6 (10.0)	92.0 (10.8)	0.553
KOOS-ADL Subscale (%)	98.1 (4.4)	97.5 (5.4)	0.637
KOOS-Sport/Rec Subscale (%)	91.1 (12.8)	89.5 (17.7)	0.638
KOOS-QoL Subscale (%)	85.9 (17.7)	77.0 (21.7)	**0.050**
Marx	8.7 (4.8)	7.0 (4.2)	0.142
TSK-11	16.2 (5.5)	19.2 (5.0)	**0.023**
ACL-RSI	8.0 (2.5)	6.7 (3.1)	0.096
Current Pain	0.2 (0.5)	0.3 (0.6)	0.482
Worst Pain	0.6 (1.1)	1.5 (1.9)	0.052
Best Pain	0.1 (0.5)	0.0 (0.2)	0.787
Effusion (Yes:No)	31:40	2:17	**0.008**
Activity Level at 5 Years (1:2:3:4)[35,81]	42:13:24:3	7:6:8:1	0.400
Currently at Pre-Injury Activity Level (Yes:No)[35,81]	50:32	11:11	0.465

Patient-reported outcomes were completed by 82 operative and 22 non-operatively managed patients. Some outcomes measures were not completed by all patients managed operatively (KOOS: 80; Marx: 79; TSK-11: 81; ACL-RSI: 80). Patients treated operatively reported higher scores on the GRS than patients treated non-operatively (p: 0.011; Op: 94.5±6.9%, Non-Op: 87.2±11.9%; ES: 0.89) and also reported higher knee-related quality of life on the KOOS (p: 0.050; Op: 85.9±17.7%, Non-Op: 77.0±21.7%; ES: 0.48). Patients managed non-operatively reported higher levels of fear on the TSK-11 (p: 0.023; Op: 16.2±5.5, Non-Op: 19.2±5.0; ES: 0.56). No group differences were present in the KOS-ADLS, IKDC, Marx, ACL-RSI, current, worst, or best pain, cutting and pivoting activity level at 5 years, return to pre-injury activity level, or any of the other 4 subscales of the KOOS (pain, symptoms, activities of daily living, sport/rec) (Table 6.6).

Peak knee angles did not differ between patients managed operatively and non-operatively during gait (Table 6.7). Patients treated non-operatively walked with a greater peak knee adduction moment in the involved limb (p: 0.002; Op: 0.26±0.08 Nm/kg·m, Non-Op: 0.33±0.08 Nm/kg·m; ES: 0.83) and asymmetrically larger knee adduction moments in the involved limb compared to symmetric adduction moments in patients treated operatively (involved minus uninvolved) (p: 0.038; Op: -0.01±0.08 Nm/kg·m, Non-Op: 0.04±0.10 Nm/kg·m; ES: 0.55). No differences in peak knee flexion moment existed (Table 6.7). Contact force data was available for 57 patients (Op: 40, Non-Op: 17). Peak medial compartment contact forces were larger in the involved limb of the non-operative group (p: <0.001; Op: 2.37±0.47 BW, Non-Op: 3.03±0.53 BW; ES: 1.35) but the interlimb difference was not statistically different (Table 6.7). The only biomechanical group difference at the hip was the interlimb

difference in peak hip extension moment (Table 6.8). Patients managed operatively walked with symmetric hip extension moments in the involved compared to the uninvolved limb but asymmetrically lower moments were present in the involved hip of patients managed non-operatively (p: 0.006; Op: 0.01±0.08 Nm/kg·m, Non-Op: -0.04±0.06 Nm/kg·m; ES: 0.74).

Table 6.7: Involved limb and interlimb differences in sagittal and frontal plane kinematics and kinetics and medial compartment contact forces during stance phase of gait between patients who underwent ACL reconstruction compared to non-operative management of ACL injury. Boldface numbers indicate statistically significant group differences. *Contact force data includes 57/91 patients (40 op, 17 non-op). Abbreviations: N, newton; m, meter; kg, kilogram; BW, body weight.

	Op (n=73)	Non-Op (n=18)	p
Peak Knee Flexion Angle (°)	22.6 (6.4)	22.9 (7.0)	0.844
Interlimb Difference (°)	-0.4 (4.2)	-0.3 (3.6)	0.941
Peak Knee Adduction Angle (°)	3.1 (2.5)	3.0 (3.0)	0.847
Interlimb Difference (°)	-0.7 (2.6)	-1.8 (3.4)	0.145
Peak Knee Flexion Moment (Nm/kg·m)	0.49 (0.13)	0.52 (0.09)	0.369
Interlimb Difference (Nm/kg·m)	-0.02 (0.10)	0.00 (0.07)	0.584
Peak Knee Adduction Moment (Nm/kg·m)	0.26 (0.08)	0.33 (0.09)	**0.002**
Interlimb Difference (Nm/kg·m)	-0.01 (0.08)	0.04 (0.10)	**0.038**
Peak Medial Compartment Contact Force (BW)*	2.37 (0.47)	3.03 (0.53)	**<0.001**
Interlimb Difference (BW)*	-0.01 (0.51)	0.27 (0.87)	0.143

Table 6.8: Involved limb and interlimb differences in sagittal and frontal plane hip kinematics and kinetics during stance phase of gait between patients who underwent ACL reconstruction compared to non-operative management of ACL injury. Boldface numbers indicate statistically significant group differences. Abbreviations: N, newton; m, meter; kg, kilogram.

	Op (n=73)	Non-Op (n=18)	p
Peak Hip Flexion Angle (°)	28.4 (7.2)	26.8 (5.8)	0.378
Interlimb Difference (°)	0.9 (3.2)	1.0 (4.2)	0.919
Peak Hip Extension Angle (°)	20.9 (6.7)	21.6 (5.4)	0.668
Interlimb Difference (°)	-0.2 (3.1)	-0.8 (1.9)	0.409
Hip Excursion Angle (°)	49.3 (5.3)	48.4 (5.4)	0.528
Interlimb Difference (°)	0.7 (4.2)	0.2 (5.1)	0.653
Peak Hip Adduction Angle (°)	8.0 (3.0)	8.4 (4.0)	0.619
Interlimb Difference (°)	0.0 (3.9)	0.3 (5.5)	0.766
Peak Hip Flexion Moment (Nm/kg·m)	0.62 (0.15)	0.63 (0.13)	0.981
Interlimb Difference (Nm/kg·m)	-0.01 (0.10)	0.02 (0.10)	0.164
Peak Hip Extension Moment (Nm/kg·m)	0.70 (0.15)	0.73 (0.15)	0.501
Interlimb Difference (Nm/kg·m)	0.01 (0.08)	-0.04 (0.06)	**0.006**
Peak Hip Adduction Moment (Nm/kg·m)	0.55 (0.10)	0.62 (0.15)	0.090
Interlimb Difference (Nm/kg·m)	0.01 (0.12)	0.05 (0.17)	0.374

Tibiofemoral knee joint OA as defined by KL grading was present in 23.4% of patients managed operatively and 5.0% of patients managed non-operatively (Table 6.9). No statistical group differences were present in the rate of medial or lateral compartment OA in the involved or uninvolved limbs (Table 6.9). Joint space width did not differ between patients managed operatively and non-operatively in either tibiofemoral compartment (Table 6.9).

Table 6.9: Radiographic characteristics between patients who underwent ACL reconstruction compared to non-operative management of ACL injury. Boldface numbers indicate statistically significant group differences. *Joint space width data includes 82/84 patients. Abbreviations: OA, osteoarthritis; JSW, joint space width; mm, millimeter.

	Op (n=64)	Non-Op (n=20)	p
Involved OA-Medial Compartment (Yes:No)	10:54	1:19	0.447
Involved OA-Lateral Compartment (Yes:No)	8:56	1:19	0.679
Involved OA-Medial or Lateral Compartment (Yes:No)	15:49	1:19	0.102
Uninvolved OA-Medial Compartment (Yes:No)	4:60	0:20	0.568
Uninvolved OA-Lateral Compartment (Yes:No)	4:60	1:19	>0.999
Uninvolved OA-Medial or Lateral Compartment (Yes:No)	6:58	1:19	0.468
Minimum JSW Difference-Medial Compartment (mm)	0.0 (1.2)	0.0 (0.9)	0.978
$JSW_{0.25}$ Difference-Medial Compartment (mm)	0.2 (1.0)	0.1 (0.8)	0.522
Minimum JSW Difference-Lateral Compartment (mm)	-0.5 (1.1)	-0.3 (1.3)	0.439
$JSW_{0.70}$ Difference-Lateral Compartment (mm)	-0.2 (0.8)	-0.1 (1.0)	0.532

6.5 Discussion

The purpose of this study was to determine if differences exist in long-term functional, biomechanical, and radiographic outcomes between subjects completing operative compared to non-operative management of ACL injury. All patients completed progressive, criterion-based rehabilitation and self-selected an operative or non-operative treatment strategy using recommendations from the orthopaedic surgeon and physical therapy team. The findings of this study indicate that 5-year functional, biomechanical, and radiographic outcomes are similar between operatively and non-operatively treated patients. However, patients managed operatively did demonstrate more knee joint effusion, higher self-report in global knee function and

quality of life and lower self-reported fear, and lower measures of knee and hip joint loading than patients managed non-operatively.

Patient-reports of knee function are important components for measuring success after ACL injury and reconstruction.[119] Patient-reported outcomes can impact patient satisfaction after ACL injury to a greater extent than clinical measures of knee function.[99] In the current study patients managed non-operatively scored 7.3% lower on the GRS and 8.9% lower on the knee-related quality of life subscale of the KOOS, both greater than minimal detectable changes of 6.5% and 7.2%, respectively.[30,85,115] The GRS asks the patient to rate current knee function compared to knee function prior to injury, while the quality of life subscale of the KOOS addresses awareness of knee problems, modifications to lifestyle to avoid potential damage to the knee, and lack of knee confidence. Patients managed non-operatively were not different from patients treated with reconstruction in level of activity, knee symptoms, or ability to complete activities of daily living as indicated by scores on the KOS-ADLS, IKDC, and the pain, symptoms, activities of daily living, and sport/recreation subscales of the KOOS. The comprehensive findings comparing patient-reported outcomes between the two contrasting surgical approaches of ACL injury may indicate a more conscientious pattern of movement adopted by patients treated non-operatively. Patients completing rehabilitation alone are potentially more careful of how they move compared to prior to injury, but this heightened awareness may not change their physical ability to complete daily and sports activities when compared to their ACL-reconstructed counterparts. Scores on the TSK-11 further corroborate this explanation for differences found in self-reported function. Patients managed non-operatively reported higher levels of fear on the TSK-11 than those treated operatively, with the

difference matching the minimal detectable change of 3.0 points.[26] Although scores on the TSK-11 have been reported at various timeframes for patients with ACL injury, it is unknown what score on this measure represents a "normal" or "healthy" level of fear. The higher level of fear reported by the patients managed non-operatively may represent an implemented strategy to safely and successfully achieve high levels of knee function and long-term knee joint health without surgical intervention.

Quadriceps strength and performance on single-legged hop testing did not differ between the operative and non-operative groups. Scores on strength and hop measures were high, with both groups demonstrating over 97% symmetry in quadriceps strength and all 4 hop tests. Further, frequency of cutting and pivoting activities as indicated by Marx scores along with participation in cutting and pivoting activities at 5 years did not differ between patients treated operatively and non-operatively. Sixty-one percent of patients treated with reconstruction and 50% of patients treated with rehabilitation alone were engaging in their pre-injury level of activity at 5 years. The current findings further rebuke the misconception of patients and clinicians that ACL reconstruction is mandatory to achieve restoration of knee function and return to high-demand sports activities.[47,106,127] The ability to return to cutting and pivoting sports undoubtedly requires a stable knee joint. ACL reconstruction is superior to non-operative management in reducing knee joint laxity.[57,58,71,126,157] However, neuromuscular control mechanisms can overcome joint laxity and provide the necessary dynamic knee stabilized required for high level activities.[51] Similar return to sport rates between patients managed operatively and non-operatively after matching by age, sex, and cutting and pivoting activity level have been reported at 1 and 2 years.[69,71] With the implementation of progressive,

criterion-based rehabilitation, return to sport and high levels of knee performance can be achieved with both operative and non-operative ACL treatment strategies.

Knee joint effusion is ubiquitous after ACL injury and reconstruction. Previous findings within our lab reported that some level of measureable knee joint effusion was present in 85% of patients at an average of 27 days after injury.[118] The rehabilitation protocols completed by subjects in this study all implemented effusion management techniques, with objective measures of effusion used as a marker for exercise progression and clearance to run and hop.[1,88] Despite attention to knee joint effusion both pre-operatively and post-operatively, 43% of patients treated operatively demonstrated an effusion grade of trace or more 5 years after reconstruction. In comparison, only 10% of patients managed non-operatively demonstrated a measureable knee joint effusion 5 years after completion non-operative rehabilitation. Group differences in effusion were present despite similar Marx activity scores and participation in cutting and pivoting sports activities at 5 years. Further, concomitant baseline meniscus, articular cartilage, and bone bruise injuries which could contribute to joint effusion were not different between the operative and non-operative groups. Prior knee joint effusion data (using the same modified stroke test methodology[167]) existed for 66 operatively managed patients measured after pre-operative rehabilitation and 17 non-operatively managed patients measured after non-operative rehabilitation. The presence of knee joint effusion after pre-operative rehabilitation did not differ between patients managed operatively with and without knee joint effusion 5 years after reconstruction (p: 0.180) (Table 6.10). Further, the presence of knee joint effusion after pre-operative or non-operative rehabilitation did not differ between patients treated operatively and non-operatively despite the higher rate of effusion in

operative patients at 5 years (p: 0.251) (Table 6.11). The mechanisms leading to chronic knee joint effusion are not understood. However, the trauma induced by surgical reconstruction may result in negative long-term effects in knee joint effusion for certain individuals. Chronic knee joint effusion may be a precipitating factor in the development of knee OA. For example, the biomarker aggrecanase-4 (ADAMTS-4) is thought to be a significant player in degenerative joint diseases.[54] Roberts et al. found both knee joint effusion (in the presence of any knee pathology) and knee joint OA to be predictive of ADAMTS-4 levels in the knee's synovial fluid.[143] Further study is warranted to determine the influence of knee joint effusion on the development of post-traumatic OA after ACL injury.

Table 6.10: Number of patients managed operatively with knee joint effusion after pre-operative rehabilitation and 5 years after ACL reconstruction.

		Effusion at 5 Years		
		Yes	No	p
Effusion after Pre-Operative Rehabilitation	Yes	23	23	0.180
	No	6	14	

Table 6.11: Number of patients managed operatively with knee joint effusion after pre-operative rehabilitation and patients managed non-operatively with knee joint effusion after non-operative rehabilitation.

		Op	Non-Op	p
Effusion after Post-Operative Rehabilitation or Non-Operative Rehabilitation	Yes	46	9	0.251
	No	20	8	

No statistically significant radiographic differences existed between patients managed operatively compared to non-operatively. A trend toward an increased rate of OA in either the medial and/or lateral tibiofemoral compartment (as defined by a KL grade of 2 or greater) in patients managed operatively was present compared to patients managed non-operatively. Only 1 of 20 patients treated non-operatively had tibiofemoral OA compared to 15 of 66 patients treated operatively at 5 years after ACL reconstruction or non-operative rehabilitation. A systematic review by Smith et al. compared outcomes between operatively and non-operatively treated patients with similarly isolated ACL injuries to those included in the current study.[157] They concluded that the risk for developing knee OA was not different between groups

during the first 10 years after injury, but ACL-reconstructed patients had a slightly higher likelihood to develop this sequelae after 10 years compared to the non-operative group. Further follow-up of patients within our cohort is needed to determine if a similar pattern of OA development emerges. Interlimb differences in JSW of patients managed operatively did not differ from those of the non-operative group in either tibiofemoral compartment. Previous studies have reported greater minimal joint space width and cartilage volume in the involved limb compared to the uninvolved limb 2 to 3 years after ACL injury.[59,95] However, increasing age mitigated the extent of interlimb cartilage volume differences.[59] A pattern of greater involved limb joint space width did not emerge in our cohort. The older age of subjects in the current study and radiographic testing at 5 years compared to 2 to 3 years earlier as in the previously mentioned studies may explain the differences in findings.

Frobell and colleagues reported outcomes at a similar 5-year time point of patients randomized either to early ACL reconstruction or to the option to having delayed ACL reconstruction if needed.[58] Forty-nine percent of patients in the latter group continued non-operative management through 5 years. Similar findings to the current study were reported by Frobell et al. when comparing the early reconstruction group to those who remained non-operatively treated at 5 years. Frobell reported the absence of group differences in any of the 5 KOOS subscales, in activity level and return to pre-injury activity level at 5 years when assessed by the Tegner activity scale, or in the presence of radiographic OA in the involved tibiofemoral joint. Mean scores for the operative and non-operative groups on each KOOS subscale were similar in magnitude between Frobell et al. and the current study. Rates of OA development were also similar between the 2 studies. Frobell reported that 16% of patients treated

with early ACL reconstruction and 12% of patients treated with rehabilitation alone demonstrated radiographic tibiofemoral OA compared to 23% and 5%, respectively, in the current study.

Consideration of long-term movement patterns are important due to their link to risk of second ACL injury, ability to return to sport after ACL injury, and development of post-traumatic knee OA.[8,80,136,164] Knee joint angles, moments, and contact forces are altered early after ACL injury[27,60,62,149,150] and presumably result in compensatory changes at the hip and ankle joint.[90] Abnormal joint angles and mechanics can persist for years after ACL reconstruction.[23,61,137,144,181,183,184,192] In the current study patients who underwent ACL reconstruction walked with symmetric sagittal and frontal plane knee angles and moments and medial compartment contact forces 5 years after surgery. The symmetric frontal plane moments of the operative group at 5 years is similar to findings by Varma et al. of reconstructed patients at 4.5 years after ACL reconstruction.[176] Others have reported asymmetrically lower knee adduction moments in the reconstructed limb but at earlier time points from surgery.[181,192] The difference in findings may indicate long-term longitudinal changes in movement patterns after ACL injury, necessitating careful comparison between studies of biomechanical findings across time points.

The knee adduction moment and medial contact force in the involved limb of patients managed operatively was lower than that of patients managed non-operatively at 5 years. Further, the symmetric knee adduction moment of the operative group differed from the asymmetrically greater peak adduction moment in the involved knee of the non-operative group. To our knowledge long-term knee joint biomechanics in patients completing non-operative management of ACL injury have not been reported.

Although greater knee adduction moments have been associated with the presence and severity of primary OA in older adults[53,107,111,129] it is unknown if higher joint loads are destructive or protective to articular cartilage after ACL injury.[8,186] Although patients managed non-operatively walked with greater involved limb knee adduction moments and medial compartment contact forces than patients treated with reconstruction at 5 years, only 5% had medial knee OA compared to 15% of operatively treated patients. These findings suggest that greater knee joint loading is not destructive in non-operatively managed patients at a macroscopic, radiographic level at this early 5-year time point for detecting post-traumatic OA. Continued investigation of joint biomechanics is needed to further tease out the role of joint loading on articular cartilage health after ACL injury.

A comprehensive study of 5-year outcomes comparing an operative to non-operative treatment strategy was presented in this study. Our findings indicate that favorable outcomes can occur following both treatment approaches when progressive, criterion-based rehabilitation is incorporated. Further evidence is provided that return to sport outcomes do not differ between operatively and non-operatively treated groups of patients, advocating against the use of patient intention to return to sport as the primary driver in early surgical decision-making after ACL injury. Despite the current findings, a huge hurdle still exists in successfully screening and identifying the best candidates for both ACL reconstruction and non-operative rehabilitation. The ability for patients who initially present with poor dynamic knee stability to improve knee function and succeed with non-operative management[128] may signal the need for extended periods of progressive rehabilitation to restore maximal knee function prior to surgical decision-making. In addition, it is not known whether outcomes at 5 years

vary in alternate ACL populations. Our findings may not be generalizable to those with more extensive concomitant injuries or less active in sports activities. However, our findings do open the door to improving the educational process between patients and clinicians regarding the expected clinical course and long-term outcomes of operative and non-operative treatment of ACL injuries.

6.6 Conclusion

Patients treated with ACL reconstruction compared to rehabilitation alone did not differ in quadriceps strength, performance on single-legged hop tests, level of sports activities, subjective reports of pain, symptoms, or activities of daily living, or the presence of knee OA 5 years after surgery or non-operative rehabilitation. Patients managed operatively did report greater global ratings of knee function, higher knee-related quality of life, and lower fear but were more likely to possess knee joint effusion than patients managed non-operatively. Patients treated non-operatively walked with higher measures of knee joint loading than patients with reconstruction. Overall outcomes were generally favorable for both surgical and non-surgical treatment approaches to ACL injury where progressive, criterion-based rehabilitation was used. Further study is needed to determine if differences in outcomes represent beneficial or deleterious consequences to each treatment group and to identify clinical algorithms for identifying the best candidates for surgical compared to conservative care after ACL injury.

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Chapter 7

IMPLICATIONS FOR THE TREATMENT OF ANTERIOR CRUCIATE LIGAMENT INJURY

7.1 Purpose

The overall goals of this body of work were 1) establish long-term knee joint health as an important goal early after anterior cruciate ligament (ACL) injury and reconstruction and 2) provide clear evidence of expected long-term functional, patient-reported, biomechanical, and radiographic outcomes after operative and non-operative management of ACL injury. Specifically, we aimed to identify factors early after ACL injury and/or reconstruction associated with the development of post-traumatic knee osteoarthritis (OA) 5 years later and to compare long-term outcomes between operative and non-operative management of ACL injury. The central hypotheses were 1) that modifiable factors present early after ACL injury and reconstruction would differ between individuals who do and do not develop post-traumatic knee OA and 2) that outcomes would not differ between patients treated with operative compared to non-operative management of ACL injury.

7.2 Biomechanical Factors Associated with Development of Post-Traumatic Osteoarthritis

Aim 1: Determine the relationship between joint biomechanics and loading early after ACL injury with the presence of knee joint osteoarthritis 5 years after ACL reconstruction

Hypothesis 1.1: Altered knee kinematics and kinetics prior to and early after ACL reconstruction and knee alignment will be associated with radiographic knee osteoarthritis 5 years after ACL reconstruction

Hypothesis 1.2: Altered hip kinematics and kinetics prior to and early after ACL reconstruction will be associated with radiographic knee osteoarthritis 5 years after ACL reconstruction

Hypothesis 1.3: Altered knee joint contact forces prior to and early after ACL reconstruction will be associated with radiographic knee osteoarthritis 5 years after ACL reconstruction

The risk of post-traumatic knee OA after ACL injury is indisputable and currently appears inevitable for most with a history of ACL disruption. The majority of patients will possess radiographic and symptomatic signs of this degenerative, irreversible disease within 10-20 years of ACL injury. The emanate question is no longer "Will post-traumatic knee OA develop?" but instead "How do we prevent, or at least delay, post-traumatic knee OA from developing?" Before precipitating premature modifications to current treatment strategies, an improved understanding of underlying mechanisms contributing to the initiation of post-traumatic knee OA after ACL injury must be established. The findings of the work in chapters 2, 3, and 5 provide groundwork data to support theories put forth earlier by others suggesting altered joint biomechanics after ACL injury may change the loading environment of the knee and lead to negative long-term consequences for the articular cartilage, i.e. osteoarthritis. All three hypotheses were supported by our work. Patients with radiographic knee OA 5 years after ACL reconstruction walked with lower involved limb knee adduction moments and medial compartment joint contact forces than those without OA early after injury and reconstruction. Patients with knee OA also demonstrated smaller sagittal plane hip angles and asymmetrically lower sagittal and frontal plane hip

moments in the ACL-injured limb compared to those without OA at 5 years. The time frame between ACL injury and 2 years after ACL reconstruction may represent a critical period during which articular cartilage health is highly sensitive to joint unloading and cartilage deconditioning. Further work is needed to determine effective rehabilitation strategies to both identify and amend these altered loading patterns associated with the later development of post-traumatic knee OA.

7.3 Clinical Factors Associated with Development of Post-Traumatic Osteoarthritis

Aim 2: Determine the relationship between baseline and functional outcomes early after ACL injury with the presence of knee joint osteoarthritis 5 years after injury

Hypothesis 2.1: Baseline characteristics and functional outcomes early after ACL injury and/or ACL reconstruction will differ between those with and without radiographic signs of knee osteoarthritis 5 years after ACL reconstruction or non-operative rehabilitation

The findings of Aim 1 established strong associations between altered joint biomechanics and subsequent development of post-traumatic knee OA after ACL injury. Although this information provides critical mechanistic information to tease out the process of articular cartilage destruction after ACL injury, a biomechanical laboratory environment is required. No clinical tools currently exist to identify patients early after ACL injury who are at greatest risk for subsequent post-traumatic OA. The findings of the work in chapter 4 establish clinically measureable patient characteristics and outcomes which can prospectively identify patients at greatest risk for early development of post-traumatic knee OA after ACL injury. Our hypothesis for

Aim 2 was supported. Poor performance in single-legged hop tests and lower subjective knee function were associated with the early development of post-traumatic knee OA 5 years after ACL reconstruction or non-operative rehabilitation. Clinical measures of knee function were most predictive of subsequent OA development following an extended period of rehabilitation early after ACL injury to restore muscle strength and neuromuscular control. In addition, a longer period of time from ACL injury to initial impairment resolution was associated with post-traumatic OA development. Further work is needed to identify cut-off levels in clinical measures to categorize highest risk patients for early OA development and determine if restoration of these clinical measures of knee function can curb the subsequent early initiation of articular cartilage degeneration.

7.4 5-Year Outcomes of Operative Compared to Non-Operative Management

Aim 3: Determine the functional, biomechanical, and radiographic differences between patients completing operative compared to non-operative management of ACL injury 5 years after injury

Hypothesis 3.1: Baseline characteristics will not differ between patients completing operative compared to non-operative management of ACL injury 5 years after injury

Hypothesis 3.2: Quadriceps strength, single-legged hop scores and knee joint effusion will not differ between patients completing operative compared to non-operative management of ACL injury 5 years after injury

Hypothesis 3.3: Patient-reported outcomes will not differ between patients completing operative compared to non-operative management of ACL injury 5 years after injury

Hypothesis 3.4: Involved limb and interlimb differences in hip and knee joint biomechanics will not differ between patients completing operative compared to non-operative management of ACL injury 5 years after injury

Hypothesis 3.5: Radiographic outcomes will not differ between patients completing operative compared to non-operative management of ACL injury 5 years after injury

Misconceptions regarding surgical reconstruction after anterior cruciate ligament (ACL) injury are common among patients and healthcare providers. Most expect that prior knee function will be restored, prior activity levels will be attained, and further injury will be avoided. Improved awareness of expected outcomes after operative compared to non-operative management strategies is needed to facilitate open decision-making regarding surgical management after injury. The findings of the work in chapter 6 revealed favorable outcomes of both surgical and non-surgical treatment approaches to ACL injury when progressive, criterion-based rehabilitation is incorporated. Hypotheses 3.1-3.4 were partially supported and hypothesis 3.5 was fully supported. Patients treated with ACL reconstruction compared to rehabilitation alone did not differ in quadriceps strength, performance on single-legged hop tests, level of sports activities, subjective reports of pain, symptoms, or activities of daily living, or the presence of knee OA 5 years after surgery or non-operative rehabilitation. After ACL reconstruction patients did report better global ratings of knee function, knee-related quality of life, and lower fear and were more likely to have knee joint effusion than non-operatively managed patients. Patients managed non-operatively walked with higher measures of knee joint loading than patients treated with reconstruction. Further study is needed to determine if differences in outcomes

represent beneficial or deleterious consequences to each treatment group and to identify clinical algorithms for identifying the best candidates for surgical compared to conservative care after ACL injury.

7.5 Clinical Relevance

The underlying theme adjoining all of the findings of this dissertation is the progressive, criterion-based rehabilitation completed by patients early after ACL injury. The use of objective measures during standardized but progressive, patient-specific pre-operative or non-operative rehabilitation enabled the identification of modifiable patient factors associated with the early development of post-traumatic knee OA and controlled for quality and standards of rehabilitation to allow valid comparisons of outcomes 5 years after operative compared to non-operative management of ACL injury. The benefits of an extended period of progressive rehabilitation to resolve initial impairments and further restore muscle strength and neuromuscular control emerged throughout this work. Asymmetrically lower moments and joint contact forces in the involved limb which were related to post-traumatic OA development after ACL reconstruction improved following extended pre-operative rehabilitation. Failure to quickly resolve impairments such as range of motion, joint effusion, and abnormal gait patterns were linked to early OA development, and a combination of objective clinical measures of knee function were most predictive of subsequent OA development after an extended bout of rehabilitation early after ACL injury. Finally, the progressive, criterion-based rehabilitation completed by patients managed non-operatively not only resulted in outcomes at 5 years comparable to their ACL-reconstructed counterparts but also to extremely high overall levels of knee function and low rates of radiographic knee OA. The progressive, criterion-based

rehabilitation completed early after injury by patients was already known to improve short-term patient outcomes.[44,69,70,72,73,78,114,115,166] The rehabilitation's clear impact on long-term patient outcomes and knee joint health provides additional rationale for inclusion of early rehabilitation in management strategies after ACL injury and provides an excellent stepping stone in identifying best practice guidelines to assure lifelong knee joint health and function after ACL injury.

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Appendix A

CLINICAL MEASURES OF KNEE FUNCTION

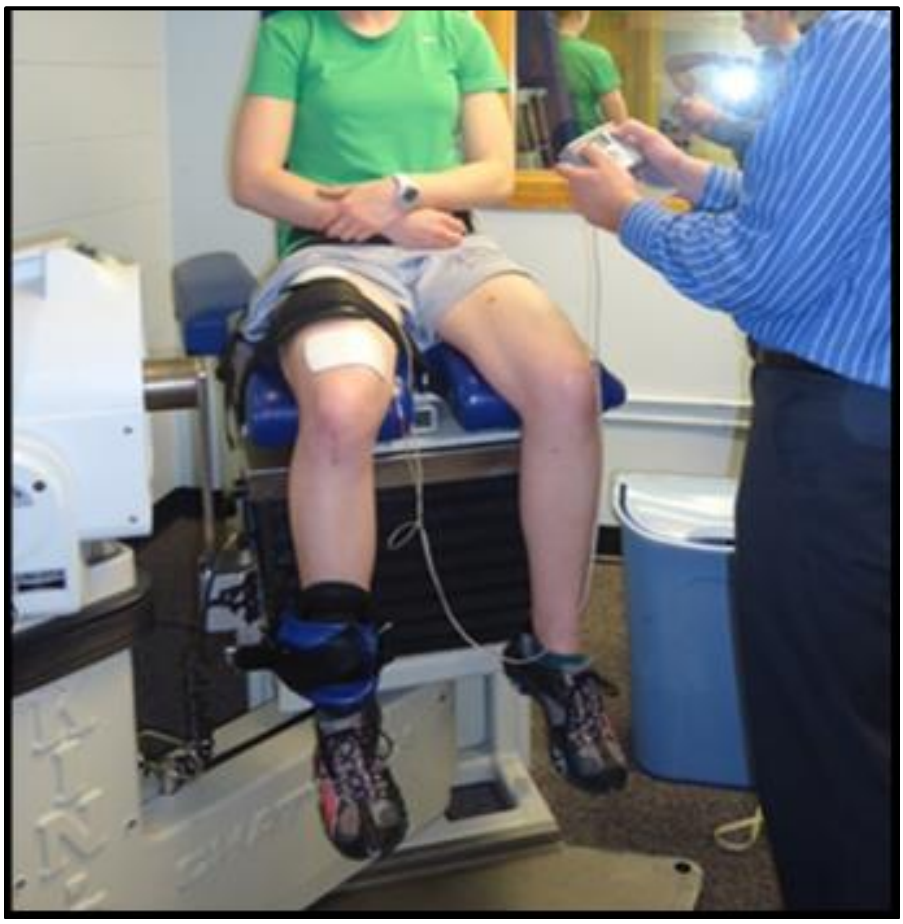

Figure A1: Patient set-up during quadriceps strength testing using the burst superimposition technique during maximal voluntary isometric contraction.

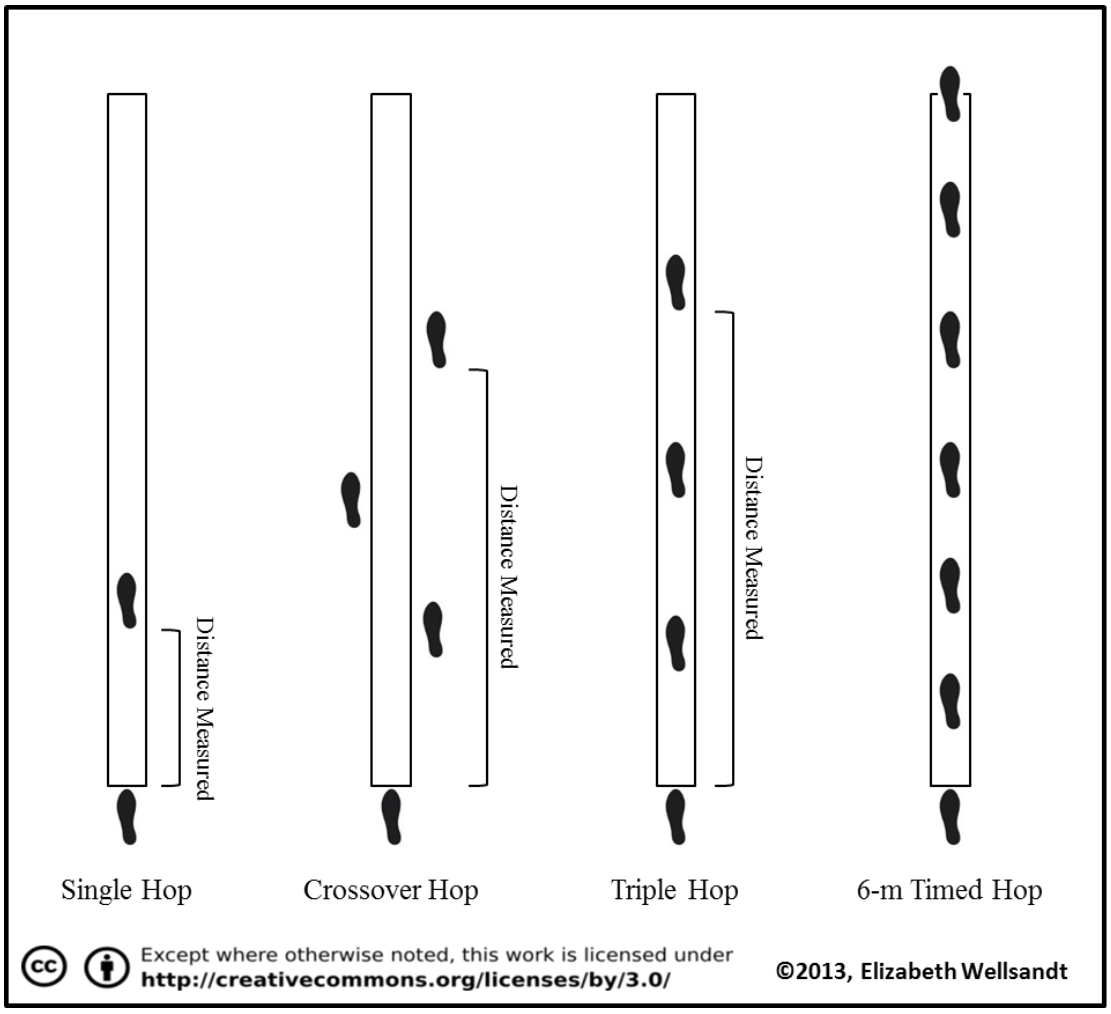

Figure A2: The 4 single-legged hop tests: single hop for distance, crossover hop for distance, triple hop for distance, and 6-meter timed hop.

Table A1: Grading scale for the modified stroke test for knee joint effusion. Taken from Sturgill et al. 2009.[168]

Grade	Test Result
Zero	No wave produced on downstroke
Trace	Small wave on medial side with downstroke
1+	Larger bulge on medial side with downstroke
2+	Effusion spontaneously returns to medial side after upstroke
3+	Not possible to move the effusion out of the medial aspect of the knee

Appendix B

INSTITUTIONAL REVIEW BOARD APPROVAL

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.

Appendix C

HUMAN SUBJECTS INFORMED CONSENTS

UD IRB Approval from 02/17/2016 to 03/14/2017

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.

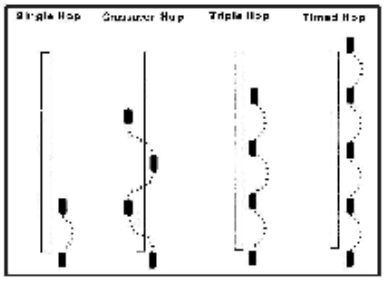

Diagram 1. Four (4) hop tests as part of the functional test protocol.

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.

Subject's Initials_____

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.

Subject's Initials_____

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

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

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PURPOSE AND BACKGROUND

You are being asked to participate in a study that will investigate knee function and structure in 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 questionnaires and x-rays. There will be a total of one to two (1-2) testing sessions: one (1) testing session 5 years after your ACL reconstruction or one to two (1-2) testing sessions for questionnaires and one (1) testing session for xrays 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 twenty-five (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

Questionnaires

You will be asked to complete a test packet which includes questions about your injury, past and current functional status, and perceived functional capabilities.

X-Rays

X-rays will take place at Abby Medical Center, One Centurian Drive, Newark, DE 19713, 5 years after your surgery or 3-7 years following your ACL injury if non-operative management was completed. You will have two types of x-rays taken while you are standing. These x-rays will allow us to look at the joint space in your injured knee, and will help a radiologist (a medical doctor specializing in medical imaging) determine the presence, severity, and location of any knee osteoarthritis you may have. These x-rays will be locked in a cabinet for research purposes only.

Risks/Discomfort

The x-rays that will be taken are the same type that physicians use during regular clinical practice. This research study involves exposure to radiation from a standard radiograph. This radiation exposure is not necessary for your medical care and is for research purposes only. The total amount of radiation that you will receive in this study is about 0.12 mSv or 12 mrem, and is approximately equivalent to a uniform whole body exposure of 15 days of exposure to natural background radiation. This use involves minimal risk per National Institutes of Health guidelines, and is necessary to obtain the research information desired. To reduce exposure all subjects will wear a lead apron to cover the rest of your body while the x-rays of your leg are captured.

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 $50 for completion of the questionnaires and xrays to compensate you for travel expenses and the time involved. Neither you, nor your insurance company will be charged for the x-rays.

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

Subject's Initials_____

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
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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.

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

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

Subject's Initials_____

Appendix D

PERMISSIONS

Google apps@UD

Elizabeth Wellsandt <ewellsan@udel.edu>

Clarifying permission
4 messages

Elizabeth Wellsandt <ewellsan@udel.edu> Tue, Mar 29, 2016 at 9:36 AM
To: permissions@sagepub.com

Good morning,

I am the first author of the manuscript entitled "Decreased Knee Joint Loading Associated with Early Knee Osteoarthritis after Anterior Cruciate Ligament Injury" published in The American Journal of Sport Medicine in Jan 2016. I am wanting to re-publish it as part of my dissertation work. When I go through the permissions page and put in "dissertation/thesis" it ends the process. To clarify, do I not need any further permission to re-use my work in my dissertation?

Thank you for your time,

--
Elizabeth Wellsandt, PT, DPT, OCS
PhD Student-Biomechanics and Movement Science
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permissions (US) <permissions@sagepub.com> Tue, Mar 29, 2016 at 1:18 PM
To: Elizabeth Wellsandt <ewellsan@udel.edu>

Dear Elizabeth Wellsandt,

Thank you for your request. You may use the published version of your article (version 3) in the printed version of your dissertation. However, if you wish to post your dissertation online, we ask that you use the version of your article that was accepted by the journal (version 2).

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Best regards,

Michelle Binur

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Appendix E

LOWER KNEE JOINT LOADING ASSOCIATED WITH EARLY KNEE OSTEOARTHRITIS AFTER ANTERIOR CRUCIATE LIGAMENT INJURY

The American Journal of Sports Medicine
http://ajs.sagepub.com/

Decreased Knee Joint Loading Associated With Early Knee Osteoarthritis After Anterior Cruciate Ligament Injury

Elizabeth Wellsandt, Emily S. Gardinier, Kurt Manal, Michael J. Axe, Thomas S. Buchanan and Lynn Snyder-Mackler

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Decreased Knee Joint Loading Associated With Early Knee Osteoarthritis After Anterior Cruciate Ligament Injury

Elizabeth Wellsandt,*† PT, Emily S. Gardinier,‡ PhD, Kurt Manal,† PhD, Michael J. Axe,†§ MD, Thomas S. Buchanan,† PhD, and Lynn Snyder-Mackler,† PT, ScD
Investigation performed at the University of Delaware, Newark, Delaware, USA

Background: Anterior cruciate ligament (ACL) injury predisposes individuals to early-onset knee joint osteoarthritis (OA). Abnormal joint loading is apparent after ACL injury and reconstruction. The relationship between altered joint biomechanics and the development of knee OA is unknown.

Hypothesis: Altered knee joint kinetics and medial compartment contact forces initially after injury and reconstruction are associated with radiographic knee OA 5 years after reconstruction.

Study Design: Case-control study; Level of evidence, 3.

Methods: Individuals with acute, unilateral ACL injury completed gait analysis before (baseline) and after (posttraining) preoperative rehabilitation and at 6 months, 1 year, and 2 years after reconstruction. Surface electromyographic and knee biomechanical data served as inputs to an electromyographically driven musculoskeletal model to estimate knee joint contact forces. Patients completed radiographic testing 5 years after reconstruction. Differences in knee joint kinetics and contact forces were compared between patients with and those without radiographic knee OA.

Results: Patients with OA walked with greater frontal plane interlimb differences than those without OA (nonOA) at baseline (peak knee adduction moment difference: 0.00 ± 0.08 N·m/kg·m [nonOA] vs –0.15 ± 0.09 N·m/kg·m [OA], $P = .014$; peak knee adduction moment impulse difference: –0.001 ± 0.032 N·m·s/kg·m [nonOA] vs –0.048 ± 0.031 N·m·s/kg·m [OA], $P = .042$). The involved limb knee adduction moment impulse of the group with osteoarthritis was also lower than that of the group without osteoarthritis at baseline (0.087 ± 0.023 N·m·s/kg·m [nonOA] vs 0.049 ± 0.018 N·m·s/kg·m [OA], $P = .023$). Significant group differences were absent at posttraining but reemerged 6 months after reconstruction (peak knee adduction moment difference: 0.02 ± 0.04 N·m/kg·m [nonOA] vs –0.06 ± 0.11 N·m/kg·m [OA], $P = .043$). In addition, the OA group walked with lower peak medial compartment contact forces of the involved limb than did the group without OA at 6 months (2.89 ± 0.52 body weight [nonOA] vs 2.10 ± 0.69 body weight [OA], $P = .036$).

Conclusion: Patients who had radiographic knee OA 5 years after ACL reconstruction walked with lower knee adduction moments and medial compartment joint contact forces than did those patients without OA early after injury and reconstruction.

Keywords: contact force; knee moment; loading; osteoarthritis; anterior cruciate ligament

The risk of knee osteoarthritis (OA) dramatically increases after anterior cruciate ligament (ACL) reconstruction (ACLR).[3,13,29] Patients with ACL injury experience higher rates of knee OA at much younger ages compared with noninjured individuals.[40] The hallmark osteoarthritic symptom of pain may be absent at the onset of knee OA,[23,41] while the presence of chronic knee pain in younger individuals is not well associated with radiographic OA.[18,40] Patient-reported outcomes of knee function are also poor discriminators for the presence of knee OA after ACL injury and ACLR.[23,41] Thus, the initial development and progression of OA after ACL injury can be difficult to predict and detect without the use of routine imaging. Evidence of altered biomechanics has been demonstrated early after ACL injury and ACLR,[44,57] and abnormal joint loading is a key mechanism that may contribute to the early development of OA. Identifying a link between joint loading and OA is a critical step in better understanding and possibly preventing early-onset knee joint OA.

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Common surrogate measures of knee joint loading are frontal and sagittal plane knee moments. Higher external knee moments have been associated with the presence and severity of idiopathic knee OA in older populations.[22,32,33,37] However, external knee adduction and flexion moments have been reported to be lower in the limb at risk for OA after ACLR.[5,0,5,4,5,7] Although it is clear that knee kinetics are altered after ACL injury and ACLR, there is a lack of information about the effect of abnormal biomechanics on the later development of OA.

The external knee adduction moment is widely used as an indicator of knee joint loading of the medial tibiofemoral compartment.[10,12,32,35,37,58] The knee adduction moment before ACLR has not been well characterized, while values higher than, equal to, and lower than the contralateral knee and healthy controls have been reported at varying points in time after ACLR.[5,39,48,51-53,57] Conflicting reports of the knee adduction moment after surgery may be due to longitudinal changes in frontal plane kinetics after ACLR.[52]

Patients initially walk with decreased external knee flexion moments after ACL injury.[16,28,43,44,54] However, it is unclear how long these alterations persist after ACLR.[24,42,52,53] As with the knee adduction moment, it is not well understood whether unresolved alterations in the knee flexion moment after ACL injury and ACLR are detrimental to long-term knee joint health.

Knee joint contact forces estimated by use of musculoskeletal models are another method to quantify knee joint loading. Models incorporating electromyographic (EMG) data may provide a more comprehensive understanding of the knee's loading environment after ACL injury than do joint moments alone, because these models can incorporate the contribution of muscular co-contraction in the estimation of joint contact forces.[4,56] Patients walk with asymmetric knee joint contact forces after ACL injury,[15] and some demonstrate persistent asymmetries 6 months after ACLR.[14] However, it is unknown whether these abnormal loading patterns precede early-onset knee OA.

The purpose of this study was to determine whether knee joint moments and contact forces early after injury and ACLR were associated with radiographic knee OA 5 years after surgery. Drawing from previous work that demonstrated lower knee joint kinetics,[16,28,43,44,54,57] muscle forces,[16] and joint contact forces[15] after ACL injury, we hypothesized that altered knee frontal and sagittal plane kinetics and medial compartment contact forces initially after injury and ACLR would be associated with medial compartment knee OA 5 years after ACLR.

METHODS

Subjects

Twenty-two subjects between the ages of 14 and 51 years with complete, unilateral ACL injury within the previous 7 months were included in this study as part of a larger randomized controlled trial of 55 patients.[20] All patients were regular participants in International Knee Documentation Committee activity level I or II cutting and pivoting activities[7,22] before injury and demonstrated dynamic knee instability after injury (noncopers).[11] Exclusion criteria included concomitant repairable meniscus injuries, grade III injury to other knee ligaments, and full-thickness articular cartilage lesion larger than 1 cm^2 diagnosed before ACLR or contralateral ACL injury after initial ACLR.

Patients were enrolled in this study after effusion, range of motion (ROM), pain, and obvious gait impairments were resolved by use of the physical therapy protocol described by Hurd et al.[26] Study approval was granted by the institutional review board at the University of Delaware, and all patients provided written informed consent. After study enrollment, patients received additional preoperative rehabilitation to further restore lower extremity strength and neuromuscular control.[20] All patients underwent ACLR by a single, board-certified orthopaedic surgeon using either a 4-bundle semitendinosus-gracilis autograft or soft tissue allograft with a medial and lateral portal and medial parapatellar tendon incision. No surgical procedures were performed on any additional ligamentous knee structures. Patients completed progressive, criterion-based postoperative rehabilitation early after surgery.[1]

Testing

Testing consisted of gait analysis with EMG at 5 time points: (1) preoperatively after rehabilitation to resolve effusion, ROM, pain, and obvious gait impairments (baseline); (2) immediately after 10 sessions of additional preoperative rehabilitation (posttraining); (3) 6 months after ACLR after criterion-based rehabilitation (6 months); (4) 1 year after ACLR; and (5) 2 years after ACLR.

Gait analysis was completed by use of an 8-camera system (VICON; Oxford Metrics Ltd) sampled at 120 Hz and 1 force platform (Bertec Corp) sampled at 1080 Hz. Retroreflective markers were placed on bony landmarks at each lower extremity, with rigid shells containing markers placed at the pelvis, thighs, and shanks.[16] Patients walked at self-selected speed, which was maintained (±5%) throughout the testing session and subsequent testing sessions. Stance phase joint angles and moments were calculated by use of inverse dynamics within commercial software (Visual 3D; C-Motion). Moments were normalized to mass (kilograms) and height (meters). Variables of interest included the peak external knee adduction moment, external knee adduction moment impulse during stance phase, and peak external knee flexion moment. Differences between limbs were calculated for each kinetic measure (involved minus uninvolved).

Surface EMG was collected at 1080 Hz (MA-300 EMG System; Motion Lab Systems) for 7 muscles on each limb (rectus femoris, medial and lateral vasti, semitendinosus, long head of biceps femoris, and medial and lateral gastrocnemii). Patients completed maximal voluntary isometric contractions for each muscle group to normalize EMG amplitude during subsequent walking trials. Raw EMG data were high-pass filtered (second-order Butterworth, 30 Hz), rectified, and then low-pass filtered (second-order Butterworth, 6 Hz), creating a linear envelope for maximal voluntary isometric contractions and walking trials.

EMG-Driven Modeling

Gait analysis and surface EMG data served as inputs to a musculoskeletal model[16,36] for the estimation of joint contact forces. This model has demonstrated good repeatability[35] and high accuracy when validated by use of in vivo contact force data recorded from an instrumented knee prosthesis.[36] In addition, sensitivity analyses conducted on varying experimental inputs to the model have demonstrated that interlimb differences in peak contact forces found within this study are much larger than estimated potential error.[15] Contact forces for 10 of these patients were included in the primary analyses of knee joint contact forces after acute ACL injury ("baseline" time point [Gardinier et al[16]]) and after ACLR ("6 months" time point [Gardinier et al[16]]).

The EMG-driven model of the knee included an anatomic model that characterizes the musculoskeletal geometry,[8] an activation dynamics model that characterizes the transformation of EMG (the neural signal) to muscle activation, and a contraction dynamics model that contains a Hill-type muscle model and characterizes the transformation of muscle activation to muscle force. The anatomic model contained pelvis, femur, tibia, and foot segments that were actuated by 10 muscle-tendon units and scaled according to subject anthropometry. The activation dynamics and contraction dynamics models contained adjustable muscle parameters (see Gardinier et al[16]) that are difficult to accurately measure in vivo, including optimal muscle fiber length and tendon slack length. These parameters were adjusted during a subject-specific model calibration and were allowed to vary within physiological bounds as described previously (see Gardinier et al[16] for limits used). After the model was calibrated, muscle forces were predicted for the stance phase of 3 novel overground walking trials.

Medial compartment contact force was calculated by balancing the external knee adduction moment (expressed about the lateral compartment contact point, which was fixed at a distance of 25% of tibial plateau width from the knee joint center) with the internal adduction moments due to the muscle forces and the contact force in the medial compartment.[5,6] The peak medial compartment contact force occurring in the first half of stance was the discrete variable of interest for this study, and the average of 3 trials was used for analysis.

Radiographs

Weightbearing posteroanterior (PA) bent knee (30°) radiographs were completed 5 years after ACLR and graded by use of the Kellgren-Lawrence (KL) system.[30] The presence of OA was defined as a KL grade $\geq$2 in the medial compartment (graded by E.W.; between-day kappa statistic: 0.904, $P < .001$; all KL grades verified by a board-certified orthopaedic surgeon). Initial radiographs after ACL injury were not obtained; however, articular cartilage lesions were assessed during arthroscopic evaluation at the time of ACLR. Two patients demonstrated chronic articular cartilage changes at the medial femoral condyle during arthroscopic evaluation during ACLR. One of these 2 patients had OA in the medial compartment at 5 years, and the other did not.

Statistical Analysis

Statistical analyses were completed with PASSW 23.0 software (SPSS Inc). Independent t tests and Fisher exact tests were performed to test differences in demographics, baseline characteristics, and concomitant injuries between patients without radiographic knee OA (nonOA group) and those with OA (OA group) in the medial compartment 5 years after ACLR. Independent t tests were used to test differences in loading measures for the involved limb between the nonOA and OA groups (peak knee adduction moment, knee adduction moment impulse, peak knee flexion moment, and peak medial compartment contact force) and interlimb differences between groups at each time point for each of these measures. Effect sizes were calculated for group differences in loading measures.[6] Previously reported minimally detectable changes were used to determine meaningful asymmetry between limbs for peak knee adduction moment (0.06 N·m/kg·m), peak knee flexion moment (0.09 N·m/kg·m), and peak medial compartment contact force (0.30 body weight [BW]).[17] Statistical significance was set at $P \leq .05$.

RESULTS

In total, 22 subjects returned for radiographic testing 5 years after ACLR (15 nonOA, 7 OA) (Figure 1). Of these 22 subjects, the number completing testing at each of the 5 earlier time points is described in Table 1. A greater proportion of subjects who completed testing at 2 years who had OA at 5 years were female (nonOA: 9 males, 2 females; OA: 1 male, 4 females; $P = .036$). No further group differences existed for sex at other time points (Table 1). No differences in age, mass, body mass index (BMI), preinjury activity level, time from injury to baseline, time from injury to ACLR, or graft type were present between groups (Table 1). The OA group walked more slowly than the nonOA group at 1 year (nonOA: 1.64 $\pm$ 0.12 m/s, OA: 1.49 $\pm$ 0.04 m/s; $P = .035$) but not at any other testing sessions (Table 1). The presence of concomitant meniscal or articular cartilage injuries identified arthroscopically during ACLR did not differ between groups at any time point for all compartments of the involved knee or specifically the medial tibiofemoral compartment (Table 1). No differences existed in additional knee injuries or surgeries sustained between the time of initial ACL injury and 5-year radiographic testing (nonOA: 1 ipsilateral retear, 1 ipsilateral partial posterior cruciate ligament tear and meniscus tear; OA: 1 ipsilateral retear) (Table 1).

The OA group walked with lower peak knee adduction moment than the nonOA group, with significant interlimb differences and large effect sizes present at baseline (peak knee adduction moment difference: 0.00 $\pm$ 0.08 N·m/kg·m [nonOA] vs -0.15 $\pm$ 0.09 N·m/kg·m [OA]; $P = .014$) (Figure 2, A and B; see also the Appendix, available online at

TABLE 1
Demographic, Baseline, and Concomitant Injury Characteristics Between Those With and Without Radiographic Medial Compartment Knee OA 5 Years After ACLR[a]

		Baseline		Posttraining		6 Months		1 Year		2 Years	
	Group	Mean ± SD	*P*	Mean ± SD	*P*	Mean ± SD	*P*	Mean ± SD	*P*	Mean ± SD	*P*
Age (baseline), y	nonOA	33.42 ± 10.85	.868	33.80 ± 10.40	.983	32.50 ± 11.16	.062	32.90 ± 11.62	.309	35.18 ± 10.14	.463
	OA	34.67 ± 14.29		33.67 ± 13.74		44.75 ± 5.56		26.00 ± 8.76		39.60 ± 12.48	
Mass, kg	nonOA	86.59 ± 19.12	.351	86.06 ± 20.73	.936	86.84 ± 15.26	.238	89.41 ± 14.47	.727	87.70 ± 13.80	.338
	OA	75.03 ± 14.52		85.24 ± 17.11		76.33 ± 10.99		86.15 ± 17.96		80.25 ± 14.30	
Body mass index	nonOA	28.13 ± 3.69	.313	27.98 ± 3.91	.591	28.07 ± 2.94	.104	28.66 ± 4.15	.853	28.77 ± 3.04	.217
	OA	25.56 ± 4.30		29.13 ± 4.23		25.15 ± 2.37		28.16 ± 5.07		26.48 ± 3.83	
Time from injury to baseline, wk	nonOA	9.75 ± 8.30	.444	9.70 ± 9.16	.687	9.80 ± 7.17	.873	8.05 ± 7.08	.542	8.45 ± 7.31	.692
	OA	5.83 ± 2.25		11.58 ± 8.33		10.50 ± 7.38		10.88 ± 9.00		10.0 ± 6.49	
Time from injury to ACLR, wk	nonOA	18.82 ± 11.02	.189	18.89 ± 12.25	.916	15.20 ± 8.38	.422	19.30 ± 22.61	.709	19.82 ± 21.52	.941
	OA	9.67 ± 2.31		19.67 ± 15.67		21.00 ± 18.57		14.75 ± 9.18		19.00 ± 16.69	
Gait velocity, m/s	nonOA	1.57 ± 0.14	.592	1.60 ± 0.12	.418	1.61 ± 0.13	.320	1.64 ± 0.12	**.035**	1.62 ± 0.12	.226
	OA	1.52 ± 0.09		1.55 ± 0.10		1.54 ± 0.08		1.49 ± 0.04		1.54 ± 0.11	
		Ratio	*P*	Ratio	*P*	Ratio	*P*	Ratio	*P*	Ratio	*P*
Sex (male:female), n	nonOA	8:4	.077	7:3	.302	8:2	.095	8:2	.520	9:2	**.036**
	OA	0:3		2:4		1:3		2:2		1:4	
Preinjury activity level (I:II),[b] n	nonOA	6:6	>.999	6:4	.608	6:4	.085	7:3	.580	8:3	.106
	OA	1:2		2:4		0:4		2:2		1:4	
Graft type (allograft:autograft), n	nonOA	9:3	>.999	8:2	.299	8:2	.520	8:2	.520	10:1	.214
	OA	2:1		3:3		2:2		2:2		3:2	
Meniscal or articular cartilage concomitant injury (no:yes), n	nonOA	5:7	.200	5:5	.633	4:6	.559	3:7	.580	4:7	.282
	OA	3:0		4:2		3:1		2:2		4:1	
Medial tibiofemoral compartment concomitant injury (no:yes), n	nonOA	8:4	.516	7:3	>.999	7:3	>.999	7:3	>.999	7:4	>.999
	OA	3:0		5:1		3:1		3:1		4:1	
Additional knee injury after initial ACL injury (no:yes), n	nonOA	10:2	.516	9:1	.625	9:1	.714	9:1	.505	11:0	.313
	OA	2:1		5:1		4:0		3:1		4:1	

[a]Boldfaced numbers indicate statistically significant baseline difference between those with and without radiographic medial compartment knee OA 5 years after ACLR ($P \leq .05$). ACL, anterior cruciate ligament; ACLR, ACL reconstruction; OA, osteoarthritis.
[b]According to International Knee Documentation Committee activity levels.[7,22]

http://ajsm.sagepub.com/supplemental). Asymmetric peak frontal plane moments improved in the OA group after preoperative rehabilitation, but significant group differences were again present at 6 months after ACLR (peak knee adduction moment difference: 0.02 ± 0.04 N·m/kg·m [nonOA] vs –0.06 ± 0.11 N·m/kg·m [OA]; $P = .043$) (Figure 2B). Both groups demonstrated symmetry in peak knee adduction moment at 1 and 2 years after surgery (Figure 2B). Large group differences for the involved limb peak knee adduction moment were present at baseline but no further time points (Figure 2A).

Additional frontal plane group differences were present in the knee adduction moment impulse (online Appendix). At baseline, the OA group had lower knee adduction moment impulse at the involved limb than did the nonOA group (0.087 ± 0.023 N·m·s/kg·m [nonOA] vs 0.049 ± 0.018 N·m·s/kg·m [OA]; $P = .023$) (Figure 2C) and underloaded the involved limb compared with the contralateral limb (knee adduction moment impulse difference: –0.001 ± 0.032 N·m·s/kg·m [nonOA] vs –0.048 ± 0.031 N·m·s/kg·m [OA]; $P = .042$) with large effect sizes exhibited (Figure 2D). Group differences in knee adduction moment impulse were absent after preoperative rehabilitation and continued through 1 year after surgery. At 2 years, no differences at the involved limbs existed between groups in the knee adduction moment impulse, but the OA group had a significantly lower interlimb

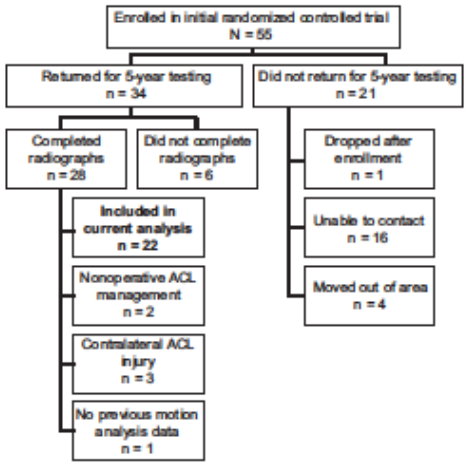

Figure 1. Flow diagram of study cohort. ACL, anterior cruciate ligament.

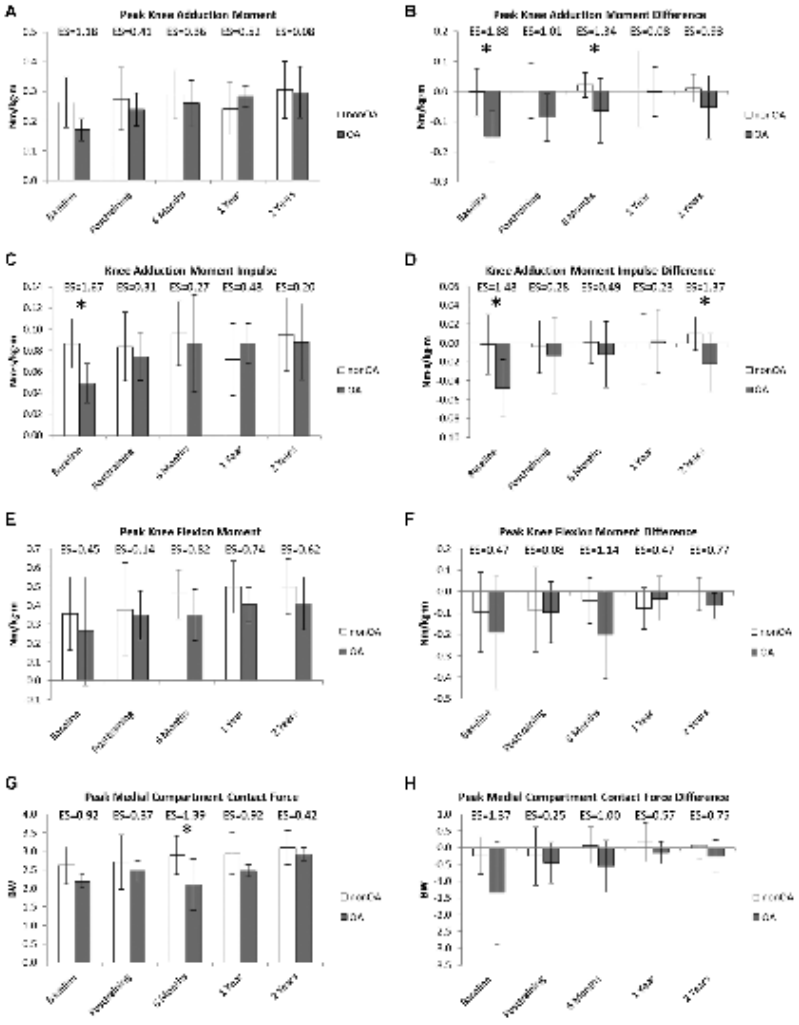

Figure 2. Mean values for involved limb and interlimb differences in kinetic measures and medial compartment contact forces between those with and without radiographic medial compartment knee osteoarthritis (OA) 5 years after anterior cruciate ligament reconstruction. Effect sizes (ES) provided. *$P \leq .05$. Whiskers represent ±1 standard deviation.

difference (lower knee adduction moment impulse on the involved limb, represented by a negative knee adduction moment impulse difference) than the nonOA group (knee adduction moment impulse difference: 0.010 ± 0.018 N·m·s/kg·m [nonOA] vs −0.021 ± 0.032 N·m·s/kg·m [OA]; P = .027) (Figure 2, C and D).

There were large differences between limbs in peak knee flexion moment for both the OA and nonOA groups

at baseline, with both groups demonstrating lower sagittal plane moments on their involved knee (Figure 2, E and F, online Appendix). Large interlimb differences continued in the OA group at 6 months. However, these differences did not reach statistical significance between groups at either time point.

Large group differences in peak medial compartment contact forces of involved limbs were seen at baseline, 6 months, and 1 year, reaching statistical significance at 6 months (peak medial compartment contact force: 2.89 ± 0.52 BW [nonOA] vs 2.10 ± 0.69 BW [OA]; $P = .036$) (Figure 2G and online Appendix). Large interlimb differences were also present between groups at baseline and 6 months (Figure 2H). Neither involved limb peak medial compartment contact force nor interlimb differences in peak medial compartment contact force were different between groups after preoperative rehabilitation.

DISCUSSION

The purpose of this study was to determine whether loading measures before and after ACLR were associated with knee OA 5 years after surgery. Results indicate that compared with subjects without radiographic OA 5 years after surgery, those who did develop radiographic OA walked with lower moments and contact forces at the involved limb and had greater interlimb differences early after injury and ACLR. Differences were largest and statistically significant before preoperative rehabilitation and 6 months after ACLR.

The current findings are consistent with a growing body of evidence suggesting that joint unloading, not overloading, may be associated with the cascade of early degenerative changes at the knee after ACL injury.[2,57] Koo and Andriacchi[31] suggested that healthy cartilage increases in thickness in response to higher repetitive loading during walking, whereas Koo et al (unpublished data, 2007) found that after ACL injury, joint unloading is associated with regional cartilage thinning. The lower joint moments and joint contact forces seen early after injury and ACLR in our subjects who went on to develop OA may be markers for underlying structural alterations to otherwise healthy articular cartilage before ACL injury. In our study, joint loading variables increased on the involved limb to levels similar to the nonOA group by 1 year after ACLR. Although it is unclear when early degenerative changes begin, the increase in loading at 2 years may not be tolerated if cartilage structures are already deconditioned or deteriorating. Further work is needed to determine whether the more symmetric loading present at 2 years will eventually lead to joint overloading as the degeneration progresses.

Seven of 22 patients demonstrated radiographic knee OA at 5 years after ACLR. A recent systematic review indicated that cartilage degeneration detected by magnetic resonance imaging (MRI) occurs before radiographic evidence.[47] Tibial cartilage thinning is evident on MRI as early as 4 months after isolated ACL injury,[46] and these changes persist despite ACLR.[25] The occurrence of preoperative articular cartilage changes highlights the importance of sufficient and purposeful rehabilitation before surgery. In the present study, despite resolution of knee joint effusion, ROM, pain, and obvious gait impairments, there were significant differences in frontal plane moments and also notable differences in medial compartment joint contact forces at baseline between subjects who later developed radiographic OA. All of these group differences were considerably smaller after an additional 10 rehabilitation sessions targeting further strength and neuromuscular improvements before surgery. It is likely that more subjects than the 7 in our study with radiographic OA exhibited early signs of cartilage degeneration. Weninger et al[55] reported that nearly 70% of patients demonstrated cartilage degeneration on MRI 2.8 years after ACLR but only 11% had radiographic knee OA. Early rehabilitation programs both before and after ACLR may be a primary modifiable component to restore knee biomechanics and modify the course of early-onset knee OA.

The knee adduction moment was lower in the OA group when compared with both the contralateral limb and the involved limb of the nonOA group early after injury and surgery. Previous conflicting evidence regarding whether the knee adduction moment is increased or decreased after ACLR may be a result of failing to dichotomize ACL-injured subjects by the presence of later knee OA and to consider longitudinal changes in frontal plane loading after ACL injury. Webster and colleagues[51,52] reported a lower knee adduction moment at 10 months after ACLR compared with both the contralateral limb and healthy controls, which improved at 3 years, which is consistent with current findings within the OA group in the present study. However, Webster et al[53] reported the absence of interlimb differences in the knee adduction moment at 20 months, while our 2-year results in the OA group show large between-limb differences for both the peak knee adduction moment and knee adduction moment impulse, consistent with 26-month findings by Zahala et al.[57] Previous research has reported that between 3.5 and 5.3 years after ACLR, patients have knee adduction moment values that are greater than, equal to, and less than those of healthy controls.[5,39,48] Further analysis is required within our cohort to determine whether this period represents a critical time when a shift to overloading patterns becomes evident.

Significant differences in peak knee adduction moment and knee adduction moment impulse between the nonOA and OA group were present at baseline but not after preoperative rehabilitation. Subjects with OA demonstrated larger asymmetries between limbs in peak knee adduction moment and knee adduction moment impulse and lower knee adduction moment impulse on the involved limb at baseline, which normalized after rehabilitation. Meanwhile, the nonOA group walked with symmetric frontal plane moments at both points in time. Early identification of individuals at high risk of early-onset knee OA and determination of sufficient preoperative rehabilitation dosages may play a key role in curbing the unloading tendencies of certain individuals and potential pathway of irreversible knee joint OA.

Sagittal plane moments undoubtedly play a role in describing the loading environment of the knee's medial

compartment.[49] Previous work has established that the peak knee flexion moment is lower both before and after ACLR.[16,36,38,42-44,54,57] The negative interlimb differences in the peak knee flexion moment found for both the nonOA and OA groups at each time point further support this trend for involved limb unloading. Although only 7 of 22 subjects had radiographic knee OA at 5 years, the majority will likely develop radiographic knee OA within 15 years of surgery.[3] It is possible that sagittal plane moments may be associated with overall long-term risk of knee OA while frontal plane moments may better differentiate subjects at risk of earlier radiographic knee OA present within 5 years of ACLR.

Six months after ACLR, differences between groups for both involved limb peak knee flexion moment and interlimb difference in peak knee flexion moment were not statistically significant, which is not consistent with the findings of others.[24,42] The limited sample size in our current study may have restricted achievement of significant findings. However, large effect sizes were present for both measures, suggesting that sagittal plane kinetics may also play a role in the early onset of knee OA.

Medial compartment joint contact forces estimated by use of an EMG-driven musculoskeletal model differed between subjects who did and those who did not develop radiographic knee OA at 5 years. An inherent strength of using this approach to describe the knee's loading environment is that it incorporates individual muscle activation patterns, which are known to be altered after ACL injury[28,43,44] in addition to joint biomechanics. The OA group walked with lower medial compartment contact forces of the involved limb and large interlimb differences at baseline and 6 months after ACLR when compared with subjects without radiographic knee OA. Large differences between groups for the involved limb contact forces also persisted at 1 year. Previous work within this cohort found that medial compartment contact forces were significantly less in the injured limb before ACLR than in the contralateral limb.[15] When these subjects were separated by the presence of knee OA at 5 years and their baseline data were analyzed, it was found that the involved medial compartment of the OA group was loaded nearly one-half BW less than the involved limb of the nonOA group at baseline. The OA group also had nearly an entire BW greater loading difference relative to the contralateral limb compared with the nonOA group at baseline. Again, these group differences were eliminated after additional preoperative rehabilitation. This relative unloading present in the OA group before and after surgery further highlights the key contributions that not only joint biomechanics but also muscle activation patterns may provide to the development of early knee OA. The more comprehensive approach undertaken by the musculoskeletal model to estimate joint loading, including the use of frontal and sagittal plane kinetics with co-contraction estimates via EMG input, may provide enhanced insight into the development of OA compared with kinetic measures alone. Further work is needed to determine whether relative contributions of muscle activation and joint biomechanics to joint contact forces differ between OA groups.

Concomitant meniscus and articular cartilage injuries increase the risk of degenerative changes in the knee after ACL injury.[3,22,29,34,47] However, no subjects within either group possessed acute cartilage injury at the time of ACLR, and the proportion of meniscal injuries did not differ between subjects who did or did not go on to develop radiographic OA by 5 years. There were also no differences in the occurrence of additional knee injuries or surgery during the time from initial ACL injury to 5-year radiographic testing between those with and without OA at 5 years. The current findings do not refute previous findings regarding the increased OA risk associated with concomitant injuries. Given our findings, however, the strong association between biomechanical alterations and future knee joint degeneration can be attributed to ACL rupture independent of additional knee joint damage.

Previous studies reported that female sex increases the risk for development of primary knee OA,[38,46] and it has been suggested that this risk factor may play a role in the risk of OA after ACL injury.[35] However, more recent studies have shown no risk factor of sex[3] and further that male patients are at higher risk of knee OA after ACL injury.[34] Of our patients who completed testing at 2 years, a larger proportion of those who went on to demonstrate OA at 5 years were female (4 females, 1 male) compared with the nonOA group (2 females, 9 males). Women are more likely than men to demonstrate dynamic knee instability after sustaining an ACL injury,[27] and within those subjects with poor dynamic stability, women demonstrate greater biomechanical asymmetries than men.[9] The altered biomechanics in individuals with poor dynamic knee stability[19,28] may place women at higher risk of early development of OA after ACL injury.

Age, obesity, and manual labor at the time of injury are additional factors that increase the risk of developing knee OA after ACL injury but are difficult to modify.[3,54] Clinical signs such as muscle weakness have been linked to the development of primary knee OA, but modifiable risk factors related to knee OA after ACL injury are largely unknown.[35] The identification of clinical tests and measures that relate either to underlying altered joint biomechanics or directly to the development of knee OA after ACL injury are needed to effectively screen patients at greatest risk for posttraumatic OA, in whom targeted prevention strategies will be most effective.

Limitations do exist within the present study. Sample sizes are limited at each time point. The small sample size likely resulted in group differences that demonstrated large effect sizes but lacked statistical significance. Caution must be demonstrated in drawing firm conclusions from effect sizes when statistically significant group differences are not present, which warrants future study with the use of a larger sample. Further, some subjects were not tested at all time points, limiting further longitudinal analysis and chronological conclusions regarding loading patterns. Despite these limitations, it is important to note that this study is the first of its kind to demonstrate a link between altered movement patterns and radiographic evidence of knee OA after ACL injury. Further work is necessary to determine whether the presence of knee OA and altered

knee joint biomechanics after ACL injury is also related to altered mechanics at the hip and ankle.

CONCLUSION

Patients with radiographic knee OA at 5 years after ACLR walked with lower knee adduction moments and medial compartment joint contact forces in the involved limb than did patients without OA early after injury and reconstruction. Knee joint loading became more similar between the groups at 1 year after ACLR. The time span between injury and 2 years after ACLR may represent a critical period during which articular cartilage health is highly sensitive to joint unloading and cartilage deconditioning. Further work is needed to determine effective rehabilitation strategies to both identify and amend these altered loading patterns associated with early-onset knee OA; in addition, research is needed to evaluate whether loading strategies differ greater than 2 years after ACLR between those who do and do not go on to develop radiographic knee OA.

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