



Relating subjective and objective knee function after anterior cruciate ligament injury through biomechanical and neuromusculoskeletal modelling approaches

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PhD Thesis

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Table of Contents

ACKNOWLEDGEMENTS	III
GENERAL ABSTRACT	IV
CONTRIBUTIONS.....	VI
LIST OF ABBREVIATIONS AND UNITS.....	VIII
LIST OF TABLES	IX
LIST OF FIGURES.....	X
CHAPTER 1: GENERAL INTRODUCTION.....	1
CHAPTER 2: LITERATURE REVIEW.....	4
2.1 KNEE JOINT STABILITY	4
2.2 MEASURES OF KNEE JOINT CONTROL	7
2.3 ACL INJURIES AND CHANGES IN JOINT FUNCTION	8
2.4 COPERS VS. NON-COPERS	10
2.5 ACL RECONSTRUCTION.....	12
2.7 NEUROMUSCULOSKELETAL MODELLING	14
2.8 ACL REHABILITATION PROGRAMS.....	16
2.9 PAST LIMITATIONS AND KNOWLEDGE GAPS	18
2.10 RESEARCH QUESTIONS AND HYPOTHESES	20
CHAPTER 3: GENERAL METHODOLOGY	24
3.1 STUDY DESIGN	24
3.2 PARTICIPANTS	24
3.3 EQUIPMENT	25
3.4 IN VIVO PROTOCOL.....	26
3.5 DATA REDUCTION.....	28
CHAPTER 4: JOURNAL ARTICLES.....	39
4.1 STUDY 1: DYNAMIC TASKS AFTER ACL INJURY	39
4.2 STUDY 2: DYNAMIC KNEE JOINT CONTROL AFTER ACL INJURY	64
4.3 STUDY 3: OBJECTIVE AND SUBJECTIVE FUNCTIONALITY AFTER ACL INJURY.....	81
4.4 STUDY 4: MRI-BASED OPENSIM MODELLING.....	102
4.5 STUDY 5: JOINT LOADING AFTER ACL INJURY	118
CHAPTER 5: GENERAL DISCUSSION	143
5.1 BIOMECHANICS ASSOCIATED WITH ACL INJURY	143
5.2 DYNAMIC KNEE JOINT CONTROL.....	146
5.3 RELATION OF SUBJECTIVE AND OBJECTIVE FUNCTIONAL ABILITY.....	147
5.4 THESIS LIMITATIONS.....	149
5.5 FUTURE DIRECTIONS	155
5.6 CONCLUSIONS.....	156
CHAPTER 6: GENERAL REFERENCES	158
APPENDIX	177

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General Abstract

Background

Knee injuries have a considerable impact on both the person's psychological and physical health. We currently have tools to address each of these aspects but they are often considered independent of each other. Little work has been done to consolidate the subjective and objective functional ability of anterior cruciate ligament (ACL) injured individuals, which can be detrimental when implementing a return-to-play decision-making scheme. The lack of understanding concerning the relationship of these two measures may account for the high incidence of re-injury rates and lower quality of life exhibited by so many of these patients.

Purpose

The purpose of this doctoral thesis is to investigate the relationship between subjective and objective measures of functional ability in ACL deficient and ACL reconstructed conditions through biomechanical and neuromusculoskeletal modelling approaches.

Methods

This thesis is comprised of five studies based on a single in vivo data collection protocol, medical imaging and in silico data analyses. The in vivo data collection was of test-retest design where ACL deficient patients participated prior to their operation and approximately ten months post-reconstruction. This experimental group was matched to a healthy, uninjured control group, which was tested a single time.

The first study of this thesis involved a descriptive analysis of spatiotemporal, neuromuscular, and biomechanical patterns during hopping and side cut tasks in addition to subjective functional ability questionnaires. Then, two novel measures of dynamic knee joint control were developed and applied along with a third measure to determine if changes in joint control exist between the three groups (Study 2). The relationships of these objective measures of functional ability to subjective measures were then examined through correlation and regression models (Study 3). Following this, a method of including magnetic resonance imaging to construct patient-specific models was developed and implemented to determine realistic kinematic and ligament lengthening profiles (Study 4). These patient-specific models were then applied to quantify knee joint loading in the form of contact and ligament forces, which were correlated to subjective measures of functional ability (Study 5).

Results

Even though no major differences in neuromuscular patterns were observed between all three groups, it was found that subjective patient-reported outcome measures scores and biomechanical measures in the form of knee flexion angles and extensor moments were lower in the ACL deficient group compared to healthy controls. These differences continued to exist 10 months post-operation as the ACL reconstructed group had not fully recovered to patterns observed in the healthy controls. The current findings also suggest a possible hierarchy in the relationships between objective and subjective measures of functional ability. Basic kinematic objective measures such as knee flexion angle show small to moderate correlations, while more comprehensive measures such as stiffness and joint compressive force show moderate to strong correlations to subjective questionnaires. Finally, this thesis developed patient-specific OpenSim models that were used to produce appropriate kinematics and ligament lengthening with the reduction in soft tissue artefact.

Conclusion

This thesis demonstrated that patients who are high-functioning in the ACL deficient state show greater improvements in subjective outcome scores after ACL reconstruction compared to objective measures. Biomechanical and neuromusculoskeletal modelling approaches identified important differences between the healthy and ACL deficient groups that were not resolved post-operatively. Our results also demonstrate that certain subjective and objective measures of functional ability are strongly correlated. The knowledge gained from this test-retest design and novel patient-specific in silico models aids clinicians in managing their expectations regarding the effectiveness of reconstruction and the respective long-term sequelae.

Contributions

Study 1: Anterior cruciate ligament reconstruction improves subjective ability but not neuromuscular biomechanics during dynamic tasks (accepted in Knee Surgery, Sports Traumatology, Arthroscopy)

The first study of this thesis was focused on the in vivo data collections collected at the University of Copenhagen from 2013 – 2016. The theoretical conception of these experiments and data collections was a concerted effort among all co-authors. During these collections, KB Smale led 65 of the 126 data collections with Dr. Teresa Flaxman and Ida Fillingsness leading the remaining 61. Vicon Nexus labelling of the hops, side cuts, and countermovement jump tasks were labelled by KB Smale. With respect to kinematic and kinetic analyses, KB Smale was responsible for writing all processing scripts and performing all OpenSim analyses. Electromyography processing scripts were written in collaboration with Dr. Flaxman while KB Smale was responsible for all statistical analyses performed regarding this study. The manuscript was written by KB Smale and edited by all co-authors.

Study 2: Assessment of objective dynamic knee joint control in anterior cruciate ligament deficient and reconstructed individuals (to be submitted to The Knee)

The second study of this thesis used the previously collected data to develop two novel measures of dynamic knee joint control and apply them along with a third (knee joint stiffness) to each group during the hop and side cut. Through discussions with collaborators and participants, KB Smale spearheaded the development of KJCE and KJCB along with their application along with knee joint stiffness, which involved writing all necessary code to implement them into the analysis. Again, KB Smale performed all statistical analyses and wrote the corresponding manuscript with co-authors providing edits.

Study 3: Relation of objective and subjective functional ability in anterior cruciate ligament deficient and reconstructed individuals (to be submitted to Medicine and Science in Sports and Exercise)

The third study related peak knee flexion angle, peak extensor moment and the three dynamic knee joint control measures from Study 2 to the self-reported outcome measures. The concept of this relationship once again arose through conversations with collaborators and participants while being spearheaded by KB Smale. All statistical analyses including correlations and regression models were performed by KB Smale. The manuscript was written by KB Smale and edited by co-authors.

Study 4: An MRI-based patient-specific articular contact model for OpenSim leads to soft tissue artifact reduction and improved ligament length estimates (under review in Journal of Biomechanics)

The fourth study of this thesis introduces a method of incorporating MRIs into OpenSim to create patient-specific models. KB Smale, along with fellow co-authors were responsible for

the conception of this study. MRIs were first manually segmented by KB Smale and then reviewed for accuracy by Dr. Michele Conconi. Alignment of the MRI bone geometries to the generic bones and OpenSim landmarks was performed by KB Smale while Dr. Conconi performed the knee joint articulation optimization. KB Smale then extracted these optimized anatomical landmarks and lengths and incorporated them into patient-specific OpenSim models. All further scaling and inverse kinematic analyses were performed by KB Smale. Statistical analyses and manuscript writing were also performed by KB Smale with edits being provided by all co-authors.

Study 5: The relationship between patient-specific knee joint contact and ligament forces and subjective function pre- and post-anterior cruciate ligament reconstruction (to be submitted to American Journal of Sports Medicine)

The final study of this thesis applied the patient-specific OpenSim models to quantify tibiofemoral contact and ligament forces and correlated these to the self-reported questionnaires. KB Smale, along with fellow co-authors were responsible for the conceptual design of the experiment. All OpenSim analyses including scaling, inverse kinematics, residual reduction analysis, inverse dynamics, static optimization, and joint reaction analysis were performed by KB Smale. KB Smale also performed all statistical analyses and wrote the respective manuscript while being supplied edits by all co-authors.

List of Abbreviations and Units

β	beta coefficient	KNEES	Knee Numeric Entity Evaluation Score
AAA	adduction/abduction angle	KOOS	Knee Injury & Osteoarthritis Outcome Score
ACL	anterior cruciate ligament	LCL	lateral collateral ligament
ACLd	anterior cruciate ligament deficient	LGAS	lateral gastrocnemius
ACLr	anterior cruciate ligament reconstructed	m	metres
APT	anterior/posterior translation	mm	millimetres
ATSF	anterior tibial shear force	MCL	medial collateral ligament
ATT	anterior tibial translation	MGAS	medial gastrocnemius
BFEM	biceps femoris	MLT	medial/lateral translation
BW	body weight	MRI	magnetic resonance imaging
cm	centimetres	MVIC	maximum voluntary isometric contraction
CON	healthy, uninjured control	N	Newton
DB	double bundle	Nm	Newton metre
dB	decibel	OA	osteoarthritis
DCT	distraction/compression translation	PCL	posterior cruciate ligament
DKJS	dynamic knee joint stiffness	PD	peak difference
DOF	degree of freedom	PROM	patient-reported outcome measure
EMG	electromyography	PT	patellar tendon
FEA	flexion/extension angle	r	Spearman or Pearson correlation coefficient
GMED	gluteus medius	R²	goodness-of-fit
GO	global objective	R3	Rajagopal 3 DOF model
GRF	ground reaction force	R6	Rajagopal 6 DOF model
GRAC	gracilis	RFEM	rectus femoris
H	hop	RM	MRI-based Rajagopal model
HT	hamstring tendon	RO	original Rajagopal model
Hz	Hertz	s	seconds
IEA	internal/external rotation angle	S	Study
IKDC	International Knee Documentation Committee	SB	single bundle
kg	kilogram	SC	side cut
KJC	knee joint centre	SPM	statistical parametric mapping
KJCB	knee joint centre boundary	STEN	semitendinosus
KJCE	knee joint centre excursion	TFL	tensor fascia latae

List of Tables

Table 4.1.1. Participant characteristics and subjective functional scores.

Table 4.1.2. Spatiotemporal variables during the hop and side cut tasks.

Table 4.3.1. Spearman correlation coefficients (r) for the hop task.

Table 4.3.2. Spearman correlation coefficients (r) for the side cut task.

Table 4.3.3. Pearson correlation coefficients (r) for the objective functional ability measures and Spearman correlation coefficients for the subjective functional ability measures

Table 4.3.4. Adjusted R^2 values for the objective functional ability measures with ACLd score as predictor variable and ACLr score as dependent variable in independent linear regressions.

Table 4.3.5. Odds ratios and Wald X^2 values for the subjective functional ability measures with ACLd score as predictor variable and ACLr score as dependent variable in independent ordinal regressions.

Table 4.5.1. Correlations between subjective questionnaires and joint loading variables.

Table 5.4.1. Mean ligament resting lengths defined as the minimum value during dynamic tasks.

Table A1. Summary of the 20-week standardized rehabilitation program undergone by all ACLr patients.

List of Figures

Figure 3.5.1. Aerial view of knee joint centre excursion (KJCE).

Figure 3.5.2. Two-dimensional aerial depiction of knee joint centre boundary (KJCB).

Figure 3.5.3. A) Sagittal view of MRI and example of manual segmentation B) Resulting three-dimensional renderings from MRI segmentation.

Figure 3.5.4. Example of MRI-segment bones to generic bones and OpenSim static pose anatomical landmarks.

Figure 4.1.1. Linear Envelopes during the hop movement.

Figure 4.1.2. Sagittal angles and moments during the hop movement.

Figure 4.1.3. Ground reaction forces for the hop and side cut.

Figure 4.1.4. Linear Envelopes during the side cut movement.

Figure 4.1.5. Sagittal angles and moments during the side cut movement.

Figure 4.2.1. Dynamic knee joint stiffness calculation.

Figure 4.2.2. A) Stiffness B) knee joint centre excursion and C) knee joint centre boundary.

Figure 4.4.1. Kinematic results of the side cut resulting from the four OpenSim models.

Figure 4.4.2. Ligament lengths of the side cut resulting from the four OpenSim models.

Figure 4.4.3. Demonstration of bone overlap in the R6 model, which is eliminated in the RM model.

Figure 4.4.4. Deviations of the four models from the contact sphere length derived from the MRI congruence motion.

Figure 4.5.1. EMG and static optimization muscle activations in the ACLd condition.

Figure 4.5.2. EMG and static optimization muscle activations in the ACLr condition.

Figure 4.5.3. Ligament forces during hopping.

Figure 4.5.4. Knee joint contact forces during hopping.

Figure A1. Flowchart detailing participant compliance and ability to complete hopping and side cut tasks.

Figure A2. Human Movement Biomechanics Laboratory cluster marker set.

Figure A3. Scatter plots of each objective measure with respect to the highest subjective measure correlation.

Figure A4. Scatter plots of the ACLd predictability of ACLr values for the two highest objective and subjective measures.

Figure A5. Calculated muscle forces during the hopping motion.

Chapter 1: General Introduction

The anterior cruciate ligament (ACL) is one of the main contributors to knee joint stability (Diermann et al., 2009; Markolf et al., 1976). Its rupture leads to marked decrease in quality of life (Lohmander et al., 2007; Oiestad et al., 2011) and injury rates vary between 0.05% in a general population to a staggering 7.3% in a professional female basketball league (Moses et al., 2012). Of these injuries to athletes, an estimated 78 – 85% of them occur from non-contact scenarios (Boden et al., 2000; Waldén et al., 2015), where an individual was not tackled but simply attempting a dynamic movement such as jump landing or defending an opponent. The injury rate does not appear to be slowing down as the incidence between 2007 to 2011 has actually increased approximately 19% in adolescents (Dodwell et al., 2014; Werner et al., 2015), with females being 2 – 8 times more likely to endure an ACL injury when activity type and exposure time are taken into consideration (Boden et al., 2010; Hewett et al., 2006).

Once injured, approximately 22% of patients undergo an ACL reconstruction surgery (Collins et al., 2013; Swenson et al., 2013) resulting in over 130 000 procedures annually in the United States (Buller et al., 2015). This amounts to approximately 1.9 billion USD each year (Hootman and Albohm, 2012) and even though reconstruction costs roughly four times as much as the conservative alternative, it is still considered the more cost-effective method in terms of patients' long term quality of life (Farshad et al., 2011). Unfortunately, the prognosis after ACL reconstruction is rather bleak as re-injury rates have been reported to range between 12 – 24% (Goddard et al., 2013; Laboute et al., 2010; Leys et al., 2012; Paterno et al., 2010) and only 55% of ACL injured patients return to competitive sport (Arden et al., 2014).

In addition to the alarmingly high re-injury rates, ACL injured patients are also more susceptible to developing early onset osteoarthritis (OA) in their injured limb. This is evident as 10 – 20 years post ACL injury, the incidence of OA ranges between 50 -71% with a majority of these patients reporting a reduced quality of life due to pain and decreased functionality (Lohmander et al., 2007, 2004; Oiestad et al., 2011; Roos et al., 1995). In humans, these radiographic degenerative changes begin between 2 – 4 years post ACL injury (Buckland-Wright et al., 2000; Wang et al., 2015). These rapid modifications are harrowing considering the most common age range of reported ACL injuries is 15 – 25 years (Griffin et al., 2000; LaBella et al., 2014), meaning these injured young adults are likely to lead less active lives causing a plethora of secondary health complications (Lohmander et al., 2004; von Porat et al., 2004).

Due to the high re-injury rate and accelerated progression of OA, ACL injured individuals are often repeat customers of the health care system. This suggests that the current treatment paradigm is not effective in maintaining a satisfactory quality of life post injury. Furthermore, these disheartening pathologies can amount to an extraordinary financial burden to either the

individual or government, depending on the country's social structure. However, before one can implement changes to a rehabilitation program, the outcomes must first be examined to identify the major differences occurring between the healthy, ACL deficient (ACLd) and ACL reconstructed (ACLr) conditions. For example, the ACLd population suffers neuromuscular damage associated with the loss of the ACL itself since it is also a sensory organ, whereas the ACLr group will, in addition, incur damage from the graft harvest site, be it a hamstring, patellar tendon or other graft type. Thus, it is reasonable to suspect that the surgery, rehabilitation, or re-injury prevention programs based upon returning the patient to the status of healthy, uninjured individuals are suboptimal. Since ACL injuries have both a mental and physical impact, it is imperative to consolidate these aspects in order for them both to be properly addressed in a rehabilitation program. By identifying how patient-related outcome measures (PROMs), movement profiles, neuromuscular control, and joint loading differ between ACL-related conditions, clinicians will be able to better assess their patients' rehabilitation progress. This consolidation will be useful in future applications such as building holistic evidence-based rehabilitation programs that better serve ACL injured populations in improving their long-term quality of life.

To this end, this doctoral thesis investigates through five studies the relationships between subjective and objective measures of functional ability in ACLd and ACLr conditions using biomechanical and neuromusculoskeletal modelling approaches. A combination of in vivo and in silico methods was implemented to achieve the three following global objectives (GO):

- GO1: Determine if muscle excitations and movement patterns differ between healthy and injured populations
- GO2: Employ three objective measures of dynamic knee joint control that represent healthy, ACLd, and ACLr movement patterns and determine if they are related to the patients' self-evaluation of functional ability
- GO3: Determine how knee joint contact and ligament forces differ between ACLd and ACLr conditions and identify any relationships between these and subjective measures of functional ability

The first objective (GO1) was addressed through Study 1 (S1), which was an in vivo test-retest design that compared PROMs, muscle excitations, kinematic, and kinetic results between healthy control (CON), ACLd, and ACLr groups. These kinematic and kinetic data were then used in Study 2 (S2) where three novel objective measures of dynamic knee joint control were used to assess functional ability amongst the three populations. GO2 was then addressed in Study 3 (S3) by combining S1 and S2 results to determine the correlations between objective and subjective measures in addition to the ACLd score's predictive ability of its respective ACLr score. Following this, in Study 4 (S4) magnetic resonance images (MRI) were used to create novel patient-specific knee joint

models to better represent the ACLd and ACLr populations. These models were then employed in Study 5 (S5) to address GO3 by relating the PROM scores to objective joint contact and ligament forces in the ACLd and ACLr populations.

Chapter 2: Literature Review

2.1 Knee Joint Stability

The knee joint is arguably one of the most complex joints in the human body and with its six degrees of freedom (DOF), it is very susceptible to injury. Internal knee injuries (e.g. ACL ruptures, meniscal tears, etc.) account for 40% of athletic injuries (Majewski et al., 2006) and can be explained in part by the large internal knee forces exhibited during dynamic tasks. These forces include tibial compressive forces as high as 7.6 N/BW in combination with anterior shear forces of 0.7 N/BW during jump landing (Cleather et al., 2013). The ability to safely oppose forces and moments acting on a joint is known as joint stability (Winter, 2004) and can be seen as maintaining a state of homeostasis (Riemann and Lephart, 2002). To resist these potentially damaging forces and maintain homeostasis, the responsibility falls upon active stabilisers (muscles) and passive components (joint geometry/alignment, menisci, and ligaments). All of these components must work in concert as any disruption can have a deleterious effect on the joint's ability to maintain stability.

Muscles

The sole active knee joint stabilisers are the surrounding musculature. These are considered to be the most important contributors to joint stability due to their compressive force generation (Hsieh and Walker, 1976). These compressive forces are even capable of maintaining in vitro joint stability when all passive structures are removed (Hsieh and Walker, 1976). Since compressive loading is known to be a crucial factor in joint stability (Markolf et al., 1981), muscular co-excitation is often used as a representation for the prospective amount of loading and thus, related to joint stability. Muscle pre- and co-excitation is speculated to help prepare the knee for loading and compensate for impaired neuromuscular functions (Hortobágyi and DeVita, 2000). Although certain levels of co-excitation appear to be important in successful stabilisation strategies (Rudolph et al., 2001), the optimum amount of co-excitation remains unclear as high levels of co-excitation are thought to be detrimental to the joint and linked to soft tissue degradation (Hubley-Kozey et al., 2009). Further issues arise when the muscular co-excitation is unbalanced since significant reductions in medial muscle activations compared to their lateral counterparts increases the risk of valgus loading (Hubley-Kozey et al., 2009).

Bone Geometry and Joint Alignment

Perhaps the simplest contributor to joint stabilisation arises from the articulations due to bone geometry and alignment during joint loading. This includes the 'screw-home locking mechanism' as described by Rajendran (1985) where at full extension, the femur medially

rotates on the tibial plateau to 'lock' into place. This is caused by the naturally occurring upslope on the medial tibial plateau and the flattened or downslope lateral tibial plateau, thus causing a medial femoral rotation. Since the distribution of joint contact is affected by these bony articulations, they directly contribute to knee stability and joint loading. For example, during the weight acceptance phase of gait, the medial load share is 73% while only 65% during the toe-off phase (Halder et al., 2012). These joint contact surfaces are also influenced by skeletal alignment as deviations from normal alignment increase knee joint loading, with the responses being highly individualized (Heller et al., 2003). For example, when the knee is in neutral and varus positions, maximum peak pressure occurs on the medial condyle, whereas knee valgus causes the majority of pressure to be placed on the lateral compartment (Bruns et al., 1993). An 8° increase in knee valgus from normal alignment increased contact force by 53% in stair climbing and 140% in level gait, while a 10° increase in knee varus from normal alignment increased joint contact force by 35% in stair climbing and 114% in level gait (Heller et al., 2003). These changes in joint loading caused by different alignments are associated with soft tissue degeneration in the form of OA. With respect to OA progression, knee varus is linked to medial OA and delays lateral OA progression. The opposite occurs with knee valgus as it is associated with lateral OA and delays medial OA progression (Sharma et al., 2010). Taking into consideration the effect bone geometry and joint alignment have on stability, joint loading, and disease progression, it is paramount that they be considered in methodological approaches when applicable, such as participant-specific parameters in neuromusculoskeletal models.

Menisci

The menisci have several functions in the knee joint that include load transmission, shock absorption, proprioception, lubrication, and joint stability (Aagaard and Verdonk, 1999; Fithian et al., 1990; Kelly et al., 1990; Makris et al., 2011). Their wedge-shape helps stabilise the round femoral condyles on the flat, central portion of the tibial plateau and effectively distribute load by converting vertical forces from the femur into horizontal hoop stresses, which enhances energy dissipation (Makris et al., 2011). Complete meniscectomies cause a 50 – 75% decrease in contact area, increase in mean and peak contact stress, and decreased shock absorption between the femur and tibia (Kelly et al., 1990; Lee et al., 2006). These factors play an important role in knee stability as after meniscectomies, anterior tibial translations (ATT) increase up to 5.8 mm and internal tibial rotation (ITR) decreases by 4.7° at 60° knee flexion (Allen et al., 2000). These objective measures of functional stability are supported by subjective measures of stability. Wu et al. (2002) found that any amount of meniscal resection increased subjective complaints concerning pain and instability, while reducing activity levels ten years following meniscus surgery. These complaints were supported by decreased International Knee Documentation Committee (IKDC) and Lysholm scores, which are subjective questionnaires pertaining to knee function (Wu et al., 2002). Finally, their dynamic stability and functionality

were also tested through one-leg hop between limb symmetries and it was found that the meniscectomy groups were 20% more likely to have poorer performance in their meniscus deficient limb (Wu et al., 2002). In terms of load-bearing, increases are seen proportionally to the amount of meniscus that is removed until hoop tension is lost. Once hoop tension is lost, the increases in load are equivalent to those seen in total meniscectomies (Lee et al., 2006). Similar trends are seen in soft tissue degradation as there are increased radiographic abnormalities in meniscectomy groups (Allen et al., 2000) and the amount of degeneration is proportional to the amount of removed meniscus (Kelly et al., 1990). This is supported by the increased incidence of OA in patients who have undergone double meniscectomies on the injured limb (Sommerlath, 1989). Finally, the importance of the menisci in knee joint stability is dependent on the integrity of other surrounding soft tissue stabilisers as well. Menisci provide considerable knee stability in ACLd knees (Kelly et al., 1990), which could be associated with the amount of load they bear: in the ACLd knee, the load placed on the medial meniscus has been shown to increase by 52% at full extension and 197% at 60° flexion compared to the ACL-intact knee (Allen et al., 2000). Therefore, even though the menisci play an integral role in healthy knee stability, there is an enormous responsibility placed on the neighbouring ligaments to maintain joint stability.

Ligaments

Determining the ACL's contribution to knee joint stability has been the driving force behind many studies. From numerous in vitro and in silico studies, it is clear that the ACL is the primary passive structure that resists anterior tibial translation (ATT). This is especially the case at full knee extension, although its contribution to reducing ATT is greatly decreased when knee angle is increased (Markolf et al., 1976; Moglo and Shirazi-Adl, 2003; Sakane et al., 1999; Shoemaker and Markolf, 1985; Woo and Fisher, 2009). It has been speculated that after an ACL rupture, significantly larger forces are seen in the medial and lateral tibiofemoral joint compartments (Moglo and Shirazi-Adl, 2003). The authors of this finite element study argued that since the ACLd knee has greater laxity, the collateral ligaments are taxed with greater tensile forces. Since these collateral ligaments are mechanically less efficient in resisting horizontal loads, these loads are transmitted axially onto the tibial plateau. Considering that an increase in compressive loads can decrease the amount of anterior laxity in ACLd knees, especially at full extension (Shoemaker and Markolf, 1985), this resulting shift of forces to the collateral ligaments (and in effect the tibial plateau) could be a mechanically-driven method to compensate for the instability observed in ACLd knees. Due to ethical limitations, this phenomenon cannot be examined through in vivo methods and thus must be explored through in vitro or in silico modelling. As such, models that are as anatomically and physiologically accurate as possible are crucial in determining the true effects ligament resection has on joint loading and stability.

2.2 Measures of Knee Joint Control

Defining knee joint control is a rather difficult task as it can be described in many ways. With respect to objective control measures, very common clinical tests of mechanical stability include the Lachman, instrumented anterior drawer (KT-1000 and Rolimeter), and pivot-shift tests that allow the clinician to measure translational and/or rotational laxity of the knee joint. Although these clinical tests of passive joint laxity provide information regarding the knee's passive mechanical stability, these assessments are done in relaxed, static and non-weight bearing situations. This may explain why they are not strongly correlated with functional tests, including Noyes' (1991) battery of hop tests in the ACLd (Eastlack et al., 1999) and ACLr state (Risberg et al., 1999; Sernert et al., 1999). Thus, their validity and transferability as dynamic knee joint control measures is questionable when the focus is on relating ACL injuries to joint control during dynamic and weight bearing tasks. To address this limitation, measures that represent joint control during dynamic scenarios should be developed in order to provide a more complete understanding of knee joint function.

One definition of dynamic control is joint stiffness, measured as the change in joint moments as a function of the change in joint angles (Davis and DeLuca, 1996; Longpré et al., 2013; Zeni Jr. and Higginson, 2009). These studies suggest an increase in joint stiffness increases the joint's robustness to perturbations since it would require greater magnitudes of applied forces to induce a displacement in joint position, thereby protecting the soft tissue from harmful amounts of tissue strain. Even though this concept of joint stiffness has been applied to the knee during elementary movements such as gait, it has yet to be used to describe the knee during more demanding dynamic tasks such as hopping and side cutting, during which injuries to the ACL may actually occur. Furthermore, the idea of increased joint stiffness being synonymous with dynamic knee joint control has yet to be directly tested. Thus, linking this objective stiffness measure to subjective subscales of stiffness contained within the PROMs can strengthen the validity of this measure.

Another simple measure of dynamic control after ACL injury is knee excursion, as defined by the total change in sagittal plane angle during a dynamic task. This knee excursion is greater in the ACL injured limb during gait and hopping (Di Stasi et al., 2015; Risberg et al., 2009), greater in poor functioning ACLd patients compared to high-functioning patients during a step task (Rudolph and Snyder-Mackler, 2004), and may improve in women between the ACLd and ACLr state (Di Stasi et al., 2015). This method is limited, though, since it only considers knee joint excursion in one dimension while it is well-known that the ACL contributes to knee joint control in more than just the sagittal flexion angle, including ATT, abduction/adduction, and internal/external rotation (Markolf et al., 1976) and non-contact injury mechanisms are a combination of forces in multiple planes (Boden et al., 2000; Griffin et al., 2006). Therefore, knee excursion's ability to represent dynamic control would likely be improved if it considered

the joint in three-dimensional space and served as a measure of movement efficiency. Through early conversations during pilot testing of this thesis, participants reporting poor control and instability often described their injured knee as “wobbly”. This measure of knee excursion that tracks the knee joint centre in three-dimensional space may prove to be a valuable metric in objectively representing this subjective concern ACL injured patients have voiced. Thus, linking an objective measure to a subjective concern may prove useful in relating physical and mental aspects associated with ACL injuries.

Finally, movement variability has also been used to assess knee control after ACL injury. It is believed that there is an optimal level of variability in human movement since a rigid system is less adaptable to perturbations, while a highly variable system is noisy and unstable (Stergiou et al., 2006; Stergiou and Decker, 2011). Through a literature review, Decker and colleagues (2011) concluded that the loss of variability, which is associated with a more rigid and repeatable movement pattern, is observed in the ACLd knee. Contrarily, increased variability beyond the optimal level, which is linked to a noisy and irregular movement pattern, is found in the ACLr knee. Even though this review indicated abnormal levels of variability, the included studies were cross-sectional and therefore it still remains unknown how or if movement consistency (i.e. variability) changes longitudinally with respect to a specific patient’s ACL status. This measure also provides conflicting results since, depending on the definition, the ACLd limb has been linked to no changes (Skurvydas et al., 2011) or decreases (Zampeli et al., 2010) in variability, while both increased (Cordeiro et al., 2015) and decreased (Pollard et al., 2015) variability have been observed in ACLr populations. Since these objective movement variability results have been inconsistent and often contradictory, linking them to subjective measures may prove to be a method of external validity. Determining optimum levels of performance based independently on variability is not possible whereas subjective scores of functional ability clearly demonstrate a hierarchy in performance. Therefore, matching a patient’s objective movement variability to their subjective functional score may elucidate the optimal level of variability.

2.3 ACL Injuries and Changes in Joint Function

Objective Measures

The healing and rehabilitation process after ACL injury is incremental and based on joint function. It begins with immobilisation required for tissue healing, pain management, and the reduction of swelling (Wright et al., 2015). Mobilisation is introduced as early as possible to avoid scar tissue and over the course of weeks and months, exercises to regain balance, strength, and stability are incrementally made more difficult and based on a patient’s performance (Wright et al., 2015). With this process inducing varying levels of physical activity over the course of months, changes to the patients’ neuromuscular biomechanics are to be

expected. When the excitations of muscle groups are examined through electromyography (EMG) during various dynamic tasks, there is a wide spectrum in findings among studies. In terms of the quadriceps, decreases in activation compared to uninjured controls after ACL injury during gait (Limbird et al., 1988), running (Lent et al., 1994), and other functional activities (Ciccotti et al., 1994) have been reported. Another study, however, reported no changes in quadriceps activation during a standing, weight-bearing task (Aalbersberg et al., 2009) in an ACL injured group. Previous studies have reported increases in hamstring activation during level (Limbird et al., 1988) and uphill (Kalund et al., 1990) gait, static weight-bearing (Aalbersberg et al., 2009), dynamic knee extensions (Alkjær et al., 2012), and a battery of functional activities (Ciccotti et al., 1994). On the contrary, other studies have observed no changes in hamstring activation during level gait (Kalund et al., 1990) or even a decrease in activity during running (Lent et al., 1994). These surface EMG results during gait have been summarized in a review by Shanbehzadeh (2015) who determined that only 7/12 studies reported activation magnitude differences in the ACL injured for the quadriceps and only 6/12 studies declared differing hamstring activation amplitudes.

Differences in movement profiles between healthy (CON) and ACL injured are somewhat more consistent than EMG findings. During walking and jogging, ACLd show decreased knee flexion angles (Chmielewski et al., 2001; Rudolph et al., 1998) and internal knee extensor moments (Andriacchi and Birac, 1993; Chmielewski et al., 2001; Rudolph et al., 2001). This trend of decreased knee flexion has also been observed in a step down and cut movement (Houck and Yack, 2003) while the decreased internal knee extension moment has been seen in hopping (Rudolph et al., 2000), stepping (Andriacchi and Birac, 1993), and a step down and cut movement (Houck and Yack, 2003).

Subjective Measures

Despite the lack of congruency among the aforementioned objective measures, subjective measures of patient function acquired through PROMs are more consistent in describing negative change following injury and positive change following ACL reconstruction and rehabilitation (Irrgang et al., 2001; Roos and Lohmander, 2003). The Knee Injury and Osteoarthritis Outcome Scale (KOOS; Roos and Lohmander, 2003), Knee Numeric-Entity Evaluation Scale (KNEES; Comins et al., 2013), International Knee Documentation Committee (IKDC; Irrgang et al., 2001), Tegner activity scale (Tegner and Lysholm, 1985), and Lysholm scale (Lysholm and Gillquist, 1982) are all used to assess a degree of self-reported symptoms, function, and ability in ACLd and ACLr populations. These questionnaires are effective in distinguishing between patient populations as scores have been reported to be significantly lower in ACLd compared to healthy counterparts (Eitzen et al., 2010; Fischer-Rasmussen and Jensen, 2000; Fitzgerald et al., 2000a; Herrington and Fowler, 2006; Lindstrom et al., 2010) and

greater in ACLr compared to ACLd (Cordeiro et al., 2015; Lentz et al., 2009; Nyland et al., 2014). Based on these subjective improvements, ACL reconstruction appears to induce a positive change in function, yet, as noted above, re-injury rates and return to pre-injury activity levels are troubling. It is plausible that subjective measures are not sensitive to the factors that may indicate when a patient is ready for a safe and optimal return to activity. Linking these subjective measures of function with objective measures of joint control may provide this insight and lead to a more informed clinical decision-making process.

Objective and Subjective Congruency

Perhaps the most basic measure of objective knee function is mechanical stability (joint laxity) determined through the Lachman and Pivot-shift tests or the instrumented anterior drawer (i.e.: KT-1000; Makhni et al., 2015). However, there is a consensus that this passive mechanical stability is not significantly correlated to subjective measures of joint function (Barrett, 1991; Christino et al., 2016; Sernert et al., 1999; Snyder-Mackler et al., 1997), possibly due to the laxity being determined in an unweighted and muscle-relaxed state, which is not reflective of a functional task or injurious scenario. Knee strength, defined by peak knee flexor torque and power experimentally measured by a dynamometer, has shown moderate correlations ($r = 0.51 - 0.54$) to KOOS subscales (Bodkin et al., 2017) but although this is a stronger relationship than clinical laxity, these measures of isometric strength are not truly indicative of a demanding dynamic task either. Subjective PROMs have nevertheless been related to performance on various timed hopping tests, which serve as surrogate measures of objective functional ability. Correlations between these hop tests and PROMs range from weak to considerably strong (6 metre timed hop – IKDC: $r = 0.72$; Bodkin et al., 2017; Logerstedt et al., 2012) but still only define knee function as the external outcome of the whole-body function. It is therefore still unclear if the lack of relationships between the physical and mental aspect of functional ability are truly non-existent or if the objective measures are not targeting the same elements of functional ability that the subjective questionnaires are trying to represent.

2.4 Copers vs. Non-copers

Definition of a coper

Prior to the work of Snyder-Mackler's group at the University of Delaware, few studies were investigating possible within ACLd group differences in functional ability (Daniel et al., 1994; Wojtys and Huston, 1994). This paradigm shifted with the seminal screening evaluation tool proposed by Fitzgerald et al. (2000a) in which they incorporated objective and subjective functional measures as a way of discriminating between potential copers and non-copers. To be classified as a potential coper, a patient must achieve a timed hop test with a score greater than 80% limb symmetry (Noyes et al., 1991), a global rating of knee function above 60%, a

KOOS-ADL score of greater than 80%, and finally, one or less episodes of “giving-way”. This tool identified 39 out of 93 participants as potential copers, of which 28 received conservative treatment and 79% (22/39) of those successfully returned to a pre-injury level of activity without any instances of dynamic instability. Many studies, including the vast majority of those from the University of Delaware that examine copers and non-copers, use these guidelines to discriminate between ACLD individuals even though this standard has been shown to have a 70% false negative rate (those rated as potential non-copers who were in fact true copers; Moksnes et al., 2008). An alternative to Fitzgerald’s screening tool is a simpler classification that defines a copers as an ACLD patient who has returned to their pre-injury level of activity without surgery or any instances of instability (Alkjaer et al., 2002; Courtney et al., 2005; Daniel et al., 1994). A third evaluation schema was put forward by Fithian and colleagues called the Surgery Risk Factor (SURF) classification system which is based upon knee joint laxity and the patient’s pre-injury level of activity (Fithian, 2005). Surgeons use this guideline to determine which patients are at a high risk of subsequent injury to the knee joint and should therefore receive operative treatment. Finally, to confound groupings further, a third group of ACLD patients is sometimes included and identified as “adapters”. These individuals opt for conservative treatment methods and are capable of returning to an activity level that is below their pre-injury state (Button et al., 2006; Courtney et al., 2005). With the variation in classification systems to determine potential copers, comparisons between studies should be taken with caution as there is a considerable range of functionality in the sample size in particular those studies that either do not screen for potential copers, or that only evaluate tasks which are non-threatening and accessible to the vast majority of ACL injured individuals, such as gait.

Functional Differences

Since a great number of studies use self-reported questionnaires of knee function (e.g. Fitzgerald (2000a): KOOS-ADL & Global Knee Rating Score) in their decision-making scheme when grouping copers and non-copers, it is of little surprise that copers consistently have significantly higher scores in Lysholm, KOOS-ADL, KOOS-Sport, and Global Knee Rating when compared to the non-copers (Eastlack et al., 1999; Herrington and Fowler, 2006; Snyder-Mackler et al., 1997). What is of particular interest is that there are no differences in knee joint laxity in copers and non-copers regardless of the passive or active state of the surrounding musculature (Hurd et al., 2008; Melnyk et al., 2007; Wojtys and Huston, 1994). Since the IKDC questionnaire uses queries for subjective joint laxity as one of its measures, this could explain why this questionnaire is not an effective tool in describing the disparity of knee joint function between copers and non-copers (Eastlack et al., 1999; Herrington and Fowler, 2006; Snyder-Mackler et al., 1997).

In terms of the surrounding musculature, only Hurd and colleagues (2008), who use the SURF coper classification, found that quadriceps strength did not differ between copers and non-copers while other publications who use the Fitzgerald coper classification observed a significantly higher quadriceps strength in the coper population (Lewek et al., 2003; Rudolph and Snyder-Mackler, 2004). This deficit in quadriceps strength has previously been noted as a hallmark characteristic of the non-coper population (Lewek et al., 2003). This is possibly due to the non-copers weaker quadriceps not being able to produce compressive loads known to increase knee joint stability (Hsieh and Walker, 1976; Markolf et al., 1981). Strength alone, however, is not sufficient to dynamically stabilise the knee joint as non-copers with good quadriceps strength also exist (Eastlack et al., 1999; Lewek et al., 2003; Rudolph et al., 2000). Instability is also associated with an imbalance in quadriceps excitation with respect to hamstrings and gastrocnemii (Sell et al., 2007; White et al., 2003) meaning that both appropriate co-excitation and raw strength are important for avoiding instability. This is supported by Eitzen et al. (2010), who found quadriceps muscle strength to be the best baseline predictor of those who would or would not need reconstructive surgery, although it only contributed 13% to the final predictive model.

2.5 ACL Reconstruction

Surgical Techniques

Once the surgical option has been chosen, the vast majority of ACL reconstructions are completed with one of two techniques: bone-patellar tendon-bone (PT) or hamstring tendon (HT) autografts (Erickson et al., 2014). The HT autografts typically come from the semitendinosus and gracilis tendons comprising single (SB) and double bundles (DB; Erickson et al., 2014). Studies are in agreement that the two techniques lead to no differences in Lysholm, and Tegner scores, nor anterior laxity or range of motion (Gong et al., 2013; Hussein et al., 2012a; Kongtharvonskul et al., 2013; Lee et al., 2012). However, a greater amount of rotational stability in the form of reduced rotational laxity has been observed in DB patients, which has been attributed to the wider insertion site on the tibial plateau in the DB technique (Kongtharvonskul et al., 2013; Lee et al., 2012; Papachristou et al., 2008). This additional rotational stability has been noted in the pivot shift tests as DB have been shown to be four times more likely to exhibit normal scores on this test compared to SB patients (Kongtharvonskul et al., 2013). This same study also found that DB patients were two times more likely to show normal IKDC scores (Kongtharvonskul et al., 2013) but this has been refuted in other studies that observed no differences in IKDC scores between groups (Gong et al., 2013; Hussein et al., 2012a).

Biological Outcomes

Since variations in surgical techniques exist, there is understandably a wide range of biological outcomes depending on the chosen technique. Pinczewski et al. (2007) tracked the osteointegration of two patients who needed revision surgery due to graft rupture. They noted that the combination of interference screws and HT graft allows for good osteointegration as evidenced by collagen fibre continuity between bone and tendon by 6 and 15 weeks. Another study that followed twelve patients who had hardware or re-rupture issues found that at three months, very few collagen fibres had formed between the bone and HT graft (Robert et al., 2003). At five and six months, collagen fibres were observed and immature woven bone had formed. Finally, at ten months, good integration had occurred between the graft and surrounding bone and the re-ruptures were mid-substance instead of at the fixation site. These studies stress the belief that osteointegration is crucial within the first few months post-operation and if bone tunnel movement occurs, the graft will not be able to mesh with the surrounding bone and the patient becomes at risk of fixation failure. Since the biological healing of tissues vary patient to patient and with respect to surgical technique, the stage of healing needs to be considered when interpreting the mechanical stability and functional performance of patients post-reconstruction.

Mechanical Stability and Functional Outcomes

With respect to mechanical stability and functional outcomes, a decreased peak in knee flexion torque has been reported between 8 – 24 months post-reconstruction but no differences outside of this range (Feller and Webster, 2003). Knee laxity asymmetry between limbs has also been observed after HT grafts, evidenced by larger KT-1000 arthrometer results in the injured limb (Feller and Webster, 2003; Goldblatt et al., 2005). This laxity asymmetry may partially be explained by femoral and tibial tunnel widening (Clatworthy et al., 1999) and still persists three years post-operation as only 32% and 44% of HT ACLr patients achieve a normal Lachman and pivot shift rating respectively (Razi et al., 2014). This laxity appears to affect a patient's return to play as only 43% HT ACLr were able to return in a 28 month follow-up (Aglietti et al., 1994). After two years, laxity, pivot shift, Lysholm score, Tegner score, and knee flexion/extension strength were no different between SB and DB but IKDC scores were higher in the DB group (Lee et al., 2012). At four years follow-up, IKDC scores were higher in the DB patients for one study (Song et al., 2004), but not for another (Hussein et al., 2012b). These studies also differed in anterior laxity, pivot shift and Lachman tests. Hussein and colleagues (2012b) observed decreased ATT and increased normal pivot shift and Lachman scores in the SB patients compared to Song et al. (2004) who detected no differences in these measures, in addition to Lysholm and Tegner scores, OA, and graft rupture rates.

Biomechanical Outcomes

After reconstruction, biomechanical differences in the form of kinematic (Deneweth et al., 2010; Oberländer et al., 2014; Pollard et al., 2015), kinetic (Holsgaard-Larsen et al., 2014; Miranda et al., 2013), and EMG (Coats-Thomas et al., 2013; Cordeiro et al., 2015; Nyland et al., 2014) persist with respect to healthy, uninjured populations. Furthermore, PROMs although show improvement from the ACLd state, rarely achieve the same level observed in healthy populations (Arderm et al., 2016; Gustavsson et al., 2006; Johnson et al., 2015; Minzlaff et al., 2018; Nyland et al., 2014). These differences likely contribute to the long-term incidences of degenerative changes observed in ACLr. After 13 years post-operation, 79% of patients were observed to have knee joint soft tissue degeneration (Salmon et al., 2006) while at 15 years, another study reported 38% of HT and 58% of PT graft to have radiographs indicating degeneration (Leys et al., 2012). These results are in line with those reported by Lohmander et al. (2007) in that 50% of ACLr patients exhibit OA 10 - 20 years post-reconstruction. These persisting biomechanical differences and high incidences of soft tissue degeneration demonstrate the ineffectiveness of the current treatment paradigm. Health researchers need to be encouraged to pursue novel research questions that help elucidate the link between objective and subjective functional ability and determine if and how these factors influence knee joint health.

2.6 Neuromusculoskeletal Modelling

It is clear from the above that ACL injury, surgery, and surgical technique will lead to altered kinematics, neuromuscular control, and thus joint kinetics. It is also clear from the literature that these parameters are linked to the development of knee OA (Lohmander et al., 2007, 2004; Oiestad et al., 2011). However, when investigating the complex interactions of the neuromuscular and skeletal systems, many research questions have gone unanswered due to the invasive nature of the experiments required to measure muscle and joint contact forces in the human body. Furthermore, if these interactions are capable of being measured, it is still difficult to discern cause-and-effect relationships due to the intricate nature of the neuromuscular and skeletal systems. Advancements in computing technology have brought in silico simulations to the leading edge of human movement analysis. Simulation software such as OpenSim (Delp et al., 2007) have addressed these issues by providing a modelling environment where individual variables (muscle parameters, joint contact surfaces, kinematics, etc.) can be manipulated and the outcomes of these interventions examined to identify cause-and-effect relationships. Other simulation software such as AnyBody, Simm, and pure mathematical modelling through programming languages exist, but since OpenSim is open-source, the user community is much larger and the source code is freely available. OpenSim is also versatile in that its easy-to-use graphical user interface can be bypassed with application program interfaces allowing for simple data import/export, batch processing, and modifications

to the existing OpenSim tools. In silico models from these software have been effective in identifying the roles of ligament and contact forces during knee motion (Nardini et al., 2016; Sancisi and Parenti-Castelli, 2011). In silico models have also been used to determine muscle force contributions (Delp et al., 1990; Hamner et al., 2010) and knee joint contact loads (Fregly et al., 2011) during walking and running.

In silico modelling has proven valuable in quantifying contact force patterns at various degrees of ACL injury, including ACLd and ACLr patient groups. When the ACL is removed, mixed results have been observed in terms of tibiofemoral contact forces. A stochastic biomechanical model has predicted a greater anterior tibial shear force (ATSF) compared to healthy controls, but this model did not consider ATT (Lin et al., 2012). When Shelburne and colleagues (2004) incorporated ATT into their model, they observed a decrease of ATSF in the ACLd condition. Differences in compressive joint loading are also apparent, as an EMG-driven musculoskeletal model has shown a decrease in compressive force in the ACLd limb compared to the uninjured limb (Gardinier et al., 2013). This model however excluded knee ligaments and testing occurred only eight weeks post-injury. Therefore, this decreased compressive force can likely be attributed to a shielding mechanism employed to protect the graft that is still in its early stages of healing. Contrarily, two finite element models that included knee ligaments and six DOF estimated significantly larger tibiofemoral compressive joint forces (Moglo and Shirazi-Adl, 2003; Vairis et al., 2015), compared to uninjured knees. The authors of this finite element study argued that since the ACLd knee has greater laxity, the collateral ligaments are taxed with greater tensile forces. This postulation has been supported by in silico models in which once the ACL is removed, the medial collateral ligament (MCL) exhibits greater tensile forces perhaps in an effort to combat the anterior laxity (Shao et al., 2011; Shelburne et al., 2004). As discussed earlier, this shift of forces to the collateral ligaments and in effect the tibia plateau could be a mechanically-driven circumvention of the stability issues observed in ACLd knees. These two models (Moglo and Shirazi-Adl, 2003; Vairis et al., 2015) however, are not based on actual in vivo data but instead knee replica scans and therefore generalize patient-specific parameters such as joint alignment, muscle wrapping, and ligament insertions.

Even with the presence of discrepancies in regards to the magnitude of contact force after ACL injury, the literature consistently agrees that in ACLd individuals, the location of contact force is shifted more posterolaterally (Scarvell et al., 2005; Van de Velde et al., 2009). This shift could be an important factor linking injury to OA as the average thickness of the newly loaded area is thinner, not conditioned to the new loading, and undergoes greater deformation compared to a healthy knee (Andriacchi and Mündermann, 2006; Van de Velde et al., 2009). ACL reconstruction has proven to be only partially effective in returning tibiofemoral contact loading back to loading conditions observed in healthy populations. One EMG-driven model has shown increased compressive forces in the ACLr group compared to healthy (Tsai et

al., 2012) while another EMG-driven model has shown normal contact forces in half (4/8) of ACLr patients (Sanford et al., 2013). An MRI-based model has detected ACLr contact mechanics similar to healthy controls but when the knee was brought to lower flexion angles, the contact area became more posterior, similar to what is seen in ACLd (Hosseini et al., 2012). When all of these results are taken into consideration, there are still large discrepancies in the tibiofemoral contact mechanics between healthy, ACLd, and ACLr patients. These differences may be attributed to different types of modelling (in vitro, EMG-driven, finite element, MRI, etc.), the functional ability of the patients being modelled (copers vs. non-copers), or even the biofidelity of the model itself. If the model is too simplistic or anatomically/physiologically inaccurate, the conclusions made with it will be limited. Thus, biofidelity is crucial to preserve external validity and allow for smooth applications to in vivo scenarios.

2.7 ACL Rehabilitation Programs

Strength, range of motion, and balance exercises are often used in standard rehabilitation programs. In addition to this, the University of Delaware rehabilitation program strongly advocates the use of perturbation training (Fitzgerald et al., 2000b). They observed that the patients who completed the standard rehabilitation program, limited to quadriceps and hamstrings resistive exercises, cardiovascular endurance training, agility skill training, and sport-specific skill training, were less likely to return to play compared to those who completed the perturbation training. During the rehabilitation process, patients were exposed to perturbations through the use of a motorized force platform, tilt board, and a roller board. With the addition of these perturbations, participants were five times more likely to successfully return to high-level physical activity, which include cutting and jumping sports that place the player at higher risk of a knee injury. These functional improvements were also observed to be more lasting as perturbation participants showed significantly higher retention rates at the six-month follow-up session in KOOS-ADL, global rating of knee function, and cross-over hop scores. Since no differences in knee joint laxity were observed between the groups prior to training and at the follow-up, more evidence is provided that the functional ability in ACLd patients is more dependent on neuromuscular patterns than mechanical stability.

Another study (Eitzen et al., 2010) that used the University of Delaware perturbation protocol also observed significant improvements in functional scores (KOOS, IKDC, and visual analog scale of global rating of knee function). Furthermore, quadriceps and hamstring strength were larger post-rehabilitation in both ACLd groups while the six metre timed hop test symmetry between limbs also increased in non-copers. Other benefits related to perturbation training include decreased amounts of knee excursion during gait in the injured limb even with both the strength and perturbation groups showing an increase in quadriceps strength after training (Hartigan et al., 2009). Perturbation training has also had a significant impact on females specifically as they had decreased hip and knee flexion angles and moments, smaller

knee and larger knee excursions pre-training. After completing the perturbation program, all of these variables except knee extensor moments were returned to levels of those recorded for healthy controls (Di Stasi and Snyder-Mackler, 2012). Finally, neuromuscular training through the use of perturbations has also shown to decrease kinesiophobia (Hartigan et al., 2013).

Rehabilitation programs post-reconstruction are typically based on the premise of symmetry between limbs. This includes the Knee Symmetry Model (Biggs et al., 2009) in which an emphasis is placed on bilateral symmetry in range of motion, strength, stability, and function. The level of symmetry is often arbitrary but usually considered to be the injured side showing 75 – 90% ability of the contralateral limb (Biggs et al., 2009; Noyes et al., 1991; Wright et al., 2015). Aside from the arbitrary definition of asymmetry, the process of evaluating a patient's progress based on objective isolated limb symmetry may be detrimental to their recovery. Firstly, it is unknown whether or not the individual was predisposed to biomechanical factors or neuromuscular patterns that lead to the injury in the first place. By assessing the injured limb function in relation to the contralateral side that performs movements in a precarious way can be viewed as setting the patient up to fail. Secondly, ACL injury is known to have an effect on the contralateral limb, particularly for dynamic balance and voluntary quadriceps activation (Zult et al., 2017). These reasons may account for why limb symmetry indexes frequently overestimate knee joint function, and the lack of injured limb restoration of function may increase the risk of secondary ACL injury (Wellsandt et al., 2017). Placing less emphasis on limb symmetry during evaluations and investing more onto neuromusculoskeletal modelling to extract joint loading information while relating these values to the patient's subjective functional performance may be a more effective alternative.

The Multicenter Orthopaedics Outcomes Network (MOON) has also developed an ACL rehabilitation protocol that is based on functional performance (Wright et al., 2015). Although progression through this program is less dependent on limb symmetry than the others, the only PROM variable it includes is the single 1 – 10 global rating of knee function question from the IKDC. Considering this subjective component of functional ability is included in the vast majority of studies pertaining to ACL injuries and functional outcomes, it is viewed in the research community as an important aspect of ACL injury recovery. However, clinicians and the current rehabilitation programs fail to effectively incorporate this mental aspect into their schemas. Incorporating more of this subjective component will help improve return to play guidelines and lower the risk of secondary injury. To do so effectively however, the relationship between objective and subjective measures of functional knee joint ability must first be better understood.

2.8 Past Limitations and Knowledge Gaps

Technical Limitations

The inconsistent results in objective variables across ACL studies/populations may be attributed to numerous reasons. This includes variability in surgical methods (Erickson et al., 2014) and across tasks (Ciccotti et al., 1994) being measured, such as walking, stair ascent/descent, level running, which are relatively easy to perform and not associated with ACL injury mechanisms unlike cutting and deceleration motions (Boden et al., 2000; i.e. low-risk, low demand which do not push their performance threshold). Another limitation of past work includes the use of cross-sectional design to determine differences between CON, ACLd, and ACLr, which could be misleading because observed variability may be attributed to differences in sample populations and not solely the reconstruction. To the authors' knowledge, a comprehensive test-retest with matched controls investigation of neuromuscular function and movement biomechanics in these populations during challenging dynamic tasks has yet to be completed. A final drawback is that many studies extract discrete variables (i.e. amplitude, onsets, time-dependent events) from highly correlated and time-dependent waveforms such as EMG, kinematics, and kinetics (Aalbersberg et al., 2009; Chmielewski et al., 2001; Limbird et al., 1988; Oberländer et al., 2014; Rudolph et al., 2001, 1998). Testing discrete variables increases the risk of erroneous conclusions including Type II error (Pataky et al., 2016, 2015) for a number of reasons. First, it is possible that peaks may remain similar between two groups but the rest of the waveform may differ, or the peaks being tested may be shifted in time so that the similar phases of the dynamic movement are not being compared. Finally, taking the peaks and ensemble averaging to extract values for these outcome scores makes the measures very susceptible to outliers and large within-measure variance. This is especially the case in studies involving human participants as the trial number and sample size are typically rather small. All of these mis-representations stemming from discrete variable testing can be resolved if the entire biological waveform is considered in the statistical analysis, which may produce more consistent findings among studies. All of these discrepancies in findings make it difficult for assessing the functionality of ACL injured patients and therefore a consensus within subjective and objective measures would be paramount in a clinician's ability to effectively aide in a patient's return to play. Therefore, this knowledge gap of cross-sectional design and discrete variable testing is addressed by GO1 of this thesis in that muscle excitation and movement waveforms will be analysed both pre and post-reconstruction while being matched to healthy, uninjured waveforms as well.

Subjective and Objective Functional Ability

With clinical joint laxity being deemed a basic measure, strength more informative, and hop performance as the most comprehensive, these results indicate a potential hierarchy in the

relationship between subjective and objective measures of knee joint control and function. It appears as though the deeper and more comprehensive definitions of objective knee joint function seem to have stronger relationships to subjective measures of function. Although passive joint laxity, strength and global function (hop performance) have been related to subjective functional ability, there has yet to be a thorough investigation of knee-specific dynamic measures of function and their relationship to subjective measures despite many of the commonly used PROMs having questions specifically targeting these variables. This includes the KNEES Slackness and Looseness subscales, KOOS stiffness-related questions, and IKDC/Lysholm questions pertaining to the knee's stability and instances of giving way. Clinical laxity and strength are not specifically addressed in these PROMs, which may account for the lack of correlations between the two types of measures. Global function is a more common inclusion in PROMs and therefore might explain the higher correlations seen between these two measures and thus supports the potential hierarchy in measures. Since control-related questions appear in the PROMS it is reasonable to postulate that objective measures of knee control and function would be related. These objective measures require higher-level biomechanical analyses such as neuromusculoskeletal modelling and using them may provide greater insight and consolidate the relationship between subjective and objective measures of knee joint function in ACL injured individuals. This knowledge gap is therefore addressed by GO2 & GO3 since objective measures of dynamic knee joint control and joint loading are related to subjective measures of functional ability to determine if the different aspects (physical and psychological) are congruent pre and post-reconstruction.

Neuromusculoskeletal Modelling Limitations

Although these in silico models have advanced our knowledge of the neuromuscular and skeletal systems, they still exhibit limitations that affect their validity. For example, the data used to build biological functions and anatomical characteristics within in silico models are primarily based on in vitro cadavre studies (Delp et al., 1990; Hamner et al., 2010) leading to a somewhat generic application of muscle parameters, bone geometry, and joint articulations. Nevertheless, recent advances in imaging and technical advances in measurement and computing have recently led to more advanced and biofidelic models. For example, the model developed by Rajagopal et al. (2016) addresses the biofidelity of their knee joint by enhancing the OpenSim one DOF hinge joint to one that prescribes motion based on cadaveric work (Walker et al., 1988). In this model, knee flexion/extension is unprescribed, while the remaining five DOF are a function of this sagittal plane angle. This approach is more complex and requires greater computing time which would have been impractical only a few years ago. Although it is more anatomically accurate than a simple hinge joint and a step in the right direction, it still lacks consideration of participant-specific bone geometries and their respective articulation, as

well as the effect of loading condition on tibiofemoral kinematics during dynamic tasks (Benoit et al., 2007).

Since muscle force and joint contact load estimations are higher level analyses in the OpenSim program flow, errors and inaccuracies in earlier analyses are propagated and perhaps multiplied when using these late-stage tools. Comparisons of generic and participant-specific models have demonstrated this with knee joint contact forces being more accurately modeled using participant-specific parameters (Gerus et al., 2013; Lerner et al., 2015). One type of participant-specific model incorporates magnetic resonance imaging (MRI) data to customize and improve bone geometry, muscle wrapping, and ligament lengths (Conconi et al., 2018). Enhancing generic models is also an effective way of reducing soft tissue artefact in kinematic results (Potvin et al., 2017; Smale et al., 2017). Soft tissue artefact is a well-established cause of kinematic error when using surface markers (Benoit et al., 2006; Reinschmidt et al., 1997) and since generic modelling procedures simply reduce error between the experimental and model markers, there is no consideration of soft tissue artefact in these general procedures. Adding kinematic constraints such as constant contact between articulating surfaces (Conconi et al., 2018) is proven to be an effective method in reducing this kinematic error and providing more biofidelic results. Furthermore, although MRIs and contact parameters can be included in OpenSim (Schmid et al., 2009; Valente et al., 2017), it remains unclear how an MRI-based knee contact model would affect lower limb kinematics and ligament lengths during dynamic tasks. This is therefore addressed by S4 and GO3 of this thesis in that a novel MRI patient-specific knee contact model is developed to determine biofidelic kinematics and ligament lengthening during a dynamic task.

2.9 Research Questions and Hypotheses

GO1: Determine how muscle excitations differ between healthy and injured populations and how these differences are reflected in their overall movement patterns

Study 1:

A common limitation amongst past studies is their cross-sectional designs. Given that each patient has a unique body type, diverse history of athletic exposures and coaching, and varying levels of injury, one cannot be confident that any differences they discern in a cross-sectional study are directly related to ACL health. To address this issue and GO1, we followed patients through their ACLd and ACLr states and examined their subjective function, muscle activation and biomechanical properties in relation to CON participants during challenging side cut and deceleration tasks (S1O1).

This study objective was specifically designed to answer the following three research questions:

- S1Q1: How does an ACL rupture affect one's subjective, neuromuscular, spatiotemporal, and biomechanical function compared to healthy controls (i.e. CON vs. ACLd)?
- S1Q2: How does reconstructive surgery impact the subjective ability, neuromuscular, spatiotemporal, and movement patterns of these patients (i.e. ACLd vs. ACLr)?
- S1Q3: How have these ACLr patients recovered in subjective, neuromuscular, spatiotemporal, and biomechanical function with respect to the healthy participants (i.e. ACLr vs. CON)?

These three research questions were then associated with three hypotheses:

- S1H1: Lower subjective scores and knee extensor moments in addition to altered muscle activations will be observed in the ACLd group compared to the CONs
- S1H2: After reconstruction, subjective function would improve but biomechanical and neuromuscular function would remain consistent with those observed in the ACLd group
- S1H3: ACLr would not fully recover subjective function and would still have altered neuromuscular and biomechanical patterns compared to the healthy, uninjured CON

GO2: Employ three objective measures of dynamic knee joint control that represent these movement patterns and determine if they are related to the patients' self-evaluation of functional ability

Studies 2 & 3:

As discussed earlier, a second limitation of past studies is the validity of variables used in the comparison of subjective and objective measures of knee joint functional ability. It is possible that the reason these measures show poor correlations is because they are designed to test different aspects of function. Thus, to address this limitation and GO2 of this thesis, S2 asked the following research question:

- S2Q1: Was the lack of consensus in past studies due to the nature of their variables and their poor ability to represent dynamic knee joint control?

To address this research question, the we computed and assessed two novel measures of knee joint control and applied a third to determine how dynamic knee joint control changes in relation to the status of the ACL (S2O1). It was then hypothesized that:

- S2H1: Control would be greatest in the healthy CON, lowest in the ACLd group, and the ACLr patients would show increased control compared to ACLd while not reaching levels seen in CON

Once these novel measures of joint control were developed and tested for the three ACL states, S3 focused on determining their relationship to the associated PROMs. Therefore, the research question asked in S3 was:

- S3Q1: How are the novel measures of dynamic knee joint control related to subjective measures of joint function (PROMs)?

To address this research question, S3 had three objectives:

- S3O1: To determine if objective biomechanical measures are related to subjective functional scores in both the ACLd and ACLr state
- S3O2: To determine if a selected objective or subjective score in the ACLd state is correlated to its corresponding score in the ACLr state
- S3O3: To determine if a variable in the ACLd state is capable of predicting its respective value in the ACLr state

These three objectives were each associated with a respective hypothesis:

- S3H1: Since both measures are aimed to indicate a patient's functional ability, it is expected that moderate correlations will be observed between the objective and subjective measures
- S3H2: It is expected that a patient's function in the ACLd state will be strongly associated with their function in the ACLr state
- S3H3: Since it is expected that measures will be related in the ACLd and ACLr states, the ACLd score is believed to have moderate ability to predict the ACLr score

GO3: Determine how knee joint contact and ligament forces differ between ACLd and ACLr conditions and identify any relationships between these and subjective measures of functional ability

Studies 4 & 5:

Given the limitations to generic models available in OpenSim, building patient-specific models would be more anatomically correct and therefore produce more valid results during dynamic tasks. To determine this and address GO3, S4 asked the following research question:

- S4Q1: What are the effects of a patient-specific MRI-based model have on kinematic profiles and ligament lengths with respect to generic OpenSim models?

To address this research question, we determined if the inclusion of an MRI-based knee contact model would elicit differences in lower limb kinematics and resulting knee ligament lengths during a side cut task (S4O1). It was then hypothesized that:

- S4H1: The original Rajagopal model would result in the smallest ranges of motion while the unconstrained six DOF model would have the largest ranges of motion for both kinematics and ligament lengths
- S4H2: The MRI-based model would reduce the ranges of motion observed in the six DOF model but ranges of motion would still be larger than those observed with the original Rajagopal model

After the patient-specific models had been built, it still needs to be determined whether or not this proposed hierarchy extends to joint contact and ligament forces. Therefore, S5 asked the following research question to address GO3:

- S5Q1: If joint loading in the form of contact and ligament forces are considered measures of objective joint function, are these variables related to subjective measures of functional ability?

This research question was addressed by (S5O1) evaluating if knee joint contact and ligament forces differed between pre and post-ACL reconstructed states; (S5O2) evaluating the relationship between these contact and ligament forces to their respective PROMs scores. These two research objectives manifested as two hypotheses:

- S5H1: Given the ACLr group have returned to play, it is hypothesized that they would apply a more demanding movement program and thereby elicit greater knee joint contact and ligament forces
- S5H2: Since the ACLr group is more confident and subjectively functional, it is expected that their objective joint loading will reflect this and show moderate to strong correlations

Chapter 3: General Methodology

3.1 Study Design

This thesis is comprised of a single in vivo data collection and subsequent imaging and in silico data analyses. The in vivo data collection was of test-retest design and completed at the University of Copenhagen from 2013 to 2016. For this data collection, ACLd patients participated prior to their operation and approximately ten months post-reconstruction (ACLr). This experimental group was matched to a healthy, uninjured control group (CON), which was tested a single time.

The current thesis is a portion of a larger investigation that aimed to identify changes in neuromuscular control patterns pre and post-reconstruction with respect to uninjured participants. Thus, participants completed a battery of movements including a force-matching protocol (Flaxman et al., 2012), one and two-leg squats, forward lunges, one-leg hops, side cuts, and countermovement jumps. Tasks were performed in order of difficulty and ballistic nature to allow for the patients' incremental progression in comfort level as the tasks became more demanding. This thesis focuses specifically on the hopping and side cut tasks as they are commonly reported to be stressful to the ACL (Boden et al., 2000).

This study was approved by both the Capital Region of Denmark (Protocol # H-3-2013-126) and University of Ottawa (H06-14-27) ethics committees (see Appendix for approvals).

3.2 Participants

Forty-seven ACLd patients were recruited from Bispebjerg-Frederiksberg Hospital to participate in the larger study program. Inclusion criteria included primary ACL injury and no history of contralateral ACL ruptures. All patients who were under the age of 18 or pregnant were excluded. Rupture of the ACL was confirmed clinically by the physician (positive Lachman or Rolimeter (Aircast Europa, Germany) tests), via magnetic resonance imaging and later confirmed arthroscopically. Each patient underwent an ACL reconstruction procedure and received a standardized 20-week rehabilitation program that focused on range of motion, balance, strength, and functional training with a ramping degree of effort throughout the program (Table A.1).

Due to the fear of further or re-injury (as expressed by participants), 27 participants refused to perform the hopping and side cut tasks in either the pre- or post-operative stage (Figure A.1). These 20 remaining participants comprised the sample for this thesis and are heretofore considered a "high functioning" cohort. All females (7/7) and the majority of males (9/13) underwent a DB hamstrings autograft procedure while two males received a PT autograft, one male received an Achilles tendon allograft, and one male received an iliotibial

band autograft. All varying graft types were found to be within one standard deviation of the mean from the hamstring graft group for each dependent variable, thus the first three studies of this thesis did not use graft type as a co-variate. Studies four and five used a subset that only includes patients who completed the hop and side cut tasks, had MRIs readily available for analysis, and underwent a double-bundle hamstring procedure. All reconstructions were performed by a total of six surgeons who had 10 – 25 years of experience. The tunnel placement was at the anatomical insertions of the ACL in that the femoral tunnel was via the anteromedial portal positioned as posterior as possible without posterior wall blowout. The tibial tunnel was placed slightly medial to the anterolateral meniscal horn. Endobuttons (Smith & Nephew, USA) with a 15 – 20 mm loop were used for femoral fixation while tibial fixations were done with Intrafix (Braun, Germany) with a plastic sheath.

The twenty patients considered in this thesis were matched to healthy, uninjured participants based on sex, height, weight, body mass index, leg tested (dominant or non-dominant), and Tegner activity scale scores. CON were recruited from the community through word of mouth with an inclusion criteria of no previous lower limb surgical operations, no additional serious lower limb injury including fractures or sprains within six months prior to testing, not pregnant, or have any diseases that might affect neuromuscular function. Matches for both sex and leg tested were 100% correct while age had a mean offset of 2.1 ± 1.9 years (range: -6.0 - +6.0 years), BMI a mean offset of 1.9 ± 1.3 kg/m² (range: -4.4 - +5.0 kg/m²), and Tegner Activity scale mean offset of 1.2 ± 1.3 (range: -5 - +3).

3.3 Equipment

Kinematics and Kinetics

Retro-reflective markers were placed on each participant's anatomical landmarks according to a whole-body HMBL cluster marker set (Mantovani and Lamontagne, 2016; Figure A.2). Marker trajectories were recorded at 100 Hz using a 10-camera motion capture system (6 MX and 4 T series, Vicon Oxford Metrics, UK) with supporting Nexus software (v 1.8.5, Vicon Oxford Metrics, UK). Ground reaction forces (GRF) were recorded from two force platforms (AMTI-OR6, AMTI, USA), which were embedded in the lab floor. GRF signals were sampled at 1000 Hz and amplified with an internal gain of 1000 (MSA-6, AMTI, USA).

Electromyography

Electromyography was recorded using surface electrodes (2DT2 Foam Dual Pre-gelled, Multi BioSensors Inc., USA) that were placed in a bipolar configuration, with a 2 cm inter-electrode distance. Electrodes were placed over the muscle bellies of the tensor fascia lata (TFL), rectus femoris (RFEM), vastus lateralis (VLAT), vastus medialis (VMED), biceps femoris (BFEM), semitendinosus (STEN), lateral gastrocnemius (LGAS), medial gastrocnemius (MGAS),

gracilis (GRAC), and gluteus medius (GMED) according to the SENIAM guidelines (Stegeman and Hermens, 1998). Electrodes were connected to a 10-channel wireless transducer system (MQAir, MARQ Medical, Denmark) and recorded with accompanying Fireworks software. Signal parameters at the transducer level included a sampling rate of 1000 Hz, 20 – 500 Hz bandwidth filter and a 6 dB/octave filter slope before A/D conversion. Signal quality and cross-talk were visually inspected during isolated exercises with manual resistance by the researcher. EMG signals were normalized to maximum voluntary isometric contractions (MVIC – section 3.4) obtained during hip flexion, extension, adduction, and abduction; knee flexion and extension; and ankle plantar flexion.

Magnetic Resonance Imaging

MRIs were taken with TR/TE: 500/14 ms, FOV 18, and a slice thickness of 3 mm (Sigma Horizon LX 1.5 Tesla, General Electric, USA). The knee joint centre was positioned in the middle of the volume and thus included approximately 8 cm of the distal femur and 8 cm of the proximal tibia. Each patient underwent imaging in both the frontal and sagittal views of T1 and T2-weighted scans including fat-saturated versions.

3.4 In Vivo Protocol

All data collections occurred at Drs. Tine Alkjaer and Erik Simonsen's Gait Laboratory at the Department of Neuroscience and Pharmacology, University of Copenhagen, Denmark.

Informed Consent, Questionnaires, and Preparation

Prior to the first data collection, each participant received a phone call from the researcher to discuss the study's purpose, equipment, and tasks they would be asked to complete. Once the participant arrived at the laboratory, they were given a brief introduction to the laboratory and equipment. All participants then read and signed an informed consent form approved by the University of Copenhagen and University of Ottawa ethics review boards. Following this, each participant completed a battery of questionnaires pertaining to their self-reported functional ability. This included the Tegner activity scale (Tegner and Lysholm, 1985), Lysholm (Lysholm and Gillquist, 1982), International Knee Documentation Committee subjective knee form (Irrgang et al., 2001), Knee injury and Osteoarthritis Score (Roos and Lohmander, 2003), and the Knee Numeric-Entity Evaluation Score (Comins et al., 2013).

Once all consent forms and questionnaires were completed, participants changed into tight-fitting spandex shorts and t-shirt and anthropometric measurements were taken. These measurements included height, weight, thigh (anterior superior iliac spine to lateral femoral epicondyle) and shank (lateral femoral epicondyle to lateral malleolus) lengths, thigh and shank circumferences, and knee and ankle widths. Participants then completed twelve trials of the

force-matching task (Flaxman et al., 2012) as a warm-up and familiarisation with the task. Finally, EMG sensor locations were prepared by shaving the hair, removing dead skin cells with sand paper, and clearing skin oil with alcohol swabs. Experiment preparation was completed with the placement of EMG sensors according to SENIAM guidelines (Stegeman and Hermens, 1998).

Maximum Voluntary Isometric Contractions

Manual maximum voluntary isometric contractions were required to normalize experimental EMG trials to allow for comparisons between participants and testing sessions. MVICs for hip musculature included hip flexion, extension, abduction, and adduction. For each action, the hip, knee, and ankle were kept in neutral positions while resistance was provided by a nylon strap wrapped around their shank and attached to the wall. For knee MVICs, each participant performed knee extension and flexion isometric contractions with a knee joint angle of 30° flexion while the researcher provided manual resistance to ensure maximal effort and an isometric position. Plantar flexion MVICs were completed with the participant standing and raising their heels while resisting upward motion using wall-mounted bars. Three trials of 5 – 10 s ramped contractions were completed with a 45 s rest period between contractions.

Dynamic Trials

Following MVICs, participants were outfitted with the whole-body cluster marker set (Mantovani and Lamontagne, 2016) and completed 72 trials of the force-matching task. Once completed, participants performed a series of dynamic movement tasks, including one and two-legged squats, forward lunges, one-leg hops, side cuts, and countermovement jumps. Tasks were performed in an increasing order of difficulty to ensure a high-level of confidence in all participants. Each movement was demonstrated by the researcher and participants were notified that they were allowed to skip the task if it caused any pain or discomfort. Five successful trials of each task were performed at a self-selected speed, with the researcher providing guidance to avoid unsafe and poor form (as defined in section 4.1), and encouragement for maximum performance.

This large data collection was divided into data sets for multiple investigations. The current thesis used the hopping and side cut tasks for further analysis. To successfully complete the hop, participants stood on their non-test limb, jumped forward landing on their test limb within the boundaries of the force plate, and maintained single-limb balance for a minimum of two seconds. To avoid stepping and ensure intensity, participants were encouraged to hop a maximal distance and speed to ensure they were eliciting a considerable amount of deceleration. In successful side cuts, the participant completed the movement as fast as they

felt comfortable, cut onto and off of the force plate at $45 \pm 10^\circ$ angles marked by taping on the floor, and had a foot strike that occurred completely within the boundaries of the force plate.

3.5 Data Reduction

3.5.1 Study 1: Dynamic Tasks after ACL Injury

Data Processing

After marker trajectories were labelled in Vicon Nexus (v1.8.5, Vicon, UK), c3d files were imported into MatLab (2013a & 2015b, Mathworks, USA) for all subsequent analysis. Trajectories and GRFs were filtered using a 4th order zero-lag low pass Butterworth filter with matching cut-off frequencies of 15 Hz (Bisseling and Hof, 2006). Filter order and cut-off frequency was chosen based on a residual analysis (Winter, 2004) and visual inspection of performance. Kinematic and kinetic data were then imported to OpenSim (v 3.3, SimTk, USA) to undergo further analyses. For Studies 1 – 3, the Rajagopal OpenSim model (2016) was modified to include three unprescribed rotational degrees of freedom at both knees. Patient-specific contact-based models were developed and used in S4 & S5 (see Chapter 4.4). Scaling, inverse kinematics, and inverse dynamics were used to compute lower limb joint angles and internal joint moments. Weight factors used in the scaling and inverse kinematics procedures were participant-specific to ensure compliance with accepted tolerances as defined by OpenSim documentation and Hicks et al. (2015). Spatiotemporal variables including impact velocity (m/s) and distance (m) for the hop in addition to stance time (s), impact velocity (m/s), push-off velocity (m/s), impact angle ($^\circ$), and push-off angle ($^\circ$) for the side cut were calculated.

All EMG data were also processed using MatLab and underwent a fourth order 20 Hz zero-lag high pass Butterworth filter. Signals were then rectified and treated with a fourth order 10 Hz zero-lag low pass Butterworth filter to obtain linear envelopes. MVIC signals were treated with the same high and low pass filters and a moving 50 ms average window was taken to determine the maximum value of each action. The greatest windowed value for each muscle, regardless of which contraction it came from was then used for amplitude normalization of the linear envelopes. Thus, linear envelopes are reported as a ratio of the MVIC value.

All EMG, kinematic, and kinetic data were synchronously collected. Hopping trials were cropped from the 100 ms prior to initial contact to 300 ms post-contact and therefore did not undergo any time normalization. Side cuts were cropped to the length of the stance phase with the addition of 10% stance time prior to initial contact. Thus, side cuts were time normalized from -10% to 100% stance. These pre-contact additions were included to display any pre-contact anticipatory strategies.

Statistical Analysis

To determine if graft type affected the results, a post-hoc analysis was completed to test for outliers (>3 standard deviations from the mean curves generated from the hamstring graft participants). This approach was chosen due to the non-discrete, continuous nature of the statistical parametric mapping (SPM) approach and it was found that all graft types (PT, iliotibial autograft, and Achilles allograft) fell within 1 standard deviation of the mean. Thus, it was concluded that graft type was not a covariate in this sample population and did not become an exclusion criterion. Since the experiment was of mixed design – patients underwent test-retest while healthy group was separate and only tested once – the statistical analysis was divided into three research comparisons instead of completing a repeated measures ANOVA. The first (S1Q1: CON vs ACLd) and third (S1Q3: ACLr vs CON) were addressed by conducting independent t-tests as they were different populations, while the second comparison (S1Q2: ACLd vs ACLr) was done with paired sample t-tests because they were the same population. Hip, knee, and ankle sagittal joint angles, moments, GRFs and EMG linear envelopes for both tasks were analyzed using one-dimensional SPM (Pataky, 2010; Penny et al., 2011) while traditional discrete independent and paired sample t-tests were used for spatiotemporal variables. Since the PROMs were ordinal data, Mann-Whitney U tests were used for the first and third research questions while Wilcoxon Signed Rank tests were used for the second research question. All SPM analyses were conducted in MatLab while the PROMs and spatiotemporal analyses were conducted in SPSS (v 22, IBM, USA). Since each group was tested twice during statistical analyses, a correction was used to set significance to $p < 0.025$.

3.5.2 Study 2: Dynamic Knee Joint Control after ACL Injury

Data Processing

This study used the kinematic and kinetic results of S1 to complete a deeper analysis of dynamic knee joint control. The first measure of control was dynamic knee joint stiffness (DKJS) and was calculated as the change in knee flexion moment over the change in knee flexion angle (Davis and DeLuca, 1996). This was done from the point of initial contact to maximum knee extensor moment (Figure 3.6.1) and reported as an absolute value.

Upon conversations with patients during the data collections and multiple focus group discussions with 10 – 15 researchers with backgrounds in biology, human movement sciences and engineering, in which four have torn their ACL, it became apparent that there were consistent subjective complaints about knee function that needed to be considered. These complaints included that their knee felt “wobbly” in that when they were completing the movement, there was excess, undesired movement of their knee. Additionally, a second complaint was that when completing the tasks, they believed their knee movement to be “inconsistent” between trials. The PROMs indirectly attempt to capture this information but to

the author's knowledge, there are no objective measures of dynamic knee joint control that represent these self-reported issues. To this end, we developed two novel measures that were directly inspired by these patient and focus group discussions.

Knee joint centre (KJC) was defined as the midpoint between the medial and lateral femoral epicondyle markers and knee joint centre excursion (KJCE) was calculated as the Euclidean distance of the KJC from the appointed start and end points of the movements in the global coordinate system (Figure 3.5.1). For the hop, KJCE was calculated from initial contact to the following 100 ms, as ACL injuries most commonly occur within this time frame (Koga et al., 2010) and we did not want the period of voluntary balance to influence our measures. For the side cut, KJCE was computed for the entire stance phase. A higher KJCE value indicates inefficient movement of the KJC while a lower value indicates a more direct and efficient movement pattern.

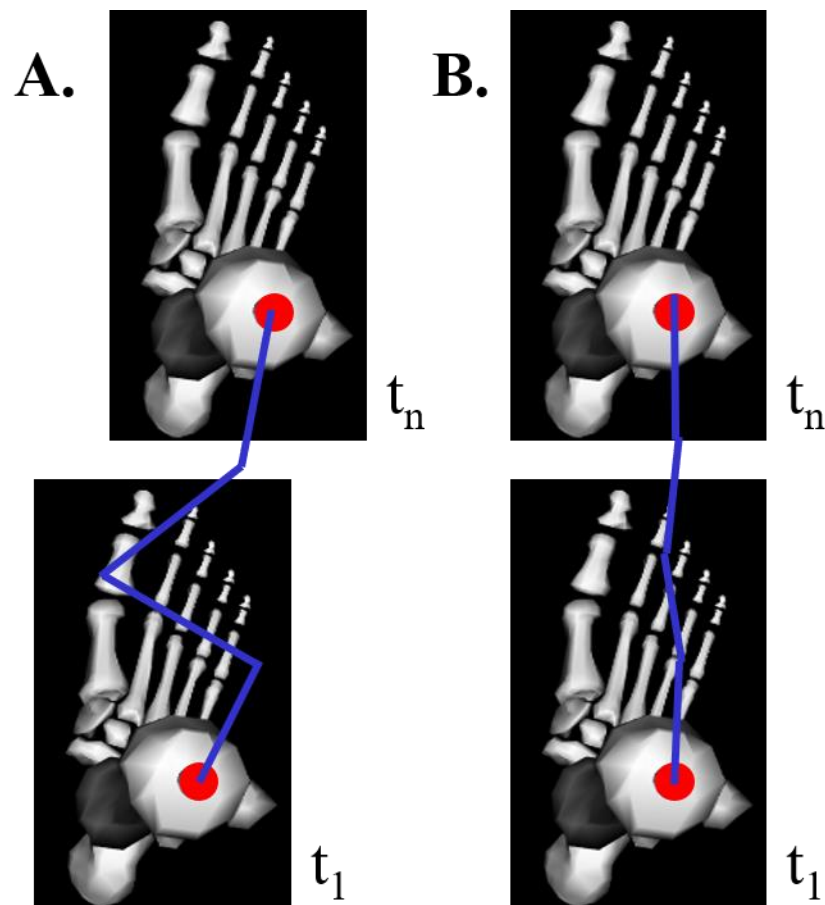


Figure 3.5.1. Aerial view of knee joint centre excursion (KJCE). A) An example of poor dynamic knee joint control (higher KJCE) and B) an example of good dynamic knee joint control (smaller KJCE).

Knee joint centre boundary (KJCB) was calculated over the same time periods as KJCE and was position normalized to allow for trials within each participant to be comparable. Since KJC was expressed in the global coordinate system, the coordinates of the initial time point of each trial were subtracted from the rest of the respective trial. This normalized each within participants' trial to an equivalent starting point. Then, at each subsequent time step, the Euclidean distance between KJC markers in all three trials were calculated and represented a boundary (Figure 3.5.2). These boundaries were then summed to achieve a total KJCB. A small Euclidean distance indicated that the KJC movement was more consistent than if the Euclidean distance was large. The boundary lengths (Euclidean distances) found at each time step were then summed and expressed in metres to represent the KJCB value for that participant.

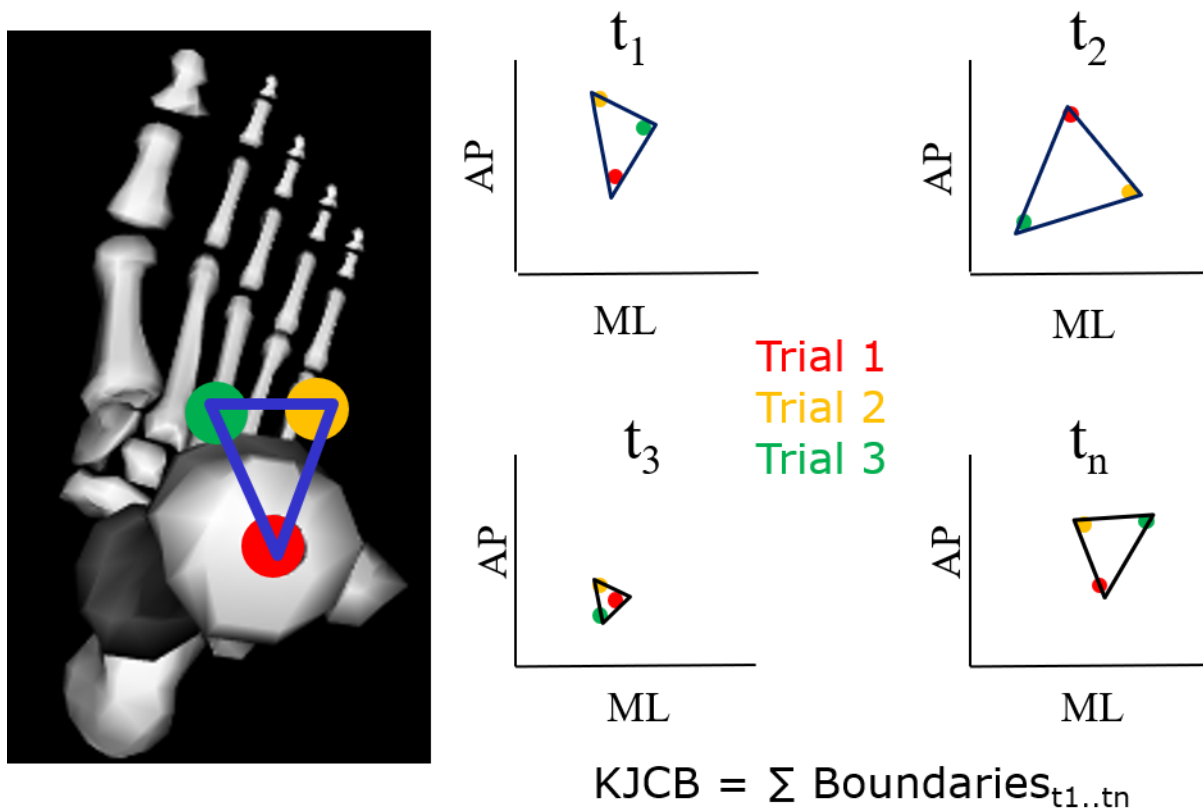


Figure 3.5.2. Two-dimensional aerial depiction of knee joint centre boundary (KJCB). Left side illustrates a participant's knee joint centre position during three trials at a single point in time. The blue shape is the boundary of these three positions. The right represents various time points in which the boundary is calculated based on the three-dimensional position of the knee joint centre positions. The total KJCB is the sum of these individual boundaries.

Statistical Analysis

Similar to S1, S2 made three comparisons: the first was CON vs ACLd (S2Q1), second was ACLd vs ACLr (S2Q2), and third was ACLr vs CON (S2Q3). Since all data were found to be normally distributed (Shapiro-Wilk test), independent t-tests were used to address the first and third comparisons while a paired sample t-test was used to address the second comparison. Due to multiple comparisons, our significance level was once again corrected to $p < 0.025$. When differences were found to be significant, Cohen's effect size (d) was calculated to quantify the size of the difference. A small effect size was considered to be $d < 0.5$, medium $0.5 < d < 0.8$, and large $d > 0.8$ (Cohen, 2013). All statistical analyses were completed in SPSS.

3.5.3 Study 3: Objective and Subjective Functionality after ACL Injury

Data Processing

Results from S1 and S2 were used for S3. The peak knee flexion angle and extensor moment were calculated for both the hop and side cut tasks. These two variables, along with DJKS, KJCE, and KJCB were considered the objective measures of knee joint control while Tegner, Lysholm, IKDC, KOOS, and KNEES scores were considered subjective measures of knee joint function. Since the CON group exhibited a ceiling effect for all subjective measures, this study only considered the ACLd and ACLr groups in its analysis.

Statistical Analysis

To determine if subjective and objective measures of function were correlated (S3O1), Spearman's rank correlations were performed between each PROM and all five objective measures. Spearman's rank correlations were chosen as PROMs are ordinal data. Spearman's rank correlations were used once again to determine if each subjective measure in the ACLd state was correlated to its respective score in the ACLr state (S3O2). Pearson correlations were used to determine the same relationship between ACL states for the objective measures of function. A weak correlation was defined as $r < 0.25$, fair $0.25 < r < 0.5$, moderate to strong $0.5 < r < 0.75$, and very strong $r > 0.75$ (Portney and Watkins, 2000). Finally, ordinal regressions were used to determine the predictive ability of each ACLd PROM scores to its respective ACLr score (S3O3) and Nagelkerke R^2 were used to determine model fit. Linear regressions were used to determine the predictive ability of each ACLd objective measure to its respective ACLr value and adjusted R^2 and standardized coefficients (β) were used to determine model fit. All tests were deemed significant if the p value < 0.05 and trending towards significance when $0.05 < p < 0.1$. All statistical tests were performed in SPSS.

3.5.4 Study 4: MRI-Based OpenSim Modelling

Data Processing

Processed marker trajectories from S1 were used for S4. This study also only used ACLd data as MRIs were only performed in this group for clinical diagnoses purposes. Four OpenSim models were compared in this study: (1) the original Rajagopal (RO) model; (2) the RO with all three rotational knee DOFs released and three translational DOFs locked to zero; (3) the RO with all six DOFs unconstrained and all motion boundaries presented by Xu et al. (2015); (4) an MRI-based model that allows for movement in all three knee joint rotations and translations (RM). This RM model used the R6 model but included two constraints representing condylar contact as two spheres on the femur and two on the tibia. The size and location of these spheres were determined specifically for each patient based on MRI data, as discussed below. Generic versions of all four models were subjected to the same scaling procedure using identical measurement set and scale factors. Once scaled, anatomical points needed to build the International Society of Biomechanics (ISB) coordinate systems (medial and lateral epicondyles; hip, knee, and ankle joint centres; medial and lateral malleoli) were represented in the global reference frame. The motion of all models was expressed according to the ISB standard reference systems (Wu and Cavanagh, 1995).

Combinations of frontal and sagittal views of T1 and T2-weighted scans including fat-saturated versions (Figure 3.5.3) were used to manually segment the femur, tibia, and fibula (Workbench 2016.11, MITK, Germany). The initial segmentation was performed by KB Smale and then reviewed for accuracy by Dr. Conconi. Femoral and tibial insertion sites for the anterior and posterior cruciate ligaments, and medial and lateral collateral ligaments were also identified from the MRIs. The three-dimensional segmented bones were then loaded into Rhinoceros (4.0, McNeel & Associates, USA) along with a generic femur and tibia. These generic bones were automatically scaled and aligned with the MRI bones based on the knee joint centre, medial epicondyle and hip joint centre markers so that coordinates for the hip and ankle joint centres could be obtained (Figure 3.5.4). Once matched, the same anatomical points as above were identified and used to automatically align the corresponding points from the OpenSim model. The ligament origin and insertion segmentations were then represented as point clouds on the respective bones to be used in the ligament optimization described below. This process resulted in the MRI-segmented bones along with ligament insertion point clouds aligned according to OpenSim static pose anatomical landmarks.

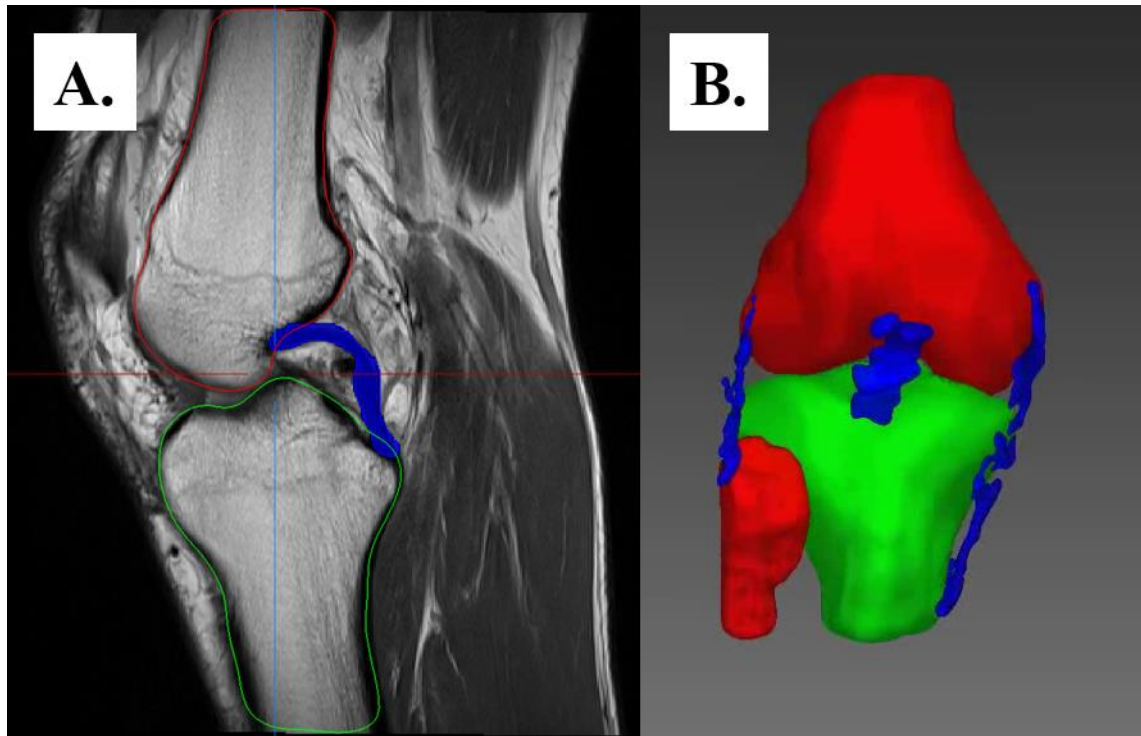


Figure 3.5.3. A) Sagittal view of MRI and example of manual segmentation B) Resulting three-dimensional renderings from MRI segmentation.

To define the patient-specific parameters of the RM model, the natural knee joint motion of each participant was first computed similar to (Conconi et al., 2018, 2015) as the envelope of tibiofemoral configurations that minimize the peak contact pressure, i.e. that maximize joint congruence (Conconi and Castelli, 2014). Thus, flexion angle was controlled from 10° extension to 120° flexion and at 2° intervals, the remaining five DoFs were optimized to maximize joint congruence. Exploiting the isometric behaviour shown by the knee ligaments along the natural motion (Victor et al., 2009; Wilson et al., 1998), the origin and insertion of the ACL, posterior cruciate ligament (PCL), MCL, and lateral collateral ligament (LCL) of each participant were determined as those associated with the most isometric fibre of the respective ligament throughout the entire flexion/extension range of motion. These insertion points had to be located within their respective point clouds located on the femur, tibia, or fibula. These origins and insertions of the four knee ligaments were incorporated into all four models but were used solely to analyze the ligament elongation and not used as kinematic constraints. Even though all patients had a complete ACL rupture, these lengths were still included as an exploratory analysis due to the ligaments' insertions still being discernible in the MRIs.



Figure 3.5.4. Example of MRI-segment bones (blue) to generic bones (purple) and OpenSim static pose anatomical landmarks (green).

The articular surfaces obtained from the MRIs were approximated with four spheres: two for the femoral and two for the tibial condyles. The radius and position of the initial sphere centres were then optimized (max variation allowed: ± 2 mm) in order to guarantee both the medial and lateral contact over the entire natural knee motion. The optimized spheres were introduced into the RM model and, assuming that both condyles remain in contact during the considered task, converted into two constant length constraints between the femoral and tibial sphere centres in both the medial and lateral knee compartments. Therefore, in the MRI-based model (RM) where motion could occur in all rotations and translations, these medial and lateral constant lengths that represented the tibiofemoral contact areas had to be preserved.

Inverse kinematics was performed on each trial with the four individual models. Marker weightings were consistent between models so that tracking errors satisfied the guidelines as outlined by Hicks et al. (2015). Kinematics obtained with the RO model were subsequently transformed from the Walker knee (Walker et al., 1988) to the ISB convention to ensure valid comparisons of the models. A point kinematics analysis was then executed to procure the ligaments' tibial insertion coordinates with respect to the femoral coordinate system. These coordinates were then used to determine the lengths over the entire movement.

Statistical Analysis

Repeated measure ANOVAs were applied through SPM for each hip, knee, and ankle DOF, to test for significance between the four models and the effect of patient-specific parameters (S4O1). If the F statistic was significant, a post-hoc analysis of paired sample t-tests with a multiple comparisons correction was used to determine between which models the significant differences occurred. All tests were deemed significant if $p < 0.05$.

To determine the clinical relevance of these differences, Cohen's d effect sizes were calculated during the peak difference between the two models. A small effect size was considered to be $d < 0.5$, medium $0.5 < d < 0.8$, and large $d > 0.8$ (Cohen, 2013). All statistical analyses were completed in MatLab.

3.5.5 Study 5: Joint Loading after ACL Injury

Data Processing

Marker trajectories, EMG linear envelopes, and GRFs from S1 were used for S5. The patient-specific models developed in S4 were used in S5, except the foot metatarsophalangeal and subtalar joints, as well as the three translational knee DOFs were locked as required for residual reduction analysis (RRA) and static optimization (SO) analyses. Since MRIs were only conducted in the ACLd condition, structural consistency between the ACLd and ACLr state for each patient was assumed to enable MRI use for the ACLr group. Due to graft harvesting, the semitendinosus (STEN) and gracilis (GRAC) maximum isometric forces were reduced by 18.7 and 8.9% respectively in the ACLr condition (Williams et al., 2004).

Scaling was the first process completed in OpenSim during which the patient-specific MRI-based models from S4 were scaled to fit the segment lengths of each participant in the ACLd and ACLr state. This was done by matching the model's markers to experimental markers from the static pose and lengthening or shortening the segment based on the segment's scale factor (ratio of model vs experimental markers). Next, inverse kinematics was completed by using the marker trajectories from the dynamic hopping trials and performing a weighted least-squares algorithm (Eq. 3.5.1):

$$\min_q \left[\sum_{i \in \text{markers}} w_i \left\| \mathbf{x}_i^{\text{exp}} - \mathbf{x}_i(\mathbf{q}) \right\|^2 + \sum_{j \in \text{unprescribed coords}} \omega_j \left(q_j^{\text{exp}} - q_j \right)^2 \right]$$

$q_j = q_j^{\text{exp}}$ for all prescribed coordinates j

where w_i is the designated marker weight, w_j is the designated coordinate weight, $\mathbf{q}$ is the vector of generalized coordinates being solved, $\mathbf{x}_i^{\text{exp}}$ is the experimental position of marker i , $\mathbf{x}_i(\mathbf{q})$ is the corresponding marker on the scaled MRI-based model, and q_j^{exp} is the experimental value for coordinate j . Since coordinates were not prescribed during this process, the second portion of Eq. 3.5.1 is set to 0. During standard practice in RRA, foot metatarsophalangeal, subtalar, and knee translational coordinates are locked due to the model's inability to account for moments occurring in these coordinates. Marker weights were prescribed based on the patient to ensure error was below the accepted tolerances (Hicks et al., 2015).

Once inverse kinematics was completed, RRA was performed to reduce the dynamic inconsistency between the motion capture data (ma ; marker and segment mass and accelerations) and the external forces (F ; GRFs). This was done by minimizing the residual forces (F_{residual}) in Newton's Second Law (Eq. 3.5.2):

$$F + F_{\text{residual}} = ma$$

Weightings of coordinates were altered to ensure errors in kinematics and residual forces both fell within the accepted error tolerances (Hicks et al., 2015).

Following RRA, these kinematics were used in combination with the GRFs to performed inverse dynamics. Once completed, static optimization was conducted for each trial with a time step of 5 ms to solve the muscle redundancy problem (Eq. 3.5.3):

$$\sum_{m=1}^n [a_m f(F_m^0, l_m, v_m)] r_{m,j} = \tau_j$$

where a_m is the activation of muscle m and the force produced is a function of the muscle's maximum isometric force (F_m^0), length (l_m), and velocity (v_m). This force is then multiplied by its respective moment around joint j ($r_{m,j}$). The sum of these internal (muscle) moments equates to the joint torque (τ_j) calculated through inverse dynamics. The muscle activations were minimized based on the objective function (Eq. 3.5.4):

$$J = \sum_{m=1}^n (a_m)^p$$

where $p = 3$. The cubed power was chosen over the second power as it distributed muscle forces more evenly and did not select one muscle from a group of agonists and activate it to its maximum (Crowninshield and Brand, 1981). The optimization procedure was not capable of finding a solution when $p = 4$. All ligament forces were passive components within the model where default OpenSim stress-strain curves were used to determine ligament force production. The resting ligament length was defined as the smallest length observed within each participant during all trials.

Finally, joint reaction analysis was conducted to determine the three-dimensional resultant forces at the knee during the hop movement (Steele et al., 2012). Joint reaction analysis is similar to inverse dynamics but considers the internal forces generated by muscles and ligaments, which are not included in inverse dynamics analyses. All forces were normalized to body weight and reaction forces were represented as the femur onto the tibia with respect to the tibia reference frame. For simplicity in relating to the literature, all reaction forces were multiplied by -1 to obtain joint contact forces and are subsequently described as such.

Statistical Analysis

Static optimization activations of ten muscles were validated against the EMG linear envelopes. These within trial waveforms were cross-correlated to each other to determine the signals' offset, which is likened to electromechanical delay. To validate these shifted activations against the EMG linear envelopes, Pearson correlations coefficients were calculated for each muscle within trial and averaged for the entire group to determine the mean correlation. To compare joint contact and ligament forces between the ACLd and ACLr state (S5O1), paired sample t-tests were performed using SPM. Finally, to determine the relationship between PROMs and peak contact and ligament forces (S5O2), Spearman correlations were conducted due to the questionnaires' ordinal nature. All statistical analyses were performed in MatLab and significance was set to $p < 0.05$.

Chapter 4: Journal Articles

4.1 Study 1: Dynamic tasks after ACL injury

ACL reconstruction improves subjective ability but not neuromuscular biomechanics during dynamic tasks

Running Title: Dynamic tasks after ACL injury

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Abstract

Purpose: The purpose of this study was to identify high functioning anterior cruciate ligament deficient (ACLd) patients and assess the effects of reconstruction (ACLr) on their self-reported functionality, muscle activations and biomechanical properties.

Methods: Twenty young and active patients participated pre (11.5 ± 14.3 months post injury) and again 10.5 ± 1.7 months post-reconstruction and were individually matched to 20 healthy controls. Participants completed hop and side cut movements while patient-related outcome measures (PROMs), lower limb electromyography, kinetic, and whole body kinematic data were collected. One-dimensional statistical parametric mapping was used to test for group differences (healthy vs ACLd; ACLd vs ACLr; ACLr vs healthy).

Results: When comparing healthy to ACLd, all PROMs indicated significant lower subjective function while the only substantial biomechanical difference between these participants was a decreased knee extensor moment in both the hop (peak difference: 0.63 Nm/kg, $p < 0.001$) and side cut (peak difference: 0.76 Nm/kg, $p < 0.001$). When comparing the patients pre and post-reconstruction, no biomechanical differences were observed while only half of the PROMs (Tegner, Lysholm, KNEES-ADL, KNEES-Slackness, KNEES-Looseness, KNEES-Sport Behaviour, IKDC, and KOOS-QoL) indicated higher function in the ACLr state. When comparing the ACLr patients to the healthy participants, all PROMs were still significantly higher in the healthy controls. The ACLr also had a smaller flexion angle (peak difference: 14.5° , $p = 0.007$) and knee extensor moment (peak difference: 0.62 Nm/kg, $p < 0.001$) during the hop and a smaller knee extensor moment (peak difference: 0.90 Nm/kg, $p < 0.001$) during the side cut task.

Conclusion: It was found that in the current high functioning patients, (1) ACLd patients had significantly lower subjective function in all PROMs and knee extensor moments; (2) half of PROMs showed an increase in function after reconstruction with no accompanying changes in neuromuscular and movement patterns; and (3) ACL reconstruction failed to return subjective function, knee flexion angles, and knee extensor moments to healthy values.

Introduction

The healing process after anterior cruciate ligament (ACL) injury includes long periods of inactivity and therefore changes to the patients' neuromuscular biomechanics are to be expected. When the activations of muscle groups are examined during various dynamic tasks, there is a wide spectrum in findings among studies. In terms of the quadriceps, decreases in activation after ACL injury during gait (Limbird et al., 1988), running (Lent et al., 1994), and other functional activities (Ciccotti et al., 1994) have been reported. Another study however reported no changes in quadriceps activation during a standing, weight-bearing task (Aalbersberg et al., 2009) in an ACL injured group. Previous studies have reported increases in hamstring activation during level (Limbird et al., 1988) and uphill (Kalund et al., 1990) gait, static weight-bearing (Aalbersberg et al., 2009), dynamic knee extensions (Alkjær et al., 2012), and a battery of functional activities (Ciccotti et al., 1994). On the contrary, other studies have observed no changes in hamstring activation during level gait (Kalund et al., 1990) or even a decrease in activity during running (Lent et al., 1994). These surface electromyography (EMG) results during gait have been summarized in a review by Shanbehzadeh (2015) who determined that only 7/12 studies reported activation magnitude differences in the ACL injured for the quadriceps and only 6/12 studies declared differing hamstring activation amplitudes. Differences in movement profiles between healthy (CON) and ACL injured have been shown to be somewhat more consistent than EMG findings. During walking and jogging, ACLd show decreased knee flexion angles (Chmielewski et al., 2001; Rudolph et al., 1998) and internal knee extensor moments (Andriacchi and Birac, 1993; Chmielewski et al., 2001; Rudolph et al., 2001). This trend of decreased knee flexion has also been observed in a step down and cut movement (Houck and Yack, 2003) while the decreased internal knee extension moment has been seen in both hopping (Rudolph et al., 2000), stepping (Andriacchi and Birac, 1993), and a step down and cut movement (Houck and Yack, 2003).

Despite the lack of congruency between objective measures including EMG and biomechanical findings, a subjective method of determining patient function is through patient reported outcome measures (PROMs). Commonly, the Knee Injury and Osteoarthritis Outcome Scale (KOOS; Roos and Lohmander, 2003), Knee Numeric-Entity Evaluation Scale (KNEES; Comins et al., 2013), International Knee Documentation Committee (IKDC; Irrgang et al., 2001), Tegner activity scale (Tegner and Lysholm, 1985), and Lysholm scale (Lysholm and Gillquist, 1982) are all used to assess a degree of self-reported symptoms, function, and ability in ACLd and ACLr populations. These questionnaires are effective in distinguishing between patient populations as scores have been reported to be significantly lower in ACLd compared to healthy counterparts (Eitzen et al., 2010; Fischer-Rasmussen and Jensen, 2000; Fitzgerald et al., 2000a; Herrington and Fowler, 2006; Lindstrom et al., 2010). After reconstruction, these questionnaire scores are generally greater than the ACLd state but still rarely achieve the same level observed

in healthy populations (Gustavsson et al., 2006; Nyland et al., 2014). Therefore, this indicates that the reconstructive process is improving the patient's subjective functional ability; however, the lack of similar improvements in how the patients objectively complete various tasks is less established.

The inconsistent results in objective variables across studies/populations may be attributed to numerous reasons. This includes variability across tasks (Ciccotti et al., 1994) being measured, such as walking, stair ascent/descent, level running, which are relatively easy to perform and not associated with ACL injury mechanisms unlike cutting and deceleration motions (i.e.: low-risk, low demand which do not push their performance threshold; Boden et al., 2000). Another limitation of past work includes the use of cross-sectional design to determine differences between CON, ACLd, and ACLr, which could be misleading because observed variability may be attributed to differences in sample populations and not solely the reconstruction. To the authors' knowledge, a comprehensive test-retest with matched controls investigation of neuromuscular function and movement biomechanics in these populations during dynamic tasks has yet to be completed. A final drawback is that many studies extract discrete variables (i.e. amplitude, onsets, time-dependent events) from highly correlated and time-dependent waveforms such as EMG, kinematics, and kinetics (Aalbersberg et al., 2009; Chmielewski et al., 2001; Limbird et al., 1988; Oberländer et al., 2014; Rudolph et al., 2001, 1998). This poses the risk of erroneous conclusions as it is possible that peaks may remain similar between two groups but the rest of the waveform may differ, or the peaks being tested may be shifted in time so that the similar phases of the dynamic movement are not being compared. Furthermore, testing discrete variables also may increase risk of erroneous conclusions including Type II error (Pataky et al., 2016, 2015). If the entire biological waveform is considered in the statistical analysis, it is possible that results may become more consistent. All of these discrepancies in findings make it difficult for assessing the functionality of ACL injured patients and therefore a consensus within subjective and objective measures would be paramount in a clinician's ability to effectively aide in a patient's return to play.

To address these limitations, the purpose of this study was to follow patients through their ACLd and ACLr states and examine their subjective function, muscle activation and biomechanical properties in relation to CON participants during challenging side cut and deceleration tasks. To this end, we will address three research questions: Q1) how does an ACL rupture affect one's subjective, neuromuscular, spatiotemporal, and biomechanical function compared to healthy controls (i.e. CON vs. ACLd)? Q2) how does reconstructive surgery impact the subjective ability, neuromuscular, spatiotemporal, and movement patterns of these patients (i.e. ACLd vs. ACLr)? Finally, Q3) how have these ACLr patients recovered in subjective, neuromuscular, spatiotemporal, and biomechanical function with respect to the healthy participants (i.e. ACLr vs. CON)? We expected to see lower subjective scores, knee extensor

moments and altered muscle activations in the ACLd group compared to the CON. After reconstruction, it was expected that subjective function would improve but biomechanical and neuromuscular function would remain consistent with findings in the ACLd state. Finally, we hypothesized that ACLr would not fully recover subjective function and would still have altered neuromuscular and biomechanical patterns compared to the healthy, uninjured CON.

Methods

This study consisted of a test-retest design of ACLd 11.5 ± 14.3 months post injury and again 10.5 ± 1.7 months post-reconstruction (ACLR). These patients were matched with healthy controls (CON) who were only tested once. The independent variable was ACL status (CON, ACLd, and ACLr) while the dependent variables included PROMs, muscle activations of ten lower limb muscles, spatiotemporal variables, and sagittal plane angles and internal moments for the hip, knee, and ankle joint of the test limb.

Participants

Forty-seven ACLd patients were recruited from Bispebjerg-Frederiksberg Hospital to participate in a larger study which included data collections prior to and 10-months post-ACL reconstruction. Inclusion criteria included primary ACL injury and no history of contralateral ACL ruptures. Rupture of the ACL was confirmed clinically by the physician (positive Lachman and Rolimeter tests) and via magnetic resonance imaging or arthroscopy, and each patient underwent an ACL reconstruction procedure. All ACLr patients received a standardized 20-week rehabilitation program that focused on range of motion, balance, strength, and functional training, with a ramping degree of effort throughout the program (Table A1).

Participants first completed a weight-bearing isometric force matching protocol (Flaxman et al., 2012), followed by one and two legged squats, forward lunges, hops, side cuts, and countermovement jumps. These tasks were performed in order of difficulty and ballistic nature to allow for the patients' incremental progression in comfort level with the demanding nature of the tasks. Throughout testing, participants completed the tasks at their own rate while being encouraged to rest between tasks to avoid fatigue. The current study is a primary analysis of a portion of this larger investigation and focuses only on the hop and side cut task as these two movements are commonly reported to be stressful to the ACL (Boden et al., 2000). Due to the fear of re-injury (as expressed by participants), 27 participants refused to perform the hop and side cut tasks in either the pre- or post-operative stage (Figure A1). We defined the remaining 20 participants as high functioning and these high-functioning participants are reported here (Table 1). All females (7/7) and the majority of males (9/13) underwent a double-bundle hamstrings autograft procedure while two males received a bone-patellar tendon-bone autograft, one male received an Achilles tendon allograft, and one male received an iliotibial

band autograft. These 20 patients were matched with healthy controls based on sex, leg tested (dominant or non-dominant), body mass index, age, and Tegner score. Healthy controls were recruited from the community through word of mouth and only tested once. Their exclusion criteria included no previous lower limb surgical operations, no additional serious lower limb injury including fractures or sprains within six months prior to testing, and any diseases that might affect neuromuscular function. This study was approved by the Capital Region of Denmark and University of Ottawa ethics committees.

Data Collection

Upon receiving written informed consent, participants then completed a battery of PROMs including the KOOS (Roos and Lohmander, 2003), KNEES-ACL (reported as percent of maximum score; Comins et al., 2013), subjective IKDC (Irrgang et al., 2001), Tegner (Tegner and Lysholm, 1985), and Lysholm scale (Lysholm and Gillquist, 1982). Participants were then asked to change into tight-fitting clothing, followed by anthropometric measurements and skin preparation for EMG electrode placement. Electrodes were placed on the muscle bellies of the gluteus medius (GMED), tensor fascia lata (TFL), gracilis (GRAC), rectus femoris (RFEM), vastus medialis (VMED), vastus lateralis (VLAT), long head of biceps femoris (BFEM), semitendinosus (STEN), medial (MGAS) and lateral gastrocnemii (LGAS) according to the SENIAM guidelines (Stegeman and Hermens, 1998). EMG data were sampled at 1000 Hz with a 20-500 Hz bandwidth using wireless sensors (MQair, Marq-Medical, Denmark). EMG data were normalized to maximum voluntary isometric contractions (MVIC), which included and performed in the following order: plantar flexion; hip flexion, extension, adduction, and abduction; and knee extension and flexion. Three trials of a five second ramped effort separated by 45 seconds of rest were completed for each action. All contractions were performed with the hip, knee, and ankle at 30°, 30°, and 90° of flexion respectively and resistance was applied by a nylon strap fixed to the wall and manually by the examiner for knee extension and flexion.

Participants were then outfitted with a cluster marker set (Mantovani and Lamontagne, 2016) and kinematic data were collected using a 10-camera motion capture system (6 MX and 4 T series, Vicon, UK) and captured at 100 Hz. Ground reaction force (GRF) data were sampled at 1000 Hz using one force plate (OR 6-5-1, AMTI, USA). To successfully complete the hop, participants stood on their non-test leg and jumped forward with their test limb onto a force plate and maintained balance for two seconds. To avoid stepping, participants were encouraged to select a comfortable speed and distance to ensure it was a forward jump. In successful side cuts, the participant completed the movement as fast as they could, cut onto and off of the force plate at the $45 \pm 10^\circ$ angles marked by taping on the floor and had a foot strike that occurred entirely within the boundaries of the force plate. Three to five successful trials of each task were collected for all participants.

Data Processing

All kinetic and kinematic data were processed through a MatLab (2013a, Mathworks, USA) – OpenSim (3.3, Simtk, USA) application program interface. Marker trajectories and GRFs were filtered using a 4th order zero-lag low pass Butterworth filter with matching cut-off frequencies of 15 Hz (Bisseling and Hof, 2006). The Rajagopal OpenSim model (Rajagopal et al., 2016) was modified to include three unprescribed rotational degrees of freedom at both knees. Scaling, inverse kinematics, and inverse dynamics were used to compute hip, knee, and ankle sagittal plane angles and internal joint moments. This study limited the analysis to the sagittal plane as our research group has shown large errors in frontal and transverse plane kinematics when collecting with surface markers, which limits the interpretation of these planes (Benoit et al., 2006). Spatiotemporal variables including impact velocity (m/s) and distance (m) for the hop as well as stance time (s), impact velocity (m/s), push-off velocity (m/s), impact angle (°), and push-off angle (°) for the side cut were calculated.

EMG data were also processed using MatLab and underwent a fourth order 20 Hz high pass zero-lag Butterworth filter and then rectified and treated with a fourth order 10 Hz low pass zero-lag Butterworth filter. MVIC signals were treated with the same high and low pass filters and a moving 50 ms average window was taken to determine the max value of each action. The greatest windowed value for each muscle, regardless of which contraction it came from was then used for amplitude normalization of the linear envelopes. Thus, linear envelopes are presented as a ratio of the MVIC value.

All EMG, kinematic, and kinetic data were synchronously collected. Hop trials were cropped from the 100 ms prior to initial contact to 300 ms post-contact and therefore did not undergo any time normalization. Side cuts were cropped to the length of the stance phase with the addition of 10% stance time prior to initial contact. Thus, side cuts are time normalized from -10% stance to 100% stance.

Statistical Analysis

Hip, knee, and ankle sagittal joint angles, moments, GRFs and EMG linear envelopes for both tasks were analyzed using one-dimensional statistical parametric mapping (SPM; Pataky, 2010; Penny et al., 2011). To determine if graft type affected the results, a post-hoc analysis was completed to test for outliers (>3 standard deviations from the mean curves generated from the hamstring graft participants). This approach was chosen due to the non-discrete, continuous nature of the SPM approach. For the EMG linear envelopes, GRFs, and joint angles and moments, we addressed Q1 (CON vs ACLd) and Q3 (ACLR vs CON) by conducting independent t-tests, while to test Q2 (ACLd vs ACLr), paired sample t-tests were conducted on the dependent variables. With the PROMs being ordinal data, Mann-Whitney U tests were used

for Q1 and Q3 while Wilcoxon Signed Rank tests were used to address Q2. All analyses of PROMs and spatiotemporal variables (hop distance, impact/push-off velocities, impact/push-off angles) were conducted in SPSS (v22, IBM, USA). Since each group was used twice during the statistical testing, a correction was used to set significance at $\alpha < 0.025$.

Results

Of the 20 remaining participants, 17 were capable of completing the side cut and 18 completed the hop in both pre- and post-reconstruction sessions and therefore results are reported for each group and task. Since graft type did not elicit any outliers, all types were included in the analysis.

Q1: CON vs ACLd

All PROMs showed significantly greater functionality scores for the control group than the ACLd participants for both the hop and side cut movements (Table 4.1.1) while no differences in spatiotemporal variables were observed (Table 4.1.2).

For the hop movement, the only difference in EMG was the MGAS, which had a greater activation in the ACLd than the CON between 91 – 103 ms after contact (peak difference (PD): 11.2% MVIC, $p = 0.018$, Figure 4.1.1). There were no differences in sagittal plane angles but the ACLd had reduced knee extensor moment from 32 – 120 ms post-contact (PD: 0.63 Nm/kg, $p < 0.001$, Figure 4.1.2). There were no differences in GRFs (Figure 4.1.3) or spatiotemporal variables (Table 4.1.2) between the two groups during the hop movement.

During the side cut manoeuvre, there were no significant differences in EMG (Figure 4.1.4) or GRFs (Figure 4.1.3), while the only significant difference in joint angles or moments between the CON vs ACLd during the side cut maneuver was a decreased knee extensor moment at 25 – 61% stance (PD: 0.76 Nm/kg, $p < 0.001$, Figure 4.1.5) in the ACLd group. CON also entered the side cut movement with a higher velocity (3.03 ± 0.42 m/s) compared to the ACLd (2.70 ± 0.38 m/s; $p = 0.018$, Table 2).

Table 4.1.1. Participant characteristics and subjective functional scores. Healthy, ACL deficient (ACLd) and ACL reconstructed (ACLr) means and (standard deviations). Pre Inj: is the patient's self-reported Tegner score prior to their injury. Inj: is the patient's self-reported Tegner scored in the ACLd state at the time of testing. [†] indicates significance ($p < 0.05$) between healthy and ACLd, * marks significance ($p < 0.05$) between ACLd and ACLr, and [‡] indicates significance ($p < 0.05$) between healthy and ACLr.

	Hops			Side Cut		
	Healthy	ACLD	ACLR	Healthy	ACLD	ACLR
Male/Female	11/7	11/7	11/7	11/6	11/6	11/6
Age (years)	26.7 (6.7)	27.5 (5.9)	28.4 (5.9)	26.6 (3.6)	27.8 (5.9)	28.7 (5.9)
BMI (kg/m²)	24.0 (3.0)	24.4 (3.2)	24.7 (3.4)	24.0 (3.0)	24.4 (3.3)	24.6 (3.6)
Time Since Injury (months)	-	12.5 (SD: 18.7; Range: 1 - 101)	-	-	10.4 (SD: 9.9; Range: 1 - 36)	-
Time Since Surgery (months)	-	-	10.5 (SD: 1.7; Range 7.5 - 12)	-	-	10.5 (SD: 1.7; Range: 7.5 - 12)
Tegner	7.2 (1.5) ^{††}	Pre Inj: 6.8 (1.5) Inj: 3.6 (1.7) ^{†*}	5.8 (1.5) ^{**}	7.6 (1.3) ^{††}	Pre Inj: 6.9 (1.6) Inj: 3.5 (1.6) ^{†*}	5.6 (1.7) ^{**}
Lysholm	99.5 (1.5) ^{††}	73.5 (9.2) ^{†*}	84.9 (8.4) ^{**†}	99.5 (1.6) ^{††}	73.4 (8.5) ^{†*}	83.1 (8.4) ^{**†}
IKDC	99.4 (1.5) ^{††}	65.6 (11.0) ^{†*}	77.4 (9.6) ^{**†}	99.3 (1.7) ^{††}	64.0 (9.2) ^{†*}	76.3 (9.8) ^{**†}
KNEES – ADL	0.3 (0.8) ^{††}	24.4 (16.6) ^{†*}	12.4 (9.6) ^{**†}	0.3 (0.9) ^{††}	24.8 (17.3) ^{†*}	14.2 (10.4) ^{**†}
KNEES – Psychosocial	0.0 (0.0) ^{††}	29.6 (21.1) [†]	18.1 (16.0) [†]	0.0 (0.0) ^{††}	33.3 (19.5) [†]	19.2 (13.7) [†]
KNEES – Symptoms	0.0 (0.0) ^{††}	24.1 (13.1) [†]	17.6 (17.0) [†]	0.0 (0.0) ^{††}	27.1 (13.9) [†]	17.3 (13.9) [†]
KNEES – Slackness	0.3 (1.1) ^{††}	33.8 (15.4) ^{†*}	16.5 (14.6) ^{**†}	0.3 (1.2) ^{††}	32.8 (16.4) ^{†*}	16.7 (15.5) ^{**†}
KNEES – Looseness	0.0 (0.0) ^{††}	32.4 (17.8) ^{†*}	15.3 (18.4) ^{**†}	0.0 (0.0) ^{††}	33.8 (17.0) ^{†*}	16.7 (17.8) ^{**†}
KNEES - Sport Behaviour	0.9 (2.9) ^{††}	74.4 (20.8) ^{†*}	43.2 (25.7) ^{**†}	0.7 (2.9) ^{††}	72.5 (20.2) ^{†*}	41.2 (25.3) ^{**†}
KNEES – Sport Physical	0.0 (0.0) ^{††}	33.8 (34.2) [†]	21.8 (26.7) [†]	0.0 (0.0) ^{††}	32.4 (31.7) [†]	22.1 (27.8) [†]
KOOS – Symptoms	97.4 (4.9) ^{††}	82.7 (11.0) [†]	82.9 (9.8) [†]	97.7 (4.8) ^{††}	82.6 (12.2) [†]	83.2 (11.6) [†]
KOOS – Pain	99.7 (1.3) ^{††}	84.6 (7.4) [†]	88.9 (8.5) [†]	99.7 (1.4) ^{††}	82.2 (15.8) [†]	87.4 (12.3) [†]
KOOS - ADL	100 (0.0) ^{††}	93.0 (5.2) [†]	94.8 (5.8) [†]	100 (0.0) ^{††}	90.6 (12.7) [†]	92.3 (11.7) [†]
KOOS – Sport/Rec	98.6 (4.1) ^{††}	63.6 (21.9) [†]	77.8 (16.3) [†]	98.5 (4.2) ^{††}	65.9 (23.8) [†]	76.5 (20.1) [†]
KOOS - QoL	99.4 (2.4) ^{††}	56.9 (6.7) ^{†*}	70.8 (10.2) ^{**†}	99.4 (2.4) ^{††}	54.7 (7.4) ^{†*}	68.2 (14.1) ^{**†}

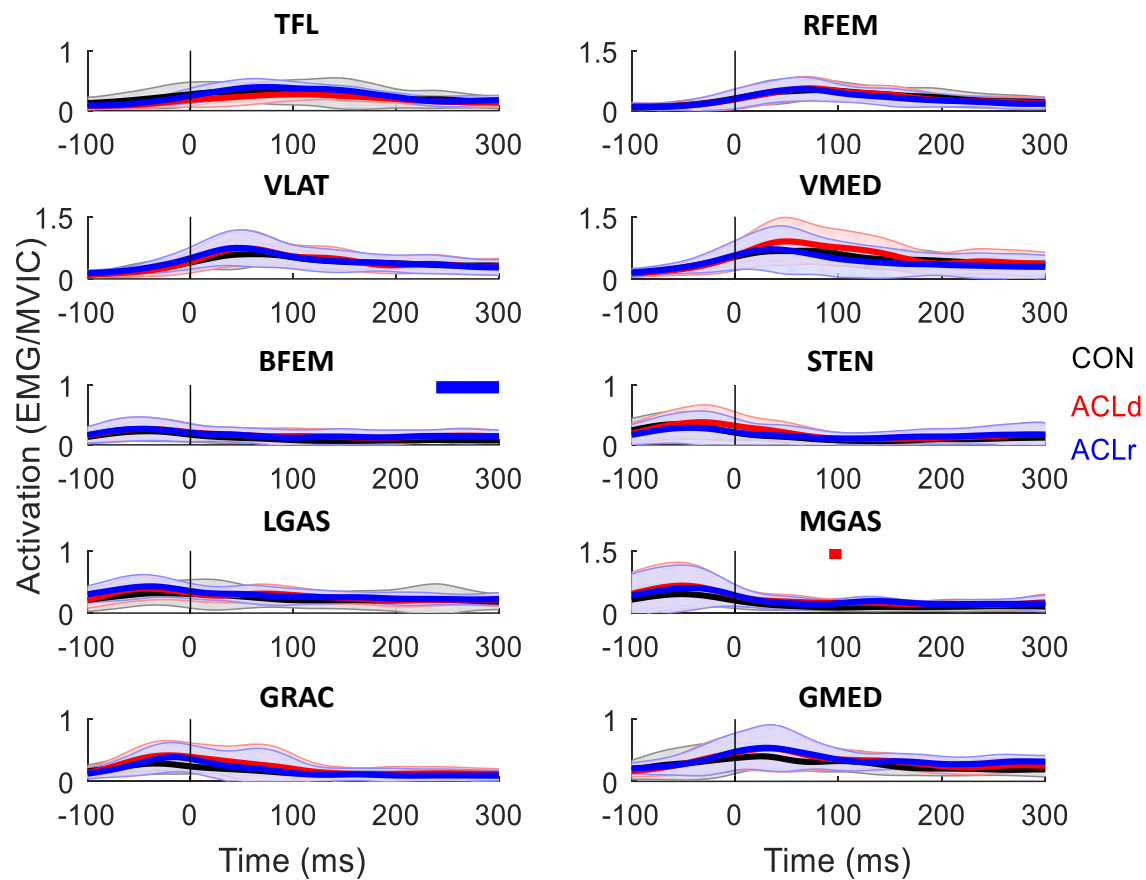


Figure 4.1.1. Linear Envelopes during the hop movement. Activation is a ratio of the trial EMG of MVIC. Black vertical line represents time at contact; red horizontal bar represents significance between healthy and ACLd; and blue horizontal bar represents significance between healthy and ACLr.

Q2: ACLd vs ACLr

For those patients who completed the hop, Tegner, Lysholm, KNEES-ADL, KNEES-Slackness, KNEES-Looseness, KNEES-Sport Behaviour, IKDC, and KOOS-Quality of Life scores indicated significantly greater functionality in the ACLr state than the ACLd state. For those who completed the side cut, Tegner, Lysholm, KNEES-Activities of Daily Living, KNEES-Slackness, KNEES-Looseness, KNEES-Sport Behaviour, IKDC, and KOOS-Quality of Life scores indicated greater functionality in the ACLr group than they were pre-reconstruction (Table 4.1.1).

No significant differences between ACLd and ACLr were observed in EMG, GRFs, joint angles and moments for either the hop or side cut movements. During the side cut however, the ACLd

pushed off from the side cut at a slightly greater angle ($39.2 \pm 6.2^\circ$) compared to the ACLr ($37.1 \pm 5.8^\circ$, $p = 0.023$, Table 4.1.2).

Table 4.1.2. Spatiotemporal variables presented as means and (standard deviations) during the hop (H) and side cut (SC) for healthy, ACL deficient (ACLd) and ACL reconstruction (ACLR) participants. Impact velocities and angle are calculated during 10% pre-contact while push-off velocities and angles are calculated during last 10% of stance. Angles are in relation to the line of forward progression and represent the angle of which the participants enter and exit the stance phase of the side cut movement. * marks significance between ACLd and ACLr ($p = 0.023$).

	CON	ACLd	ACLR
H Impact Velocity (m/s)	1.93 (0.27)	1.79 (0.27)	1.84 (0.21)
H Distance (m)	1.27 (0.18)	1.16 (0.16)	1.21 (0.12)
SC Stance Time (s)	0.401 (0.086)	0.421 (0.070)	0.412 (0.073)
SC Impact Velocity (m/s)	2.96 (0.39)	2.76 (0.41)	2.84 (0.43)
SC Push-off Velocity (m/s)	2.99 (0.42)	2.81 (0.38)	2.91 (0.43)
SC Impact Angle ($^\circ$)	35.0 (2.2)	36.6 (5.8)	35.9 (5.6)
SC Push-off Angle ($^\circ$)	36.5 (3.2)	39.2 (6.2)*	37.1 (5.8)*

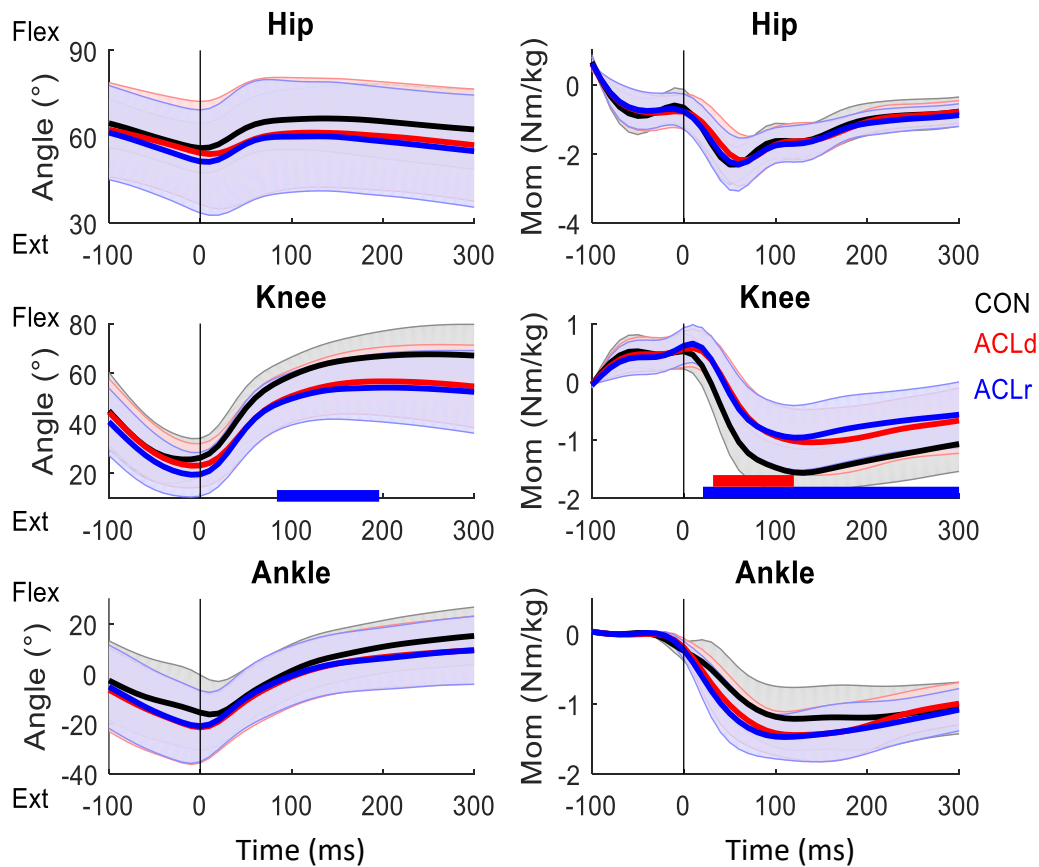


Figure 4.1.2. Sagittal angles and moments during the hop movement. Positive values are flexion while negative values are extension. Black vertical line represents time at contact; red horizontal bar represents significance between healthy and ACLd; and blue horizontal bar represents significance between healthy and ACLr.

Q3: ACLr vs CON

All PROMs indicated that subjective functionality was significantly greater for the control group than the ACLr participants for both the hop and side cut movements (Table 4.1.1) while no differences were observed in spatiotemporal values (Table 4.1.2).

After reconstruction, the BF was significantly more activated in the ACLr group compared to the CON from 239 – 300 ms post-contact of hop (PD: 6.1% MVIC, $p < 0.001$, Figure 1). The ACLr also had a decreased knee flexion angle 84 – 196 ms post-contact (PD: 14.5°, $p = 0.007$, Figure 4.1.2) and a decreased knee extensor moment 21 – 300 ms post-contact (PD: 0.62 Nm/kg, $p < 0.001$, Figure 4.1.2).

No EMG differences were observed in the side cut but again, the ACLr had a decreased knee extensor moment from 23 – 83% of the stance phase (PD: 0.90 Nm/kg, $p < 0.001$, Figure

4.1.5). Moreover, the ACLr also had a decreased medial GRF 68-69% of the stance phase (PD: 1.09 N/kg, $p = 0.022$).

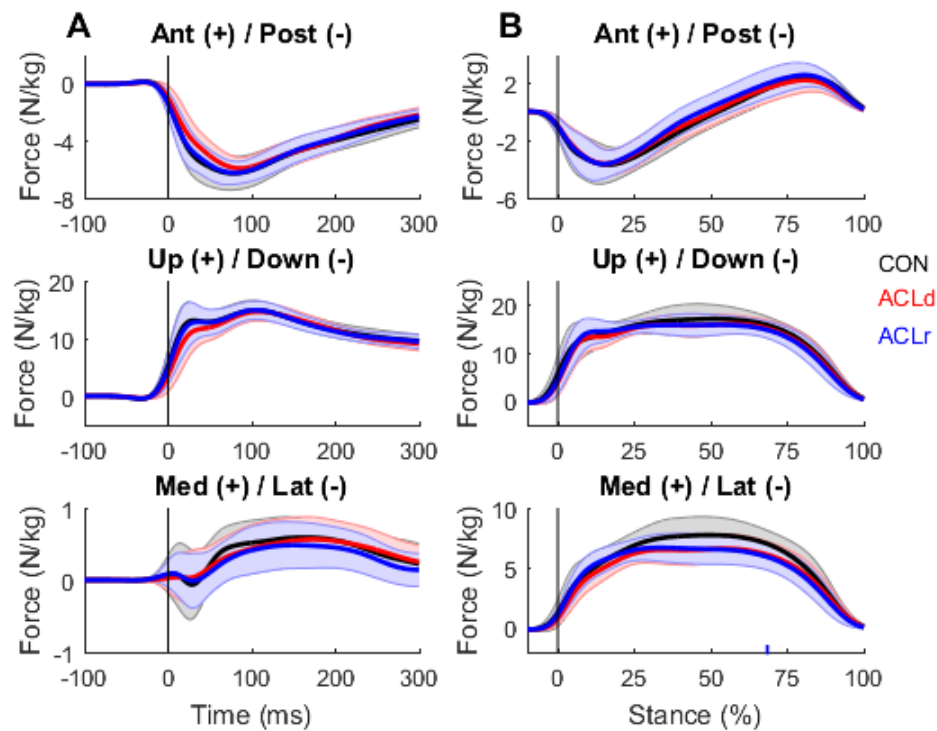


Figure 4.1.3. Ground reaction forces for the A) hop and B) side cut. Black vertical land indicates initial contact while blue horizontal bar indicates significant ($p < 0.05$) difference between the healthy (CON) and ACL reconstructed (ACLR) groups. ACLd – Anterior cruciate ligament deficient.

Discussion

The purpose of this study was to implement a test-retest design that had ACL injured patients complete challenging dynamic tasks pre- and 10 months post ACL reconstruction to evaluate their neuromuscular and biomechanical strategies. The injured cohort was taken from a larger group of 47 ACL injured participants. We considered this cohort high-functioning since only they were willing or able to complete the hop and side cut tasks. Note that they still may be classified as non-copers since they elected to undergo ACL reconstruction (Daniel et al., 1994). These participants reported significant subjective improvement in function after ACL reconstruction; however, surgical intervention led to very few changes in the objective movement and muscle activation measures between the ACLd and ACLr states of these patients.

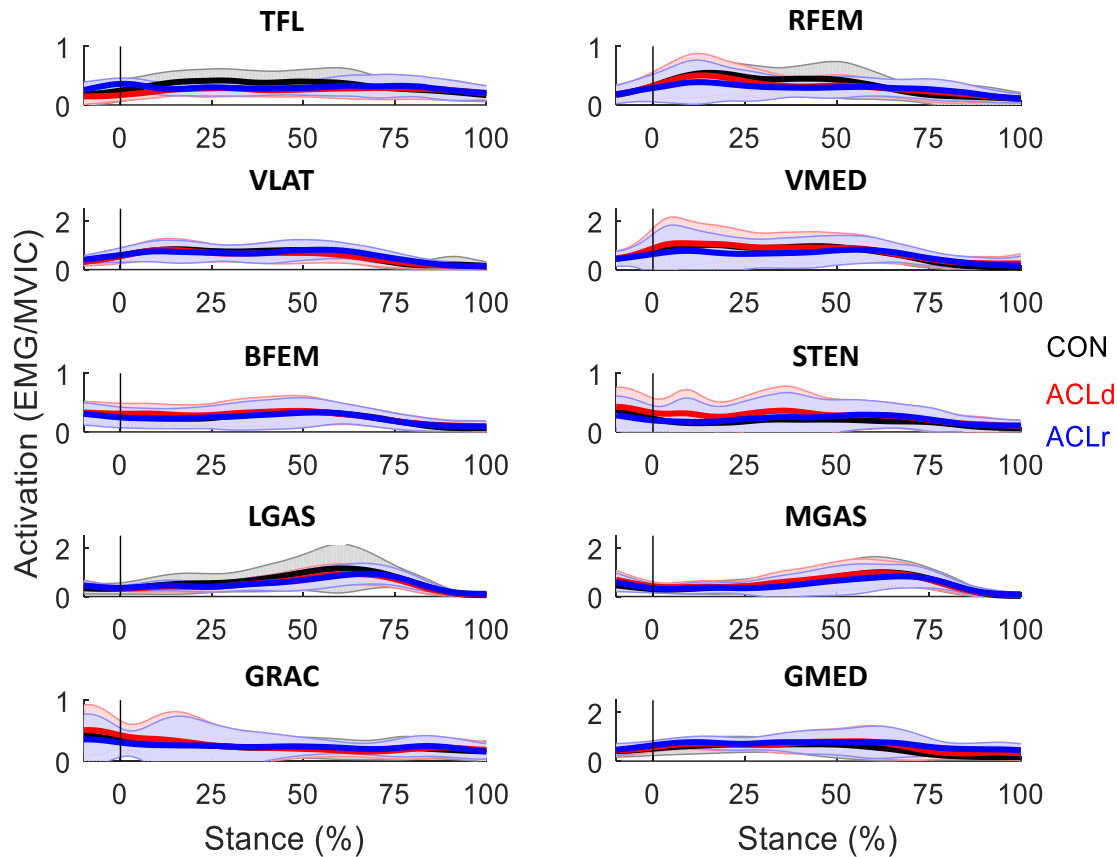


Figure 4.1.4. Linear Envelopes during the side cut movement. Activation is a ratio of the trial EMG of MVIC. Black vertical line represents time at contact.

Hop

During the hop, both patient groups completed the movement with a smaller knee extensor moment while only the ACLr group had a decreased flexion angle compared to the CON. These results support previous studies (Di Stasi and Snyder-Mackler, 2012; Rudolph et al., 2000) where hopping motions were also examined. Increased activation was observed in the MGAS for the ACLd group during a brief period 100 ms after contact, which corresponds to peak vertical GRF. This differs from the BF of ACLr as it was significantly more activated compared to the CON 239 ms post contact, which is during force absorption. Considering past studies have noted that ACL injuries occur within the first 50 ms post contact (Koga et al., 2010; Krosshaug et al., 2007), these relatively small differences 100 and 239 ms post contact indicate that they may not have an effect on ACL injury mechanisms. Our results support two earlier studies, which found ACLd patients had earlier onsets and longer durations for the BFEM and MGAS during gait (Lass et al., 1991; Limbird et al., 1988; Sinkjaer and Arendt-Nielsen, 1991). Increases in these specific muscles for ACLd patients have also been reported during stair ascent (Rudolph and Snyder-Mackler, 2004) and for ACLr patients during functional activities

that included walking, ramp ascending, stair ascending and stair descending (Ciccotti et al., 1994). Furthermore, elevated gastrocnemii muscle forces have been shown to compensate for weakened hamstring muscles during a similar single-leg landing (Morgan et al., 2014). Considering hamstring muscles have shown to be weakened in low-functioning ACLd (Tsepis et al., 2004) and ACLr (Konrath et al., 2016; Nakamura et al., 2002), in theory this increased MGAS activity could compensate for this decreased hamstring activity. Contrarily, since in this study the increase occurred considerably long after landing and at relatively low levels of activation, the impact of this increased activation is having on knee joint stability and injury prevention is questionable.

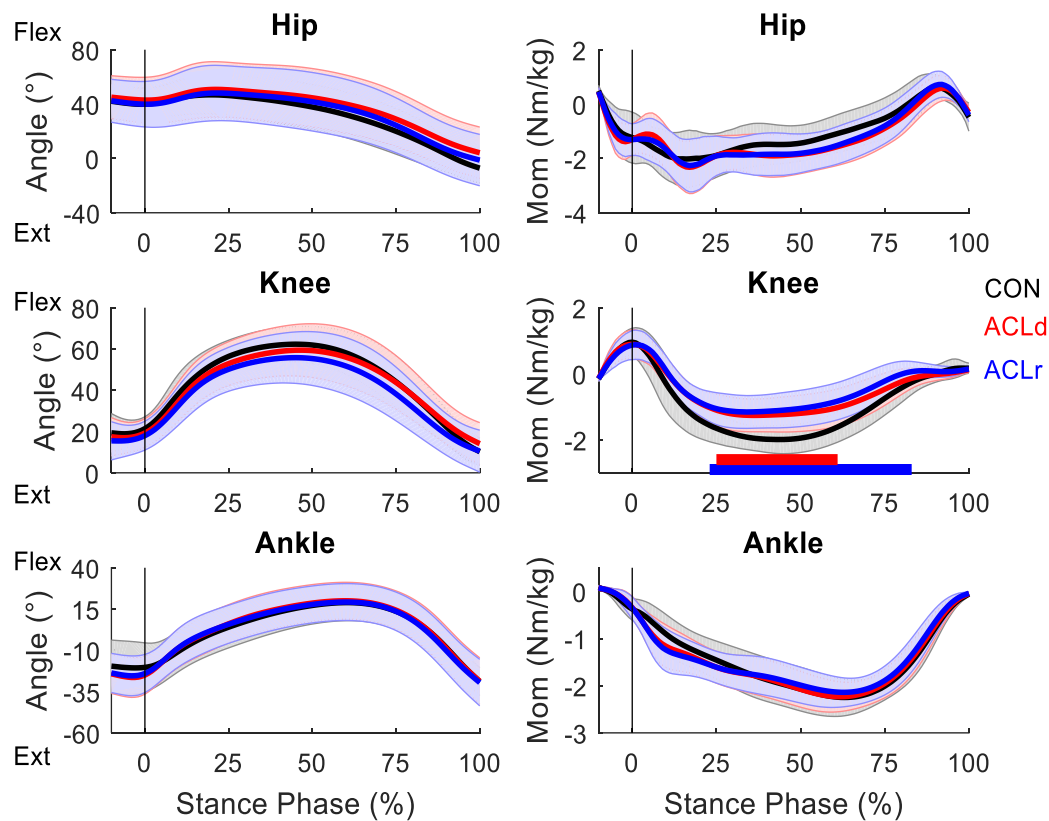


Figure 4.1.5. Sagittal angles and moments during the side cut movement. Positive values are flexion while negative values are extension. Black vertical line represents time at contact; red horizontal bar represents significance between CON and ACLd; and blue horizontal bar represents significance between CON and ACLr.

Side Cut

For the side cut, no differences between the three groups in hip, knee, and ankle kinematics were observed for the entire stance phase, while similarly to the hop both injured populations had a decreased knee extensor moment for a vast period of stance. Houck et al.

also reported reduced knee extensor moments during a cutting motion in ACL deficient participants (Houck and Yack, 2003) although these were observed along with decreased flexion angles, which we did not see during our side cut movement. The decreased internal knee extensor moment in our injured populations corresponds to an increase in external knee extension moment, leading to a more extended knee, which is a more injurious knee position (Krosshaug et al., 2007). Unfortunately without these injured patients' baseline measures prior to injury, no conclusions can be made as to whether this was a cause or effect of the injury. Moreover, no differences in EMG existed between the three groups to account for this kinetic difference, while medial GRF was greater in the CON than ACLr group for only 1% of stance during the push-off phase. Even though medial GRF was not reported in the work of Miranda and colleagues (Miranda et al., 2013), their vertical GRF results differed from ours as they detected lower vertical GRF in the ACLr compared to healthy controls. It is worth noting that differing results between the current study and (Miranda et al., 2013) may be due to their ACLr group being five years post-reconstruction and a considerably higher filter cut-off (100 Hz) than what was used in the current study (15 Hz). The decrease in lateral pushing by the ACLr may be related to frontal and transverse plane joint angles and moments but since these degrees of freedom cannot be accurately measured by surface markers (Benoit et al., 2006), we chose not to report them and further any misconceptions.

Subjective Function

As expected, PROMs were significantly lower in the ACLd population than in the CON. This supports various past studies (Eitzen et al., 2010; Fischer-Rasmussen and Jensen, 2000; Fitzgerald et al., 2000a; Herrington and Fowler, 2006; Lindstrom et al., 2010). Interestingly however, there was no significant improvement between the ACLd and ACLr reported using KNEES – Psychosocial, KNEES – Symptoms, KNEES – Sport Physical, KOOS – Symptoms, KOOS – Pain, KOOS – ADL, KOOS – Sport/Rec. This finding was not expected. One commonality between the KNEES and KOOS that the IKDC does not share is that they are divided up into subscales instead of a total sum for the entire questionnaire. While it is possible to have varying results between the different subscales it is not clear what these subscales represent in terms of the functional capacity of the participants. The use of subscales to obtain a more meaningful and concise answer also becomes ambiguous after considering that our high functioning (those who completed the hop and side cut) patients did not differ from our low functioning patients (those who did not complete these tasks) in the majority of the subscales (Table A.2). Interestingly however, following surgery, rehabilitation and return to activity clearance, subjective function remained significantly lower in ACLr than in the CON group, indicating that patients are still not fully comfortable with their own perceived abilities despite the capacity to perform our demanding tasks. This finding aligns with the biomechanical results as it was found that knee flexion angle and extensor moment exhibited by ACLr were also significantly smaller

than those of the uninjured CON, indicating that ACL reconstruction did not return subjective function and biomechanical variables to levels observed in uninjured CON.

Clinical Implications

Since the majority of ACLr patients in this study underwent a hamstring autograft procedure, it is worth noting that no EMG differences were observed for the ST and gracilis muscles that had their tendons completely harvested. Past research has also shown that when the graft is procured from the ST and gracilis tendons, the surrounding synergistic muscles have shown hypertrophy (Macleod et al., 2014) but knee flexion strength is significantly lower in the surgical limb two years after graft harvesting (Konrath et al., 2016). Furthermore, ST and gracilis volume, cross-sectional area, and length were all significantly correlated to knee flexion strength (Konrath et al., 2016). The clinical relationship between EMG muscle activations and force production has been shown to be vulnerable to cross-sectional area, force-length and force-velocity relationships (Hug et al., 2015). Thus, even though it is possible that any force transmission lost by the harvested tissue is compensated by tissue growth rather than greater activation of the remaining tissue, surface EMG cannot conclusively support this assertion.

The ACLd participants in this study represent a biased group since they were capable of performing the demanding tasks measured here. After careful consultation with their physician, they opted to have ACL reconstruction. This reconstruction led to increased subjective measures of function and, 10 months after surgery and having passed their clinical assessments, they were cleared for full activity. Despite this, and from a purely objective assessment of their biomechanical measures (joint angles and moments), during hops and side cuts they have not returned to 'normal' healthy characteristics; nor have they significantly changed from their pre-operative state. There are many reasons a patient would seek ACL reconstruction including self-efficacy and improved mechanical stability; there are also many reasons why a surgeon would recommend surgery and discussing those reasons goes beyond the scope of this paper. Our results suggest, however, that if the patient is already able to complete these challenging tasks, the intervention will likely lead to increases in their self-perceived functional ability but not their movement strategies and neuromuscular control. This highlights the importance of the patient's psychological state throughout the rehabilitation process and that a long-term follow-up to determine if these patients remain healthy despite residual biomechanical differences would have great value to the research community. This insight may further educate the decision making process.

While PROMs may further inform the decision-making process, our findings that improved subjective function do not lead to improved movement patterns and neuromuscular control in ACLr highlight the dangers of using self-reported assessments when determining return to play status. The current findings that differences in subjective function and movement

patterns still exist between ACLr and CON also highlight the dangers of comparing ACLr to healthy uninjured individuals when determining return to play status. Popular performance-based clinical tests in ACL rehabilitation include items like the single leg hop test, which compare the injured and uninjured limbs of patients in a test of asymmetry. This comparison of injured and uninjured limbs though could be misleading however, since the uninjured limb can also be compromised after ACL injury (Nyland et al., 2016). Ideally subjectivity would be removed from the process, and a patient's status would be assessed next to a gold-standard. To do so would require further research to identify the neuromuscular and biomechanical strategies implemented by those who have undergone ACL reconstruction and safely returned to play, or alternative strategies that would lead to optimal joint stabilisation based on the individual patient. To supplement the neuromuscular and biomechanical characteristics of a rehabbing patient, this study highlights the importance of self-perceived function. Upon examination of current return to play guidelines such as the MOON protocol (Wright et al., 2015), the goals and benchmarks of each phase are based on mechanical achievements while little to no attention is attributed to the patient's psychological state. Our results indicate that these patients were cleared to return to play even though their self-perceived function was still significantly lower than uninjured CON. Further examination of the impact of a patient's subjective function on their long-term health could prove extremely valuable to both the research and clinical community because if these considerations are made when assessing novel cases, it is possible that the high incidence of re-injury and osteoarthritis can be mitigated.

Limitations

This study was test-retest design, with a control group. The healthy controls were matched to the ACL patients based on five descriptive parameters; however, they are still different people with varying exposures to activity and training throughout the lifespan which may have led to different movement and neuromuscular strategies. All patients of the Bispebjerg Hospital Department of Sports Traumatology waiting to undergo a reconstruction were contacted to participate and therefore patients were not selected based off of any performance measures. Of the total patient population who volunteered to participate (47), less than half were comfortable completing the side cut and hop (this includes 12 and 13 patients who completed the hop and side cut tasks respectively in the ACLr but not ACLd state and thus were not included). Our 10 month timeframe for post-operative testing was based on the findings of Erickson et al. (2014). We believe this was appropriate since of the 38 participants who returned for their post-operative testing, 35 and 36 of these completed the side cut and hop, respectively.

We chose to analyse difficult tasks as these are movements that need to be safely done in order to safely return to play and have shown to be ACL-injurious (Boden et al., 2000). We acknowledge that they were anticipatory in nature but this was done mainly as a safety and comfort concern for the injured patients. Of the 47 patients that participated in the ACLd state, only 22 and 24 were comfortable/capable of completing the side cut and hop tasks, respectively. Thus, since only half of our patients were able to complete the anticipated movements, we deemed the unanticipated versions to be too risky and demanding for these patients.

Of the participants included in this study, 14/20 had one or more concomitant injuries including 2/20 with MCL tears, 9/20 with medial meniscus damage, 6/20 with lateral meniscus damage, and 1/20 with cartilage injury. Since isolated ACL ruptures are not as common as injuries occurring to multiple structures, we believe that our cohorts are a valid representation of an ACL injured population.

Regarding our analysis of the muscle activation data, previous studies have identified decreases in maximum voluntary activation due to pain and, therefore, if the ACLd or ACLr patients were experiencing pain due to their injury their maximum activation may be decreased, causing an overestimation of activation during the dynamic trials. Many types of EMG normalization techniques have been explored (Benoit et al., 2003) but normalization to MVIC has been shown to be most reliable measure in ACLd populations (Knutson et al., 1994) and was therefore our choice. This limitation was further mitigated by the use of SPM over traditional discrete peak activation testing: if the increases in peak activation previously observed in injured populations was caused by their inability to produce a true maximum activation, SPM also incorporates the waveform pattern into the testing, thus providing an alternative technique that analyzes both the time varying pattern and its amplitude.

Conclusions

This study presents an intentionally biased group of ACL injured patients who are, based on their performing hop and side-cut tasks in their ACL deficient state, considered high functioning. Through the implementation of the current three research question framework, it was found that (1) ACLd patients had significantly lower subjective function in all PROMs and knee extensor moments; (2) half of PROMs showed a significant increase in function after reconstruction with no accompanying changes in neuromuscular and movement patterns; and (3) ACL reconstruction failed to return subjective function, knee flexion angles, and knee extensor moments to healthy values. These results indicate that the patient may experience an increase in self-perceived function, but improvements to objective dynamic functionality during the hop and side-cut are very few. This information may help inform the decision-making

process regarding treatment options of those ACL deficient patients who are considered to be high function.

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Conflict of Interest

The authors have no professional relationships that stand to gain from the current study. The results of the present study do not constitute endorsement by ACSM and the results are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

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4.2 Study 2: Dynamic knee joint control after ACL injury

Assessment of objective dynamic knee joint control in anterior cruciate ligament deficient and reconstructed individuals

Running Title: Dynamic knee joint control after ACL injury

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Abstract

Background: There is a current lack of objective dynamic knee joint control measures that can be related to the status of the anterior cruciate ligament (ACL). Thus, the purpose of this study was to introduce two novel measures and apply a third to determine how dynamic knee joint control changes in relation to the status of the ACL during the hop and side cut movements.

Methods: Twenty ACL deficient (ACLd) patients were tested prior to reconstruction and approximately ten months post-reconstruction (ACLR). Each patient was matched to a healthy uninjured participant (CON). Three objective control measures including dynamic stiffness, knee joint centre excursion (KJCE), and knee joint centre boundary (KJCB) were assessed for each participant when completing the side cut and hop tasks. Kinematics and kinetics were computed.

Results: During the side cut, stiffness was found to be significantly lower in both injured groups ($p = 0.013$) compared to the healthy CON, while there were no differences in stiffness during the hop. No significant differences were observed in the KJCE during the side cut, while KJCE was significantly greater ($p = 0.006$) during the hop in CON compared to the ACLd. There were no differences in KJCB.

Conclusions: In both the pre and post-operative state, these high-functioning ACL injured were able to complete the hop and side cut with similar dynamic control and spatiotemporal values as the healthy controls. Even though these patients have been previously reported to have dramatic improvements in self-perceived control between the deficient and reconstructed state, these lack of improvements in objective control demonstrate a gap between a patient's self-efficacy and the level of control they implement while completing two demanding tasks.

Introduction

With the increasing rates of anterior cruciate ligament (ACL) ruptures during physical activity (Agel et al., 2016), a better understanding of knee joint control and the lack thereof leading to injury is imperative. Many past studies have examined the biomechanics of ACL deficient (ACLd) and reconstructed (ACLR) patients during various dynamic tasks and have arrived at a general consensus that these injured groups complete the same movement with reduced knee flexion angles and knee extensor moments (Andriacchi and Birac, 1993; Chmielewski et al., 2001; Di Stasi and Snyder-Mackler, 2012; Houck and Yack, 2003; Oberländer et al., 2014; Rudolph et al., 1998, 2000, 2001). Unfortunately, these kinematic and kinetic variables are only representations of the movement and are not indicative of the patient's dynamic knee joint control. Therefore, patients could have altered kinematic and kinetic patterns but still maintain an appropriate amount of knee joint control, which remains unknown to the researcher or clinician until true measures of control are implemented.

Defining joint control is a rather difficult task as it can be described in many ways. With respect to objective stability measures, very common clinical tests include the Lachman and pivot-shift tests that allow the clinician to measure translational and rotational laxity of the knee joint. Unfortunately, a simple measure of passive anterior laxity whether by manual Lachman or KT-1000 instrumentation has been found to be uncorrelated with various functional tests including Noyes' (1991) battery of hop tests in the ACLd (Eastlack et al., 1999) and ACLr state (Risberg et al., 1999; Sernert et al., 1999). Furthermore, even though these clinical tests provide information regarding the knee's mechanical stability, these assessments are done in static and non-weight bearing situations. Therefore, their validity as dynamic knee joint control measures is questionable when the focus is on relating ACL injuries to joint control during dynamic and weight bearing tasks.

One definition of dynamic control has been joint stiffness, measured as the change in joint moments as a function of the change in joint angles (Davis and DeLuca, 1996; Longpré et al., 2013; Zeni Jr. and Higginson, 2009). These studies suggest an increase in joint stiffness increases dynamic joint control since it would require greater magnitudes of applied forces to induce a displacement in joint position, and therefore protecting the soft tissue from harmful amounts of tissue strain. Even though this concept of joint stiffness has been applied to the knee during elementary movements such as gait, it has yet to be used to describe the knee during more demanding dynamic tasks.

Another simple measure of dynamic control after ACL injury has been knee joint angular excursion as defined by the change in sagittal plane angle during various dynamic tasks. This knee excursion is greater in the ACL injured limb during gait and hopping (Di Stasi et al., 2015; Risberg et al., 2009), greater in poor functioning ACLd patients during a step task (Rudolph and

Snyder-Mackler, 2004), and may improve in women between the ACLd and ACLr state (Di Stasi et al., 2015). This method is limited though as it only considers knee joint angular excursion in one dimension while it is well-known that ACL contributes to knee joint control in more than just the sagittal plane (Markolf et al., 1976) and non-contact injury mechanisms are a combination of forces in multiple planes (Boden et al., 2000; Griffin et al., 2006). Thus, a measure of three-dimensional knee joint centre (midpoint between the two femoral epicondyles) excursion (KJCE) in the global coordinate system is warranted. Since this KJCE measure considers the knee movement in three dimensions, it provides more information than the traditional unidimensional sagittal plane knee angle. Furthermore, since KJCE is rooted in the global reference frame, it is a better representation of the holistic knee joint motion including the unwanted “wobble” exhibited by an unstable knee during dynamic tasks. This measure of control has the potential to be a better representation of knee joint movement and therefore could be a powerful objective representation of a patient’s subjective report.

Finally, movement variability has also been used to assess knee control after ACL injury. It is believed that there is an optimal level of variability in human movement as a rigid system is less adaptable to perturbations while a highly variable system is noisy and unstable (Stergiou et al., 2006; Stergiou and Decker, 2011). Through a literature review, Decker and colleagues (2011) concluded that the loss of variability, which is associated with a more rigid and repeatable movement pattern is observed in the ACLd knee while increased variability beyond the optimal level, which is associated with a noisy and irregular movement pattern is found in the ACLr knee. Even though this review indicated abnormal levels of variability, the included studies were cross-sectional and therefore it still remains unknown how or if movement consistency (i.e. variability) changes longitudinally with respect to a specific patient’s ACL status. This measure also provides conflicting results since depending on the definition, the ACLd limb has been linked to no changes (Skurvydas et al., 2011) or decreases (Zampeli et al., 2010) in variability, while both increased (Cordeiro et al., 2015) and decreased (Pollard et al., 2015) variability has been observed in ACLr populations. This issue can be addressed by a novel measure that quantifies a knee joint centre boundary (KJCB) within a participant’s dynamic task trials. Since identifying the optimal level of variability is difficult, one consideration that can be made is that since a healthy population has yet to endure a knee injury, their variability can be considered optimal. Therefore, a simple measure of movement consistency that can be compared amongst healthy, ACLd, and ACLr groups could provide insight into how variability, and in effect knee joint control, change throughout the ACL injury and recovery process.

Since dynamic knee joint control remains relatively unknown in relation to ACL injury, the primary purpose of this study was to compute and assess two novel measures of knee joint control (KJCE and KJCB) and apply a third (stiffness) to determine how dynamic knee joint control changes in relation to the status of the ACL. To address this purpose, we assessed three

objective measures of control during hop and side cut manoeuvres that were performed by healthy, ACLd, and ACLr individuals. It was hypothesized that for all measures, control would be greatest (high stiffness, and low KJCE and KJCB) in the healthy participants, lowest in the ACLd group, and the ACLr patients would show increased control compared to ACLd patients while not reaching levels seen in the healthy controls.

Methods

Participants

As part of a larger project, 47 ACL injured participants were tested at the University of Copenhagen (ACL rupture was confirmed via arthroscopy and all patients underwent a reconstruction procedure). Of these, 20 participants were included in this study based on their agreement to perform side cut and hop movements (see Chapter 4.1 for details). Of these 20 participants, 17 were comfortable completing the side cut and 18 completed the hop movement in both the ACLd and ACLr state (Table 4.1.1). Each of these 20 patients were matched with a healthy control (CON) based on sex, leg tested (dominant or non-dominant), body mass index, age, and Tegner score. The inclusion criteria for CON included no previous lower limb surgical operations, no additional serious lower limb injury including fractures or sprains within six months prior to testing, and any diseases that might affect neuromuscular function. This study was approved by the local ethics committee for the Capital Region of Denmark and the University of Ottawa Research Ethics Board.

Protocol

Upon arrival, participants received an introduction to the laboratory space and equipment and then provided informed consent. Participants next changed into tight-fitting spandex and were outfitted with a whole-body marker set that includes clusters on each thigh and lower leg (Mantovani and Lamontagne, 2016). The full protocol included static (Chapter 4.1) and dynamic tasks performed in order of incremental difficulty.

Kinematic data were collected using a 10-camera motion capture system (6 MX and 4 T series, Vicon, UK) at a sampling frequency of 100Hz. Ground reaction force (GRF) data were synchronously sampled at 1000Hz using one force plate (OR 6-5-1, AMTI, USA). For a hop attempt to be deemed successful, participants began on their non-test limb and jumped forward, landing with their test limb within the boundaries of the force plate and maintained balance. Distance was self-selected but needed to be greater than stepping distance to ensure it was a jump. Participants were asked to complete the movement at the maximum speed they were comfortable with, which caused them to drive their mass forward into the landing and abruptly arrest their momentum instead of completing a relaxed hopping motion. As for the side cut, participants were again instructed to complete the movement as fast as they were

comfortable with, cut onto the force plate at a 45° angle, have their entire foot plant within the boundaries of the force plate, and then cut off from the force plate again at a 45° angle. Three successful trials were considered for each participant.

Data Analysis

All data analysis was completed using a MatLab (2013a, Mathworks, USA) – OpenSim (3.3, Simtk, USA) application program interface. Marker trajectories and GRFs were filtered with matching 4th order zero-lag low pass Butterworth filters with cut-off frequencies of 15Hz. A whole-body OpenSim model (Rajagopal et al., 2016) was modified to include three unprescribed rotational degrees of freedom at each knee. Scaling, inverse kinematics, and inverse dynamics were used to compute hip, knee, and ankle angles and internal joint moments.

Dynamic knee joint stiffness was calculated as the change in knee sagittal moment over the change in knee sagittal angle (Davis and Deluca 1996) from the point of initial foot contact to the maximum knee extensor moment (Figure 4.2.1) and reported as an absolute value. Knee joint centre (KJC) was defined as the midpoint between the medial and lateral femoral epicondyle markers and KJCE was calculated as the Euclidean distance of the KJC from the appointed start and end points of the movements. Thus, KJCE was the Euclidean distance that the KJC travelled throughout the task of interest. For the side cut, KJCE was computed for the entire stance phase while for the hop, KJCE was calculated from initial contact to the following 100 ms as ACL injuries most commonly occur within this time frame (Koga et al., 2010) and we did not want the period of voluntary balance control to influence our measures.

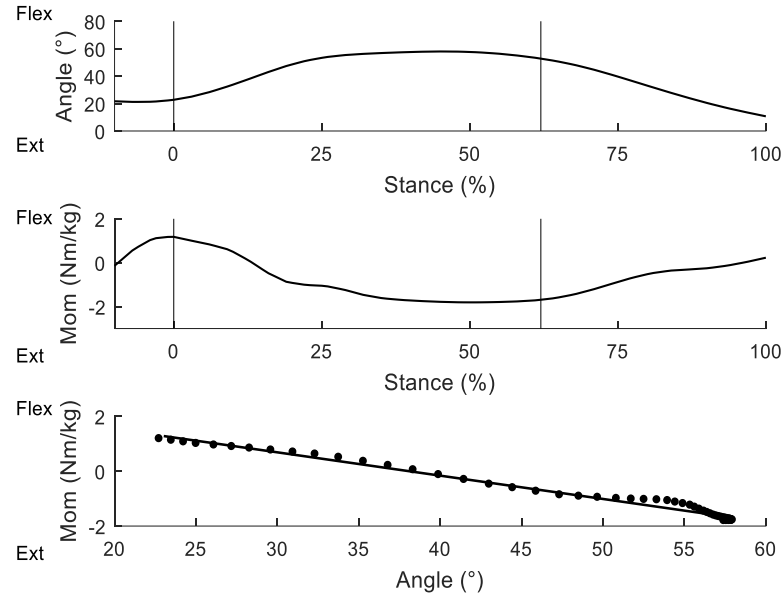


Figure 4.2.1 Top plot is knee sagittal plane angle of an example side cut trial, middle plot is sagittal plane knee internal joint moment, and the bottom plot is knee moment as a function of knee angle. Each dot represents a time point from initial contact to max knee extensor moment (vertical lines on top two plots). Stiffness is quantified as the slope of the line of best fit from the angle-moment scatter plot.

Finally, the KJCB was calculated over the same time periods as the KJCE and was position normalized to allow for the trials within each participant to be comparable. Since KJC was expressed in the global coordinate system, the coordinates of the initial time point of each trial were subtracted from the rest of the respective trial, which normalized each within participants' trial to an equivalent starting point. Then, at each subsequent time point, the Euclidean distance between KJC markers in all three trials was calculated and represented a boundary (Eq. 4.2.1):

$$\sum_{i=1}^n \sqrt{(x_2 - x_1)^2 + (y_2 - y_1)^2 + (z_2 - z_1)^2} + \sqrt{(x_3 - x_2)^2 + (y_3 - y_2)^2 + (z_3 - z_2)^2} \\ + \sqrt{(x_3 - x_1)^2 + (y_3 - y_1)^2 + (z_3 - z_1)^2}$$

where n is the last time point in the trial, i is the frame number, x , y , z are the global knee joint center coordinates for the three trials (1, 2, 3).

A small Euclidean distance indicates that the KJC movement was more consistent than if the Euclidean distance was large. The boundary lengths (Euclidean distances) found at each time point were then summed and expressed in metres to represent the KJCB value for that participant.

Statistical Analysis

All statistical analyses were performed using SPSS (22.0, IBM, USA). Since the injured groups are dependent, while the healthy controls were independent of these groups, we implemented a three research question approach: Q1) did the healthy and ACLd patients differ in dynamic knee joint control? Q2) Did the ACLd patients differ from the ACLr? Q3) Did the ACLr differ from healthy controls? Since all data were found to be normally distributed (Shapiro-Wilk test), independent t-tests were used to address Q1 & Q3, whereas a paired samples t-test was used to address Q2. Due to multiple comparisons, our alpha level of significance was reduced to 0.025. When differences were found to be significant, Cohen's effect size (d) was calculated to quantify the size of the difference.

Results

Q1: CON vs ACLd

For the hop, there was no difference in dynamic knee joint stiffness between CON (0.06 ± 0.01 Nm/kg/°) and ACLd (0.06 ± 0.02 Nm/kg/°). KJCE was significantly greater ($p = 0.006$, power = 0.82, $d = 1.0$) in the CON (0.20 ± 0.02 m) than in the ACLd (0.18 ± 0.02 m). Finally, as for KJCB, no significant difference was found between the CON (4.89 ± 3.10 m) and ACLd (5.82 ± 3.46 m).

In the side cut task, stiffness was significantly greater ($p < 0.0005$, power = 0.99, $d = 1.51$) in the CON (0.08 ± 0.02 Nm/kg/°) than in the ACLd group (0.06 ± 0.01 Nm/kg/°; Figure 4.2.2A). There was no difference in KJCE between the CON group (0.55 ± 0.07 m) and the ACLd (0.53 ± 0.05 m; Figure 4.2.2B), nor in the KJCB between CON (10.50 ± 5.18 m) and ACLd (10.72 ± 7.46 m; Figure 4.2.2C).

Q2: ACLd vs ACLr

No significant differences were found in stiffness, KJCE, or KJCB during the hop or side cut tasks.

Q3: ACLr vs CON

For the hop, stiffness was similar between CON (0.06 ± 0.01 Nm/kg/°) and ACLr (0.06 ± 0.01 Nm/kg/°). The KJCE trended towards being greater ($p = 0.054$, power = 0.49, $d = 1.0$) in the CON (0.20 ± 0.02 m) than in the ACLr (0.18 ± 0.02 m), while no difference in KJCB was found between the CON (4.89 ± 3.10 m) and ACLr (5.52 ± 2.97 m).

During the side cut, stiffness was significantly greater ($p = 0.013$, power = 0.72, $d = 0.9$) in the CON (0.08 ± 0.02 Nm/kg/°) than in the ACLr group (0.07 ± 0.02 Nm/kg/°). KJCE did not

differ significantly between the CON group (0.55 ± 0.07 m) and the ACLr (0.52 ± 0.06 m), nor did it differ for the KJCB between CON (10.50 ± 5.18 m) and ACLr (8.31 ± 4.24 m).

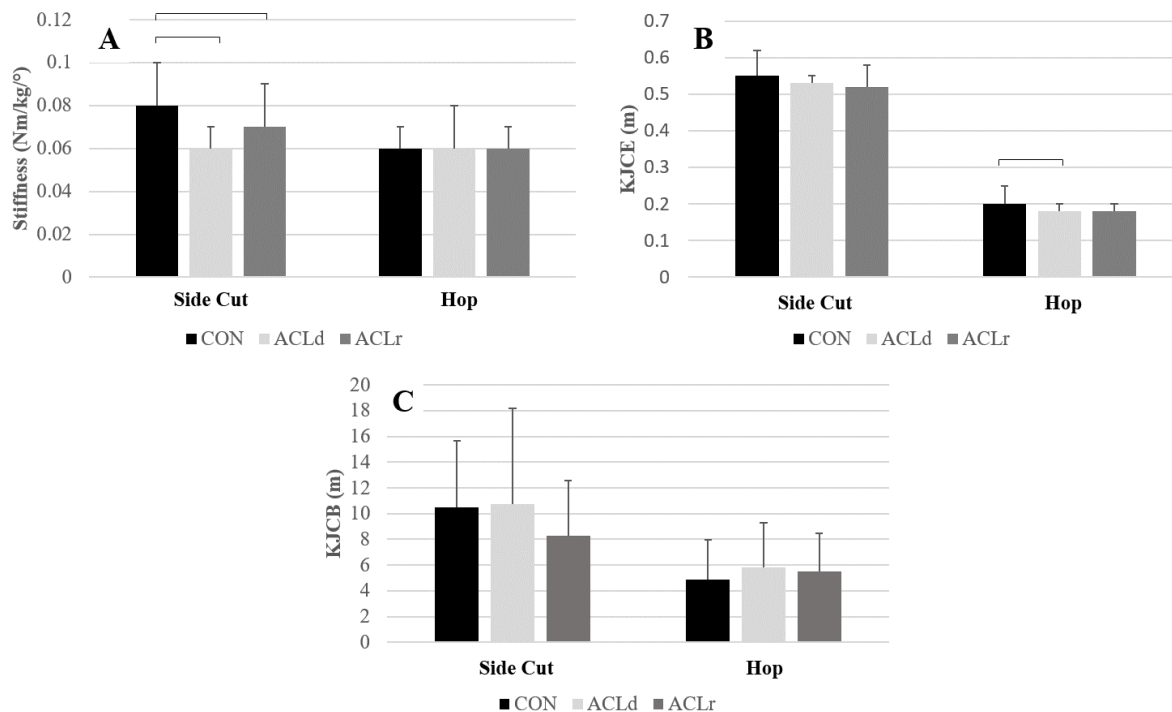


Figure 4.2.2 A) Stiffness **B)** Knee joint centre excursion (KJCE) and **C)** knee joint center boundary (KJCB) means and standard deviation bars for healthy (CON), ACL deficient (ACLd), and ACL reconstructed (ACLR) patients during the side cut and hop movements. Horizontal bars denote significance ($p < 0.025$) between groups.

Discussion

The purpose for this study was to compute and assess two novel measures of dynamic knee joint control (KJCE and KJCB) and apply a third (stiffness) to determine how these measures change in relation to the status of the ACL during two demanding tasks. This was done by comparing dynamic joint stiffness, KJCE, and KJCB between healthy CON, ACLd, and ACLr participants throughout hop and side cut movements. It was found that 1) healthy matched participants have greater stiffness during the side cut and KJCE during the hop compared to the ACLd. 2) There were no statistically significant differences between ACLd and ACLr, while 3) stiffness was significantly greater in the CON during the side cut and KJCE trended towards significance during the hop when compared to ACLr.

From our past work (See Chapter 4.1), the ACLd patients exhibited significant deficits in self-reported functional ability, assessed through questionnaires including Lysholm, IKDC,

KOOS, and KNEES. Many of these deficits significantly improved after ACL reconstruction indicating that this procedure provided an increase in self-efficacy, as evidenced in significantly greater outcome scores in daily living and sporting activities domains. Even though this subjective increase was observed, the current results found few differences in all three objective control measures regardless of ACL status. The ACL injured participants were tested once approximately 10 months post-reconstruction. This time frame was chosen as 56% of surgeons recommend waiting at least six months, 12% recommending waiting at least nine months, while 32% didn't recommend a certain time minimum but rather relied on subjective and objective movement performance (Erickson et al., 2014). Even though the majority of these surgeons have recommended return to play after six months post-reconstruction, this is likely not enough time for reinnervation to occur within the knee. In a study of six canines, only two exhibited the regeneration of free nerve endings six months post-reconstruction (Barrack et al., 1997). In humans, reinnervation has been observed to occur after ACL reconstruction but the level of nerve signal has yet to reach those exhibited by healthy controls even after seven years (Ochi et al., 1999; Young et al., 2016). This would imply that our study participants, despite being cleared for full activity, would not have complete reinnervation and thus be performing with a sensory deficit. Thus, at this stage the main role of the ACL would be mechanical in nature, meaning clearance to return to play is often based on the ACL's mechanical role and not its neural input. Those patients who contemplate undergoing reconstruction will likely experience improved confidence in their abilities, which may be related to the regained ACL mechanical stability but since they are still lacking that neural input, their kinematics and objective control when performing dynamic tasks may not improve a great deal.

The most sensitive measure of dynamic control to ACL status appeared to be stiffness during the side cut movement. A significantly less stiff knee was observed in the ACLd group and continued to be less stiff after reconstruction when compared to CON. This finding resembles that of Zeni Jr. and Higginson (2009) who observed greater stiffness values in their control group compared to the participants with moderate osteoarthritis. Contrarily, no differences in knee joint stiffness were observed in the hop task. Since this variable is derived from flexion angle and joint moment, it is pertinent to acknowledge our past work (See Chapter 4.1). Here the injured patients were found to complete the hop with a significantly smaller amount of knee flexion and a decreased extensor moment, while during the side cut, only extensor moment was observed to decrease. Thus, if stiffness can truly be considered a measure of joint control, the approach of decreasing both angle and moment taken by both ACLd and ACLr groups during the hop appears to be effective at maintaining joint stiffness and therefore control. Furthermore, this appears to be more effective than the approach of only reducing joint moment as seen in the side cut where significant decreases in joint stiffness were observed between the CON and both injured groups. This knowledge of maintaining the relationship between joint angle and moment to preserve an appropriate level of stiffness and

joint control is useful in not only designing an effective rehabilitation program but has the potential to be used in return to play assessments.

Throughout the self-reported questionnaires and conversations with the patients, a recurring explanation of their lack of control or instability was that it felt “wobbly” or had “extra” movement. We attempted to quantify this perceived lack of control through the calculation of KJCE. Contrary to our hypothesis, no differences in KJCE were observed during the side cut while it was found to be greatest in the CON during the hop task. Since this perceived lack of control is not present in the objective quantification of the task in hand, it warrants further investigation as to whether or not these objective measures of control are related to the patient’s self-perceived level of ability. Furthermore, these patients were considered high-functioning as they were able and willing to complete the side cut and hop in both the ACLd and ACLr state. Therefore, it would be very interesting to see if this measure of control is more sensitive in injured populations displaying lower physical function and thus could also be used in return to play assessments.

As stated earlier, the literature is inconclusive about variability in ACLd and our results of similar KJCB boundaries across groups within each task were contrary to our hypothesis. Although it is believed that there is an optimal level of variability (Stergiou et al., 2006; Stergiou and Decker, 2011) and an extensive review has concluded that this optimal variability level paradigm appears to exist in ACL injured populations, what exactly this optimal level is has yet to be established. The lack of differences in our current results could be interpreted in two ways: the first is that our novel measures are not sensitive to either the groups or tasks that they were applied to. The second is that since our patients are functioning at such a high level, they are currently operating similar to the CON and at an optimal level of variability. To determine which one of these possible explanations is true, future work will be conducted to examine KJCB in a more inclusive study population that is comprised of a stratification of patients based on their level of perceived and objective functional ability.

One of our study’s strengths is its test-retest design in which any confounding factors due to testing different participants (anthropometric, experience, etc.) are eliminated as the same patient was tested in both the ACLd and ACLr state. A limitation of this approach is that the participant pool was limited to only high functioning participants and therefore the results of the current study cannot be projected onto the group of patients unwilling to complete these movements in one or either ACL state. That stated, since these high functioning patients have relatively equal dynamic control and spatiotemporal values to healthy controls, their previously reported altered movement strategies (See Chapter 4.1) could be used as benchmarks in the rehabilitation of patients with less function.

A second limitation is that only three trials were used to calculate stiffness, KJCE, and KJCB for each participant. This trial number is especially low for traditional variability measures but unlike a simple gait task, high trial numbers of hops and side cuts induces fatigue very rapidly, which in turn would influence the results. Although calculating variability on a small number of trials may provide inconsistency among testing sessions, the aspect of clinical feasibility needs to be considered. A simple measure of variability that is easy to implement is crucial for clinicians as they don't have the time or resources to collect, process and analyze large amounts of trials. Therefore, the costs and benefits need to be considered when applying variability measures to small samples.

A third limitation to these measures is the amount of error induced by soft tissue artifact. Sagittal plane angles have been shown to be reliable but considerable errors are observed in the frontal and transverse planes (Leardini et al., 2005; Peters et al., 2010). Since our stiffness measure was confined to the sagittal plane, these angles and moments should not have been greatly influenced by soft tissue artifact. KJCE and KJCB however are three-dimensional measures and could contain error during these dynamic tasks. Fortunately, these measures are based on the KJC, which is defined as the midpoint between the two femoral epicondyle markers relative to the global reference system. Therefore, since the markers are placed on bony landmarks and not on top of considerable soft tissue, the average of these two values should to a certain extent mitigate the noise experienced by the markers during these tasks.

In conclusion, very few differences in three objective measures of control were observed between healthy, ACLd, and ACLr participants during hop and side cut movements despite considerable kinematic and kinetic differences between healthy and both injured states (Chapter 4.1). Even though these patients had dramatic improvements in self-perceived control between the deficient and reconstructed state, the lack of improvements in objective control demonstrate a gap between a patient's self-efficacy and the level of control they implement while completing two demanding tasks. Given the considerably high level of re-injury (Goddard et al., 2013; Laboute et al., 2010) and low level of return to pre-injury activity (Ardernd et al., 2014), the gap between perceived control and objective control warrants further investigation.

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Conflict of Interest

The authors have no conflicts of interest to declare.

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4.3 Study 3: Objective and subjective functionality after ACL injury

Relation of objective and subjective functional ability in anterior cruciate ligament deficient and reconstructed individuals

Running Title: Objective and subjective functionality after ACL injury

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Abstract

Background: The decision of returning to play after anterior cruciate ligament (ACL) injury is based on objective and subjective standards; however, the relationship between these diverse measures remains ambiguous. The purposes of this study were to quantify their relationships and determine if measures in the deficient (ACLd) state were correlated to, and capable of predicting a patient's functional score in the reconstructed (ACLr) state.

Methods: Twenty participants with an ACL injury completed hop and side cut movements prior to and 10 months post-reconstruction. Their self-reported questionnaire (Tegner, Lysholm, International Knee Documentation Committee, Knee Injury and Osteoarthritis Outcome Survey (KOOS), and Knee Numeric Entity Evaluation Scale) measures were related to objective measures of functional ability (peak knee flexion, peak knee extensor moment, dynamic knee joint stiffness, knee joint centre excursion (KJCE), and knee joint centre boundary during two dynamic tasks. Spearman and Pearson correlations were used to determine relationships between variables while linear and ordinal regressions were used to identify ACLd score's predictive ability of an ACLr score.

Results: Relationships between objective and subjective measures were task and ACL status dependent with KJCE and stiffness most commonly being related to subjective scores. The strongest correlation observed was between knee stiffness and Tegner in the ACLr group during the side cut ($r = 0.69$, $p = 0.002$). Peak knee flexion angle ($r = 0.66 - 0.83$, adj. $R^2 = 0.4 - 0.66$) was the best objective predictor between ACLd and ACLr states while KOOS-ADL had the strongest correlations ($r = 0.70 - 0.77$) and Tegner had the greatest predictive power (Odds Ratio: 1.46 -1.86) between states in both tasks.

Conclusion: Objective dynamic measures show a stronger relation to subjective functional ability measures compared to clinical laxity. Furthermore, objective measures are more correlated and more often capable of predicting ACLr scores than the self-reported functional measures.

Introduction

Returning to pre-injury levels of play after enduring an anterior cruciate ligament (ACL) rupture is an arduous task as on average 81% of patients are capable of returning to play while only 55% return to a competitive level (Ardern et al., 2014). The decision in returning to play is often based on a series of objective and subjective standards (Wright et al., 2015) but the relationship between these diverse measures remains ambiguous and it is unclear if they are harmonious in indicating a patient's level of function before and after ACL reconstructive surgery.

There are many patient-reported outcome measures (PROM) designed to assess the subjective functional ability of a patient with a knee injury. Commonly, the Knee Injury and Osteoarthritis Outcome Scale (KOOS; Roos and Lohmander, 2003), Knee Numeric-Entity Evaluation Scale (KNEES; Comins et al., 2013), International Knee Documentation Committee (IKDC; Irrgang et al., 2001), Tegner activity level (Tegner and Lysholm, 1985), and Lysholm scale (Lysholm and Gillquist, 1982) are all used to assess a degree of self-reported symptoms, function, and ability in ACL deficient (ACLd) and ACL reconstructed (ACLr) populations. These questionnaires are effective in distinguishing between patient populations as scores have been reported to be significantly lower in ACL injured populations compared to healthy counterparts (Eitzen et al., 2010; Fitzgerald et al., 2000a; Herrington and Fowler, 2006; Lindstrom et al., 2010). After reconstruction, these questionnaire scores are generally higher than the ACLd state but still rarely achieve the same level observed in healthy populations (Fischer-Rasmussen and Jensen, 2000; Gustavsson et al., 2006; Nyland et al., 2014; Chapter 4.1). Therefore, this indicates that the reconstructive process is significantly improving the patient's subjective functional ability; however, corresponding improvements in how the patients objectively complete various tasks are considerably less clear.

Common ACL rupture diagnosis techniques are joint laxity tests including the Lachman and Pivot-Shift tests, which are designed to assess the amount of passive laxity (mechanical stability) in the knee of interest. Issues with these tests include 1) the uninjured knee acts as a control value despite the evidence that contralateral legs are also possibly affected by injury (Hannon et al., 2017; Wellsandt et al., 2017); 2) these tests are completed in a static non-weight bearing position and thus disregarding the role of compressive force caused by body weight on knee joint stability (Markolf et al., 1981); 3) the body is supine in a static position with movement occurring only in the test limb, which is a situation not commonly associated with ACL injuries (Boden et al., 2000); and 4) the knee is relaxed and therefore the well-established muscular contribution to knee stability (Potvin and Brown, 2005) is not taken into consideration. These characteristics might account for the discrepancies observed between objective clinical measures and subjective ability measures during dynamic and weight-bearing

tasks. For example, laxity is often reported to be uncorrelated to Lysholm, Tegner, KOOS, and global function scores in both the ACLd and ACLr state (Barrett, 1991; Kocher et al., 2004; Sernert et al., 1999; Snyder-Mackler et al., 1997). Since these PROMs and in effect self-reported functional ability, do not appear to be related to unweighted mechanical stability (joint laxity), it would be beneficial to examine the relation between the characteristics of dynamic movements associated with ACL injury (Boden et al., 2000) and these self-reported function scores.

One-legged hops are a common objective assessment of a person's ability to function with inflicted with knee pathologies such as ACL injury (Noyes et al., 1989). Thus, it is logical to determine how a patient's performance on different hopping tasks relates to their perceived functional ability. To this end, a comprehensive subjective questionnaire score has shown to be correlated to timed hop and cross-over hop performance (Wilk et al., 1994), while Lysholm scores have shown correlation to one-legged hop distance (Sernert et al., 1999). Even though these objective functional performance measures are showing a stronger relation than laxity with respect to a patient's subjective evaluation, they are still not indicative of the patient's movement profile and intrinsic level of knee joint control.

Strong symptoms of ACL injury include decreased peak knee flexion angles and decreased peak extensor moments in the injured limb during a variety of dynamic tasks such as walking, running, steps and side cuts (Andriacchi and Birac, 1993; Chmielewski et al., 2001; Di Stasi and Snyder-Mackler, 2012; Houck and Yack, 2003; Oberländer et al., 2014; Rudolph et al., 2001, 2000, 1998). This difference between ACLd and healthy controls is mitigated but not fully restored after reconstruction (Oberländer et al., 2014). Since flexion angle and extensor moments are foundational characteristics of describing movement patterns, it is reasonable to suspect both measures to be more related to a patient's self-reported function than passive joint laxity.

Even though flexion angles and extensor moments can effectively describe a movement pattern, they are not measures of dynamic knee joint control. With the low rate of return to sport and high incidence of graft rupture and osteoarthritis, our rehabilitation programs are missing an important aspect of ACL injury recovery. This discrepancy and lack of relationship between objective and subjective functional ability may hold the key to determine which patients are truly performing and functioning better than others. The lack of moderate to strong correlations between objective and subjective measures is perhaps that the objective measures of functional ability (passive joint laxity, limb symmetry index, etc.) are not representative of the types of questions the PROMs are asking. For example, the KOOS, IKDC, and KNEES have in some form or another, questions concerning the patient's knee slackness/looseness during dynamic tasks. It is unsurprising that these basic kinematic and

kinetic objective measures of joint function are not related to subjective scores because they are addressing different aspects. Therefore, if deeper objective measures that better represent knee joint function and control can be determined, we will likely see stronger relationships between them and the subjective scores as they are attempting to address the same features. To this end, our group has previously applied or developed three measures of knee joint control (Chapter 4.2). These include dynamic knee joint stiffness (Davis and DeLuca, 1996), which has been shown to differ in pathological populations (Collins et al., 2014), as well as knee joint centre excursion (Rudolph and Snyder-Mackler, 2004) and knee joint center boundary (KJCB) - a rudimentary measure of movement variability, which have also indicated differences in ACLr populations (Cordeiro et al., 2015; Pollard et al., 2015). This consolidation of objective and subjective functional ability can then be used in improving rehabilitation programs so that they are more effective of returning athletes to competition and reducing secondary injuries like graft rupture and osteoarthritis.

To address the research question of whether or not dynamic objective functional ability measures are related to self-reported levels of function, the current study had three purposes. The first was to determine if objective biomechanical measures are related to subjective functional scores in each of the ACL states. Since both of these types of measures are aimed to indicate a patient's functional ability, it is reasonable to hypothesize that mainly weak - moderate correlations will be observed between the two measures as they are aiming to test a similar phenomenon but have varying definitions of said measure. The second aim was to determine if a selected objective or subjective score in the ACLd state is correlated to its corresponding score in the ACLr state. It is hypothesized that strong correlations will exist in many of the variables between both ACL states. Finally, the third purpose of this study was to determine if a variable in the ACLd state is capable of predicting its respective value in the ACLr state. If such a relationship can be established in any of the variables between the ACLd and ACLr state, a clinician could assess a patient prior to reconstruction and have a benchmark of where that patient's functional ability should be post-operation. It is hypothesized that ACLd scores will have moderate predictive ability of the post-operative condition.

Methods

Participants

The current study is a continuation of a larger study described in Chapters 4.1 and 4.2 which contain additional results and methodological details. Forty-seven ACL injured patients participated in the larger study but due to longitudinal drop-out and self-efficacy in these tasks (see Chapter 4.1 for details), 20 were eligible and included here. ACL injured patients were tested once in their ACLd state prior to their reconstruction and once again approximately 10-months post-operation in their ACLr state. Ten months was chosen as this is a common return

to play time frame for athletes and recommended by a majority of surgeons (Erickson et al., 2014). Of these 20 patients, 18 and 17 chose to complete the hop and side cut movements respectively, in both the ACLd and ACLr conditions (Table 4.1.1). All data collections occurred at the University of Copenhagen and this study was approved by the local Danish and Canadian ethics committees.

Protocol

Once participants arrived at the laboratory, they were introduced to the equipment and procedures and then asked to provide written informed consent. They then completed a battery of subjective functional questionnaires including the KOOS (Roos and Lohmander, 2003), KNEES (Comins et al., 2013), IKDC (Irrgang et al., 2001), Tegner (Tegner and Lysholm, 1985), and Lysholm scale (Lysholm and Gillquist, 1982). Once finished, participants changed into tight-fitting lycra shorts and t-shirt, which was followed by anthropometric measurements and marker placement according to a whole-body cluster marker set presented in Mantovani & Lamontagne (2016).

Kinematics were sampled at 100 Hz using a 10-camera motion capture system (6 MX and 4 T series, Vicon, UK) while ground reaction forces were sampled at 1000 Hz using one force plate (OR 6-5-1, AMTI, USA). Participants completed a target match protocol (Flaxman et al., 2012), and three successful trials each of one- and two-legged squats, lunges, countermovement jumps, hops, and side cuts. This study focused on the hop and side cut tasks as these are commonly seen as ACL injury inducing movements (Boden et al., 2000) and would test the participants' functional ability. A hop was considered successful when the participant took off from their non-test leg, jumped forward onto their test limb and landing with their foot fully within the force plate perimeter, while being completely capable of arresting their momentum and maintaining balance. Distance and speed were self-selected but verbal encouragement was provided for the participants to jump as quickly as they were comfortable with and that the motion was not a relaxed hopping or stepping motion. A side cut was deemed successful when the participant took 3-5 approach steps, cut onto the force plate with their test limb at approximately 45° angle, their whole foot was contained within the force plate perimeter, and they left the force plate at approximately 45° angle. Again, speed was not regulated but participants were encouraged to complete the movement at the fastest speed they were comfortable with.

Data Analysis

Kinematic and ground reaction force data were processed using a MatLab (2013a, Mathworks, USA) – OpenSim (3.3, Simtk, USA) application program interface. Marker trajectories and ground reaction forces were filtered using matching 4th order zero-lag low pass

Butterworth filters with cut-offs set to 15 Hz. A generic whole-body OpenSim model (Rajagopal et al., 2016) was altered to include three independent knee degrees of freedom instead of the sagittal plane only degree of freedom knee. This model was scaled to the static trial of each participant, followed by inverse kinematics and inverse dynamics analyses to compute hip, knee, and ankle joint angles and internal joint moments.

Peak sagittal knee flexion angles and knee extensor moments were calculated for the hop and side cut tasks. Additionally, sagittal knee joint dynamic stiffness as defined by Davis & DeLuca (1996) as the change in knee flex/extensor moment over the change in knee flexion angle calculated from the point of initial foot contact to the maximum extensor moment. The absolute value of dynamic stiffness was taken, in such a greater magnitude indicated a greater stiffness. Knee joint centre was defined as the mid-point between the medial and lateral femoral epicondyle surface markers and the Euclidean distance, knee joint centre excursion (KJCE), was calculated for each movement. For the hop, KJCE was calculated for the first 100 ms following initial contact while in the side cut, KJCE was calculated for the entire stance phase. These time periods were chosen as ACL injuries are most common during the loading phases that occur shortly after foot contact with the ground (Koga et al., 2010). Finally, the three within-participant trials for each task were time and position normalized so that the Euclidean distance between the KJC markers could be used as a measure of movement consistency. This distance was taken for each frame and summed for the same time periods as described for the KJCE and is named the KJC boundary (KJCB).

Since reduced ACL strain is observed at greater knee flexion angles (Markolf et al., 1998), higher flexion angles and smaller knee extensor moments are considered to be better outcomes. Greater stiffness and lower KJCE and KJCB are also considered better objective outcomes of knee joint function. Furthermore, higher Tegner, Lysholm, IKDC, and KOOS scores indicate better subjective function while decreased KNEES scores indicate better subjective function.

Statistical Analysis

All statistical tests were performed in SPSS (22.0, IBM, USA). The first aim was addressed by performing correlations between each PROM score and the five objective movement variables as outlined above for each ACL state. Due to the PROMs being ordinal data, Spearman's rank correlations were used. For the second purpose of this study, Spearman's rank correlations were again used to assess the relationship between each PROM score in the ACLd condition to its respective score in the ACLr state. Pearson correlations were used to assess this same relationship between the objective measures as these are interval in nature. A weak correlation was defined as $r < 0.25$, fair $0.25 < r < 0.5$, moderate to strong $0.5 < r < 0.75$, and very strong $r > 0.75$ (Portney and Watkins, 2000). Finally, to address our third purpose, an

ordinal regression was used to determine the predictive ability of each ACLd PROM score to its respective ACLr score and Nagelkerke R^2 were used to determine model fit. Linear regressions were used in determining the predictive ability of each ACLd objective measure to its respective ACLr score and adjusted R^2 and standardized coefficients (β) were used to determine model fit. All tests were deemed significant if the p value < 0.05 and trending towards significance when p < 0.1.

Results

Objective – Subjective Correlations

With respect to peak knee flexion angle during the hop, the only significant correlation in either the ACLd or ACLr state was to ACLr's Tegner score ($r = 0.51$, $p = 0.031$; Table 4.3.1 & Figure A.3). There were no significant correlations between peak knee extensor moment and any PROMs while stiffness had moderate correlations to KOOS-ADL ($r = -0.52$, $p = 0.028$), KNEES-Slackness ($r = 0.60$, $p = 0.006$), and KNEES-Sport Behaviour ($r = 0.68$, $p = 0.002$) all in the ACLr state. The KJCE was only correlated to IKDC ($r = 0.5$, $p = 0.029$) in the ACLd state while no moderate to strong correlations were observed between the KJCB and PROMs during the hop in either state.

Table 4.3.1. Spearman correlation coefficients (r) for the hop task. KJCE: knee joint center excursion; KJCB: knee joint center boundary. * indicates p value < 0.1 while ** indicates p value < 0.05.

	Peak Flexion Angle		Peak Extensor Moment		Stiffness		KJCE		KJCB	
	ACLd	ACLR	ACLd	ACLR	ACLd	ACLR	ACLd	ACLR	ACLd	ACLR
Tegner	.22	.51**	.25	.31	.16	-.09	.46*	.46*	.01	-.12
Lysholm	-.14	.14	-.29	.20	-.09	-.24	.18	.06	-.05	-.30
IKDC	.08	.24	-.02	.03	.03	-.07	.51**	.10	-.27	-.19
KOOS-Symptoms	-.23	.06	-.35	.11	-.26	-.27	.35	-.05	-.40	-.06
KOOS-Pain	.02	.05	-.07	-.01	-.19	-.48**	.42*	-.27	-.19	.14
KOOS-ADL	.11	.05	-.01	.18	-.19	-.52**	.31	.06	-.18	.02
KOOS-Sport	.21	.30	.13	.06	.23	-.31	.43*	.14	-.22	-.23
KOOS-QOL	.20	.10	.44	-.08	.34	-.43*	.20	.02	.15	.00
KNEES-ADL	.24	-.06	.35	.11	.18	.45*	-.26	-.08	.35	.07
KNEES-Psychosocial	.07	-.04	.01	.24	-.17	.42*	-.05	-.00	.25	-.21
KNEES-Symptoms	.09	-.11	.07	.16	.06	.42*	-.30	.04	.33	.08
KNEES-Slackness	.18	-.19	.03	-.01	-.16	.60**	-.12	-.07	.37	-.41*
KNEES-Looseness	.40	-.03	.32	-.04	.20	.34	-.01	.10	.144	.01
KNEES- Sport Behaviour	-.15	-.05	.30	.19	.26	.68**	-.42**	-.13	.11	-.16
KNEES- Sport Physical	-.17	-.36	-.35	-.13	-.48**	.31	.04	.00	.32	.19

In the side cut, peak knee flexion angle was moderately correlated to both the KOOS-Symptoms ($r = -0.6$, $p = 0.01$) and KNEES – Psychosocial ($r = 0.51$, $p = 0.037$) in the ACLd state (Table 4.3.2). With respect to peak knee extensor moment, the only moderate correlation was observed in KNEES – Sport Behaviour ($r = -0.52$, $p = 0.032$) in the ACLd state. Stiffness was only moderately correlated with Tegner ($r = 0.68$, $p = 0.02$) in the ACLr state while KJCE was moderately correlated with KOOS – Quality of Life ($r = -0.58$, $p = 0.015$) and KNEES – Psychosocial ($r = 0.65$, $p = 0.004$) in the ACLr state. No moderate or strong correlations were observed between KJCB and any of the PROMs.

Table 4.3.2. Spearman correlation coefficients (r) for the side cut task. KJCE: knee joint center excursion; KJCB: knee joint center boundary. * indicates p value < 0.1 while ** indicates p value ≤ 0.05.

	Peak Flexion Angle		Peak Extensor Moment		Stiffness		KJCE		KJCB	
	ACLd	ACLr	ACLd	ACLr	ACLd	ACLr	ACLd	ACLr	ACLd	ACLr
Tegner	.01	-.22	.13	.32	.40	.69**	-.18	-.29	.09	.14
Lysholm	-.11	-.34	.06	-.07	.48*	.18	-.36	-.19	.39	.28
IKDC	-.10	-.21	-.02	.09	.10	.32	-.23	-.24	.11	.18
KOOS-Symptoms	-.60**	-.40	-.16	-.18	.23	-.05	-.37	-.36	.39	.01
KOOS-Pain	-.45*	-.25	.09	-.05	.07	-.01	-.35	-.05	.49**	.14
KOOS-ADL	.01	-.26	.26	-.02	.27	.06	-.07	-.15	.10	.03
KOOS-Sport	.01	-.11	.3	.29	.24	.38	-.17	.03	.31	.07
KOOS-QOL	.33	-.40	.33	.26	.19	.13	-.10	-.58**	.24	.03
KNEES-ADL	.37	.23	-.03	-.09	-.01	-.14	.38	-.02	-.28	-.14
KNEES-Psychosocial	.51**	.40	.08	.25	-.14	-.26	.46*	.65**	-.30	-.41
KNEES-Symptoms	.48**	.29	.15	-.04	-.37	.04	.25	.03	-.24	-.10
KNEES-Slackness	.03	.42*	-.36	.05	-.32	-.10	-.17	.48*	.17	.01
KNEES-Looseness	.24	.37	-.30	.31	-.46*	-.11	-.03	.38	-.12	-.30
KNEES- Sport Behaviour	-.04	.28	-.52**	.07	-.17	-.20	-.35	.37	.33	-.08
KNEES- Sport Physical	-.04	-.01	-.40	-.23	-.26	-.23	.17	-.02	.35	-.21

ACLd – ACLr Correlations

In the hop, only four variables demonstrated a strong relationship between the ACLd and ACLr state (Table 4.3.3 & Figure A.4). This includes the peak knee flexion angle ($r = 0.66$, $p = 0.003$), peak knee extensor moment ($r = 0.62$, $p = 0.006$), KJCE ($r = 0.63$, $p = 0.005$), and KOOS – ADL ($r = 0.70$, $p = 0.001$). In the side cut, KJCB ($r = 0.47$, $p = 0.058$), Tegner ($r = 0.44$, $p = 0.092$), and KOOS – Symptoms ($r = 0.42$, $p = 0.097$) demonstrated fair correlations that trended towards significance, while peak knee flexion angle ($r = 0.83$, $p < 0.0005$), KJCE ($r = 0.82$, $p < 0.0005$), and KOOS – ADL ($r = 0.77$, $p < 0.0005$) were all very strong and significant correlations.

Table 4.3.3. Pearson correlation coefficients (r) for the objective functional ability measures and Spearman correlation coefficients for the subjective functional ability measures. Results display the relationship between the ACLd and ACLr state for the jump lunge and side cut tasks.

* indicates p value < 0.1 while ** indicates p value ≤ 0.05.

Measure	Hop	Side Cut
Peak Flexion Angle	.66**	.83**
Peak Extensor Moment	.62**	.37
Stiffness	.20	.40
KJCE	.63**	.82**
KJCB	-.20	.47*
Tegner	.21	.44*
Lysholm	-.32	.10
IKDC	-.19	-.17
KOOS – Symptoms	.37	.42*
KOOS – Pain	.27	.37
KOOS – ADL	.70**	.77**
KOOS – Sport	.25	.38
KOOS – QOL	.14	.24
KNEES - ADL	.23	.38
KNEES – Psychosocial	.19	.20
KNEES – Symptoms	-.04	.10
KNEES – Slackness	.35	.33
KNEES – Looseness	-.06	.21
KNEES – Sport Behaviour	.09	-.04
KNEES – Sport Physical	.22	.18

ACLd – ACLr Linear Regressions (Objective Measures)

In the hop, three of the five objective functional ability measures had ACLd values that were significantly capable of predicting its corresponding ACLr value (Table 4.3.4). This includes the peak knee flexion angle (adj. $R^2 = 0.40$, $\beta = 0.66$, $p = 0.003$), peak knee extensor moment (adj. $R^2 = 0.34$, $\beta = 0.62$, $p = 0.006$), and KJCE (adj. $R^2 = 0.36$, $\beta = 0.63$, $p = 0.005$). In the side cut, peak knee flexion angle (adj. $R^2 = 0.66$, $\beta = 0.83$, $p < 0.0005$) and KJCE (adj. $R^2 = 0.64$, $\beta = 0.82$, $p < 0.0005$) were also significant while KJCB (adj. $R^2 = 0.17$, $\beta = 0.47$, $p = 0.058$) was trending towards significance.

Table 4.3.4. Adjusted R^2 values for the objective functional ability measures with ACLd score as predictor variable and ACLr score as dependent variable in independent linear regressions. * indicates p value < 0.1 while ** indicates p value ≤ 0.05 .

	Hop			Side Cut		
	R^2	Intercept	Beta	R^2	Intercept	Beta
Peak Flexion Angle	0.40**	16.55	0.66	0.66**	12.92	0.83
Peak Extensor Moment	0.34**	0.42	0.62	0.08	0.81	0.37
Stiffness	-0.02	0.05	0.20	0.10	0.03	0.40
KJCE	0.36**	0.09	0.63	0.64**	0.03	0.82
KJCB	-0.02	6.51	-0.20	0.17*	5.46	0.47

ACLd – ACLr Ordinal Regressions (Subjective Measures)

In the hop, only KOOS – ADL had a significant odds ratio (OR; Nag. $R^2 = 0.46$, OR = 1.37, Wald $X^2 = 8.56$, $p = 0.003$) while the odds ratio associated with Tegner scores was approaching significance (Nag. $R^2 = 0.16$, OR = 1.46, Wald $X^2 = 2.81$, $p = 0.094$; Table 4.4.5). In the side cut, Tegner (Nag. $R^2 = 0.35$, OR = 1.86, Wald $X^2 = 5.84$, $p = 0.016$), KOOS – Pain (Nag. $R^2 = 0.33$, OR = 1.10, Wald $X^2 = 5.42$, $p = 0.02$), KOOS – ADL (Nag. $R^2 = 0.66$, OR = 1.38, Wald $X^2 = 8.27$, $p = 0.004$), KOOS – Sport (Nag. $R^2 = 0.21$, OR = 1.04, Wald $X^2 = 4.17$, $p = 0.041$) all had significant and positive odds ratios. Additionally, KOOS – Symptoms (Nag. $R^2 = 0.18$, OR = 1.07, Wald $X^2 = 2.79$, $p = 0.095$), KOOS – QOL (Nag. $R^2 = 0.15$, OR = 1.13, Wald $X^2 = 3.34$, $p = 0.068$), and KNEES – ADL (Nag. $R^2 = 0.15$, OR = 1.05, Wald $X^2 = 3.11$, $p = 0.078$) were all approaching significance.

Table 4.3.5. Odds ratios and Wald X^2 values for the subjective functional ability measures with ACLd score as predictor variable and ACLr score as dependent variable in independent ordinal regressions. * indicates p value < 0.1 while ** indicates p value ≤ 0.05 .

Measure	Hop		Side Cut	
	Odds Ratio	Wald X^2	Odds Ratio	Wald X^2
Tegner	1.46*	2.81	1.86**	5.84
Lysholm	.94	1.34	1.05	1.45
IKDC	.97	.59	1.01	.15
KOOS – Symptoms	1.05	1.57	1.07*	2.79
KOOS – Pain	1.07	1.33	1.10**	5.42
KOOS – ADL	1.37**	8.56	1.38**	8.27
KOOS – Sport	1.02	.70	1.04**	4.17
KOOS – QOL	1.04	.37	1.13*	3.34
KNEES - ADL	1.02	.79	1.05*	3.11
KNEES – Psychosocial	1.02	.69	1.03	2.34
KNEES – Symptoms	.99	.18	1.04	2.65
KNEES – Slackness	1.04	2.18	1.04	1.76
KNEES – Looseness	.99	.36	1.02	.49
KNEES – Sport Behaviour	1.01	.05	.99	.11
KNEES – Sport Physical	1.01	.58	1.01	.57

Discussion

The purposes of this study were 1) determine if objective and subjective assessments of functional ability were related to each other, 2) determine if ACLd scores in objective or subjective functional ability measures were correlated to their corresponding ACLr value, and 3) determine if these ACLd scores could predict their corresponding ACLr value. Many moderate to strong correlations between objective and subjective measures were found but they appear to be task-dependent with no single match superior to others. With respect to the ACLd – ACLr correlations, the strongest relationships were found in the side cut and objective measures. Finally, with respect to the ACLd scores ability to predict ACLr scores, the side cut was once again more effective as demonstrated by the higher adjusted R^2 and odds ratio values.

When interpreting the correlations between subjective scores and objective measures, the structure of the questionnaire needs to be considered. For example, a lower KNEES score demonstrates greater functional ability in a patient whereas in the other questionnaires, a higher score signifies greater function. This is represented in the correlations as the relationships involving the KNEES, often have the opposite sign as the other scores, which is exemplified in ACLr hop stiffness. Another consideration is how the questionnaires are designed. The Tegner is a single question activity scale and does not assess subjective knee function, while the others involve the combination of multiple questions to establish a rating of

subjective ability. Additionally, even though the Lysholm and IKDC consist of multiple questions spanning over a wide range of topics, they are summed into a final score unlike the KOOS and KNEES. This subscale approach may be more appropriate as few or no correlations between Lysholm/IKDC and our objective measures were detected while many significant correlations to the individual KOOS and KNEES subscales were observed. This may possibly demonstrate a “washing out” effect when the questionnaire sums various aspects of self-reported function together.

In those who were willing to complete the hop, the highest correlations occurred in the ACLr state and were between peak flexion angle and Tegner ($r = 0.51$) and stiffness to KOOS-Pain ($r = -0.48$; as stiffness increases, more pain exhibited), KOOS-ADL ($r = -0.52$; as stiffness increases, poorer KOOS-ADL performance), KNEES-Slackness ($r = 0.60$; as stiffness increases, self-reported slacker knee) and KNEES-Sport Behaviour ($r = -0.68$; as stiffness increases, better sport behaviour). Therefore, out of the five objective measures tested, stiffness during a rapid deceleration appears to be the most related to self-perceived function. The meaning of this relationship remains rather ambiguous but the current results suggest that a stiffer knee is detrimental as it is associated with more pain, poorer ability to complete activities of daily living, and a self-reported slacker knee. Although no causal relationships can be defined, it is possible that the patients who perceive more slackness in their knee implement an objectively noticeable stiffening strategy. Previously, self-reported function has only be poorly correlated with clinical laxity (Barrett, 1991; Snyder-Mackler et al., 1997) or one-legged hop performance (Sernert et al., 1999). Stiffness also displayed higher correlations to self-perceived function than Lysholm to one-legged hop performance (Sernert et al., 1999) and also a generic subjective evaluation to timed hop performance (Wilk et al., 1994) where the correlation coefficients ranged between 0.31 – 0.48. It is of interest to note that increased stiffness was associated with decreased subjective functional ability (decreased KOOS scores and increased KNEES scores). Since the current methods can only describe relationships, it is unclear whether the greater stiffness is causing the subjective apprehension or if the decreased perceived ability is causing a stiffening response during the hop perhaps in a prophylactic precaution.

The side cut movement resulted in considerably different findings than the hop as the strongest correlations were more evenly dispersed between the objective measures and ACL status. Here the strongest correlations were observed between ACLd peak flexion angle and KOOS-Symptoms ($r = -0.60$) and KNEES-Psychosocial ($r = 0.51$), ACLr stiffness and Tegner ($r = 0.69$), and ACLr KJCE and KOOS-QOL ($r = -0.58$) and KNEES-Psychosocial ($r = 0.65$). With respect to the knee flexion angle relationships, a higher peak flexion angle during the side cut was associated with poorer self-perceived functional ability as indicated by smaller KOOS-Symptoms and greater KNEES-Psychosocial scores. Past work has identified smaller peak flexion angles in ACLd populations (Chmielewski et al., 2001; Rudolph et al., 1998; Chapter 4.1) and since this

decrease is associated with better KOOS-Symptoms and KNEES-Psychosocial function, they may perhaps be trying to increase the direct axial loading onto the knee joint that has been shown to enhance stiffness and therefore stability (Markolf et al., 1981). After reconstruction, a greater amount of KJCE during the side cut was considerably related to patients reporting a decreased quality of life and more psychosocial stress. Past work involving KJCE found that the poorly functioning ACLd (non-copers) demonstrated a greater KJCE during a stepping task than those who were capable of coping with their ACL injury (Rudolph and Snyder-Mackler, 2004). Thus, it seems as though excess movement of a patient's knee joint centre is related to a decrease in both their objective and subjective functional ability.

The low amount of strong correlations in the subjective functional measures between the ACLd and ACLr state was not expected. In this analysis, the significant correlations in both tasks were found to range between $r = 0.62 - 0.83$, with peak knee flexion angle and KJCE being the most robust correlations between the two tasks. This suggests that objective measures of function that the patients are not self-reporting appear to be more consistent between the two ACL states. With respect to the subjective measures, only the KOOS-ADL was significant in both tasks, which needs to be interpreted with caution as a ceiling effect is likely to have occurred. Ceiling effects are commonly defined as when $>15\%$ of respondents achieve the maximum possible score (Lim et al., 2015; McHorney and Tarlov, 1995). Following these criteria, the KOOS-ADL and all KNEES sub scales except sport behavior exhibited a ceiling effect in the ACLr state.

With respect to the ACLd predictive ability of ACLr scores, the objective functionality scores again seem to outperform the subjective functional measures although direct comparisons between the objective and subjective measures are difficult though because of the differences between linear and ordinal regressions. Similar to the correlations, peak knee flexion angle and KJCE showed the highest adjusted R^2 ($0.36 - 0.66$) and were robust between both tasks. The best and most robust predictors of the subjective measures were the Tegner (OR: $1.46 - 1.86$) and KOOS – ADL (OR: $1.05 - 1.37$), which is interesting considering that the Tegner scale differs from the other subjective measures as it is a measure of physical activity level rather than the direct functionality of the knee (Tegner and Lysholm, 1985). The predictive power of KOOS-ADL also must be taken into consideration again due to the ceiling effect previously mentioned. The IKDC had very little predictive power indicating that these results were varied pre- and post-reconstruction within the participants. This is not surprising as the IKDC has been previously shown to have an insignificant relationship to clinical measures (Snyder-Mackler et al., 1997).

There are some limitations that need to be discussed when considering the results of the current study. The first is that not all questionnaires included in the current study are

specifically designed for measuring subjective functional ability in ACLd and ACLr patients. In particular, the KOOS was validated in an osteoarthritic population (Roos and Lohmander, 2003), while the IKDC was developed for a range of knee injuries including ACL injury (Irrgang et al., 2001). Despite not being specifically designed for ACL injuries like the KNEES (Comins et al., 2013), these questionnaires have been validated in ACL populations (Irrgang et al., 2001; Salavati et al., 2011) and are both commonly used in ACL-related studies (Theisen et al., 2016), it was thus important to include them in the current analyses. Furthermore, the KNEES is currently only valid in Danish and therefore its international scope is rather limited. A second limitation is that the participants included in the current study were high functioning as demonstrated by their ability to complete the rather difficult hop and side cut tasks in both the deficient and reconstructed state. It is in our group's interest to examine a variety of tasks that include arguably easier movements such as squatting and lunging. These more ballistic tasks were chosen for the current study to avoid the possibility of shielding of the injured limb that might occur in a bipedal task. Additionally, it was believed that the more difficult tasks would elicit greater differences between the injured states and would thus improve the correlational and predictive ability of the objective measures.

To our knowledge, this study was the first to determine how objective functional measures taken from dynamic and weight-bearing tasks are related to an ACL patient's self-perceived functional ability obtained through a battery of questionnaires. Using these dynamic functional measures led to stronger correlations than what have been observed for non-weight bearing clinical laxity and other functional performance measures. Furthermore, we also established the relationships between these objective measures in the ACLd state and their corresponding score in the ACLr state. Finally, by quantifying the predictive power that ACLd results have with respect to their respective post-reconstruction outcome we demonstrated that, given the task, some scores in the ACLd state are in fact effective at predicting the performance of the same patients once they have received their elected operations. These findings encourage an open dialogue between the clinician and patient regarding their expectations of subjective and objective functional ability post-reconstruction.

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Conflict of Interest

The authors have no conflicts of interest to declare.

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4.4 Study 4: MRI-based OpenSim modelling

An MRI-based patient-specific articular contact model for OpenSim leads to soft tissue artifact reduction and improved knee ligament length estimates

Running Title: MRI-based OpenSim contact model

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Abstract

The validity of generic OpenSim models can be enhanced by incorporating magnetic resonance imaging (MRI) to satisfy participant-specific parameters. The purpose of this study was to determine if the inclusion of an MRI-based knee contact model would elicit differences in lower limb kinematics and resulting knee ligament lengths during a side cut task. MRIs were obtained from 11 participants and the popular Rajagopal model was altered to include three and six knee degrees of freedom (DOF), and MRI-based contact knee models with six unprescribed kinematic components. These models were used in an inverse kinematics analysis of a side cut task and the resulting lower limb kinematics and knee ligament lengths were analyzed. The MRI-based contact model was more responsive to the movement task than the original Rajagopal model while less susceptible to soft tissue artefact than the unconstrained six DOF model. Ligament isometry was greatest in the original Rajagopal model and smallest in the six DOF model. When using musculoskeletal modelling software, one must acutely consider the model choice as the resulting kinematics and ligament lengths are dependent on this decision. The MRI-based knee contact model appears to be responsive to the kinematics and ligament lengths of highly dynamic tasks and may prove to be the most valid option for continuing with late-stage modelling operations such as static optimization.

Introduction

Advancements in computing technology have brought *in silico* simulations to the leading edge of human movement analysis. When investigating the complex interactions of the neuromuscular and skeletal systems, many research questions have gone unanswered due to the invasive nature of these experiments as muscle and joint contact forces are not easily measured in the human body. Furthermore, if these interactions are capable of being measured, it is still difficult to discern cause-and-effect relationships due to the intricate nature of the neuromuscular and skeletal systems. Simulation software such as OpenSim (Delp et al., 2007) has addressed these issues as it provides a modeling environment where individual variables can be manipulated and the outcomes of these interventions examined to identify cause-and-effect relationships. These *in silico* models have been effective in identifying the ligament and contact roles during knee motion (Nardini et al., 2016; Sancisi and Parenti-Castelli, 2011). *In silico* models have also been used to determine force contributions (Delp et al., 1990; Hamner et al., 2010) and knee joint contact loads (Fregly et al., 2011) during walking and running.

Although these human movement simulations have advanced our knowledge of the neuromuscular and skeletal systems, they still exhibit limitations that affect their validity. For example, *in silico* models are primarily based on *in vitro* cadavre studies (Delp et al., 1990; Hamner et al., 2010; Rajagopal et al., 2016) leading to a somewhat generic application of muscle parameters, bone geometry, and joint articulations. The Rajagopal model (Rajagopal et al., 2016) addresses the biofidelity of their knee joint by enhancing the OpenSim one degree of freedom (DOF) hinge joint to one that prescribes motion based on cadaveric work (Walker et al., 1988). In this model, knee flexion/extension is unprescribed, while the remaining five DOF are a function of this sagittal plane angle. Although this is more anatomically accurate than a simple hinge joint, it still lacks consideration of participant-specific bone geometries and their respective articulation, as well as effect of loading condition on tibiofemoral kinematics during dynamic tasks (Benoit et al., 2007).

Since muscle force and joint contact load estimations are higher level analyses in the OpenSim program flow, errors and inaccuracies in earlier analyses are propagated and perhaps multiplied when using these late-stage tools. Comparisons of generic and participant-specific models have demonstrated this with knee joint contact forces being more accurately modeled using participant-specific parameters (Gerus et al., 2013; Lerner et al., 2015). One type of participant-specific model incorporates magnetic resonance imaging (MRI) data to customize and improve bone geometry, muscle wrapping, and ligament lengths (Conconi et al., 2018). Although MRIs can be included in OpenSim (Schmid et al., 2009; Valente et al., 2017), it remains

unclear how an MRI-based knee contact model would affect lower limb kinematics and ligament lengths during dynamic tasks.

To address this knowledge gap, the purpose of this study was to determine if the inclusion of an MRI-based knee contact model would elicit differences in lower limb kinematics and resulting knee ligament lengths during a side cut task. A novel, MRI-based participant-specific knee model featuring knee ligament origins and insertions, as well as joint contact surfaces replicating the participant tibiofemoral articulation was developed and compared to the standard Rajagopal model and two other Rajagopal models adapted to contain three and six unprescribed knee DOF. It was hypothesized that the original Rajagopal model would result in the smallest range of motion while the unconstrained six DOF model would have the largest range of motion for both kinematics and ligament lengths. It was further anticipated that the MRI-based contact model would reduce the range of motion observed in six DOF model but range of motion would still be larger during the side cut task than the original Rajagopal model.

Methods

In vivo data

This *in silico* work was based on 11 anterior cruciate ligament (ACL) deficient patients (4 female, 7 male; 28.3 ± 5.4 years; 175.1 ± 8.5 cm; 77.2 ± 14.3 kg). Inclusion criteria included primary ACL injury and no history of contralateral ACL ruptures. Rupture of the ACL was confirmed clinically by the physician (positive Lachman and Rolimeter tests) and via MRI or arthroscopy. All data collections occurred at the University of Copenhagen and this study was approved by the Capital Region of Denmark and University of Ottawa ethics committees.

Participants were outfitted with a whole-body cluster marker set (Mantovani and Lamontagne, 2016) with kinematic data being collected at 100 Hz by a 10-camera motion capture system (6 MX and 4 T series, Vicon, UK). Ground reaction forces were sampled at 1000 Hz using one force plate (OR 6-5-1, AMTI, USA). To successfully complete the side cut task, participants performed the movement as fast as they could, cutting onto and off of the force plate at a $45 \pm 10^\circ$ angles marked by taping on the floor. The entire foot strike had to occur within the boundaries of the force plate and the cuts were performed with the injured leg. Three to four successful side cuts were recorded for each participant.

All data were processed with MatLab (2015b, Mathworks, USA) and OpenSim (3.3, Simtk, USA). Marker trajectories and ground reaction forces were filtered with a 4th order zero-lag low pass Butterworth filter with matching cut-off frequencies of 15 Hz (Bisseling and Hof, 2006). The side cut movement was time normalized to 100% stance phase with the addition of 10% stance time prior to initial contact. Thus, the movement spans from -10% stance to 100% stance.

OpenSim models

Four OpenSim models were compared in this study: (1) the original Rajagopal (RO) model (Rajagopal et al., 2016); (2) the RO with all three rotational knee DOFs released and three translational DOF locked to zero (R3); (3) 6-DOF system (R6) using the six DOF motion boundaries presented by Xu et al. (Xu, 2013); (4) a 6-DOF MRI-based model (RM). This RM model used the DOF of the R6 model but included two constraints representing condylar contact as two spheres on the femur and two on the tibia. The size and location of these spheres were determined specifically for each patient based on MRI data, as discussed in below. Generic versions of all four models were subjected to the same scaling procedure using identical measurement set and scale factors. Once scaled, anatomical points needed to build the International Society of Biomechanics (ISB) coordinate systems (medial and lateral epicondyles; hip, knee, and ankle joint centers; and medial and lateral malleoli) were represented in the global reference frame.

The motion of all models was expressed according to the ISB standard reference systems (Wu and Cavanagh, 1995).

MRI acquisition and analysis

MRIs were taken with TR/TE: 500/14ms, FOV 18, and a slice thickness of 3 mm (Sigma Horizon LX 1.5 Tesla, General Electric, USA). Images were centered on the knee joint with the view including approximately 8 cm of the distal femur and 8 cm of the proximal tibia. Combinations of frontal and sagittal views of T1 and T2-weighted scans including fat-saturated versions were used to segment the femur, tibia, and fibula (Workbench 2016.11, MITK, Germany). Femoral and tibial insertion sites for the anterior and posterior cruciate ligaments and medial and lateral collateral ligaments were designated as point clouds on their respective surfaces.

The three-dimensional segmented bones were then loaded into Rhinoceros (4.0, McNeel & Associates, USA) along with a generic femur and tibia. These generic bones were scaled and aligned with the MRI bones so that coordinates for the hip and ankle joint centers could be obtained. Once they were matched, the same anatomical points as above were identified and used to align the corresponding points from the scaled OpenSim model. These resulting coordinates expressed the points in the MRI reference frame.

Construction of MRI-patient-specific (RM) model

To define the patient-specific parameters of the RM model the natural motion of each participant was first computed similar to (Conconi et al., 2018, 2015) as the envelope of tibiofemoral configurations that minimize the peak contact pressure, i.e. that maximize joint

congruence (Conconi and Castelli, 2014). Exploiting the isometric behavior shown by the knee ligaments along the natural motion (Victor et al., 2009; Wilson et al., 1998), the origin and insertion of the ACL, PCL, MCL, and LCL of each participant were determined as those associated with the most isometric fiber of the respective ligament. These origins and insertions of the four knee ligaments were incorporated into all four models but were used solely to analyze the ligament elongation and not used as kinematic constraints. Even though all patients had a complete ACL rupture, these lengths were still included as an exploratory analysis due to the ligament's insertions still being discernible in the MRIs.

The articular surfaces obtained from MRIs were approximated with four spheres: two for the femoral and two for the tibial condyles. The radius and position of the centers of these initial spheres were then optimized (max variation allowed: ± 2 mm) in order to guarantee both the medial and lateral contact over the entire natural knee motion. The optimized spheres were introduced into the RM model and, assuming that both the condyles remain in contact during the considered task, converted into two constant length constraints between the femoral and tibial sphere centers in both the medial and lateral knee compartments.

Inverse and Point Kinematics

Inverse kinematics was performed on each trial with the four individual models. Care was taken to maintain the same marker weightings between the models so that tracking errors satisfied the guidelines as outlined by Hicks et al. (2015). Kinematics obtained with the RM model were subsequently transformed from the Walker knee (Walker et al., 1988) to the ISB convention to ensure valid comparisons of the models. A point kinematics analysis was then executed to procure the ligaments' tibial insertion coordinates with respect to the femoral coordinate system. These coordinates were then used to determine the ligament lengths over the entire side cutting trial.

Statistical Analyses

To test for significance between the four models, repeated measures ANOVAs were applied through statistical parametric mapping (Pataky, 2010) for each hip, knee, and ankle DOF. This technique allows for the entire waveform to be tested instead of having to test discrete points of the side cut movement. If the F statistic was found to be significant, a post-hoc analysis of paired sample t-tests with a multiple comparisons correction were used to determine between which models the significant differences occurred. All tests were deemed significant if $p < 0.05$. To determine the clinical relevance of these differences, Cohen's d effect sizes were calculated during the peak difference between the two models. A $d = 0.2$ is considered small, 0.5 considered medium, and $d = 0.8$ considered large (Cohen, 2013).

Results

For the sake of brevity, only significant differences between RM and the other three models with medium or larger ($d > 0.5$) effect sizes are reported.

Kinematics

Although significant differences occurred in all three joints (effect size ranged from $d = 0.67$ to 3.00), the only DOF to have clinically relevant effect sizes between RM and the other three models were knee adduction/abduction, knee internal/external rotation, and the three knee translations (Figure 4.4.1). During the side cut, RM resulted in knee abduction angles for the majority of stance while the other three models resulted in knee adduction. RM differed from RO between 6 - 93% stance ($p < 0.0001$) with the peak difference of 4.52° occurring at 71% stance ($d = 2.01$). RM also differed from R3 between -10 - 93% stance ($p < 0.0001$) with the peak difference of 5.16° occurring at 38% stance ($d = 1.51$). Finally, RM differed from R6 between -10 - 84% stance ($p < 0.0001$) with the peak difference of 6.59° occurring at 39% stance ($d = 2.12$). Clinically relevant significant difference in knee internal/external rotation were noted between RM and RO. RO is significantly more internally rotated between -10 – 55% of stance ($p < 0.0001$) with a peak difference of 11.42° occurring at -10% stance ($d = 2.58$).

With respect to translations, the RM tibia was significantly more posterior than the RO tibia between -10 – 62% of stance ($p < 0.0001$) with a peak difference of 3.7 mm at 3% stance ($d = 1.12$). Differences between R6 and RM were even greater as RM was more posterior between -10 – 88% ($p < 0.0001$) and 98 – 100% ($p = 0.021$) stance with the peak difference of 10.8 mm occurring at 9% stance ($d = 3.00$). Knee medial/lateral translation was similar between R6 and RM but RM was significantly more lateral than RO between -10 – 100% stance ($p < 0.0001$) with the peak difference of 2.4 mm occurring at 36% stance ($d = 2.15$). Finally, RM was significantly different from both RO and R6 models in knee distraction/compression. RM followed the same pattern as RO but was significantly more distracted between 61 – 85% of stance ($p = 0.014$) with a peak difference of 3.6 mm occurring at 72% stance ($d = 0.67$). RM was significantly difference from -10 – 8% ($p = 0.018$), 48 – 71% ($p < 0.0001$), and 84 – 100% ($p = 0.023$) stance with a peak difference of 5.4 mm occurring at 60% stance ($d = 0.92$).

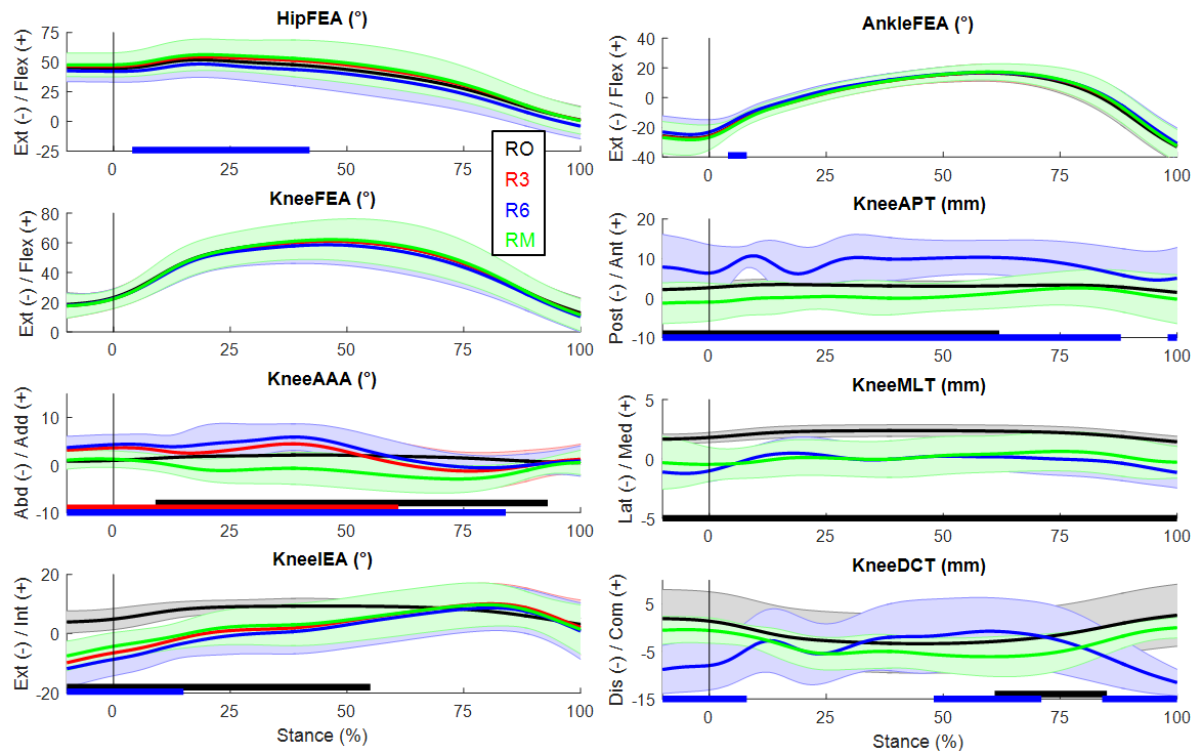


Figure 4.4.1. Kinematic means and standard deviation clouds of the side cut resulting from the four OpenSim models. Vertical bar represents initial contact while horizontal bars denote significance between RM and a respective model: RM vs RO (black), RM vs R3 (red), and RM vs R6 (blue).

Ligament Lengths

There were no clinically relevant significant differences between RM and the RO and R3 models for any ligaments (effect size ranges from $d = 0.70$ to 1.29). However, the ACL length significantly differed between RM and R6 from $-10 - 3\%$ ($p < 0.0001$), $30 - 72\%$ ($p = 0.008$), and $91 - 100\%$ ($p < 0.0001$) stance. The peak difference of 9.8 mm occurred at 100% stance ($d = 1.29$). For the PCL length, RM significantly differed from R6 between $13 - 75\%$ ($p < 0.0001$) and $99 - 100\%$ ($p = 0.028$) stance with a peak difference of 5.0 mm at 100% stance ($d = 0.70$). For the MCL length, RM significantly differed from R6 between $16 - 79\%$ ($p < 0.0001$) and $95 - 100\%$ ($p < 0.0001$) stance with a peak difference of 7.9 mm occurring at 100% stance ($d = 0.99$). Finally, LCL length differed between RM and R6 between $31 - 72\%$ ($p = 0.006$) and $97 - 100\%$ ($p = 0.011$) stance with a peak difference of 7.3 mm occurring at 100% stance ($d = 0.75$).

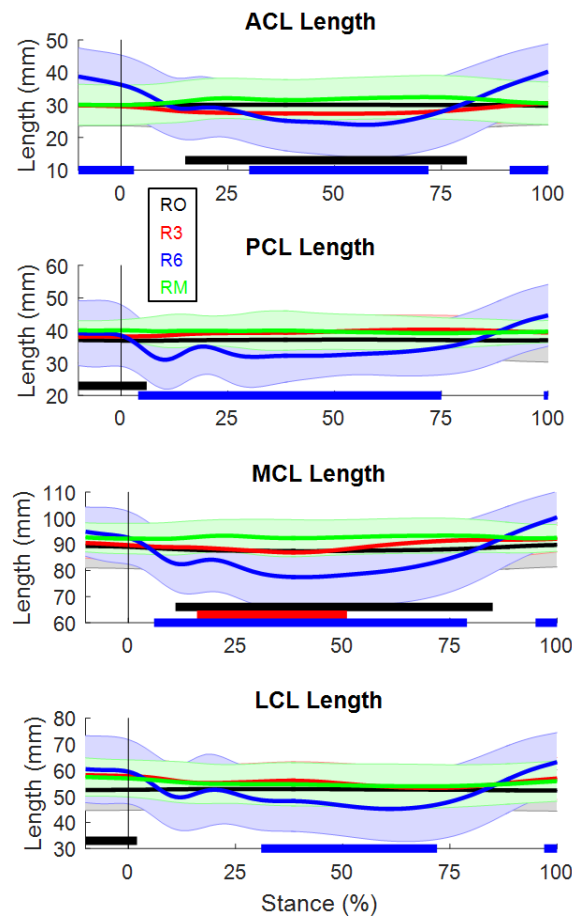


Figure 4.4.2. Ligament lengths means and standard deviation clouds resulting from the four models. Vertical bar represents initial contact while horizontal bars denote significance between RM and other models: RM vs RO (black), RM vs R3 (red), and RM vs R6 (blue).

Discussion

The purpose of this study was to determine the effects of implementing an MRI-based knee contact model on lower limb kinematics and knee ligament lengths during a side cut task. Even though many differences in kinematics were observed between RM and RO and R3, there were few clinically relevant differences in ligament lengths between them. There were however, significant and clinically relevant differences between RM and R6 in both lower limb kinematics and ligament lengths.

Kinematics

Flexion angles among all four models were similar for the sagittal plane in all three joints. The largest differences occurred in the knee ab/adduction and in/external rotations as well as the three translational components. Interestingly, RO, R3, and R6 all resulted in knee

adduction during the cutting task while RM resulted in knee abduction. In methods that use direct kinematics, participants have considerable peak abduction during the side cut task (Beaulieu et al., 2009; Pollard et al., 2004), which supports the use of the MRI-based contact RM model.

As expected with respect to knee translations, the R6 model was highly volatile and appeared to be influenced by soft tissue artefact, which is manifested as oscillations following initial contact (Smale et al., 2017; Figure 4.4.1). Although generic OpenSim models visually describe articulating bone geometry as solid shapes, inverse kinematics does not treat them as such and therefore may solve for joint positions with considerable overlap of bones (Figure 4.4.3). The introduction of a MRI-based contact model with a constant length constraint appears to not only reduce the oscillations in translational DOFs but also eliminate bone overlapping (Figure 4.4.3). This overlapping is especially apparent in R6 as the constant lengths derived from the MRI contact spheres show up to 15 mm of deviation from these lengths (Figure 4.4.4).

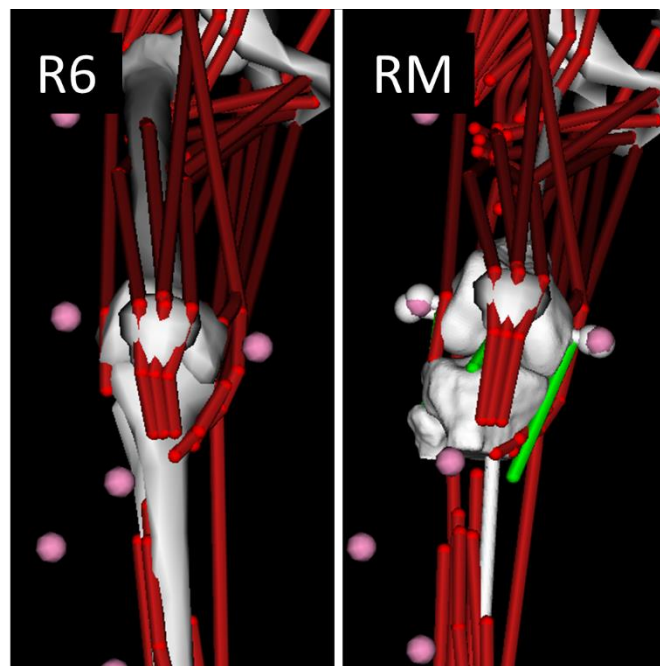


Figure 4.4.3. Demonstration of bone overlap in R6 model, which is eliminated in RM model.

During the side cut movement, there was very limited motion in the knee abd/adduction, ant/posterior and medial/lateral motion using the RO model, which is based on Walker et al (Walker et al., 1988). The Walker motion functions are not only based on cadaveric specimens but only a 7.5 kg simulated quadriceps force was applied to the specimens to produce the motions (Harding et al., 1977). Given the large ground reaction forces, expected whole-body rotations in the global lab space, and that loading alters knee joint kinematics

(Andriacchi and Dyrby, 2005; Benoit et al., 2007), it appears as though the functions derived through the cadaveric work of Walker et al (Walker et al., 1988) may be unsuitable for highly dynamic tasks such as the side cutting movement.

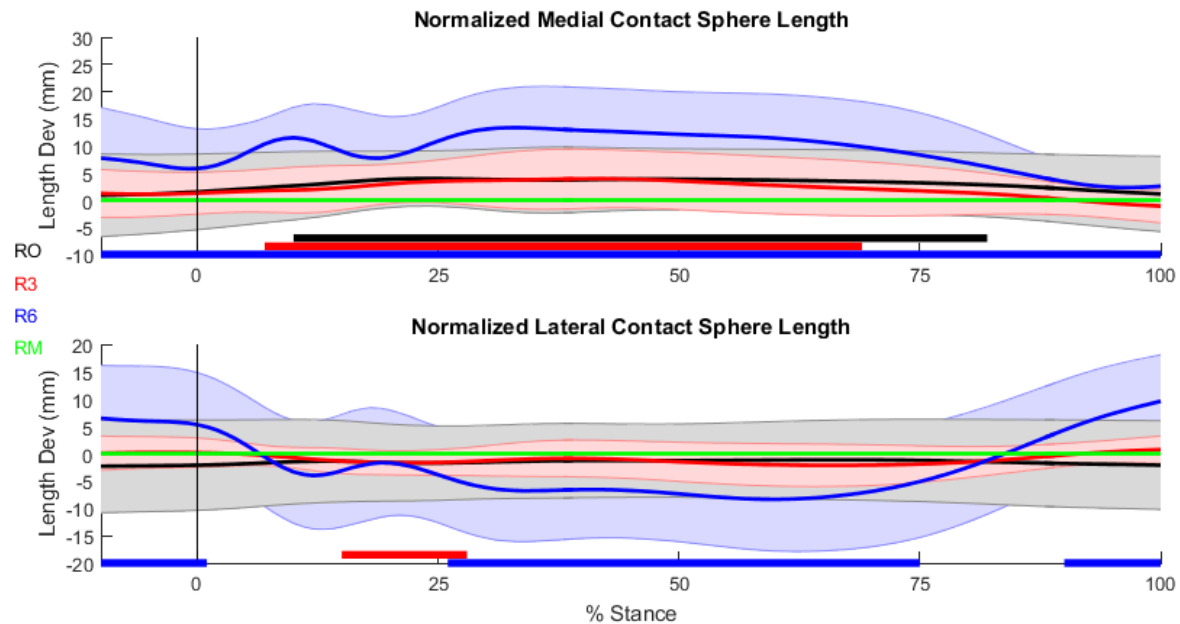


Figure 4.4.4. Deviations of the four models from the contact sphere length derived from the MRI congruence motion. Values are presented as means and standard deviations through the side cut stance phase and represent co-penetration if negative and distraction if positive. Vertical bar represents initial contact while horizontal bars denote significance between RM and other models: RM vs RO (black), RM vs R3 (red), and RM vs R6 (blue).

Ligament Lengths

As expected, the R6 kinematics with large ranges of motion produced highly volatile ligament lengths while the RO kinematics with small ranges of motion produced unresponsive ligament lengths (Figure 4.4.2). In vivo dynamic MRI studies indicate that ACL and PCL lengths range from 25 to 35 mm in length throughout knee flexion during a quasi-static lunge (Li et al., 2017), while the MCL and LCL ranged from 65 – 90 mm and 45 – 60 mm in length respectively (Park et al., 2006). Our estimated lengths for RM fall within the high end of those ranges for all four ligaments. During dynamic tasks, human knee ligaments typically have in vivo strain values ranging up to 5% original ligament length (Luque-Seron and Medina-Porqueres, 2016). The ligaments in the current model are kinematically driven, meaning their ligament force is determined by the amount of strain they exhibit. Thus, our results indicate that the unresponsive nature of the RO ligament lengths may underestimate ligament strain and ultimately true ligament force, while the R6 may result in overestimating ligament strain and

true force. The R3 or RM models would therefore seem the most biofidelic approach when using static optimization to derive ligament forces.

Limitations

Even though ligament insertions sites on the MRI are identified as point clouds, a single point within these clouds to produce the most isometric fibre of each ligament is used to determine the optimum insertion points and length. This naturally leads to a more conservative estimate in length changes but was a necessary assumption when trying to implement patient-specific parameters into an OpenSim model. A more advanced MRI analysis that considers multiple bundles for each ligament would likely yield a more detailed model but is beyond the scope of this study. A second limitation is that even though considerable differences were observed amongst the four different models, the actual in vivo motions remain unknown and thus which model is the most accurate in simulating the kinematics of the underlying bones and true ligament lengths. Based on current in vivo research (Potvin et al., 2017; Smale et al., 2017) and the reduction of STA using the RM model, we believe that it is the most biofidelic however when deciding which model to use in OpenSim we recommend evaluating the costs and benefits of biofidelity and analysis time, which are always based on the research question to be answered.

Conclusion

When using musculoskeletal modelling software, one must critically evaluate which model to choose since the resulting kinematics and ligament lengths are dependent on this decision. Including an MRI-based knee contact model allows for three unprescribed rotations and translations that are responsive to a highly ballistic task such as the side cut while having limited susceptibility to soft tissue artefact, unlike a completely unconstrained six DOF model. The MRI-based contact model also results in reasonable ligament length estimates that again are responsive to the task. These are important factors to consider especially if the user's end goal is muscle and ligament force quantification as errors in these early analyses are propagated on to late-stage analyses.

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4.5 Study 5: Joint Loading After ACL Injury

The relationship between patient-specific knee joint contact and ligament forces, and subjective function pre- and post-anterior cruciate ligament reconstruction

Running Title: Joint forces after ACL injury

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Abstract

Background: Knee injuries have both a psychological and physical impact on a patient. The psychological component can be assessed through a battery of questionnaires while the physical aspect can be determined through basic anatomical (passive laxity), generic functional (strength, hop test performance, etc.), and knee-specific objective measures (joint contact and ligament forces) of functional ability. Although these basic and generic measures have been related to subjective measures, associations between knee-specific objective and subjective measures have yet to be completed.

Hypotheses/Purpose: The first objective was to determine if knee joint contact and ligament forces differ between pre (ACLd) and post-ACL reconstructed (ACLr) states. The second objective was to determine the relationship between these contact and ligament forces to their patient's respective subjective functional ability scores. It was hypothesized that in the post-reconstructed state, patients would induce greater compressive and ligament forces during the hop landing and that these forces would be moderately to strongly correlated with the various subjective questionnaires.

Study Design: Case series

Methods: Twelve patients performed a hopping task pre and post-ACL reconstruction. Magnetic resonance images and OpenSim were used to develop patient-specific models, which were used for static optimization and joint reaction analyses. Questionnaires concerning each patient's subjective functional ability were also collected and correlated to knee joint contact and ligament forces (objective measures of functional ability).

Results: No significant differences were observed between ACLd and ACLr with respect to knee joint contact or ligament forces. There were several moderate to strong correlations between subjective and objective measures including Tegner activity level score to contact force in both states ($r = 0.67 - 0.76$) and IKDC to compressive and anterior shear forces ($r = 0.64 - 0.66$).

Conclusion: Knee specific objective measures of a patient's functional capacity can represent their subjective ability, which consolidates this relationship to a greater extent than past anatomical and gross objective measures of function. These findings can be used to develop a more holistic rehabilitation program that incorporates and finds agreement between the physical and psychological components of ACL injuries and recovery.

Clinical Relevance: The consolidation of subjective and objective functional ability assessments is imperative if the rehabilitation schema is going to improve. With poor validation of subjective function against objective measures of function, the re-injury rate is unlikely to diminish, continuing the heavy financial burden on our health care systems.

Key Terms: Knee, Musculoskeletal modelling, Rehabilitation

What is known about the subject: Subjective measures of functional ability are known to be uncorrelated to basic anatomical measures (passive knee joint laxity) and only weakly - moderately correlated to other generic objective measures of knee joint function (strength and timed hop tests). Associations between knee-specific objective and subjective measures of function have yet to be explored.

What this study adds to existing knowledge: To our knowledge, this is the first study to examine knee joint contact and ligament loads in the ACLd and ACLr state using a test-retest design. Furthermore, even though subjective measures have been associated with basic objective measures of joint function such as strength, this study is the first to relate these subjective scores to phenomena occurring directly within the knee joint during a dynamic task.

Introduction

With the rise of evidence-based and -informed practice, there is a growing need to include subjective and objective measures related to anterior cruciate ligament injuries in the clinical decision making process. This is all the more critical when one considers the re-injury rates of ACL reconstructed participants (Goddard et al., 2013; Leys et al., 2012), the rate of participants returning to pre-injury activity (Arderm et al., 2014) and the sequelae leading to reduced quality of life and knee joint osteoarthritis (Lohmander et al., 2007; Oiestad et al., 2011). One area that is being considered in light of the above is the influence of psychological factors influencing treatment success. A successful return-to-play following ACL injury is heavily influenced by the psychological state including levels of self-esteem and internal locus of control (Christino et al., 2016).

There are numerous patient reported outcome measures (PROMs) aimed at quantifying a patient's subjective functional ability and psychological state including the Tegner Activity Scale (Tegner and Lysholm, 1985), Lysholm (Lysholm and Gillquist, 1982), subjective International Knee Documentation Committee (IKDC; Irrgang et al., 2001), Knee Injury and Osteoarthritis Score (KOOS; Roos and Lohmander, 2003), and Knee Numeric-Entity Evaluation Score (KNEES; Comins et al., 2013). These questionnaires typically address the patient's self-perceived function by assessing symptoms, pain, limitations, confidence, and control related to their knee joint. They therefore represent the patient's psychological health with respect to their rehabilitation, self-efficacy, and coping strategies. Even though certain questions of them are specifically meant to reflect objective physical manifestations such as episodes of giving way or looseness, these objective measures were not directly involved in the development of these questionnaires. This therefore makes the relationship between psychological and physical states rather nebulous as it is unknown how these two aspects interact in an injured individual and contribute to their rehabilitation.

In terms of objective measures, these can be classified as anatomical (passive knee laxity tests) or functional (some quantification of movement quality). Anatomical measures are typically used in the diagnosis and as early benchmarks in rehabilitation programs (Eck et al., 2013). Objective measures of functional ability become the prominent benchmarks throughout the rest of the rehabilitation and return to play guidelines (Fitzgerald et al., 2000b; Wright et al., 2015). Perhaps the most basic anatomical objective measure is passive knee joint laxity determined through the Lachman and Pivot-shift tests or the KT-1000 (Makhni et al., 2015). There is a consensus that these objective measures are not significantly correlated to subjective measures of joint function (Barrett, 1991; Christino et al., 2016; Sernert et al., 1999; Snyder-Mackler et al., 1997) possibly due to the laxity being determined in an unweighted and muscle-relaxed state, which is not reflective of dynamic, demanding, and possibly harmful scenarios. A

step closer to functional capacity, knee strength, defined by peak knee flexor torque and power experimentally measured by a dynamometer, has shown moderate correlations ($r = 0.51 - 0.54$) to KOOS subscales (Bodkin et al., 2017). Although this is a stronger relationship than passive laxity, measures of isometric strength are not truly indicative of a demanding dynamic task. Dynamic tasks including various hop tests, which serve as surrogate measures of objective functional ability have been related to subjective PROMs. Correlations between these hop tests and PROMs range from weak to considerably strong (6 meter timed hop – IKDC: $r = 0.72$; Bodkin et al., 2017; Logerstedt et al., 2012) but still only define knee function as the external outcome of the whole-body function. Describing a functional objective measure by simply time is a coarse measure for determining how the knee joint is truly functioning as it can be influenced by a multitude of other factors including fitness and technique. Therefore, clinicians would benefit from objective measures of functional ability that are isolated solely to the knee joint, which removes these confounding variables.

Even though simplistic measures of objective stability (joint laxity), isometric function (strength) and global function (timed hop tests) have been related to subjective functional ability, there has yet to be a thorough investigation of knee-specific measures of function during dynamic movements and their relationship to subjective measures. Our group has previously examined the relationship between peak flexion angles and moments, dynamic knee joint stiffness (Davis and DeLuca, 1996) and measures of knee joint centre excursion and movement consistency to subjective PROMs. Here it was determined that not only did moderate to strong relationships exist between many objective and subjective measures, but the ACLd score had considerable predictive power of the respective ACLr outcome (Chapter 4.3). These results indicate a potential hierarchy in the relationship between subjective and objective measures of knee joint function as the deeper and more comprehensive definitions of objective knee joint function seem to have stronger relationships to subjective measures of function. Thus, higher-level biomechanical analyses such as neuromusculoskeletal modelling may provide greater insight and consolidate the relationship between subjective and objective measures of knee joint function in ACL injured individuals. If ACLr patients are more confident and functional as indicated by their subjective scores, it is possible that they would place greater demands on their knee post-operatively compared to pre-operatively. These greater demands would take the form of greater joint contact loads and knee ligament forces.

Many research questions regarding the intrinsic nature of the neuromusculoskeletal system have yet to be answered due to the invasive methodologies that these investigations would require. With improvements in computing technology and the advent of simulation software such as OpenSim (Delp et al., 2007), researchers are now able to explore many research questions previously left unanswered by modeling the neuromusculoskeletal system. These models, however, still hold many limitations that can affect their biofidelity. Firstly, the

majority of model parameters such as anatomy and muscle mechanics are primarily based on *in vitro* cadavre studies (Delp et al., 1990; Hamner et al., 2010; Rajagopal et al., 2016) thereby causing a rather generic approach when modelling various human body types. Furthermore, many of these models also simplify various joints, such as the reduction of knee joints to one degree of freedom (DOF) hinge joints (Delp et al., 1990; Hamner et al., 2010). Patient-specific models tune a generic model to be more representative of each participant being examined. This can be done through the incorporation of magnetic resonance images (MRI) data to specialize bone geometry, muscle wrapping, ligament insertions, and joint articulations (Brito da Luz et al., 2017; Conconi et al., 2018). Although patient-specific models increase processing time, they are more anatomically accurate and better represent the true knee joint kinematics during dynamic tasks (Chapter 4.4). Since PROMs generally assess the construct of knee stability through questions relating to episodes of the knee giving way or feeling loose, applying patient-specific neuromusculoskeletal models during dynamic tasks to assess contributors to joint control such as ligament forces and joint loading may reveal relationships to function previously obscured by non-functional or gross metrics. A comprehensive analysis of knee joint function can be undertaken in order to better elucidate the relationship between objective knee joint function and the patient's self-reported subjective functional ability.

The objective of this study was therefore two-fold: (1) to determine if knee joint contact and ligament forces differed between pre and post-ACL reconstructed states; (2) to determine the relationship between these contact and ligament forces to their patient's respective PROMs scores. These objectives were achieved by developing patient-specific OpenSim models with the use of MRIs and applying static optimization and joint reaction analysis to the whole-body kinematic and kinetic data during a rapid deceleration task (Chapter 4.4). Since these ACLr patients are known to have improved levels of self-confidence and functional ability compared to their ACLd condition (Chapter 4.1), it was hypothesized that the ACLr conditions would elicit a more demanding movement program with respect to the knee joint. This would manifest as the ACLr condition inducing greater compressive and ligament forces during the deceleration and that these forces would be correlated with the various subjective questionnaires.

Methods

In vivo data

This *in silico* work was based on *in vivo* measures of 12 ACL injured patients (5 female, 7 male; 27.8 ± 5.3 years; 1.76 ± 0.09 m; 76.9 ± 13.0 kg) recruited from Bispebjerg-Frederiksberg Hospital. Data collections were completed pre (ACLd) and 10 months post-reconstruction (ACLR). Inclusion criteria included primary ACL injury and no history of contralateral ACL ruptures. Complete ACL rupture was confirmed clinically by the physician (positive Lachman and Rolimeter tests) and via magnetic resonance imaging (MRI) or arthroscopy. All patients

underwent a double-bundle hamstring autograft and received a standardized 20-week rehabilitation program that focused on range of motion, balance, strength, and functional training. The test leg for all participants was the limb with the ACL rupture. All data collections occurred at the University of Copenhagen and approved by the Capital Region of Denmark and University of Ottawa ethics committees.

Upon receiving written informed consent, participants completed a battery of PROMs including the KOOS, KNEES-ACL (reported as a percent of maximum score), subjective IKDC, Tegner, and Lysholm scale. Participants then changed into tight-fitting clothing, followed by anthropometric measurements and skin preparation for EMG electrode placement. Electrodes were placed on the muscle bellies of the gluteus medius (GMED), tensor fascia lata (TFL), gracilis (GRAC), rectus femoris (RFEM), vastus medialis (VMED), vastus lateralis (VLAT), long head of biceps femoris (BFEM), semitendinosus (STEN), medial (MGAS) and lateral gastrocnemii (LGAS) according to the SENIAM guidelines (Hermens et al., 2000). EMG data were sampled at 1000 Hz with a 20-500 Hz bandwidth using wireless sensors (MQair, Marq-Medical, Denmark). EMG data were normalized to maximum voluntary isometric contractions performed in the following order: plantar flexion; hip flexion, extension, adduction, and abduction; and knee extension and flexion. Three trials of a five second ramped effort separated by 45 seconds of rest were completed for each action. All contractions were performed with the hip, knee, and ankle at 30°, 30°, and 90° of flexion respectively and resistance was applied by a nylon strap fixed to the wall and manually by the examiner for knee extension and flexion.

Participants were then outfitted with a whole-body cluster marker set (Mantovani and Lamontagne, 2016) with kinematic data being collected at 100 Hz by a 10-camera motion capture system (6 MX and 4 T series, Vicon, UK). Ground reaction forces (GRF) were sampled at 1000 Hz using one force plate (OR 6-5-1, AMTI, USA). To successfully complete the hop, participants stood on their non-test leg, jumped forward with their test (ACL injured) limb onto a force plate and maintained balance for two seconds. To avoid stepping, participants selected a comfortable speed and distance to ensure it was a forward jump although they were encouraged to drive into the motion making it as ballistic as they were comfortable with. Jump lunge trials were cropped from 100 ms prior to initial contact to 300 ms post-contact. Three to four successful trials of each task were collected for all participants.

All data were processed with MatLab (2015b, Mathworks, USA) and OpenSim (3.3, Simtk, USA). Marker trajectories and GRFs were filtered with a 4th order zero-lag low pass Butterworth filter with matching cut-off frequencies of 15 Hz (Bisseling and Hof, 2006). EMG data were first subjected to a 4th order zero-lag high pass Butterworth filter at 20 Hz, rectified, and then treated with a 4th order zero-lag low pass Butterworth filter at 10 Hz. A moving 50 ms average window was also calculated from the MVIC trials to determine the maximum activation

value of each action. The greatest windowed value for each muscle, regardless of trial, was then used to normalise the EMG linear envelopes as a ratio of the MVIC value.

Patient-specific modeling

MRIs were taken with TR/TE: 500/14 ms, FOV 18, and a slice thickness of 3 mm (Sigma Horizon LX 1.5 Tesla, General Electric, USA) in the ACLd state and were used for the ACLr state of each patient as well. Images were segmented (Workbench 2016.11, MITK, Germany) to produce three-dimensional renderings of the distal femur and proximal tibia and fibula, including attachment sites of the ACL, posterior cruciate ligament (PCL), medial collateral ligament (MCL), and lateral collateral ligament (LCL). The knee natural motion was computed from these renderings by maximizing joint congruence over the whole flexion arc (Conconi et al., 2015). Origins and insertions for the ACL, PCL, MCL, and LCL were defined as the points producing the most isometric fibre during the natural motion (Victor et al., 2009; Wilson et al., 1998). Articular contacts were approximated with two sphere-on-sphere constraints optimized about the patient anatomy similarly to Conconi et al. (2018). The Rajagopal OpenSim model (Rajagopal et al., 2016) was used as the generic base and then had the standard generic knee model replaced for each participant with their patient-specific contact constraints and ligaments (see Chapter 4.4 for greater detail on model development). Due to graft harvesting, the semitendinosus and gracilis maximum isometric forces were reduced by 18.7 and 8.9% respectively in the ACLr condition (Williams et al., 2004). Ligament physiological cross-sectional areas and stiffness values were taken from past modelling work (Blankevoort and Huiskes, 1991; Pandey et al., 1998), while the ligament reference lengths were based on the minimum value observed in all trials with respect to each participant.

Scaling, inverse kinematics, and inverse dynamics were all performed for each trial using the patient-specific models. Inverse kinematics results were then subjected to a residual reduction algorithm to reduce the dynamic inconsistency between motion capture data and GRFs. During this process, the foot metatarsophalangeal and subtalar joints were locked as well as the three translational DOF at the knee leaving a three rotational DOF spherical joint. Next, static optimization (SO) was conducted for each trial, which included the ligament forces in its solution. The step interval was set to every 5 ms, objective function was the sum of muscle activation to the third power (Crowninshield and Brand, 1981), and muscle force-length-velocity relationships were used (Millard and Delp, 2012). Finally, joint reaction analyses were performed to determine the three-dimensional joint reaction (contact) forces at the knee during the movement. All forces were normalized to body weight (BW) and contact forces are the femur onto the tibia with respect to the tibia reference frame.

Statistics

Static optimization activations of the ten muscles were validated against the EMG linear envelopes. There is typically an offset in the time-domain between EMG and SO-estimated muscle activations; the difference between the signals is typically attributed to electromechanical delay. To validate the SO-activations against EMG, the within trial waveforms of corresponding muscles were therefore cross-correlated to each other to reduce the offset in the time domain (Lund et al., 2012). Pearson correlations were calculated for each muscle within trial and averaged for the entire group to determine the mean correlation. To compare joint contact and ligament forces between the ACLd and ACLr state, paired sample T-tests were performed using statistical parametric mapping (Pataky, 2010). Finally, to determine the relationship between PROMs and peak contact and ligament forces, Spearman correlations were conducted due to the questionnaires' ordinal nature. All statistical analyses were conducted in MatLab and significance was set to $p < 0.05$.

Results

Force Modelling Results

Before accounting for the timing offset, the correlations between the SO-activations and EMGs ranged between -0.33 – 0.25 in the ACLd state and -0.31 – 0.21 in the ACLr group. The average lag of the SO activations in the ACLd condition was 104 ms and 111 ms in the ACLr state. Once shifted with respect to these lags, the correlations between SO-activations and EMGs improved in the ACLd to 0.39 – 0.71 (Figure 4.5.1) and 0.24 – 0.70 in the ACLr group (Figure 4.5.2). The resulting muscle forces from the activations for the ACLd and ACLr groups can be found in the appendix (Figure A.5), in which the ten lower limb muscles that EMG was collected from are illustrated.

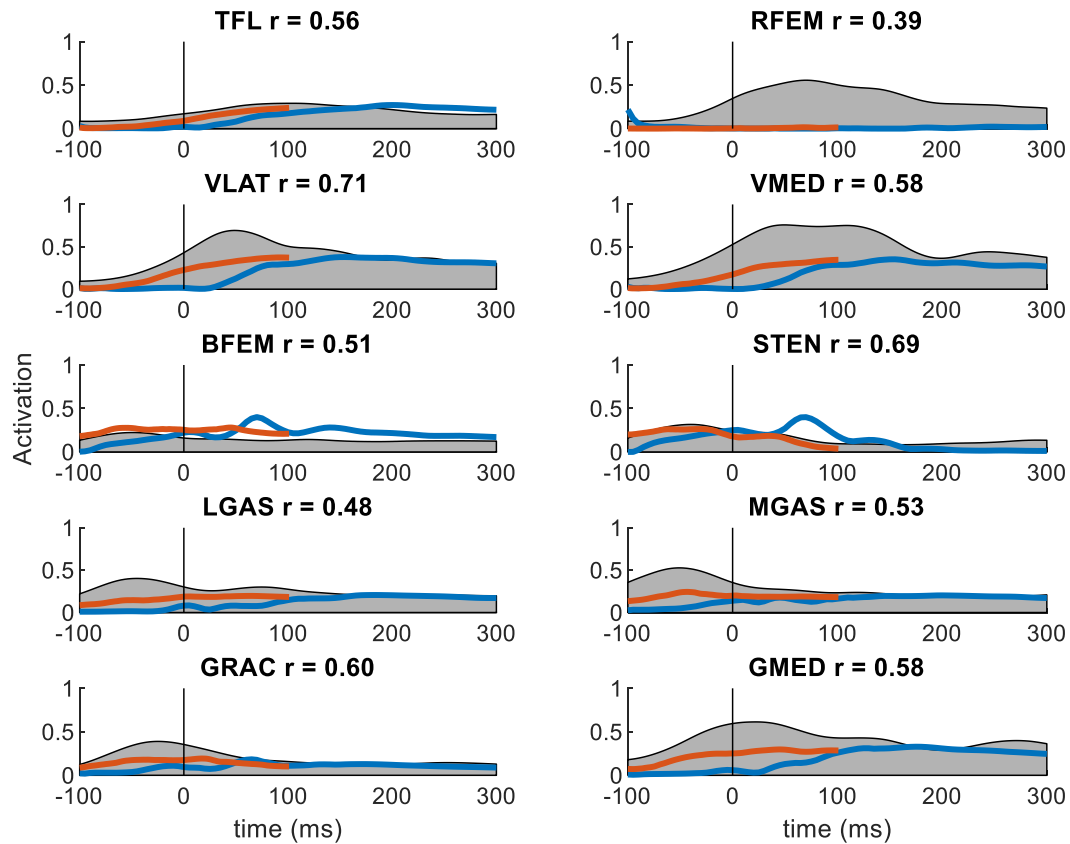


Figure 4.5.1. Mean EMG linear envelopes (grey shading) compared to original (blue) and time-shifted static optimization activations in the ACLd condition. Vertical black bars represent time of initial contact during landing (time = 0) while r (Pearson correlations) is the mean of within trial correlations between the EMG linear envelope and shifted static optimization activation. Shifted activations are shorter due to the time lag removal.

In the ACLr state, the mean ACL force peaked at 0.3 ± 0.32 N/BW while the ACL was excluded in the ACLd condition. The mean PCL peaked at 0.18 ± 0.15 N/BW in the ACLd and 0.18 ± 0.17 N/BW ACLr conditions and the mean MCL peaked at 0.17 ± 0.11 N/BW and 0.15 ± 0.12 N/BW in the ACLd and ACLr state, respectively. Finally, the mean LCL peaked at 0.08 ± 0.09 N/BW in the ACLd condition and reached 0.16 ± 0.16 N/BW in the ACLr state. There were no significant differences between ACLd and ACLr for any of the ligaments (Figure 4.5.3).

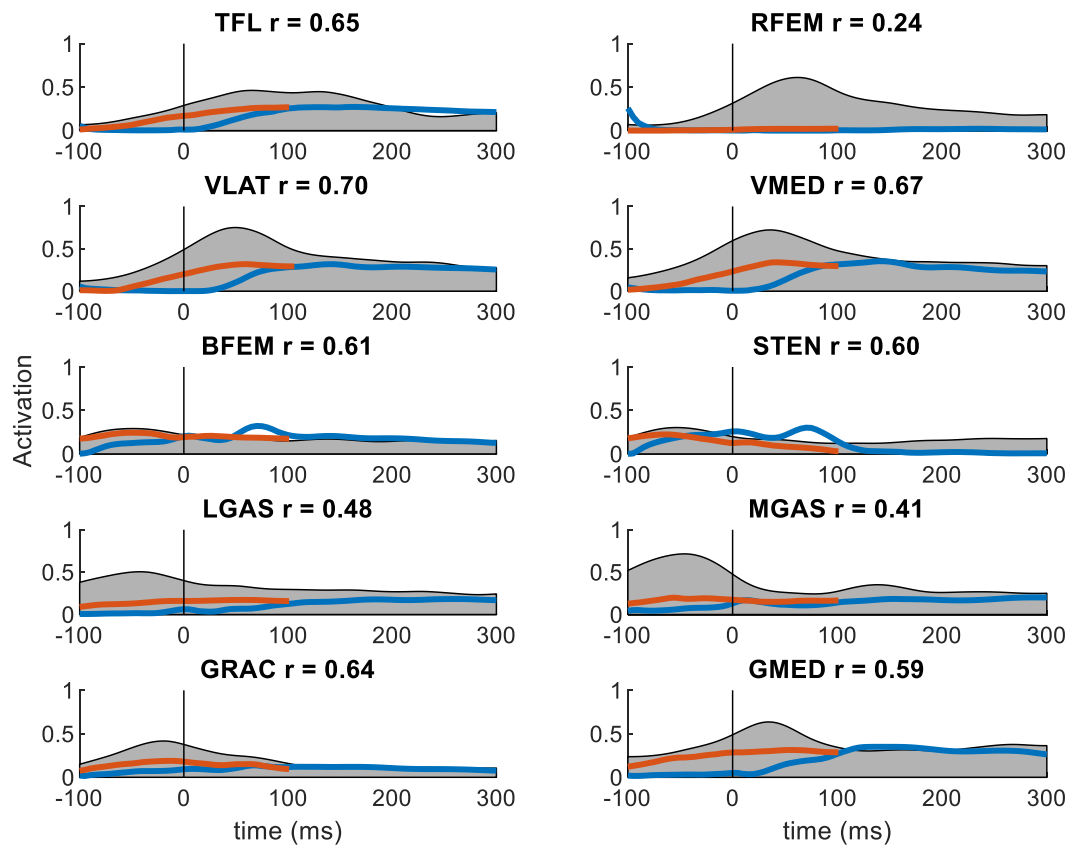


Figure 4.5.2. Mean EMG linear envelopes (grey shading) compared to original (blue) and time-shifted static optimization activations in the ACLr condition. Vertical black bars represent time of initial contact during landing (time = 0) while r (Pearson correlations) is the mean of within trial correlations between the EMG linear envelope and shifted static optimization activation. Shifted activations are shorter due to the time lag removal.

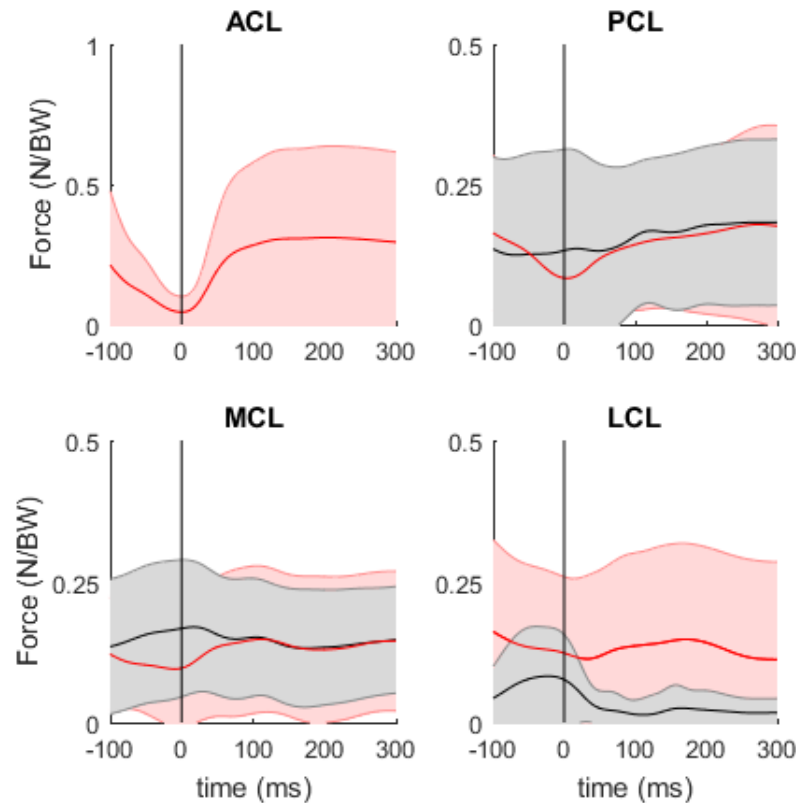


Figure 4.5.3. Mean ligament forces and standard deviation clouds in the ACLd (black) and ACLr conditions (red). Vertical lines represent time of initial contact during landing (time = 0).

The contact force was represented by three components: anterior, compressive and medial force components. SPM found no significant differences throughout the entire hopping task for any of the three contact forces. The decelerating motion caused a peak anterior tibial shear force of 0.48 ± 0.40 N/BW in the ACLd state compared to the 0.36 ± 0.96 N/BW observed in the reconstructed state. The peak compressive force at the knee joint was 7.37 ± 1.65 N/BW in the ACLd state compared to the 6.49 ± 1.11 N/BW observed in the ACLr state. Finally, the peak medial shear force of 0.51 ± 0.22 N/BW in the ACLd state was similar to the peak medial shear force of 0.53 ± 0.44 N/BW observed in the ACLr condition (Figure 4.5.4).

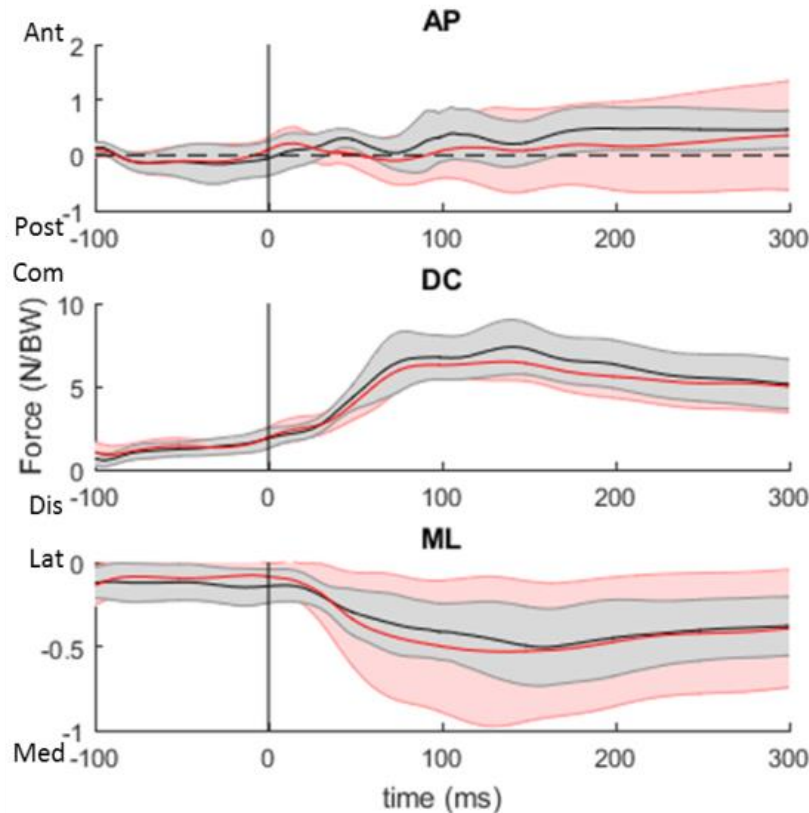


Figure 4.5.4. Knee joint contact forces for the ACLd (black) and ACLr (red) conditions. Vertical lines represent time of initial contact during landing (time = 0).

Objective and Subjective Correlations

With respect to the subjective PROMs between the ACLd and ACLr conditions, Lysholm, Tegner, IKDC, KNEES – Slackness, KNEES – Looseness, KNEES – Sport Behaviour, and KOOS – QOL showed increased functional ability in the ACLr state. The remaining PROMs (KNEES – Psychosocial, KNEES – Symptoms, KNEES – Sport Physical, KOOS – Symptoms, KOOS – Pain, KOOS – ADL, and KOOS – Sport/Recreation) all showed no significant difference between the two states.

Lysholm and KOOS – Quality of Life in the ACLd state were the only PROMs correlated to any ligament forces (Table 4.5.1). Lysholm ACLd was associated with PCL force ($r = -0.69$, $p = 0.019$) and MCL force ($r = -0.62$, $p = 0.044$) while KOOS – Quality of Life was associated with PCL force ($r = 0.68$, $p = 0.015$) and LCL force ($r = -0.66$, $p = 0.02$). In the ACLd state, IKDC was moderately correlated to peak compressive force ($r = 0.64$, $p = 0.025$) and Tegner activity scale was strongly correlated to peak compressive force ($r = 0.76$, $p = 0.007$; Figure A.4) and peak medial shear force ($r = 0.67$, $p = 0.025$). KNEES – Sport Physical was also correlated to peak

medial shear force ($r = -0.59$, $p = 0.045$). All other correlations between PROMs and contact forces in the ACLd state were insignificant.

Table 4.5.1. Exhaustive list of Spearman correlations between subjective questionnaires and knee joint contact and ligament forces. Bold font denotes significance ($p < 0.05$).

	Ant. Force	Post. Force	Med. Force	Comp. Force	ACL Force	PCL Force	MCL Force	LCL Force
IKDC ACLd	0.22	0.20	0.32	0.64	-	0.06	-0.20	0.21
IKDC ACLr	0.53	0.66	-0.21	-0.15	-0.27	-0.07	0.61	0.33
Tegner ACLd	-0.01	0.43	0.67	0.76	-	0.18	-0.12	0.00
Tegner ACLr	0.05	0.07	0.00	0.70	0.06	0.28	-0.05	0.27
Lysholm ACLd	0.11	0.31	0.29	0.17	-	-0.69	-0.62	0.51
Lysholm ACLr	-0.24	0.29	-0.74	0.07	0.15	-0.22	0.30	0.26
KOOS-Sym ACLd	0.22	-0.06	-0.14	0.23	-	-0.12	-0.27	0.32
KOOS-Sym ACLr	0.43	0.50	-0.40	-0.18	0.07	0.18	0.36	0.26
KOOS-Pain ACLd	0.22	-0.10	0.13	0.30	-	0.05	-0.19	0.21
KOOS-Pain ACLr	0.47	0.10	-0.29	-0.15	-0.03	0.15	-0.07	-0.04
KOOS-ADL ACLd	-0.08	-0.28	-0.01	0.29	-	0.35	0.30	-0.26
KOOS-ADL ACLr	0.51	0.01	-0.30	-0.09	-0.13	0.00	-0.18	-0.15
KOOS-SpRec ACLd	0.04	0.35	0.61	0.51	-	-0.07	-0.32	0.26
KOOS-SpRec ACLr	0.46	0.09	-0.32	0.18	0.21	0.40	0.10	0.17
KOOS-QOL ACLd	-0.30	0.16	0.36	0.27	-	0.68	0.60	-0.66
KOOS-QOL ACLr	-0.01	0.17	-0.56	0.12	-0.21	-0.30	0.11	-0.03
KNEES-ADL ACLd	-0.36	0.34	0.13	-0.17	-	0.29	0.22	-0.31
KNEES-ADL ACLr	-0.50	-0.13	0.21	0.11	-0.01	-0.31	-0.11	-0.18
KNEES-PsySoc ACLd	-0.29	-0.01	-0.21	-0.17	-	-0.24	0.06	-0.12
KNEES-PsySoc ACLr	-0.01	-0.52	-0.05	0.16	0.55	0.07	-0.30	0.13
KNEES-Sym ACLd	-0.10	0.38	-0.07	-0.11	-	-0.26	-0.12	0.11
KNEES-Sym ACLr	-0.25	-0.14	0.63	0.00	-0.22	-0.31	-0.16	-0.13
KNEES-Slack ACLd	-0.34	-0.05	-0.35	-0.44	-	-0.13	0.23	-0.09
KNEES-Slack ACLr	-0.48	-0.20	0.18	-0.05	0.18	-0.42	-0.60	-0.12
KNEES-Loose ACLd	-0.03	0.03	-0.15	-0.13	-	-0.10	0.09	0.08
KNEES-Loose ACLr	0.01	-0.11	0.30	-0.13	0.19	0.37	-0.14	0.11
KNEES-Sport Beh ACLd	-0.04	-0.02	-0.34	-0.46	-	-0.53	0.13	-0.03
KNEES-Sport Beh ACLr	-0.19	-0.45	0.04	-0.15	0.42	0.07	0.25	0.15
KNEES-Sport Phys ACLd	0.22	-0.20	-0.59	-0.09	-	-0.22	0.03	0.23
KNEES-Sport Phys ACLr	-0.10	-0.16	0.33	-0.45	0.05	0.02	0.29	0.58

In the ACLr condition, the only correlation between PROMs and ligament forces was peak LCL force to KNEES – Sport Physical ($r = 0.58$, $p = 0.048$). Tegner activity scale was again strongly correlated to the peak compressive force ($r = 0.70$, $p = 0.012$) while IKDC was moderately correlated to the peak anterior shear force ($r = 0.66$, $p = 0.02$). Medial shear force was also correlated to Lysholm ($r = -0.74$, $p = 0.009$) and KNEES – Symptoms ($r = 0.63$, $p = 0.028$). No other PROMs were found to have significant correlations to peak contact forces.

Discussion

To the authors' knowledge, this is the first in silico modelling study driven by kinematic and kinetic in vivo data collected pre and post-ACL reconstructed in a test-retest design. Our first objective of this study was to determine if differences exist in knee joint contact and ligament forces between the pre and post-reconstruction states while the second aim was to determine if these contact and ligament forces were correlated to the patient's subjective functional ability. Although it was hypothesized that greater contact and ligament forces would occur post-reconstruction due to their greater self-perceived functional abilities, this was not the case as there were no significant differences compared to the ACLd group. It was also hypothesized that these contact and ligament forces (measures of objective knee function) would be moderate – strongly correlated to PROMs scores (measures of subjective knee function). We found that only the Tegner Activity Scale, Lysholm, and IKDC were correlated with our objective measures.

Biomechanical Outcome Measures

The lack of significant differences in ligament forces between the ACLd and ACLr conditions is likely due to the large within-group variation, as evidenced by the standard deviation clouds in Figure 4.5.3. OpenSim ligament forces are defined kinematically in that their level of strain dictates the amount of stress (hence force) they produce during a given trial. We attribute much of this variability to our use of a three DOF knee joint which, by definition, would lead to greater kinematic variability compared to a traditional OpenSim single DOF joint. Nevertheless, our peak of mean ACL force corresponds to approximately 226 N in the ACLr state, which agrees with ACL forces measured during dynamic tasks through in silico (Kar and Quesada, 2012; Pflum et al., 2004; Shelburne et al., 2004) and in vivo (Holden et al., 1994; Hosseini et al., 2011; Roldán et al., 2017) methods. The peak of mean PCL force was approximately 136 N in both states, which agrees with previous in vitro (Markolf et al., 2006) and in vivo PCL (LaPrade et al., 2015) loading. In the ACLd state, the peak of mean MCL force was 128 N while the peak of mean MCL force was 113 N in the ACLr condition. Finally, the peak of mean LCL force in the ACLd condition was 60 N and 121 N in the ACLr state. These values are comparable to those observed by Shelburne et al. during gait, where MCL and LCL forces reached peaks of approximately 125 N (Shelburne et al., 2004). Our ligament forces also all fall well below ultimate axial tensile strengths for the ACL (2160 N; Woo, 1991), PCL (1600 N; Race and Amis, 1994), MCL (799 N; Wilson and et al., 2012), and LCL (392 N; Wilson and et al., 2012), indicating that the current model provided reasonable estimations of ligament forces, given that no participants sustained injury during testing.

During our deceleration task, the knee experienced a peak of mean anterior tibial shear force (ATSF) of 0.48 N/BW (~361 N) and 0.36 N/BW (~271 N) in the ACLd and ACLr state,

respectively. ATSFs in previous studies have been highly variable and dependent on task, ranging from 0.45 – 0.7 N/BW during a landing task (Bennett et al., 2008; Cleather et al., 2013), 0.51 – 0.92 N/BW during level walking (Costigan et al., 2002; Kuster et al., 1994), and up to 1.73 N/BW during downhill walking (Kuster et al., 1994). Shelburne and colleagues have also examined in silico ATSF in healthy populations during gait and again during those same gait trials with the ACL removed to represent the ACLd condition. Through this method they observed peak ATSF to decrease from 259 N in the healthy knee to 76 N in the ACLd knee (Shelburne et al., 2004). They attributed this decrease in ATSF to the greater anterior tibial translation occurring in the ACLd state, which cannot be expressed by our three rotational DOF model. Our simulations also resulted in knee joint compressive forces 7.37 and 6.49 N/BW in the ACLd and ACLr state, respectively. Other modelling studies have quantified tibiofemoral compressive forces to range between 3.46 – 9.92 N/BW depending on the task and population (Cleather et al., 2013; Kuster et al., 1994; Tsai and Powers, 2012). Instrumented knee implants have also provided valuable data with respect to knee joint loading as of late. D’Lima and colleagues have measured tibiofemoral contact forces during a variety of daily living and sporting activities (D’Lima et al., 2008) and observed compressive forces reaching a maximum of about 4 N/BW during running and skiing. These values coincide with the OrthoLoad group who have also examined compressive force readings during routine activities and noted compressive forces of approximately 2.7 – 3.5 N/BW depending on the task (Kutzner et al., 2010; Taylor et al., 2017). Although the in silico models may seem to be over-predicting in vivo compressive forces, it should be noted that these in vivo instrumented implant forces are from older populations who have undergone knee arthroplasty and therefore likely have reduced muscle strength and agility, which would decrease the knee contact loads, while our study also included a highly ballistic task.

Clinical Implications

A large battery of PROMs were collected in the pre and post-reconstructive conditions and even though they have all been developed to target the psychology of ACL injured patients, there were relatively few significant correlations to knee joint contact and ligament forces. The two best measures appear to be the Tegner activity scale and the IKDC as they both showed moderate to strong correlations to contact forces in either or both states. Although the Tegner score is not a direct measure of subjective function but rather a tool to discern the highest level of participant’s activity, it inherently indicates how confident the patient is to complete daily living and sporting activities at the various levels. There is agreement in the literature that the Tegner score is not associated with clinical joint laxity (Barrett, 1991; Christino et al., 2016; Sernert et al., 1999), which makes the current findings that Tegner scores show correlations of $r = 0.70 - 0.76$ to the peak compressive force during a hopping movement very intriguing. Although we cannot discern whether this relationship is caused by the patient’s pre-injury

characteristics such as strength, we are confident in interpreting this as those who induce greater compressive loading are also capable of playing intensive sports at a higher level.

The IKDC has also shown no correlation to clinical joint laxity (Christino et al., 2016; Snyder-Mackler et al., 1997), but has shown moderate to strong correlations with hopping functional tests (Bodkin et al., 2017; Logerstedt et al., 2012). The relationship we found between IKDC and contact forces supports this relationship of IKDC to global functional performance, meaning that the IKDC might be the most effective PROM in consolidating subjective and objective levels of functional ability. Considering the Tegner, Lysholm, and IKDC all showed the greatest correlations to objective functional measures, it is encouraging to know that these three questionnaires are the most commonly reported in ACL literature (42%, 63%, 71%, respectively; Makhni et al., 2015). Furthermore, it is interesting to note that the non-subscale questionnaires (Tegner, Lysholm, IKDC) had a higher percentage of correlations to objective measures than the questionnaires that are broken down into subscales (KOOS and KNEES). These subscales may be more effective at identifying a specific psychological aspect but were not as strongly related to our objective measures of functional ability (loading demands placed on knee joint).

With these same participants, our group has previously noted little clinical significance in kinematic or kinetic (Chapter 4.1), dynamic knee joint stiffness or knee motion consistency (Chapter 4.2) variables. These findings are despite major improvements in self-reported subjective functional ability from the ACLd to ACLr state (Chapter 4.1). Even though the kinematics and kinetics of a trial drive the static optimization and joint reaction analyses, small differences in the input can have a considerable impact on the results of these higher-level analyses. Since the current ACLr patients responded with greater self-confidence during dynamic tasks, we had hypothesized that the ACLr group would exhibit greater knee joint forces, which would perhaps explain their higher perceived ability. Conversely however, the opposite was observed in that although not significant, the ACLr had lower ATSF and tibiofemoral compressive forces during this hopping task. These results may seem counter-intuitive, but the nature of the task must be taken into consideration. This was a unilateral task and we have no way of computing limb asymmetry. Previous work has discovered substantial asymmetrical loading in ACLr patients throughout a variety of dual-leg tasks and have described it as a shielding mechanism (Thomson et al., 2018). Therefore, when the participants are responding to the PROMs, they may be reflecting on scenarios in which they were shielding their injured limb, causing an inflated self-confidence and in effect PROMs scores. They may be over-rating their objective physical ability, which could lead to premature return to play or exposure to deleterious knee joint scenarios. This all lends support to the high re-injury rates after reconstruction that can reach as high as 24% (Paterno et al., 2010). Although the patient's psychological health is a crucial aspect in appropriate return-to-play, validating this subjective

measure may reduce successive re-injury rates. The consolidation of subjective and objective functional ability assessments is imperative if the ACL rehabilitation schema is going to improve. With poor validation of subjective function against objective measures of function, the re-injury rate and incidence of related osteoarthritis are unlikely to diminish, resulting in subsequent lowered quality of life.

Limitations

Firstly, we had to lock the three translations of our patient-specific models and only consider the three rotational DOFs when calculating ligament and contact forces. This was required in order for residual reduction analysis and static optimization procedures to find solutions during this dynamic task. Furthermore, Joint reaction analysis is not possible in a free-moving six DOF joint and therefore, the reduction in translations was needed to quantify joint translational forces. While this is generally more freedom than previous studies using OpenSim (Delp et al., 1990; Hamner et al., 2010; Rajagopal et al., 2016), we acknowledge that this reduces the biofidelity of our model. Unprescribed six DOF knee versions of the current model show considerable soft tissue artefact after loading that manifests as oscillations in kinematics (Chapter 4.4). The current three DOF version was effective in mitigating these oscillations and therefore reduced the amount of soft tissue artefact. Furthermore, our decision was based on Chapter 4.4 where we reported no statistically significant differences in the elongation of the most isometric fibers between our patient-specific and the three rotational DOFs models. We therefore concluded that the impact of a spherical pair knee model on the ligaments forces can be considered limited. The use of the rotational kinematics from the original model also allowed us to perform OpenSim's residual reduction and static optimization analyses results, while still providing a more anatomically accurate model than the most common alternatives.

Secondly, our patient-specific models treat each knee ligament as a single bundle, in which they represent the most isometric fibre (Conconi et al., 2018; Chapter 4.4). This knowingly simplifies the knee joint but discerning multiple bundles from MRIs is an arduous task and our choice of the most isometric fibre likely resulted in conservative values as they will be less responsive to length changes as other fibres found within that ligament. This means our ligament force estimates are still valid, although they may be underestimating the true amount of strain exhibited during dynamic tasks. Thirdly, our MRIs for each patient were only taken in the ACLd state prior to their surgery as they were used as a diagnostic tool. We accept that minor changes to the patient's bone geometry or ligament insertions may occur between two the data collections which may result in slight errors due to the joint alignment in the ACLr condition. Finally, the validation of our static optimization muscle activations consisted of correlations to EMG linear envelopes of the respective trial. Although this is a common and accepted practice in the neuromusculoskeletal modelling community (Hicks et al., 2015; Lund et

al., 2012), EMG excitations and the OpenSim activations are not the same phenomena. Static optimization does not consider muscle and kinematic states and assumes that activation corresponds to instantaneous force production, whereas processes such as the electromechanical delay disrupt the relationship between EMG and force production, which is the reason we induced a shift of our activations during the validation procedure. With this in mind and the inherent limitations of SO in predicting synergistic muscle activations, our results corresponded well with the literature (Hoffrén et al., 2011; Wibawa et al., 2016).

Conclusion

This test-retest design examined knee joint contact and ligament forces and their relationship to subjective functional ability pre and post-ACL reconstruction. Although no significant differences were found in contact or ligament forces between the two conditions, the Tegner activity scale and IKDC showed moderate to strong correlations with knee joint contact forces. Therefore, knee specific objective measures of a patient's functional capacity can represent their subjective ability, which consolidates this relationship to a greater extent than past anatomical and gross objective measures of function. These findings can be used to develop a more holistic rehabilitation program that incorporates and finds agreement between the physical and psychological components of ACL injuries and recovery.

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Conflict of Interest

The authors have no professional relationships that stand to gain from the current study and that the results are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

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Chapter 5: General Discussion

The overarching aim of this doctoral thesis was to develop a better understanding of the relationship between subjective and objective measures of functional ability in ACLd and ACLr individuals. To address this aim, both biomechanical and neuromusculoskeletal approaches were taken and three specific objectives were identified. The first (GO1), was to determine how muscle activations differ between healthy and injured populations and how these differences were reflected in their overall movement patterns. This was achieved through an in vivo test-retest data collection (S1) that analyzed spatiotemporal, electromyographic, kinematic, kinetic, and patient-reported data. The second objective (GO2) was to employ three objective measures of dynamic knee joint control that represent these movement patterns and determine if they were related to the patients' self – evaluation of functional ability. This objective was addressed by conducting secondary analyses (S2 & S3) on the data collected in S1. The final thesis objective (GO3) was to determine how knee joint contact and ligament forces differ between ACLd and ACLr conditions and identify any relationships between joint loading and subjective measures of functional ability. For this, patient-specific models were developed with the use of MRIs (S4), applied to the biomechanical data of S1, and related to their respective PROMs scores (S5). The results in this thesis therefore contribute to the understanding of ACL injuries and how they manifest as both physical and psychological features.

5.1 Biomechanics Associated with ACL Injury

The first hypothesis (S1H1) was that lower subjective scores and knee extensor moments in addition to altered muscle activations would be observed in the ACLd group compared to the CON. With respect to the subjective scores, this hypothesis was supported as every PROM score indicted reduced functional ability in the ACLd group compared to the matched CON (Table 4.1.1). This finding supports the current literature in which PROMs are lower in the ACLd cohorts (Eitzen et al., 2010; Fischer-Rasmussen and Jensen, 2000; Fitzgerald et al., 2000a; Herrington and Fowler, 2006; Lindstrom et al., 2010). This hypothesis was also supported in terms of the reduced knee extensor moment as in both the hopping and side cut tasks, smaller knee extensor moments were observed in the ACLd group during the loading phase of both movements. Again, this finding supports past work of reduced knee extensor moments in ACLd patients with respect to CON observed during hopping (Di Stasi and Snyder-Mackler, 2012; Rudolph et al., 2000) and side cuts (Houck and Yack, 2003). As for muscle activations, the only difference in all ten muscles for both tasks was the ACLd group having greater MGAS activity for 12 ms during the hop landing. Thus, since the vast majority of muscle excitations had no changes in amplitude, this aspect of the hypothesis was rejected. As previously discussed, there is a lack of consistency amongst studies examining muscle

activations in ACLd populations. In a review of EMG studies requiring ACLd participants to perform level gait, only 7/12 studies reported activation magnitude differences in the ACLd quadriceps while 6/12 studies observed differing hamstring activation amplitudes (Shanbehzadeh et al., 2015). We purposely chose to analyse demanding dynamic tasks that were more difficult than level gait as these are the scenarios in which ACL ruptures are most likely to occur. Furthermore, we believed that the higher level of required effort would elicit differences in EMG between the two groups. This does not appear to be the case in this cohort of high-functioning ACLd patients.

The second hypothesis (S1H2) was that after reconstruction, subjective function would improve but biomechanical and neuromuscular function would remain consistent with those observed in the ACLd group. This was only partially supported as Lysholm, Tegner, IKDC, KNEES – Slackness, KNEES – Looseness, KNEES – Sport Behaviour, and KOOS – QOL showed increases in functional ability between the ACLd and ACLr state. The remaining PROMs (KNEES – Psychosocial, KNEES – Symptoms, KNEES – Sport Physical, KOOS – Symptoms, KOOS – Pain, KOOS – ADL, and KOOS – Sport/Recreation) all showed no significant difference between the two states. Although having the questionnaire divided into subscales as in the KOOS and KNEES provides advantages in identifying specific problem areas, it adds ambiguity in cases such as these. It is also unclear what physical manifestations these subscales represent and was therefore the motivation behind S3 & S5 of this thesis. The current results also support S1H2 in that biomechanical and neuromuscular changes would not exist between ACLd and ACLr. Few studies have directly compared ACLd and ACLr patients and with test-retest designs being even rarer (Aragão et al., 2015). Ciccotti et al. (1994) conducted an EMG analysis of ACLd, ACLr, and CON but their design was cross-sectional, therefore, even though significant differences were observed, they may have been due to participants themselves and not the actual ACL status. The test-retest design and comparison to matched controls is a strength of the current thesis as the comparison between ACLd and ACLr is not influenced by athletic exposure, coaching, training, and a myriad of other factors associated with between-participant comparisons.

In terms of biomechanical function, joint angles and moments are relatively simple variables and do not necessarily represent joint loading. This was the reasoning to include neuromusculoskeletal modelling in this thesis to evaluate whether joint loading in the form of contact and ligament forces differed pre and post-reconstruction. Our first hypothesis in S5 was that since patients had greater subjective functional ability post-reconstruction, they would load their injured knee to a greater extent than in the ACLd state and thereby elicit greater knee joint contact and ligament forces. This hypothesis was rejected as no differences in contact or ligament forces were observed between the groups. Although multiple studies have applied *in silico* models to ACLd scenarios and compared results to healthy CON (Moglo and Shirazi-Adl, 2003; Vairis et al., 2015; Weinhandl et al., 2016; Xu et al., 2015), ours is the first in

silico work implemented in an ACL test-retest design with respect to dynamic, weight-bearing tasks. Weinhandl et al. (2016) implemented an OpenSim model to examine how perturbations to GRFs influence ACL loading during side cuts. They found that peak ACL loading occurred almost immediately after initial ground contact and was therefore dependent on initial joint position. As shown in Figure 4.5.3, in the reconstructed state our ACL loading rapidly increases immediately after contact, plateauing 75 – 100 ms later. This rapid ACL loading within the first 50 ms following initial contact supports video analysis work in which real-case ACL ruptures occurred within this same time frame following initial contact (Koga et al., 2010; Krosshaug et al., 2007). A finite element model examining the effects of joint contact forces after resection observed significant increases in the collateral ligaments resulting in larger overall contact forces in the ACL transected condition (Moglo and Shirazi-Adl, 2003). This may help explain the higher incidence of OA in ACLd populations as higher contact loads are associated with OA progression (Griffin and Guilak, 2005; Kumar et al., 2012). Although we lack the CON population in our modelling due to MRI availability, there were no significant differences in loading patterns between the ACLd and ACLr conditions (Figure 4.5.4). Thus, if the past notion of increased loading in ACLd with respect to CON holds true, we would expect increased contact forces in the ACLr with respect to CON as well. This further questions the objective effectiveness ACL reconstruction has on high-functioning patients as neuromuscular, biomechanical, and joint contact patterns remain similar between the pre and post-operation state.

The first study of this thesis had a final hypothesis (S1H3), which was that ACLr patients would not fully recover subjective function and would still have altered neuromuscular and biomechanical patterns compared to the healthy, uninjured CON. With respect to the subjective questionnaires, all PROMs indicated that functional ability was still significantly lower in the ACLr compared to the CON participants. Since very few differences in EMG were observed between CON and ACLd, it was not surprising to see similar results in the ACLr and CON comparison. As for biomechanical measures, ACLr still had lower knee extensor moments and knee flexion angles in the hop compared to the healthy CON. This supports past work by Oberlander et al (2014) in which during a 12 month longitudinal study, they also observed that the ACLr group did not restore normal knee kinematics during hop landing. This potentially helps explain the low return to competitive sport (Arderne et al., 2014), high incidence of re-injury (Goddard et al., 2013; Laboute et al., 2010; Leys et al., 2012; Paterno et al., 2010) and rapid progression of OA (Lohmander et al., 2007, 2004; Oiestad et al., 2011; Roos et al., 1995). A possible explanation for the lack of restoration after reconstruction is that even though reinnervation has been observed to occur after ACL reconstruction, the level of nerve signal does not reach those exhibited by healthy controls even after seven years (Ochi et al., 1999; Young et al., 2016). Therefore, during reconstruction, the ACL's mechanical role may be restored but its neural, proprioceptive role is not being fulfilled. This also questions the

appropriateness of comparing ACLr to uninjured standards during the rehabilitation process. If the residual deficit in neural input is considered with the structural alterations of the graft harvest site, it is unreasonable to expect the knee joint to mirror an uninjured joint with respect to function. Therefore, alternative rehabilitation methods and guidelines may be more effective and eventually help reduce the incidence of secondary pathologies.

5.2 Dynamic Knee Joint Control

Since a joint's flexion angle or joint moment is not a complete representation of knee joint control, this thesis included the development of two novel control measures and the application of a previous ankle control measure to the knee. It was hypothesized (S2H1) that control would be greatest in the healthy CON, lowest in the ACLd group, and the ACLr patients would show increased control compared to ACLd while not fully recovering to levels seen in the CONs. This hypothesis could not be supported as there were relatively few differences in control measures between the three groups for both tasks. Stiffness during the side cut exhibited the most substantial difference and was significantly greater in the CON compared to ACLd and ACLr however no difference between ACLd and ACLr was observed (Figure 4.5.2A). The developers of this DKJS measure (Davis and DeLuca, 1996) suggested that an increase in this measure of stiffness represents an increase in dynamic joint control. Our finding of CON exhibiting the highest DKJS during the side cut supports this proposition. No differences were observed in KJCB (movement consistency) between the three groups for either task while KJCE was only significantly greater in the CON than the ACLd during the hop movement. This was not expected but perhaps could be attributed to the high-functional ability of the patients. These ACLd and ACLr participants were deemed highly functional as they were willing/able to complete these demanding tasks in both pre and post-operative states. Therefore, it is reasonable to conclude that these patients may be controlling their knee movement pattern with the efficiency and consistency of the healthy, uninjured CON.

Given that the injured patients performed the same tasks with similar neuromuscular, biomechanical, and control patterns both pre and post-reconstruction, the effectiveness of their reconstruction in improving functional capacity is questionable. Their choice in opting for surgery is influenced not only by medical (e.g. swelling, pain, giving-way) factors, but may also include societal (e.g. professional medical opinions) and cultural (e.g. mimicry of professional athletes) factors that could induce a placebo effect. This placebo effect may have caused the increased subjective functional ability but could not change objective functionality pre and post-reconstruction. Although this procedure objectively improves the passive laxity of the knee joint, changes to dynamic knee joint control were simply not present. A possible placebo effect cannot be confirmed by our studies, but if we consider our lack of objective improvement biomechanical measures, combined with past findings of poor return to play rates (Arder et al., 2014), high probability of re-injury (Goddard et al., 2013), and increased

incidence of OA (Lohmander et al., 2004), it is a plausible explanation that warrants a true randomized control trial to elucidate.

Although these previously discussed measures of joint control (KJCE, KJCB, stiffness) are relatively easy to implement and interpret, they are basic measures that often consider kinematics and kinetics independently. Neuromusculoskeletal modelling allows for a deeper analysis of knee joint function and control as it is a more holistic approach that integrates anthropometrics, kinematics, kinetics, and muscular contributions to arrive at a solution. These models can range in complexity but they often sacrifice biofidelity for more simplistic designs that allow for reasonable processing and optimization times. These generalized approaches can have a considerable impact on the anatomical correctness and therefore knee joint control. In S4, we applied four different OpenSim models and depending on the constraints placed on the model, the resulting control was greatly affected. As shown in Figure 4.4.1, an unprescribed six DOF model can have large amounts of ATT and distraction reaching up to 15 mm. These values are improbable based on gold standard studies using intra-cortical bone pins (Benoit et al., 2006) and dynamic MRI (Barrance et al., 2006) that report a posterior tibial position with respect to the femur for a variety of dynamic tasks. These deviations in translational DOFs are likely more of a result of soft tissue artefact rather than a manifestation of decreased joint control. This is evidenced by the unprescribed six DOF model resulting in oscillating knee joint translations that resemble a mass-spring-damper system (Figure 4.4.1). When the MRI-informed contact constraints were introduced, these oscillations were mitigated by forcing the model to follow rigid body assumptions instead of surface marker inertia. This reduction in soft tissue artefact oscillations has also been accomplished through bone pin derived kinematic ranges applied to OpenSim models (Potvin et al., 2017; Smale et al., 2017). Non-contact ACL injury mechanisms are a combination of knee abduction and internal rotation with the leg in an extended position (Boden et al., 2000; Krosshaug et al., 2007) and injury prevention programs often focus on proper knee abduction alignment (Hewett et al., 2012). The emphasis on abduction and internal rotation needs to be cautioned however, as kinematic error due to soft tissue artefact is up to 70 and 63% for these DOFs, respectively (Reinschmidt et al., 1997). Therefore, it is clear that the choice in model influences kinematic results and thus the interpretation with respect to knee joint control. As a result, given that all other in vivo studies to date are affected by this artefact, purported instability could in fact be the manifestations of kinematic error (Leardini et al., 2005).

5.3 Relation of Subjective and Objective Functional Ability

As previously discussed, a simple measure of stability is clinical joint laxity through Lachman, Pivot Shift, or KT-1000 tests (Makhni et al., 2015). These simplistic measures have been consistently shown to be uncorrelated to subjective measures of functional ability (Barrett, 1991; Christino et al., 2016; Sernert et al., 1999; Snyder-Mackler et al., 1997) possibly

due to the unweighted, static, muscle-relaxed state the patient must assume. Knee strength, as defined by peak knee flexor torque and power is arguably a more progressive measure of objective knee joint function. These measures have shown moderate correlations ($r = 0.51 - 0.54$) to KOOS subscales (Bodkin et al., 2017), which outperform clinical laxity, but in their isometric state, still fail to truly represent the dynamic ability required to complete demanding, injury-associated movements. A befitting measure of whole body functional ability has been a series of hop tests (Noyes et al., 1991) that are often used in rehabilitation and return to play guidelines (Fitzgerald et al., 2000b). These hop tests have correlations to PROMs ranging from weak to strong with the maximum ($r = 0.72$) being the 6 metre timed hop to IKDC (Bodkin et al., 2017; Logerstedt et al., 2012). Thus, there appears to be a hierarchy in the relationship between objective and subjective measures of functional ability: simpler objective measures show weak to no relationship to subjective measures while more comprehensive objective measures appear to show stronger relationships to subjective measures. This paradigm became a building block of this doctoral thesis and was directly tested in S3 and S5.

In S3, five variables of objective knee joint function were related to subjective PROMs scores. The first two objective variables were peak knee joint flexion and extensor moment as these variables have consistently shown to be decreased in ACL injured populations (Di Stasi and Snyder-Mackler, 2012; Houck and Yack, 2003; Rudolph et al., 2000). They were seen as the most basic measures of joint function and are not specifically assessed through any PROMs. The remaining three variables (DKJS, KJCE, KJCB) were designed to target specific categories in the PROMs questionnaires or represent general comments made by participants. These include the KNEES – Slackness and Looseness subscales; KOOS, IKDC, and Lysholm questions regarding stiffness and instances of giving way, as well as general concerns including a “wobbly” or “inconsistent” movement pattern. Peak extensor moment and KJCB were not strongly related to PROMs as they both showed very few significant correlations (Table 4.3.1 & Table 4.3.2). Peak flexion angle performed better than expected as between the two movements, it held significant correlations ($r = .42 - .6$) with KOOS – Symptoms being the highest. KJCE correlations were mediocre as the significant relationships ranged from ($r = .42 - 0.65$) with KNEES – Psychosocial having the strongest relationship during the side cut. Stiffness during the hop was significantly correlated to the majority of PROMs (see Table 4.3.1) including KNEES – Slackness ($r = 0.6$) but not KNEES – Looseness. The opposite held true for stiffness during the side cut as it was correlated to KNEES – Looseness ($r = -.46$) but not KNEES – Slackness. This stiffness correlation to KNEES – Slackness during the hop was not expected as better scores in KNEES subscales are indicated by lower scores. Thus, this correlation is portraying that patients who have more complaints about their knee slackness also exhibit a stiffer knee during hop landing. This demonstrates the continued disconnect between the objective measures and the subjective questionnaires designed to target these measures. This could be caused by three reasons: 1) the objective measure is not effectively capturing the patient’s concern and own

definition of stiffness, 2) the questionnaires are doing a poor job of capturing the objective stiffness occurring, or 3) the patient falsely believes the knee to be loose when in actuality it is stiff/stable. Unfortunately, this thesis does not have the ability to resolve this disconnect and will have to concede to future validations of these approaches.

As there was a considerable amount of moderate to strong correlations in S3, this thesis further explored the proposed hierarchy and examined the PROM relationships to patient-specific knee joint loading as defined as contact and ligament forces (S5). With respect to ligament forces, Lysholm ACLr had moderate negative correlations to PCL ($r = -.69$) and MCL force ($r = -.62$) while KOOS – QOL ACLd had moderate correlations to PCL ($r = 0.68$) and LCL force ($r = -.66$). With respect to compressive force, IKDC ACLd, and Tegner in both ACLd and ACLr states showed strong correlations ($r = .64 - .76$). Posterior shear force was also moderately correlated to IKDC ACLr ($r = .66$) while Lysholm ACLr ($r = -.74$) and KNEES – Symptoms ACLr ($r = .63$) were associated with medial shear force. Although these strong correlations were sparse given the large number of PROMs, they are the strongest reported relationships between objective and subjective measures and even outperform IKDC to functional hop tests (Bodkin et al., 2017; Logerstedt et al., 2012).

Although we cannot examine these relationships in a healthy population due to the stark ceiling effect within the CON PROMs responses, the field of biomechanics with respect to ACL injury prevention and rehabilitation would greatly benefit from more consistency amongst methods. Considering the Tegner, Lysholm, and IKDC all showed the greatest correlations to objective measures, it is heartening to see that they are the most commonly reported questionnaires in ACL literature (42%, 63%, and 71% respectively; Makhni et al., 2015). Since current ACL rehabilitation programs are primarily focussed on physical function (Fithian, 2005; Fitzgerald et al., 2000a; Wright et al., 2015), they would likely benefit from the inclusion of more in-depth psychological assessments of the patients self-reported function. Thus, if future work can further consolidate the relationships between these measures, rehabilitation programs can become more holistic and likely reduce the high rate of re-injury and OA progression.

5.4 Thesis Limitations

Aside from limitations mentioned in their respective studies, this thesis has some general limitations that need to be considered.

Participants

There are many considerations with respect to human participants and even more so when they are a pathological group. Our ACL injured patients had a considerable large range of time since injury (1 – 100 months), which could have influenced the results due to secondary

changes to joint health associated with ACL injury. For example, deterioration of articular cartilage in mice species was observed within months post-injury (Christiansen et al., 2012) whereas radiographic degeneration can begin between 2 – 4 years post-injury in humans (Buckland-Wright et al., 2000; Wang et al., 2015). Although no major degeneration was observed in the patient MRIs, it is possible that undetected changes that influenced their neuromuscular and biomechanical profiles were present. Participants also completed their ACLr session approximately 10 months post-reconstruction. Patients take varying lengths of time to recover from ACL reconstruction, which could have influenced the current results. There was some standardization however, as each patient completed the 20-week rehabilitation program (Table A1) and were cleared for return to play. This 10 month time frame is supported by Erickson et al. (2014) who reported that 68.1% of surgeons recommend at least 9 months before returning to play.

Although our injured population were individually matched to healthy CON based on sex, age, weight, height, BMI, Tegner score, and leg tested (dominant vs. non-dominant), there were could still be many differences with respect to their attitudes and psychological state, previous playing, injuries, and coaching experience. Thus, these controls cannot be treated as a true baseline measure. Therefore, any changes that were observed between the CON and injured groups cannot be considered entirely symptoms of the injury but could also have been prior patterns that may have caused the injury itself. This was accounted for to a certain extent in S1 and S2 as any test between CON and injured were considered as independent samples unlike the ACLd and ACLr which were treated as paired samples.

A third limitation with respect to the participants is their activity level. All participants included in this dissertation were fit and active individuals. This limits the scope of the thesis and biases the results as no sedentary participants volunteered for the study. Although physical activity level (da Fonseca et al., 2006) and type (Lattier et al., 2003) are known to influence muscle activations, we tried to account for this by including Tegner activity scores in our participant matching protocol. A further bias with respect to our population occurred when we decided to only include those who were capable of completing the hop and side cut both pre and post-operatively. Although, these participants had opted for reconstruction and therefore are deemed non-copers, they likely could have easily been classified as copers due to their high functional ability. This high level of function is expected to have biomechanical and neuromuscular differences compared to low functioning groups as copers and non-copers are known to have considerable differences in their neuromuscular and movement patterns (Lewek et al., 2003; Rudolph and Snyder-Mackler, 2004; Wojtys and Huston, 1994). Our lab group is currently exploring the neuromuscular and biomechanical patterns employed during a variety of dynamic tasks in relation to their functional ability.

The final limitation with respect to the participants in this thesis is that sex was not controlled for. Sex-related differences are known to exist in muscle activation patterns in healthy (Flaxman et al., 2014) and ACL injured populations (Sigward and Powers, 2006) in addition to biomechanical patterns in ACL injured populations (Miranda et al., 2013; Orishimo et al., 2014). Although sex was not controlled for, it is not expected to have a major bias on results since S1, S2, and S5 used paired comparisons between ACLd and ACLr states, which negate the effect of sex because they are within-participant comparisons. It still remains unclear if there are sex-related differences in PROM responses in healthy and injured populations.

Muscles Analyzed

The studies contained in this thesis considered 10 superficial muscles that were accessible with surface EMG. This is only a small fraction of total muscles in the human body, in which they all play a role in generating the required forces to complete a movement. There are multiple smaller muscles that cross the knee joint (semimembranosus, sartorius, vastus intermedius, short head of biceps femoris, etc.) that have an influential contribution to knee moment generation (Buchanan et al., 1996) but were not considered in the neuromuscular analysis of this thesis. Furthermore, surrounding hip musculature was minimally represented in this thesis but is known to influence femoral positioning and motion (Geiser et al., 2010; Jacobs et al., 2007). As discussed earlier, joint alignment and position has a sizeable impact on joint loading so the unknown activation of these hip muscles is a limitation to the current thesis. Finally, muscles that cross the ankle joint that were not considered in this thesis, such as the soleus, also influence tibiofemoral motion (Elias et al., 2003). Since the human body is a kinetic and kinematic chain, any changes in muscle activations have an effect that is propagated to the joint of interest. Although we considered the entire lower limb in our analyses, trunk position is also known to affect knee joint loading (Donnelly et al., 2012). During the hopping task, participants were instructed to maintain an upright trunk with their hands on their hips to reduce the effects of trunk position. During the side cuts however, participants were allowed to freely move their torso. Current work in our lab is exploring the effect of upper body centre of mass on these dynamic tasks.

Errors Associated with Multiple Comparisons

The studies forming this thesis contain multiple comparisons as there are a considerable number of dependent variables (e.g. joint angles, moments, PROMs) and an independent variable with three factors (CON, ACLd, and ACLr). This places the statistical results at a high risk of specious significant differences, when in actuality they are type 1 errors due to probability theory. To make some accommodation for this possibility, we reduced our alpha value to 0.025 but do acknowledge that this correction still leaves us susceptible to type 1 errors. Although

alternative post-hoc corrections exist, we believe they would be too conservative and result in type 2 errors. When considering one's choice in post-hoc corrections, it is imperative to determine how the selected correction would alter the study's conclusion. In S1 for example, the vast majority of objective variables were insignificant ($p > 0.025$) so a greater reduction of p would not alter this conclusion. Additionally, if a traditional Bonferroni, Sidak, or Holm-Bonferroni method were chosen here, our flexion angle, extensor moment, CON-ACLD and CON-ACLR PROMs would still be significant as they had p values below 0.0007. If these alternate corrections were chosen however, all ACLd-ACLR PROMs comparisons become statistically insignificant. We believe this is a false conclusion given the differences in means, which result in large effect sizes. For example, IKDC (mean ACLd: 65.6; mean ACLr: 77.4) had an effect size of 1.14 while KNEES Sport Behaviour (mean ACLd: 74.4; mean ACLr: 43.2) had an effect size of 1.33. To a clinician, these pre and post subjective scores represent substantial improvements in functional ability and to consider them insignificant, would be a costly type 2 error in our opinion. Furthermore, SPM currently can only apply a traditional Bonferroni correction and can in fact result in multiple significant clusters making the number of comparisons ambiguous. This was a motivator for including effect sizes and so we encourage the reader to consider the means, standard deviations, effect sizes, and p values when drawing conclusions about whether a comparison should be deemed statistically and clinically significant.

Neuromusculoskeletal Modelling

As neuromusculoskeletal modelling is a cutting-edge research method in the field of biomechanics, it still holds many limitations. With respect to its application to this thesis, and despite our model being one of the more advanced OpenSim applications in the literature at this time, major simplifications were made even with the inclusion of MRIs for patient-specific modelling. These MRIs were originally purposed for ACL health diagnosis and not modelling. Therefore, only approximately a 7 – 8 cm window of the knee joint was visible for the femur, tibia, and fibula. Other bone and muscle geometries were indiscernible from the images, which limits the specificity of the models. Nevertheless, we were able to include the four major knee ligaments and menisci as they are known to play a major role in joint stability (Allen et al., 2000; Markolf et al., 1976). Furthermore, since the MRIs were originally purposed for ligament diagnosis, they do not include the full lengths of the femur, tibia, and fibula. This required us to implement an additional step in which we align the MRI bones to a generic femur and tibia. Then, to orient the MRI bones in the OpenSim reference system, the knee joint centre, medial epicondyle, and generic hip joint centre were used. The knee joint centres and medial epicondyle markers between the MRI and generic bones were coincident but there is an unknown about the hip joint centre with respect to each participant that may caused error in our alignment. Since the femur's distal-proximal component of the ISB coordinate system is aligned with the mechanical axis (knee joint centre to hip joint centre), this could introduce

introduce kinematic cross-talk in the resulting knee joint angles. Given the available data, the correct hip joint positioning is an assumption that had to be made. We believe this to be an appropriate assumption as this error between hip joint centre positions should be relatively small as we appropriately scaled and aligned the MRI and generic bones.

A second limitation of the applied models was that even though the MRI-based contact model in S4 had movement in all three rotations and translations, this had to be simplified to only three rotational DOF in S5. Even though inverse kinematics and dynamics are capable of being performed with a six DOF knee joint, residual reduction analysis, static optimization, and joint reaction analysis all required further constraints. During residual reduction and static optimization, small knee joint translations require large muscle forces that are not producible with the small moment arms of the surrounding muscles. These knee joint translations can become quite large due to soft tissue artefact (see Chapter 4.4; Potvin et al., 2017; Smale et al., 2017) rendering the muscle forces ineffective in finding a solution. One can introduce a contact constraint to represent the surrounding soft tissue, but this would have to be modelled as a reserve actuator. These reserve actuators have an immense effect on outputted muscle force profiles and unfortunately there is no way to determine an accurate proportion of joint contact attributed to surrounding soft tissue. Additionally, since joint reaction analyses cannot be conducted on free-moving bodies (such as those in a six DOF joint), the reduction of our model in S5 allowed us to calculate compressive and shear forces.

Another limitation to our neuromusculoskeletal models is the lack of information regarding the joint contact and ligament loads. During dynamic tasks, knee joint loads are unevenly distributed between the medial and lateral compartments (Bruns et al., 1993; Halder et al., 2012). The current joint reaction analysis output only provides a singular force value for the entire joint and is not capable of breaking it down based on compartment. Other mathematical methods have been capable of doing so (Manal and Buchanan, 2013) and have effectively related their findings to compartmental OA progression. Moreover, the current analyses are incapable of identifying the contact area and location on the tibia plateau. Finite element models have found for this contact position to move posterolaterally (Scarvell et al., 2005; Van de Velde et al., 2009) and being unable to confirm that in the current population is a limitation.

With respect to ligament forces, they are modelled in OpenSim as a passive element and therefore function based on stress-strain curves. The ligament length at each time step is determined by the joint's geometry and kinematics but to establish a proper relative strain value, the user needs to establish the ligament's resting/slack length. Generic OpenSim models use ligament origins and insertions as well as resting lengths from Blankevoort and Huiskes (1991). However, since our MRI-based models have patient-specific ligament origins and

insertions, these generic resting lengths are unsuitable. To compensate, we used the minimum length observed for each ligament during each participant's dynamic trials. These resulted in resting length values agreeable to the literature (Table 5.4.1; Blankevoort and Huiskes, 1991). This method however results in ligaments never being slack during the dynamic movement, which is unlikely to be true. This could overestimate the amount of force produced but given our ligaments are conservative in their representation of the most isometric fibre, this possibility of overestimation was deemed a reasonable assumption given the available information.

Table 5.4.1. Mean ligament resting lengths defined as the minimum value during dynamic tasks

Ligament	Resting Length (mm)
ACL	31.7 ± 6.9
PCL	37.2 ± 5.7
MCL	88.9 ± 8.4
LCL	56.2 ± 8.2

Finally, there are known limitations associated with static optimization. Although static optimization has resulted in similar muscle force profiles compared to computed muscle control (Lin et al., 2012), it still considers each time step independently while not factoring in kinematic and muscle states. It is, however, a computationally simpler and more time-efficient approach. Other modelling methods include EMG-driven approaches (Kumar et al., 2012; Manal and Buchanan, 2013; Sartori et al., 2012) but are more computationally inefficient and are limited to analyzing only the muscles for which EMG data are present. Hybrid frameworks have also been implemented in neuromusculoskeletal modelling studies (Shourijeh et al., 2016; Sartori et al., 2014) that combine the EMG-driven and forward dynamics approaches. These models are also computationally inefficient and have only been applied to basic human movements such as level gait. To solve the muscle redundancy problem, static optimization employs an objective function for which the default in OpenSim is to minimize the muscles' activations to the square power. This concept of minimizing the activation is based on the concept that the human body wants to work as efficiently as possible and therefore minimize how much different muscles need to be activated (Pedotti et al., 1978; Rasmussen et al., 2001). During simple gait and other rudimentary tasks this is a reasonable assumption but concerning hopping motions in injured populations, the body may not prioritize efficiency but rather some sort of stability criterion. Objective functions used in OpenSim analyses that try to maximize stability (e.g. maximize joint compression or minimize joint shear loading) are known to influence the resulting muscle activations (Potvin, 2016). Unfortunately, it is unknown which method the human body uses when deciding on muscle activations. Therefore this thesis

choose the simplest method that produced reasonable activations (minimize cubed activations).

5.5 Future Directions

As this thesis was primarily focussed on two dynamic tasks (hops and side cuts) associated with ACL injuries (Boden et al., 2000), it was limited to high-functioning individuals. Further work is currently being undertaken to analyze the other dynamic movements included in this study (two and one-leg squats, forward lunges, and countermovement jumps). This will allow for future conclusions with respect to the low functioning patients and may yield interesting relationships to their subjective scores. Since considerable differences have been observed in coper and non-coper populations (Lewek et al., 2003; Rudolph and Snyder-Mackler, 2004; Wojtys and Huston, 1994), it is expected that the low functioning patients will be distinguishable from the high-functioning in terms of their neuromuscular, movement, and joint loading patterns.

This thesis only considered an adult population for which the conclusions may not be applicable to pediatric or adolescent populations. Injury rates are the same for males and females prior to the age of 12, then show a dramatic disproportional increase of up to eight times in females (Boden et al., 2010; Hewett et al., 2006; Shea et al., 2004; Werner et al., 2015). Furthermore, the incidence of ACL injuries increased by 19% in these young populations between 2007 – 2011 likely due to the increased exposure time and intensity of sport training programs (Werner et al., 2015). This is harrowing given the high prevalence of OA and reports of reduced quality of life 10 – 20 years post ACL injury (Lohmander et al., 2007, 2004; Oiestad et al., 2011; Roos et al., 1995). Given the injury occurring early in their life, their quality of life is already markedly reduced by the time they reach their mid-twenties. Our research group has begun addressing this with a longitudinal pediatric ACL study. Patients are recruited from the local surgeons and undergo similar tasks and methods as reported here. The goal of this work is to be able to relate the current adult findings to these younger populations in hopes of identifying what is responsible for this increasing risk of injury.

The findings in this thesis indicate that there are considerable differences in subjective function, and biomechanical variables between uninjured and ACLd populations. These differences continue to exist after ACL-reconstruction and in combination with the high incidence of graft rupture (Goddard et al., 2013; Laboute et al., 2010; Leys et al., 2012; Paterno et al., 2010) and low return to play (Ardern et al., 2014), the efficacy of current rehabilitation programs is called into question. Furthermore, with the increased incidence of ACL injuries in today's youth, the current preventative programs (Dargo et al., 2017; Hewett et al., 2012; Nessler et al., 2017; Pollard et al., 2017) are performing sub-optimally. Therefore, the current thesis findings in that ACLr patients do not recover to movement patterns and subjective

function observed in uninjured controls by the time of return to play can be used to identify a more holistic approach to prevention/rehabilitation programs that incorporate both objective and subjective measures of functional ability.

Future work can also be conducted with the development of more sophisticated and biofidelic models that better represent the tibiofemoral joint motion during dynamic tasks. This includes the addition of multiple bundles per knee ligament and optimization approaches that are capable of incorporating a knee model with all three rotations and translations. Our lab group has previously developed a hybrid modelling framework that combines EMG-driven and forward dynamics solutions for optimal quantification of muscle and joint contact forces (Shourijeh et al., 2016). This framework has yet to be applied to pathological participants or highly-demanding dynamic tasks and therefore holds great potential for impactful contributions to the field of biomechanics.

Finally, our lab group has also been developing an in vitro loading system capable of applying physiologically-appropriate muscle loads. This quasi-static set-up allows for the dynamic application of simulated muscle and ground reaction forces while simultaneously recording the motion capture and joint contact forces through tibiofemoral pressure sensors. Since the current validation procedure of neuromusculoskeletal models involve the comparison of recorded EMG profiles to muscle activations and relationship of instrumented implants to contact loads (Hicks et al., 2015; Lund et al., 2012), an alternative method of validation would be invaluable. The human leg specimens could be loaded with profiles derived from the in silico models and the resulting contact forces between each method could be compared as a validation of approaches.

5.6 Conclusions

This doctoral thesis was comprised of five studies that investigated the relationships between subjective and objective measures of functional ability in ACLd and ACLr conditions through biomechanical and neuromusculoskeletal modelling approaches. Even though no differences in neuromuscular patterns were observed, it was found that subjective PROM scores and biomechanical measures in the form of knee flexion angles and extensor moments were lower in the ACLd group compared to healthy controls. These differences continued to exist post-reconstruction as the ACLr group never fully recovered to patterns observed in the healthy CON. Our findings also suggest a possible hierarchy in the relationship between objective and subjective measures of functional ability. Simple objective measures such as passive laxity show no correlations to subjective measures, more progressive measures such as flexion angle and strength show small to moderate correlations, while deeper level measures such as stiffness and joint compressive force show moderate to strong correlations to subjective PROMs. Finally, this thesis featured a method of developing patient-specific OpenSim

models through the inclusion of MRIs and contact constraints. These models were used to produce appropriate kinematics and ligament lengthening with the reduction in soft tissue artefact.

Our finding that ACLr patients do not recover to movement patterns and subjective function observed in uninjured controls by the time of return to play can be instrumental in improving ACL prevention and rehabilitation programs and call for the consolidation of objective and subjective measures when progressing through return to play benchmarks. Furthermore, this thesis lays the groundwork for more advanced in silico models that could simulate biomechanical outcomes of various reconstruction approaches and aid clinicians in making objective evidence-based decisions. Ultimately, this thesis was designed to contribute to the current body of knowledge to help reduce secondary ACL injuries through a test-retest design, provide clarity for the relationship to OA progression by developing an in silico procedure to quantify joint loading, and assist in improving the patients' quality of life after sustaining an ACL rupture by consolidating the patient's subjective evaluation with objective functionality scores.

Chapter 6: General References

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Appendix

Table A.1. Summary of the 20-week standardized rehabilitation program undergone by all ACLr patients.

Number of weeks post-reconstruction	Exercises
1	Range of motion (ROM) and hyperextension exercises, shorter walks, cooling bandages
2-3	Straight leg raises, unloaded flexion exercises, active extension exercises, exercise bike.
4-7	ROM, strength (mainly unloaded), balance (1 leg exercises balance board, trampoline), functional (walking, stairs, raising from chair), and circuit (steps, balance board, trampoline) training
8-12	Swimming, running on stairs, interval training on bike, use of fitness machines starting with 20 rep max and gradually increasing to 15 rep max, training of hamstrings (pelvis lift, foot gliding on square of carpet, hip extensions, exercise ball curls), quadriceps training (squat, ski-exercises, step machine, leg press (25 to 10 rep max)), calf muscle training (heel lifts), balance training (on 1 leg, balance board, trampoline, etc.), functional training (stairs, running on stairs, jogging on trampoline, landing on operated limb), training of gluteus medius and maximus.
12-20	Increasing hamstrings training, quadriceps training on machines and standing. Running (stairs, regular ground, on trampoline, sports-specific training), hop training, increasing balance exercises.

Table A.2. Comparison of subjective scores in low-functioning patients (those who were not willing to complete either hop (H) or side cut (SC) tasks in either of the ACL deficient (ACLd) or reconstructed (ACLr) state) and high-functioning patients (those willing to complete either H or SC tasks in both ACL states). * indicates trend towards significance ($0.05 < p < 0.1$) between low-functioning and those able to complete H. ** indicates significance ($p < 0.05$) between low-functioning and those able to complete H. † indicates trend towards significance ($0.05 < p < 0.1$) between low-functioning and those able to complete SC. †† indicates significance ($p < 0.05$) between low-functioning and those able to complete SC.

	Low ACLd	JL ACLd	SC ACLd	Low ACLr	JL ACLr	SC ACLr
Tegner	3.5 (1.1)	4.4 (2.2)	4.3 (2.2)	5.0 (1.3)	5.8 (1.5)	5.6 (1.7)
Lysholm	75.1 (15.3)	73.5 (9.2)	73.4 (11.4)	83.9 (9.7)	84.9 (8.4)	83.1 (12.8)
IKDC	54.7 (11.6)***†	65.6 (11.0)**	64.0 (13.6)††	74.6 (11.1)	77.4 (9.6)	76.3 (13.5)
KNEES – ADL	38.8 (21.7)***†	24.4 (16.6)**	24.8 (17.3)††	17.0 (11.7)	12.4 (9.6)	14.2 (10.4)
KNEES – Psychosocial	41.3 (26.7)	29.6 (21.1)	33.3 (19.5)	18.7 (20.7)	18.1 (16.0)	19.2 (13.7)
KNEES – Symptoms	28.3 (20.6)	24.1 (13.1)	27.1 (13.9)	15.6 (15.6)	17.6 (17.0)	17.3 (13.9)
KNEES – Slackness	37.6 (17.6)	33.8 (15.4)	32.8 (16.4)	27.6 (24.3)	16.5 (14.6)	16.7 (15.5)
KNEES – Looseness	42.5 (26.7)	32.4 (17.8)	33.8 (17.0)	21.7 (18.3)	15.3 (18.4)	16.7 (17.8)
KNEES - Sport Behaviour	68.3 (27.2)	74.4 (20.8)	72.5 (20.2)	57.22 (33.9)	43.2 (25.7)	41.2 (25.3)
KNEES – Sport Physical	42.5 (29.2)	33.8 (34.2)	32.4 (31.7)	20.0 (22.5)	21.8 (26.7)	22.1 (27.8)
KOOS – Symptoms	81.4 (12.9)	82.7 (11.0)	82.6 (12.2)	84.8 (9.1)	82.9 (9.8)	83.2 (11.6)
KOOS – Pain	82.2 (11.5)	84.6 (7.4)	82.2 (15.8)	85.2 (9.4)	88.9 (8.5)	87.4 (12.3)
KOOS - ADL	91.5 (5.7)	93.0 (5.2)	90.6 (12.7)	94.0 (4.4)	94.8 (5.8)	92.3 (11.7)
KOOS – Sport/Rec	52.0 (20.3)*††	63.6 (21.9)*	65.9 (23.8)††	56.7 (22.6)***†	77.8 (16.3)**	76.5 (20.1)††
KOOS - QoL	52.6 (11.9)	56.9 (6.7)	54.7 (7.4)	59.7 (15.1)**†	70.8 (10.2)**	68.2 (14.1)†

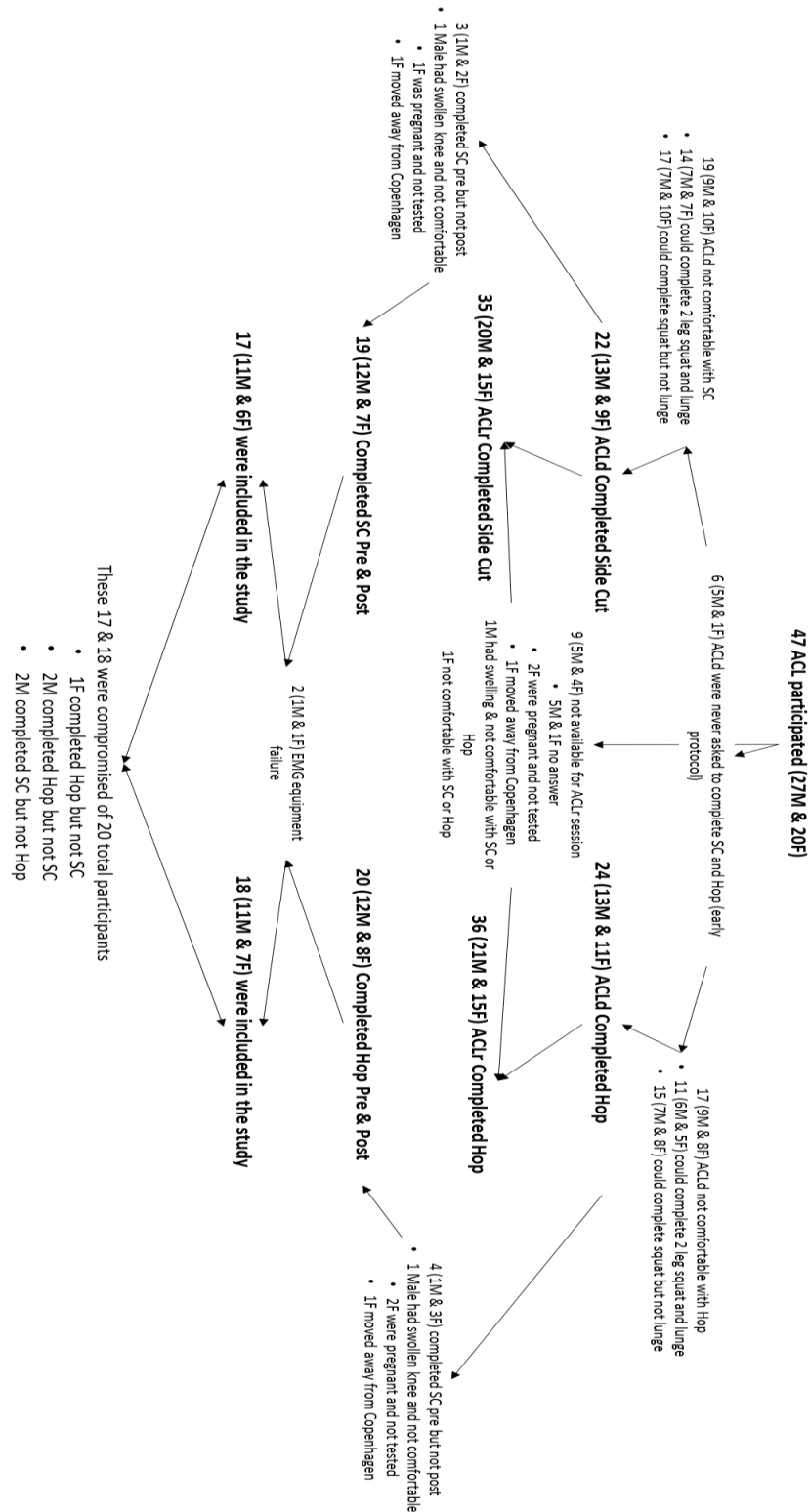


Figure A.1. Flowchart detailing participant compliance and ability to complete hopping (HL) and side cut (SC) tasks. M – Males; F – Females; ACLd – Anterior cruciate ligament deficient; ACLr – anterior cruciate ligament reconstructed.

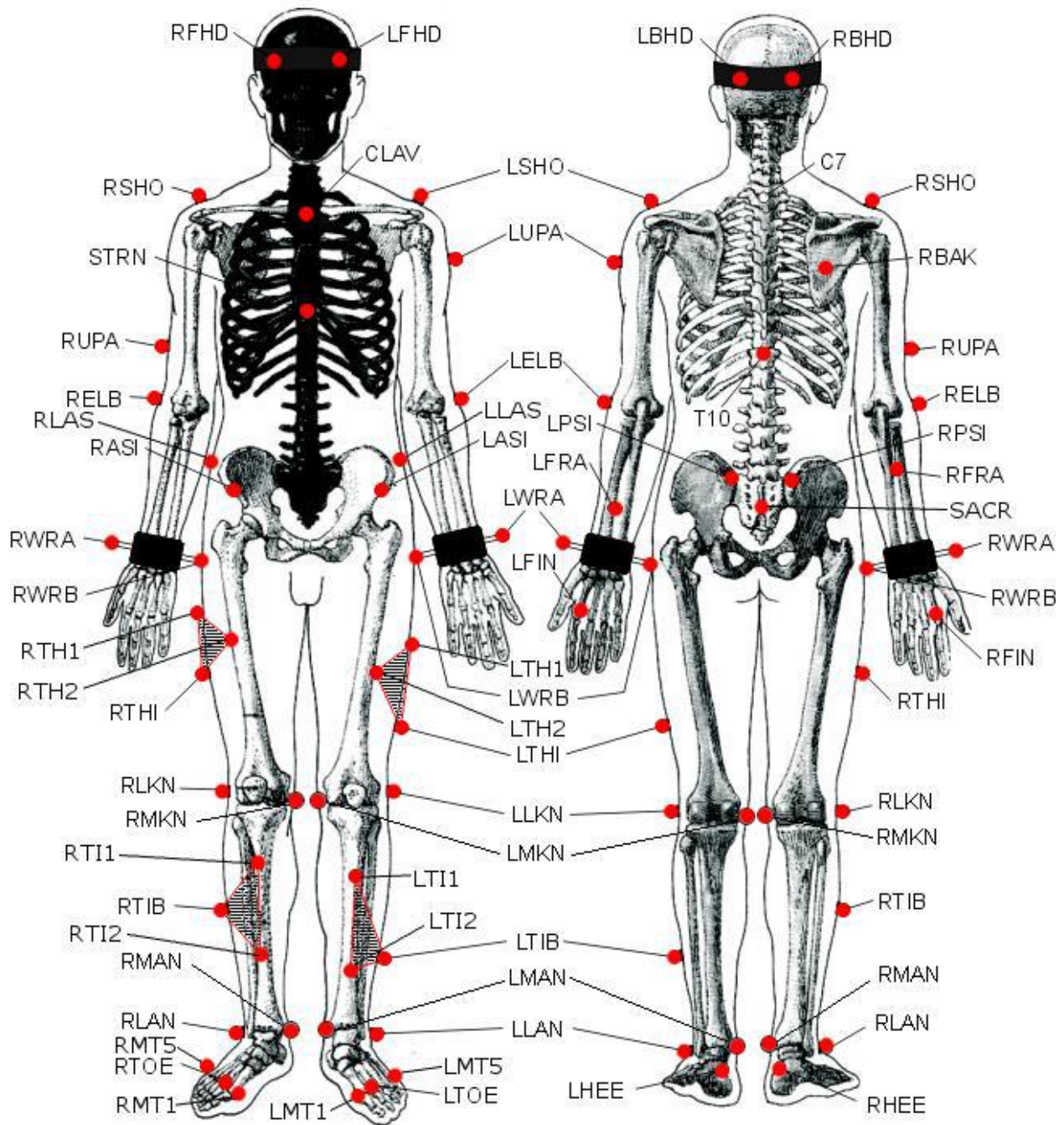


Figure A.2. Human Movement Biomechanics Laboratory (HMBL) cluster marker set. Plug-in-Gait marker set acts as the basis with the additions of medial knee and ankle (LMKN, RMKN, LMAN, RMAN) markers, two thigh (RTH1, RTH2, LTH1, LTH2), two tibial (RTI1, RTI2, LTI1, LTI2), and two metatarsal (RMT1, RMT5, LMT1, LMT5) markers. RTHI, LTHI, RTIB and LTIB are used as part of the cluster for right and left thigh, and right and left tibia segments, respectively (figure adapted from Mantovani and Lamontagne, 2016).

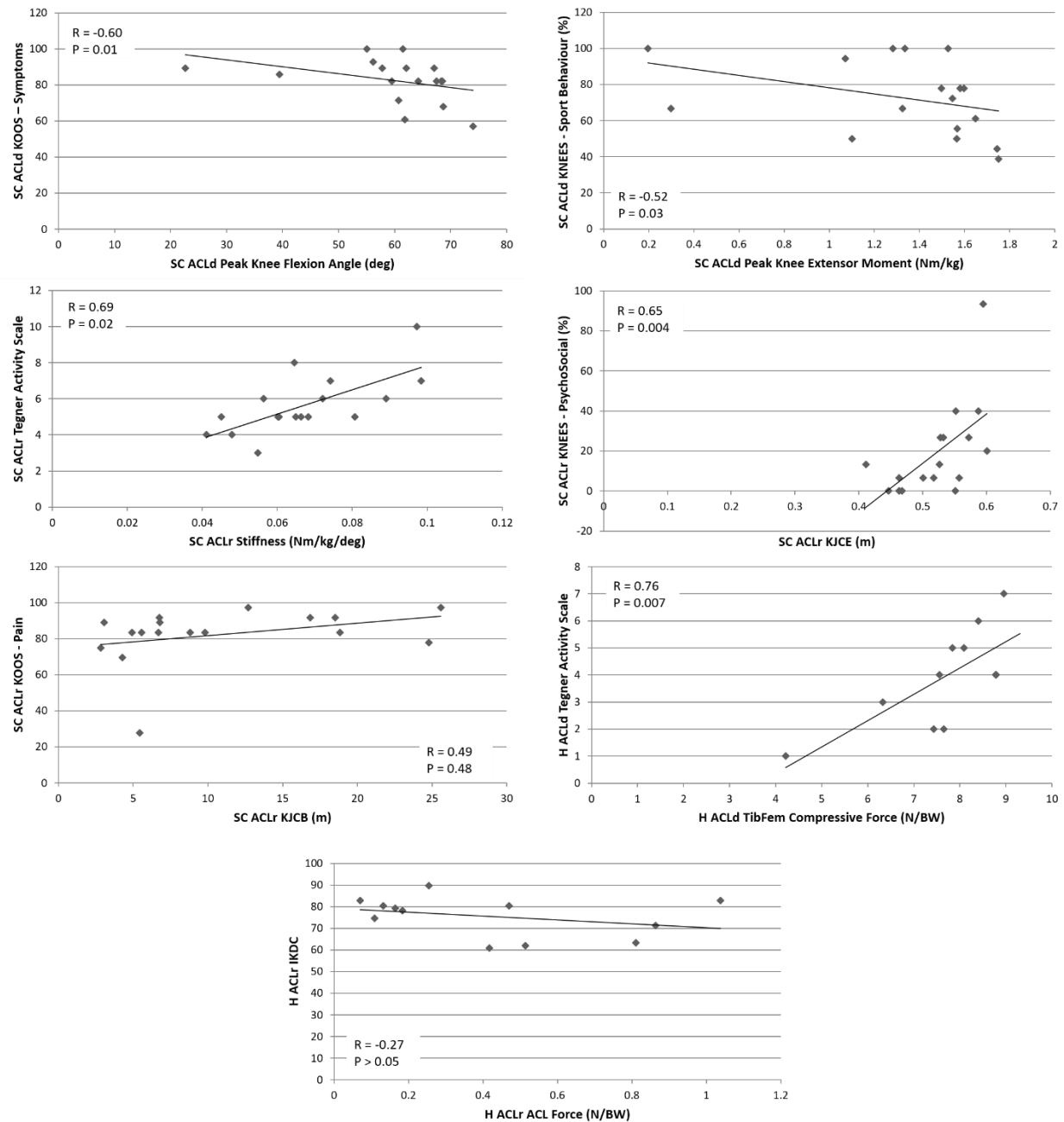


Figure A.3. Scatter plots of each objective measure with respect to the highest subjective measure correlation.

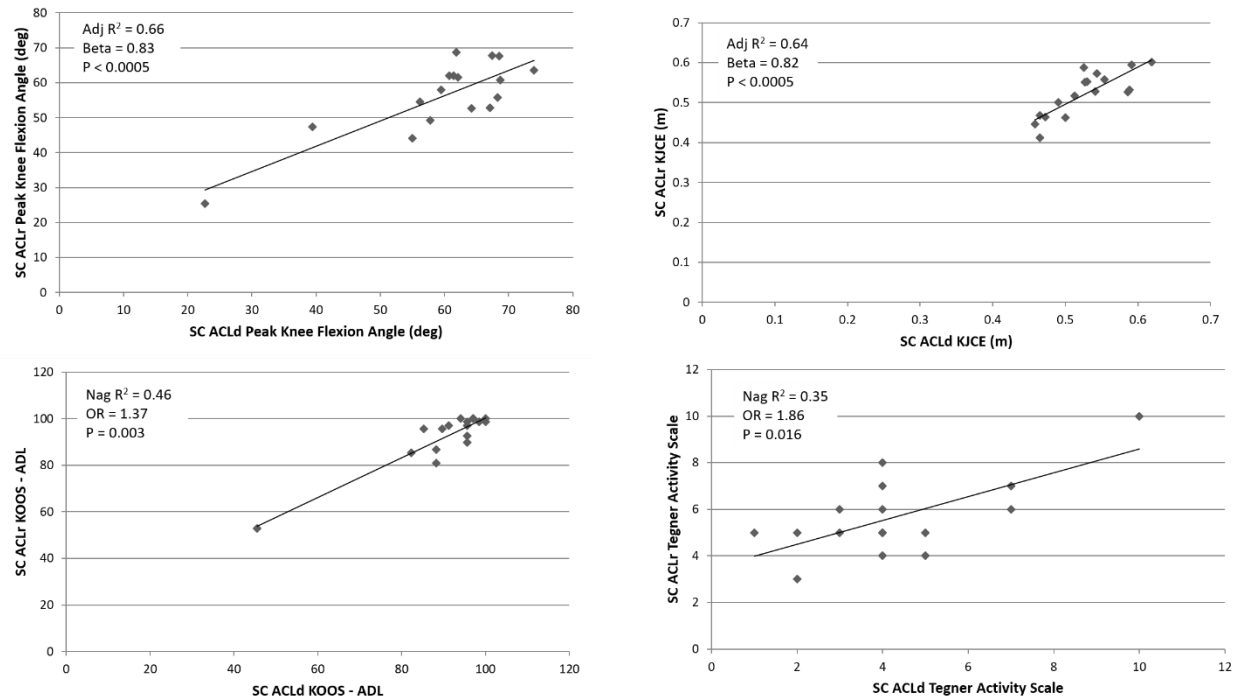


Figure A.4. Scatter plots of the ACLd predictability of ACLr values for the two highest objective and subjective measures.

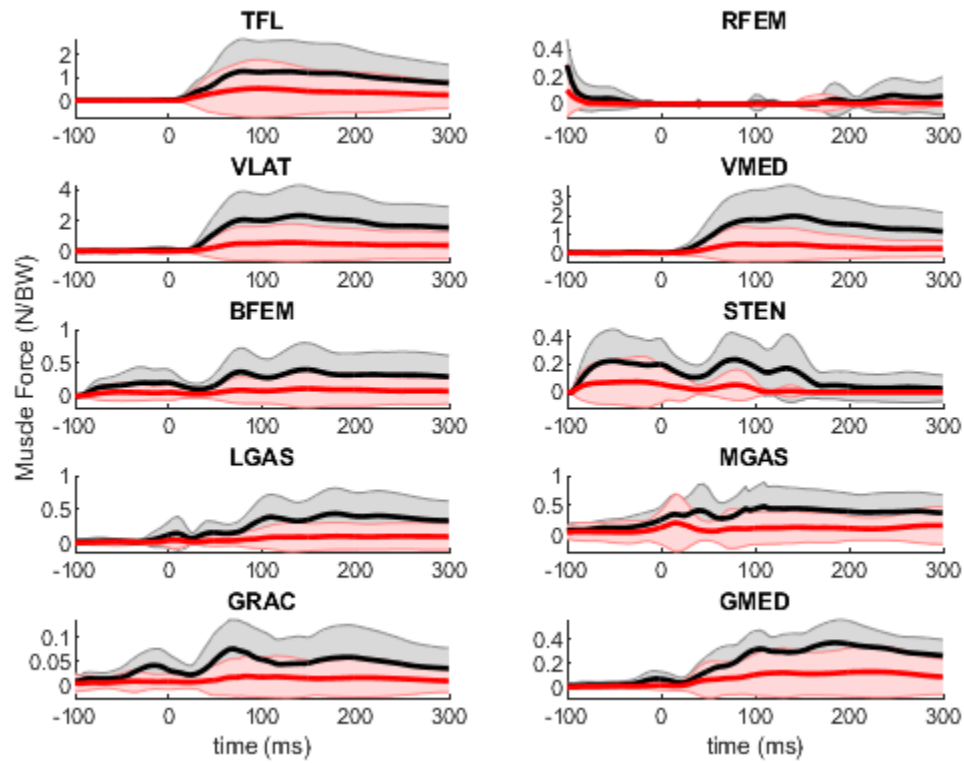


Figure A.5. Calculated muscle force mean and standard deviation clouds for ten muscles during the hopping motion. Time 0 represents initial contact while black indicates ACLd and red represents the ACLr groups.

File Number: H06-14-27

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Office of Research Ethics and Integrity

Ethics Approval Notice

Health Sciences and Science REB

Principal Investigator / Supervisor / Co-investigator(s) / Student(s)

<u>First Name</u>	<u>Last Name</u>	<u>Affiliation</u>	<u>Role</u>
Daniel	Benoit	Health Sciences / Physiotherapy	Principal Investigator
Tine	Alkjaer Eriksen	Others / Others	Co-investigator
Erik	Bruun Simonsen	Others / Others	Co-investigator
Teresa	Flaxman	Health Sciences / Others	Co-investigator
Michael	Rindom Krogsgaard	Others / Others	Co-investigator
Brent	Smale	Health Sciences / Human Kinetics	Co-investigator

File Number: H06-14-27

Type of Project: Professor

Title: Knee joint stability and neuromuscular control of the healthy and injured knee

Approval Date (mm/dd/yyyy)	Expiry Date (mm/dd/yyyy)	Approval Type
12/12/2014	12/11/2014	Ia

(Ia: Approval, Ib: Approval for initial stage only)

Special Conditions / Comments:

This project is taking place in Denmark, is lead by a Danish researcher and received ethics approval from the University of Copenhagen in September 2013. Due to confusion about process, Professor Benoit who was on sabbatical in Denmark, submitted the project for review in summer 2014 instead of submitting it immediately following the Danish approval. The University of Ottawa REB accepts that this was an honest error and following ethics review of the project has agreed to approve the submission.



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**Betydningen af led-instabilitet og nedsat motorisk kontrol for funktion og slid-
 gigtsudvikling i knæet hos kvinder og mænd
 – en ny metode med sigte på intervention**

Den Videnskabetiske Komite B for Region Hovedstaden har behandlet sagen på sit møde den 26. september 2013 og truffet følgende

Afgørelse:

Projektet godkendes i henhold til lov nr. 593 af 14. juni 2011 om videnskabetisk behandling af sundhedsvidenskabelige forskningsprojekter med senere ændring.

Godkendelsen gælder for de anmeldte forsøgsteder, den anmeldte forsøgsansvarlige i Danmark samt for den angivne forsøgsperiode.

Godkendelsen gælder til den 31. december 2014 og omfatter følgende dokumenter:

Protokol af 25.7.2013, version 1

Deltagerinformation incl. samtykkeerklæring af 25.7.2013, version 1

Annoncetekst, Opslag af 25.7.2013, version 1

Spørgeskemaer godkendt til brug i projektet: Spørgeskema til personer med korsbåndsskade, Subjektivt spørgeskema til evaluering af knæpatienter, Lysholm Score, dansk version okt. 2006, KOOS Spørgeskema til knæpatienter nov 1997

Godkendelsen gælder for de anmeldte forsøgsteder og den anmeldte forsøgsansvarlige i Danmark.

Iværksættelse af projektet i strid med godkendelsen kan straffes med bøde eller fængsel, jf. komitélovens § 41.

Ændringer:

Foretages der væsentlige ændringer i protokolmateriale under gennemførelsen af projektet, skal disse anmeldes til komiteen i form af tillægsprotokoller. Ændringerne må først iværksættes efter godkendelse fra komiteen, jf. komitélovens § 27, stk. 1.