TIBIOFEMORAL CONTACT AND ALIGNMENT USING UPRIGHT, OPEN MAGNETIC RESONANCE IMAGING (UO-MRI) IN PATIENTS WITH ANTERIOR CRUCIATE LIGAMENT (ACL) RUPTURE

by

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Abstract

Problem: Surgery to reconstruct the Anterior Cruciate Ligament (ACL) does not mitigate the elevated risk of arthritis after ACL rupture. There is indirect evidence of persistent contact and alignment changes in the tibiofemoral articulation post-reconstruction, but this has not been quantified with direct measurements in standing, weightbearing positions. Our aims were: 1) to establish the reliability and accuracy of a direct method of determining tibiofemoral contact with Upright, Open Magnetic Resonance Imaging (UO-MRI), 2) to assess differences in knees with ACL rupture treated nonoperatively versus operatively, and 3) to assess differences in knees with ACL rupture versus healthy knees.

Methods: Using UO-MRI, we investigated tibiofemoral contact area, contact centroid location, and alignment under standing, weightbearing conditions with knees extended. We assessed the inter-rater, test-retest, and intra-rater reliability in 5 participants with ACL rupture. We assessed accuracy by comparing the contact area of bovine osteochondral blocks axially loaded in a custom jig in the UO-MRI against a high resolution 7T MRI. We then conducted a biomechanical study involving 8 participants with ACL rupture treated nonoperatively and 10 treated operatively, all of whom were high functioning and had returned to sport. We compared contact area, centroid location, and alignment between the operative and nonoperative cohort, and in ACL-ruptured knees versus healthy contralateral control knees.

Results: Our methods demonstrated acceptable reliability for contact area and centroid location measurements, with intra-class correlation coefficients of 0.83 to 1.00 in the sagittal plane. Contact area measurement was accurate to within 4.8% measurement error. At a mean 2.7 years after injury, knees with ACL rupture had a 10.4% larger contact areas and a medial contact centroid that was located 5.2% more posterior. The tibiae of knees with ACL rupture

were 2.3mm more anterior, and 2.6° less externally rotated relative to the femur, than contralateral control knees. We found no differences between ACL-reconstructed and nonreconstructed knees.

Conclusion: ACL rupture was associated with significant mechanical changes 2.7 years out from injury, which ACL reconstruction did not restore. These findings may partially explain the equivalent risk of post-traumatic osteoarthritis in patients treated operatively and nonoperatively after ACL rupture.

Lay Summary

Anterior Cruciate Ligament (ACL) reconstruction does not mitigate the elevated risk of arthritis after ACL rupture, possibly because of persistently abnormal knee mechanics. We used an upright, open Magnetic Resonance Imaging (MRI) machine that allows for standing, weightbearing scans to investigate this. We first established that our measurements (contact area, location of contact, and knee alignment) were reliable and accurate. We then investigated a group of participants with ACL rupture, some of whom had undergone reconstruction and some had not. We found that ACL rupture led to greater contact between the tibia and femur bones, and altered the alignment of the tibia relative to the femur. These changes were present regardless of surgical reconstruction. Our results may partially explain the increased risk of arthritis after ACL rupture, and they provide motivation to identify surgical techniques that better restore healthy knee mechanics.

Preface

All of the work presented henceforth was conducted at the Centre for Hip Health and Mobility. All projects and methods were conducted under the ethical approval of the UBC Clinical Research Ethics Board (#H18-01459-A002) and under the operational approval of the Vancouver Coastal Health Research Institute (#V18-01459).

Statement of authorship:

This thesis represents the original work of David Stockton. David Wilson guided the development of the investigative methods and revised the thesis. The following individuals contributed to Chapter 3: Andrew Schmidt (collected accuracy data and drafted the Introduction and Discussion), Andrew Yung (implementation of T2 MRI sequence), Bas Masri (investigative methods and chapter editing), Michael Hunt (investigative methods and chapter editing), and David Wilson (senior author). David Stockton planned the study, collected and analyzed the data, and wrote and edited the manuscript which was submitted for publication in a peer-reviewed journal. The following individuals contributed to Chapter 4: Andrew Schmidt (scan segmentation and MATLAB code for tibial plateau reference frame), Andrew Yung (implementation of T2 MRI sequence), Jane Desrochers (investigative methods and chapter editing), Honglin Zhang (implementation of joint coordinate system and MATLAB code for alignment), Pierre Guy (participant recruitment and chapter editing), Bas Masri (investigative methods and chapter editing), and David Wilson (senior author). David Stockton planned the study, obtained ethics and funding, collected and analyzed the data, and wrote and edited the manuscript which was submitted for publication in a peer-reviewed journal.

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List of Abbreviations

ACL	Anterior cruciate ligament
DESS	Double energy steady state
LET	Lateral extra-articular tenodesis
MRI	Magnetic resonance imaging
RSA	Roentgen stereophotogrammetric analysis
UO-MRI	Upright, open MRI

Glossary

- Intraclass correlation coefficient (ICC):

A descriptive statistic used for quantitative measurements made on units that are organized into groups. The coefficient describes how strongly units in the same group resemble each other. For the purpose of this thesis, <0.50 is poor; 0.50 to 0.75 is moderate, 0.75 to 0.90 is good, and >0.90 is excellent.

- Smallest Detectable Change with 95 Percent Confidence (SDC_{95}):

An estimate of the smallest amount of change that can be detected by a measurement; alternatively called minimal detectable change or minimal important change.

$$SDC_{95} = 1.96 \times SEM \times \sqrt{2}$$

- Standard error of measurement (SEM):

A reliability measure that assesses response stability, it estimates the amount of error in a set of repeated scores.

$$SEM = standard\ deviation \times \sqrt{(1 - ICC)}$$

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To my wife Kaitlin and daughter Ella,

Thank you for your incredible support.

Chapter 1: Introduction

Over 20 years ago Dr. Cy Frank remarked that, "Very few subjects in contemporary orthopaedic surgery have evoked as much controversy, thought, and opinion as that of when and how to optimally reconstruct the anterior cruciate ligament of the knee" [1]. This observation was as true then as it is now. It is an injury that sparks curiosity in researchers in different fields, from physiotherapists to basic scientists to surgeons, but no one is more affected by the advancement of ACL research than the patients themselves. There is continued debate surrounding the role and timing of ACL reconstruction[2, 3], the re-emergence of adjunct extra-articular procedures that aim to improve kinematics and ACL survivorship[4, 5], and sustained discussion about ACL graft selection and reconstruction technique[6]. All of these treatment decisions are critically informed by basic science research around contact mechanics, alignment, kinematics, and gait. This injury is perhaps one of the best examples of the tight link between research "at the bench" and treatment "at the bedside."

ACL rupture is one of the most prevalent knee injuries, with an estimated incidence of 69 per 100,000 person-years[7] leading to over 100,000 ACL reconstructions yearly in the United States[8]. The diagnosis carries with it long-term consequences that no intervention has been able to successfully mitigate, as approximately 50% of affected patients develop osteoarthritis within 10-20 years[9]. The most popular treatment, surgical reconstruction, aims to restore the compromised ACL's anatomy and function including normal knee mechanics. While surgery has proven effective at reducing symptoms of dynamic instability, surprisingly,

it has not been shown to mitigate the risk of post-traumatic osteoarthritis[10]. Many of these patients truly become "young patients with old knees" [9].

Several theories attempt to explain the pathogenesis of post-traumatic osteoarthritis. Altered knee mechanics have been put forward as a leading theory, as a change in the loading and shearing patterns of articular cartilage may result after anatomic constraints that guide normal knee motion are compromised[11]. Knee hyaline cartilage is an avascular, aneural, viscoelastic structure that distributes load and lubricates tibiofemoral motion[12]. The local mechanical environment guides the structural organization of cartilage regions, therefore if a shift in loading pattern occurs with an ACL rupture, the newly loaded regions may not be able to sufficiently adapt[13]. Other theories have been put forward as well. The inflammatory reaction that develops after injury and the blunt cartilage impact that occurs at the time of injury have both been implicated[14], as have injuries to associated structures, in particular the menisci[15] and anterolateral capsule[16].

To date, no method has successfully used a single imaging modality to directly examine *in vivo* weightbearing changes associated with ACL rupture, or the effect of reconstruction. This is critical to support or refute the theory that implicates altered knee mechanics in the development of post-traumatic osteoarthritis. Upright, open MRI (UO-MRI) is a promising method in that regard. It has demonstrated excellent reliability and has been successfully applied to the study of the patellofemoral joint[17, 18]. Clinically important outcome measures that are implementable in UO-MRI include contact area, contact centroid location, and 6 degrees of freedom tibiofemoral alignment.

1.1 Research aims

We do not understand the mechanical changes that exist between high-functioning individuals with ACL rupture that have been treated operatively versus nonoperatively. Such mechanical changes have not been directly measured *in vivo* under physiologic weightbearing conditions. We have the ability to pursue this question using UO-MRI. This promising technique is well-suited to advance knowledge in this area, as knee cartilage behaviour appears to be highly dependent on the magnitude and direction of load applied.

The aims of the present study are:

I. To establish the reliability and accuracy of *in vivo* tibiofemoral contact area and centroid location in a fully extended, weightbearing posture in the UO-MRI.

II. To examine differences in contact area, centroid location, and alignment between individuals with ACL rupture who have been treated with reconstruction versus nonreconstruction.

III. To examine differences in contact area, centroid location, and alignment between knees with ACL rupture and healthy control knees.

Following a literature review in Chapter 2, Chapter 3 of the thesis addresses Aim I and presents the reliability and accuracy of our methods. Chapter 4 addresses Aims II and III and presents the results of a unique biomechanical study that was designed to address these aims. Chapter 5 concludes the work completed and lays the groundwork for future investigations.

Chapter 2: Literature Review

2.1 Normal knee anatomy with reference to the ACL

The ACL is the most commonly injured knee ligament and consists of 90% Type I collagen and 10% Type II collagen. It is composed of an anteromedial and posterolateral bundle. The ACL originates on the posteromedial surface of the lateral femoral condyle and inserts anteriorly and slightly medial to the midline on the tibial plateau. The primary function is as a restraint against anterior tibial translation relative to the femur, and it also has important secondary functions resisting internal rotation and varus in full extension[19].

Hyaline cartilage is the nonlinear, anisotropic, viscoelastic connective tissue that, under normal conditions, provides a nearly frictionless surface for the transmission and distribution of joint loads[12, 20]. There is strong evidence that abnormal joint loading can significantly affect the composition, structure, metabolic activity, and mechanical properties of articular hyaline cartilage[20], ultimately resulting in arthritis. For this reason, transection of the ACL has been the most widely used animal model for studying degenerative processes in the knee. Following ACL transection, the ensuing alterations in joint loading have been associated with a multitude of changes in articular cartilage, leading to the hypothesis that there is a causal link. Morphologic and histologic changes include fibrillation of the articular surface and loss of collagen fibril organization[21]. Compositional changes include an increase in water content, decreased concentration of collagen cross links, and alterations in the number and size of proteoglycan aggregates[22-24]. Biomechanical properties change, including

decreases in the tensile, compressive, and shear moduli, and increased hydraulic permeability of the tissue[25, 26].

2.2 Mechanism of injury

In vivo, ACL rupture is rarely an isolated event. Meniscal tears, especially of the lateral meniscus, can occur at the same time, as can injury to the anterolateral capsule[16]. Post-injury MRI often reveals osteochondral lesions, or bone bruises, most commonly on the posterolateral tibial plateau and anterolateral femoral condyle[14]. Taken together, the injury itself seems to occur often in non-contact situations, with the knee at or near full extension during a pivoting movement with axial loading[27]. Once the elastic limit of the ACL is surpassed, rupture occurs, resulting in subluxation of the knee with excessive internal rotation and anterior translation such that the posterolateral tibial plateau contacts the anterolateral femoral condyle, with varying degrees of injury to associated soft tissues.

2.3 Joint biomechanics measurement using MRI

Human joints serve a primarily biomechanical purpose[28]. Our ability to measure the role of biomechanics after ACL injury is limited by the challenge of measuring important biomechanical parameters *in vivo* under physiologic weightbearing conditions[11]. Non-MRI methods are useful but are limited in the assessment of cartilage behaviour. Two current MRI approaches include using dual modalities that combine standing biplanar radiography with supine MRI or using supine MRI with simulated weightbearing. Combining biplanar radiographs matched, or registered, to MRI images is a popular method that yields information about contact area, contact centroid location, and alignment[29-31]. MR-only

methods have used loading rigs to simulate weightbearing in supine MRI and can yield similar quantitative biomechanical measurements[32, 33].

2.3.1 Non-MRI methods

Much of our early understanding of knee biomechanics stems from cadaveric studies using simulated loads, which are limited by the difficulty of replicating physiologic load in living tissue. Mathematical models, including finite element analysis and inverse dynamics approaches, are limited by the simplifications and assumptions required[28]. Roentgen stereophotogrammetric analysis (RSA) involves the implantation of tantalum beads onto the bone during surgery followed by kinematic assessment with biplanar radiography during functional tasks like running[34]. This method is invasive and only allows for the study of surgically treated conditions. Motion-capture methods of kinematic assessment that use either optoelectric or video-based system rely on superficial skin markers that can shift relative to underlying bone by as much as 30mm[34]. All of these methods are limited in their assessment of cartilage behaviour *in vivo*, whereas MR-based methods are much better able to assess joint cartilage.

2.3.2 Supine MRI

The biomechanics of the knee after ACL rupture have been investigated under weightbearing conditions using standard clinical MRI machines with the addition of an MR-compatible load-bearing apparatus[32, 33, 35]. In this method, the participant lies supine on the table with the knee supported between two plates of a knee coil. The participant's feet rest against a foot plate that imparts an axial load to the leg via an MR-compatible loading rig that

uses pulleys and weights (Figure 2.1). Regions of cartilage-to-cartilage contact are segmented from MR images resulting in contact area and centroid measurements. The implementation of a joint coordinate system using bony landmarks allows for the determination of joint alignment and kinematics. This method has been a useful, non-invasive method of evaluating cartilage behaviour *in vivo*, with excellent ability to visualize cartilage without ionizing radiation[28].

This method is limited by the simulated nature of the 'weightbearing' axial load. The loads applied are usually low[11], and the effect of gravity in a supine MRI is orthogonal to that experienced in a standing position. This may have an unintended effect on the position of the tibia relative to the femur, and may result in postural muscle recruitment that is different from that experienced when a person is standing.

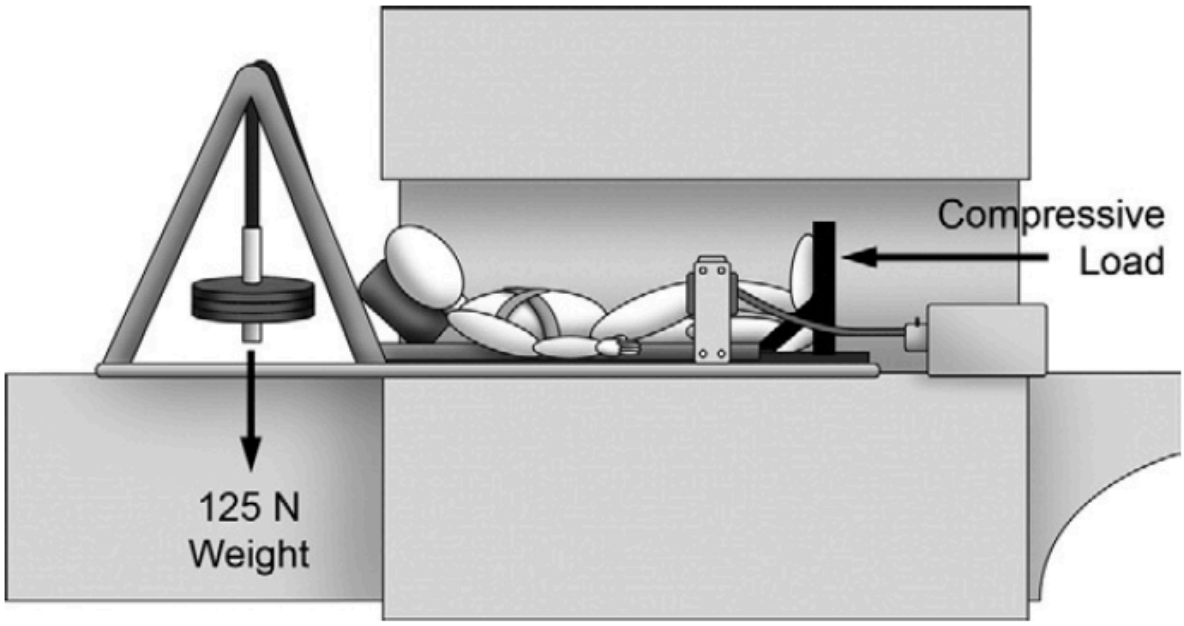

Figure 2.1 Experimental setup for knee biomechanical assessment using supine MRI. Weights are hung behind the patient in the MRI system, and a set of pulleys and a loading plate transfer the force into a compressive load at the foot. The phased-array paddle coil is attached to the medial and lateral sides of the knee, and a knee-positioning plate provides feedback to help ensure a consistent angle of knee flexion. *Reprinted from Carpenter RD, Majumdar S, Ma CB. Magnetic resonance imaging of 3-dimensional in vivo tibiofemoral kinematics in anterior cruciate ligament-reconstructed knees. Arthroscopy. 2009 Jul;25(7):760-6. © 2009 Arthroscopy Association of North America, with permission from Elsevier.*

2.3.3 Dual modality biplanar radiography with MRI image matching

The addition of biplanar radiographic assessment overcomes some of the limitations of supine MRI. In this dual modality method, participants are first scanned in the supine position using standard clinical MRI. MR images are processed using filters that detect edges and knee models are created using solid-modeling software. Next, participants are imaged in upright, weightbearing postures using a biplanar radiographic system. The participant pauses for 5 seconds at varying degrees of knee flexion while the orthogonal X-ray machines capture images (Figure 2.2). These biplanar images are then imported into the solid-modeling software and matched, or registered, to the MRI images. From these matched images, the positions of the tibia relative to the femur at varying degrees of knee flexion are calculated using a joint coordinate system. Areas of cartilage overlap are inferred to represent cartilage contact area, from which contact centroid can be calculated[29, 30].

This method is limited by the indirect method of inferring cartilage contact. The need for dual modalities and the subsequent step of combining and synthesizing the data that each produce may make the process onerous and difficult to implement on a larger scale.

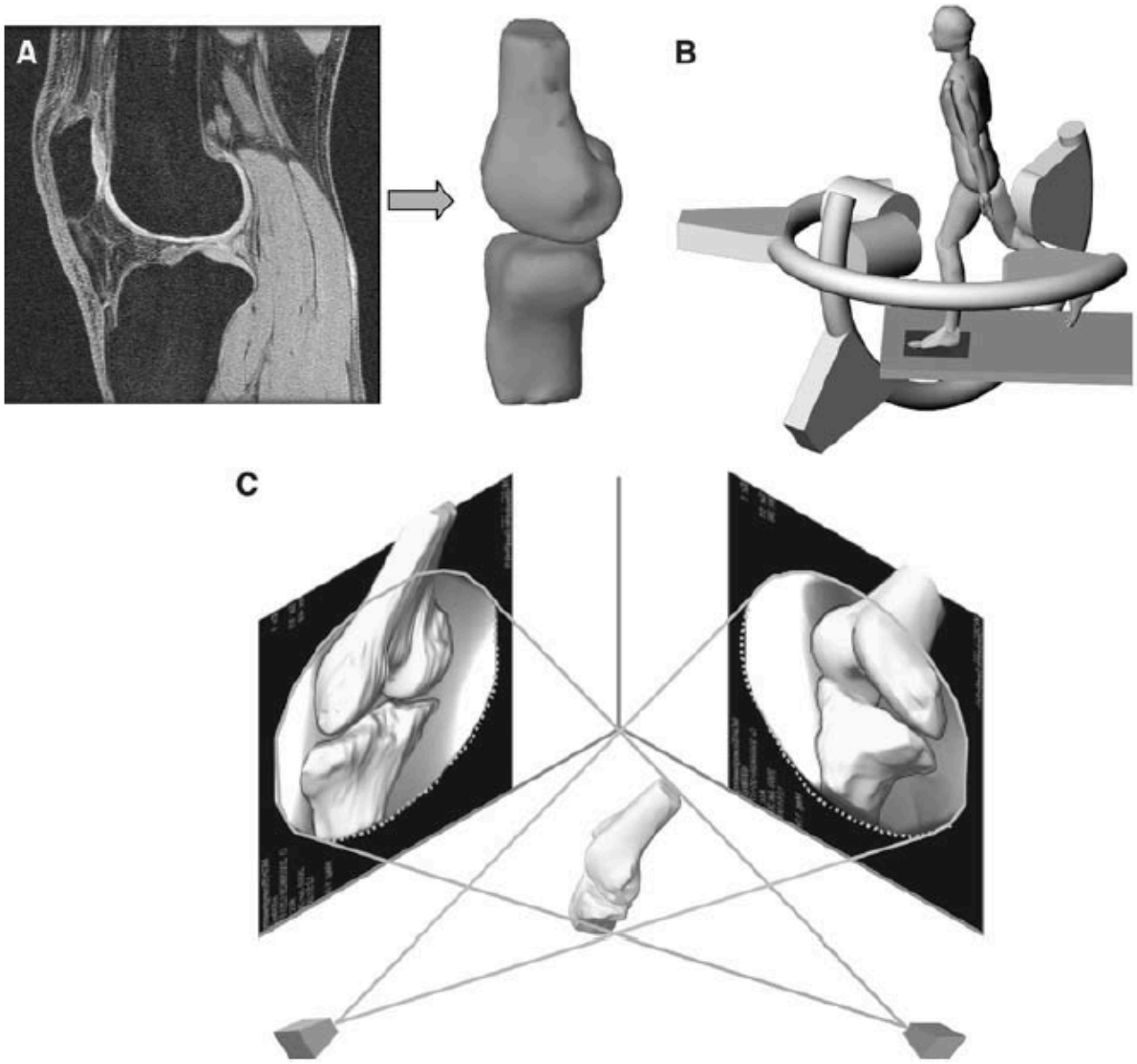

Figure 2.2 Method using biplanar radiography and supine MRI. A, an MRI-based knee model from a typical specimen. B, schema of a patient performing the quasi-static lunge inside the dual orthogonal fluoroscopic imaging system. C, schema of the virtual environment used to reproduce the knee joint kinematics of the patients. *Reprinted from Defrate LE, Papannagari R, Gill TJ, Moses JM, Pathare NP, Li G. The 6 degrees of freedom kinematics of the knee after anterior cruciate ligament deficiency: An in vivo imaging analysis. Am J Sports Med. 2006 Aug;34(8):1240-6. © 2006 SAGE Publications, with permissions gratis reuse from SAGE Publications.*

2.3.4 Upright, open MRI

Open bore MRI scanners allow for images to be acquired under upright, physiologic, weightbearing conditions (Figure 2.3). Scanning in an open bore configuration also allows for greater flexion angles, which are usually limited to <50° in closed bore scanners[11]. A knee coil is suspended from a belt, and support bars are placed to minimize participant motion. The UO-MRI has been successfully used to study patellofemoral osteoarthritis[17, 18]. The open bore method was uniquely suited for that application because patellofemoral osteoarthritis is typically exacerbated during upright weightbearing tasks[18].

There are some drawbacks to MRI scanning in functional postures. The scan sequences typically have to be shorter in order to minimize movement artifact[11]. Additionally, the magnetic field of 0.5T is lower than most clinical MRI scanners. This is currently the maximum achievable magnetic field strength that can be achieved with an open bore MRI.

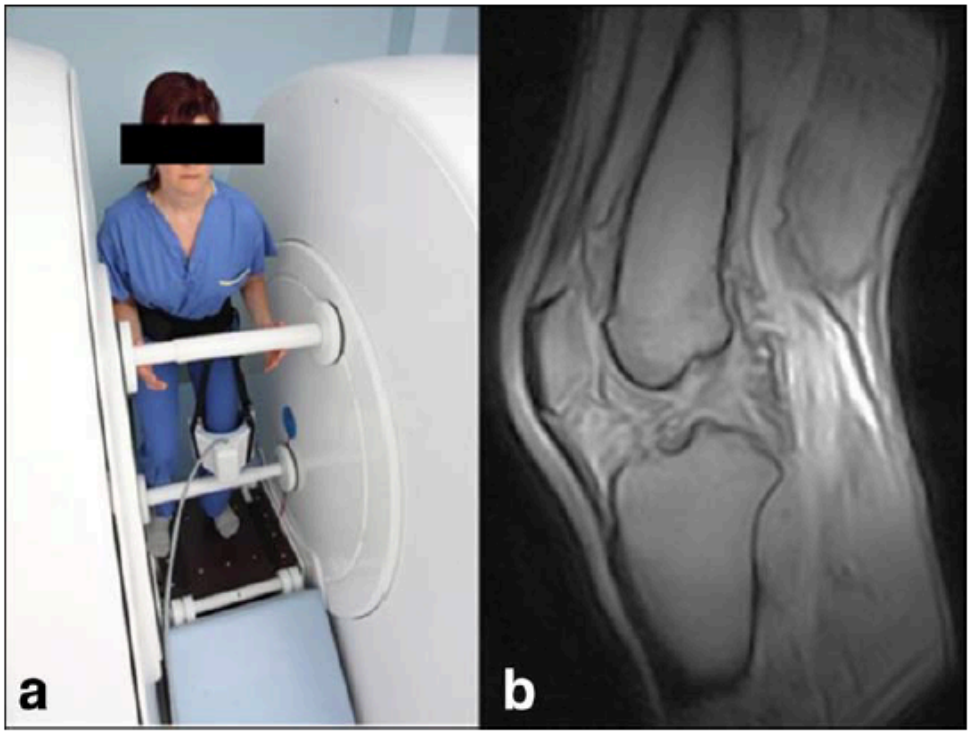

Figure 2.3 Upright, open MRI assessment. **a:** Standing with 30° knee flexion using support bars (goniometer and foot map not shown). **b:** Sample image taken from 0.5T scanner in upright weight-bearing position. *Reprinted from Macri EM, Crossley KM, d'Entremont AG, Hart HF, Forster BB, Wilson DR, Ratzlaff CR, Goldsmith CH, Khan KM. Patellofemoral and tibiofemoral alignment in a fully weight-bearing upright MR: Implementation and repeatability. J Magn Reson Imaging. 2018 Mar;47(3):841-7. © 2017 International Society for Magnetic Resonance in Medicine, with permission from John Wiley & Sons, Inc.*

2.4 Outcome measures

The most common outcome measures produced by methods that involve MRI include cartilage contact area, contact centroid location, and joint alignment. For the purpose of this discussion, the reader may assume that the position of the knee in which these measures were assessed was full extension, unless otherwise stated. Extension is the position in which the most marked mechanical differences have been noticed in previous studies[30, 31, 36], and it is the position of the knee in midstance of gait when the majority of body weight is transmitted through the knee. It is therefore the position around which our experiments are based.

2.4.1 Contact area and contact centroid location

Cartilage contact area is critical to understanding load transmission through the joint[11]. Alteration in the magnitude and location of tibiofemoral joint contact is hypothesized to contribute to the development of knee osteoarthritis following ACL injury[37, 38]. The magnitude of tibiofemoral joint contact can be represented as the area of directly opposing cartilage, both in the medial and lateral compartments of the knee. Semi-automated and manual methods of contact area determination have been described. The manual method, which involves tracing the regions of cartilage contact in a slice-by-slice manner, demonstrated less error in the UO-MRI[39]. Centroid location is found by calculating the geometric center of the contact area.

MRI determination of tibiofemoral contact area and centroid location has demonstrated reliability when performed in a 3T MRI. For contact area, Chen et al. reported ICCs of 0.90 medially and 0.92 laterally for inter-rater reliability; and 0.973 medially and

0.973 laterally for intra-rater reliability[33]. For centroid location, they reported ICCs of 0.991 medially and 0.909 laterally for inter-rater reliability; and 0.996 medially and 0.905 laterally for intra-rater reliability[33]. These estimates were made using a sample of 10 cases with inter-rater reliability determined between two raters, and intra-rater reliability determined by one rater repeating the analysis 2 weeks apart. Scans were taken supine with the knees in extension, with 25% artificial body weight applied.

Bingham et al. tested the accuracy of contact area determination using biplanar radiography and 3T MRI. They tested the medial and lateral compartment contact areas of 3 human cadaveric knee specimens against a 'gold standard' silicone casting method. The measurement error was determined to be 14±11% between the two methods[40].

2.4.2 Alignment

Joint alignment refers to the relative positions of bony segments to each other, described by the 6 degrees of freedom, at a single position. One of the most widely used conventions is the joint coordinate system proposed by Grood and Suntay (Figure 2.4)[41]. This consists of two Cartesian coordinate systems, one assigned to the femur and one to the tibia, based on standardized bony landmarks. To briefly explain its implementation, capitalized letters *X*, *Y*, and *Z* denote the femoral axes with **I**, **J**, **K** as the respective base vectors, and *x*, *y*, and *z* for the tibial axes with base vectors **i**, **j**, **k**.

The clinical motion of interest in the tibia that helps define its coordinate system is internal/external rotation (also referred to as the body fixed axis). This, the *z* axis, is defined

as the point passing midway between the two intercondylar eminences proximally and through a point midway between the tips of the medial and lateral malleoli distally (i.e. the centre of the ankle). The tibial anterior direction, or *y* axis, is taken as the cross product of the *z* axis and a line connecting the centre of each tibial plateau. The final *x* axis is obtained by completing a right-handed coordinate system.

The clinical motion of interest in the femur that helps define its coordinate system is flexion/extension (i.e. the body fixed axis). To obtain this, the *X* axis, one first defines the *Z* axis. Proximally, the *Z* axis passes through the centre of the femoral head. At the knee, it passes through the most distal point on the posterior surface of the femur that is also midway between the medial and lateral condyles. Then, the *Y* axis is defined which is the cross product of the Z axis and a line connecting the two points on the posterior surface of the femoral condyles. Finally the X axis is the cross product of **J** and **K**, the base vectors of the femoral anteroposterior (*Y*) and mechanical (*Z*) axes.

The elegance of the Grood and Suntay method comes in the incorporation of the tibial and femoral coordinate systems into an overall joint coordinate system. The cross product of **k** (base vector for tibial *z* axis) and **I** (base vector for femoral *X* axis) equals **F**, which corresponds to the 'floating' axis about which abduction/adduction occurs. Thus, two coordinate systems are defined for the tibia and femur and combined into a joint coordinate system. With regards to description of alignment, the 3 rotations are derived from the axes previously mentioned. The 3 translations (superior/inferior, anterior/posterior, and medial/lateral) can be derived by keeping the origin of one segment constant (the femur), and calculating the movement of the tibial origin relative to it.

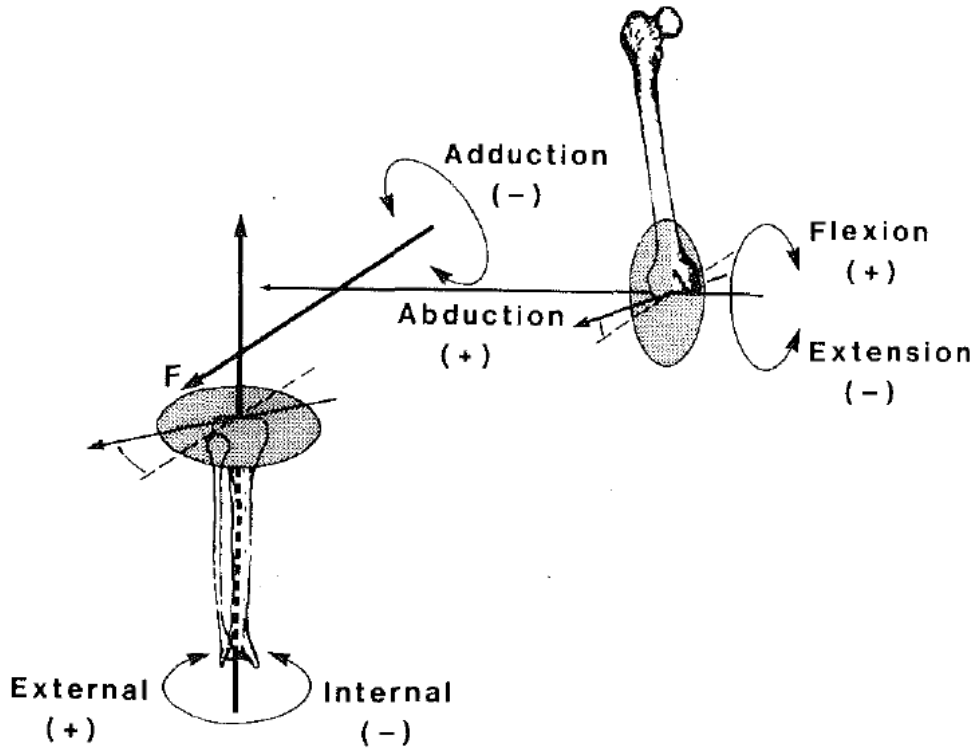

Figure 2.4 Joint coordinate system. Joint angles are defined by rotations occurring about the three joint coordinate axes. Flexion extension is about the femoral body fixed axes. External/internal tibial rotation is about the tibial fixed axis and ab/adduction is about the floating axis (F). *Reprinted from Grood ES, Suntay WJ. A joint coordinate system for the clinical description of three-dimensional motions: Application to the knee. J Biomech Eng. 1983 May;105(2):136-44. ©1977 American Society of Mechanical Engineers ASME, with permission from the American Society of Mechanical Engineers ASME.*

Macri et al. assessed the test-retest repeatability of using this joint coordinate system in the UO-MRI[17]. ICCs for the 3 rotations and 3 translations ranged from 0.95 to 0.99. The smallest detectable change with 95% confidence (SDC_{95}) for flexion was 3.24°; adduction: 1.47°; internal rotation: 3.41°; proximal translation: 0.80mm; lateral translation: 0.91mm; and anterior translation: 1.30mm.

MR-based measures of determining knee alignment have been rigorously tested for accuracy. These methods have used the dual modality technique of obtaining upright, weightbearing biplanar radiographs and matching those models to supine MRI images. Using this technique, DeFrate et al. reported measurement errors for translation of 0.04±0.06mm, and for rotation of <0.3° [29]. These estimates were obtained by comparing their dual modality method against a materials testing machine (QTest 5, MTS, Minneapolis, MN).

2.5 Knee biomechanics in ACL injury

2.5.1 Healthy knees

Reference data for contact area in healthy knees is scant, but some information can be gleaned from healthy control knees used in previous studies. In full knee extension, Van de Velde et al. reported a medial contact area of 314.4±113.6mm^2 in healthy control knees, and a lateral contact area of 193.4±75.2mm^2 [(31)]. Carpenter et al. found a medial contact area of 298±63mm^2 and a lateral contact area of 195±45mm^2 [(32)]. These studies, however, used the dual modality method to determine contact area. The contact area was therefore interpolated using supine MRI images from radiographic models under weight-bearing conditions. This was done as part of a quasi-dynamic lunge task, with the participant pausing for 5 seconds in varying degrees of flexion while the biplanar radiographs were acquired. This method may not allow for cartilage creep, that is, time-dependent cartilage deformation for a given compressive load[42], whereas a method using standing MRI accounts for this phenomenon as the upright scan sequences are usually a few minutes long. Additionally, different MRI

sequences have an effect on the observed contact area. In a group of female subjects with medial knee arthritis imaged supine with artificial axial loads, Shin et al. observed a contact area of 238.8±20.7mm^2 in the medial compartment and 138.3±17.6mm^2 in the lateral compartment using a 3D SPGR (spoiled gradient-recalled) sequence. However, using a T2 FSE (fast spin-echo) sequence, the observed contact areas in the same subjects were 186.0±15.5mm^2 medially and 93.0±11.6mm^2 laterally[43]. This was likely due to the differential abilities of the sequences to enhance cartilage signal.

Reference data for centroid location in healthy knees does not exist due to the lack of a standard reference frame for the tibial plateau on which to represent the data. Previous studies have fit ovals to the medial and lateral compartments and used their midlines in the anteroposterior and mediolateral direction as references[30, 32].

There is a paucity of MRI-based measures of normal knee alignment. With no consensus on a reference frame in which to represent the 3 translations (anterior/posterior, medial/lateral, and superior/inferior), there is no reference data that reports the position of the tibia relative to the femur. There are, however, some reference data for the 3 rotations (internal/external rotation, flexion/extension, and varus/valgus) that have been derived using biplanar fluoroscopy models matched to MRI images. In healthy knees in full extension, Defrate et al. found the tibiae to be 4.9±7.2 degrees externally rotated relative to the femur, and in 3.2±4.4 degrees of valgus[29]. Papannagari et al. found the tibiae to be in 5.4±7.6 degrees of external rotation relative to the femur[44]. These measurements may vary slightly based on the bony landmarks used to define the planes of translation and the axes of rotation.

2.5.2 ACL deficiency

Recent studies have generally found that ACL deficiency is associated with a smaller contact area especially in the medial compartment, with translation of the medial centroid posteriorly. In a study of 31 patients that used supine MRI with 25% body weight applied, at full knee extension, ACL-deficient knees had a smaller contact area by 14.3mm^2 in the medial compartment with non-significant changes in the lateral compartment[33]. In another study that used the dual modality method in 8 patients imaged 4.4 months after their injuries, ACL-deficient knees had a smaller contact area by 94.8mm^2 medially and 56.3mm^2 laterally[31].

The posterior translation in centroid location appears to correspond with an anterior translation of the tibia relative to the femur. DeFrate et al. found that tibiae in ACL-deficient knees were 3.5mm more anterior relative to the femur than in healthy controls, in a study of 8 patients imaged 7 months after their injury and prior to undergoing ACL reconstruction[29]. Shefelbine et al. similarly found that the tibiae of ACL-deficient knees were 2.6±1.7mm more anterior relative to the femur than healthy controls[35]. Differences in the other translations and rotations were less commonly reported. DeFrate et al. noted an approximate 4° less external rotation in ACL-deficient knees, but this finding was not significant.

2.5.3 ACL reconstruction

Earlier assessments of knee alignment used static three-dimensional RSA, which evolved over many years to allow dynamic testing. This became especially useful in assessing the degree to which ACL reconstruction restores normal tibiofemoral kinematics.

Tashman et al. utilized this type of analysis under dynamic, stressful loading in a population of 6 patients with unilateral ACL ruptures that had been reconstructed, using the contralateral healthy knee as a control[34]. Small tantalum spheres were permanently attached intra-operatively to various locations on the femur and tibia intra-operatively, and biplanar dynamic RSA was used to provide 3D kinematic analysis of the subjects during a downhill run on a treadmill at moderate speed. After ACL reconstruction, they found that anterior stability was restored, but the tibiae of ACL-reconstructed knees were 3.8° more externally rotated relative to the femur and 2.8° more adducted than healthy control knees. They concluded that ACL reconstruction failed to restore normal 3D rotational tibiofemoral motion under dynamic, stressful loading[34].

MRI-based methods support these invasive RSA investigations, showing that mechanical changes persist in contact and alignment post-ACL reconstruction. Hosseini et al. followed up post-ACL reconstruction on the same cohort reported on preoperatively by Van de Velde et al.[31]. They showed that contact area remained significantly decreased by 77.4mm^2 medially and 38.4mm^2 laterally relative to healthy contralateral knees[36]. These changes were present at the 6 month postoperative mark. Chen et al. followed their ACL-reconstructed cohort postoperatively, and at 6 months they reported that the medial contact area remained smaller by 18.32mm^2, with no statistically significant changes laterally compared to the healthy contralateral side[33]. Interestingly, the authors continued to follow their cohort for 2 years, at which point there was no difference in the medial contact area compared to the healthy side, and the lateral contact area showed a larger contact area by 24.5mm^2. The medial centroid locations also remained posteriorly translated in both studies. Hosseini et al. reported not just a posterior shift of the medial centroid, but also a lateral shift

by 4.5mm, towards the tibial spine[36]. The authors remarked that the medial tibial spine is often an area that experiences significant arthritic changes, and a shift in the loading location may partially account for that[31].

Alignment changes were less commonly reported. Papannagari et al., in an MR-based study examining post-ACL reconstruction knee alignment in 7 participants, reported that the tibiae remained 2.9mm more anterior than the healthy contralateral side post-surgery[44]. They also noted that ACL-reconstructed knees were 2.7° less externally rotated than healthy knees (tibia relative to femur). However, Carpenter et al. observed that ACL-reconstructed knees were 5° more externally rotated than healthy knees[32]. Carpenter et al. used artificial loading in a supine MRI, whereas Papannagari et al. used the dual modality method combining standing biplanar fluoroscopy with supine MRI images. It is likely that the positioning, postural, and gravitational effects on the knee joint in each of these methods partially accounts for some of the discrepancies in their findings. In this respect, each of these methodologies are somewhat limited in their external validity.

2.6 Literature summary and gaps in knowledge

The consequences of ACL rupture can be summarized as follows:

- Animal models have shown histologic, biochemical, structural, and biomechanical changes that occur as a result of ACL transection, leading to the final common pathway of cartilage degeneration and osteoarthritis[20-24].

- Clinical studies with long term follow-up have shown a significantly increased risk of knee arthritis after ACL rupture, whether treated with surgery to reconstruct the ACL or not[9, 45].
- Non-MRI based methods of knee kinematic assessment *in vivo* (RSA, optoelectric tracking, finite element analysis, etc.) suggest persistently abnormal knee kinematics post-ACL reconstruction[34, 37].
- MRI-based methods permit assessment of tibiofemoral cartilage biomechanics. Soon after ACL rupture, studies show that contact area in the medial and lateral tibiofemoral compartments decreases, and the location of contact in the medial compartment shifts posteriorly and possibly laterally. There is less consensus on the lateral centroid, but some studies have shown that it shifts posteriorly as well[29-31, 33, 35, 36, 44].
- After ACL rupture, the tibia is positioned more anterior relative to the femur, and there is evidence this is not always restored after ACL reconstruction. There is no consensus on internal/external rotation. These differences are most notable in full knee extension[29, 32, 35, 44].
- UO-MRI permits the direct assessment of contact area, centroid location, and alignment in physiologic weightbearing conditions. It has demonstrated reliability and accuracy in studying the patellofemoral joint, but the methods have not been fully developed for the tibiofemoral joint[17, 18].

The literature has the following gaps in knowledge:

- To date, MR-based measures used either indirect determination of contact area (in the dual modality method) or simulated weightbearing (in the supine MRI method) to

draw conclusions about tibiofemoral contact area, centroid location, and alignment. No direct MRI measure of tibiofemoral biomechanics in upright, weightbearing conditions has been used to study ACL rupture *in vivo*.

- All MR-based assessments on the effect of ACL deficiency have been made in patients who eventually went on to have ACL reconstruction. This implies that there was an indication to proceed with surgery. Following ACL injury, this was likely due to the presence of dynamic instability[46]. However, there is an important subset of patients who have an ACL injury and do not develop dynamic instability. These patients have been termed 'ACL copers'[47]. Presently, there are no data on the mechanics of their knees that may permit them to function at a high level without an intact ACL.

The aims of this thesis were to address these limitations. We first proceeded by determining the reliability and accuracy of our UO-MRI protocol.

Chapter 3: Reliability of Tibiofemoral Contact Area and Centroid Location in the UO-MRI

3.1 Introduction

Magnetic resonance (MR) has been used to assess knee joint mechanics for a number of applications, including explaining how acute injury such as anterior cruciate ligament (ACL) rupture increases the risk for osteoarthritis (OA)[13, 30, 33, 48, 49]. Measurements made include kinematics[13, 29, 50, 51], cartilage contact area, and centroid location[33, 39, 43, 49, 51].

Most biomechanical studies have been performed using conventional closed-bore MR, which has necessitated simulating weightbearing load on the joint. Approaches include positioning the participant supine in the scanner with an axial load applied to the foot (closed kinetic chain)[33, 43, 52], registering unloaded MRI-based models of cartilage to measurements of bones from loaded fluoroscopic evaluations[40, 53], and MR imaging in supine before and after a knee loading activity is performed[54, 55]. Open kinetic chain loading has also been used, such as applying a torque to the shank while the participant lies supine[51].

The reliability and accuracy for contact area and centroid location from studies with simulated loading have been estimated. The coefficient of variation (CV) for tibiofemoral contact area and centroid location, which indicates the extent of variability between multiple testing sessions, has ranged between 3.1-9.0% and 0.3-3.3% respectively[33, 43, 49, 51, 53]. Determining contact area by combining MRI with biplanar radiography has shown a slightly larger standard error of measurement of 14±11% in a cadaveric validation study[40].

The clinical applicability of these biomechanical findings is unclear because of the limitations of simulating weightbearing in conventional scanners. Supine scans with simulated weightbearing may not represent joint behaviour under physiologic load, because the supine position does not reproduce the effect of postural muscles on joint position. Assessments pre- and post-activity provide information about acute changes that result from activity, but not necessarily the biomechanical cartilage changes that occur during it.

Upright, open MRI (UO-MRI) addresses the limitations of simulated weightbearing in supine scanners by allowing joint imaging during weightbearing[39, 51, 56]. However, it is not clear how reliably measurements of contact area and centroid location can be made in upright weightbearing postures.

The aims of this study were: 1) to assess the reliability and accuracy of tibiofemoral cartilage contact area and centroid location acquired both sagitally and coronally 2) to describe the implementation of an UO-MRI protocol that permits acquisition of these measures *in vivo* under physiologic weight-bearing conditions.

3.2 Materials and methods

This study was approved by the UBC Clinical Research Ethics Board (H18-01459). All participants provided informed, written consent (Appendix B).

3.2.1 Participants

A sample of 5 patients from a larger comparative cohort study volunteered for reliability analysis. The cohort study was a convenience sample of 18 patients with prior ACL rupture. Patients were recruited through posted notifications and targeted e-mails (Appendix A).

Inclusion criteria for the cohort study were: 1) adult participants between the ages of 18-50 years old with unilateral, isolated ACL ruptures; 2) intact cartilage and evidence of complete ACL rupture on MRI; 3) reported ACL rupture within the last 5 years and if reconstructed, done within 1 year from injury; and 4) have completed a full rehabilitation program and returned to regular sport or recreational activities.

Exclusion criteria were: 1) associated ligament rupture other than the ACL (though incomplete MCL ruptures were not excluded); 2) known knee osteoarthritis diagnosed by a physician; 3) presence of other joint disease; 4) incompletely rehabilitated injury, defined as a range of motion less than 0-130 degrees, quadriceps atrophy, or persistent mechanical symptoms; 5) individuals prohibited from undergoing MRI based on the MRI screening form (Appendix C); 6) history of fainting, or evidence of change in orthostatic blood pressure; 7) prior or subsequent knee surgery other than diagnostic arthroscopy; 8) history of corticosteroid injection to either knee; and 9) bilateral ACL rupture or ACL re-rupture.

Demographic data from participants were collected including age, height, body mass, date of injury, time from injury to surgery (if applicable), and time from injury to study participation. Validated outcome questionnaires were administered to characterize knee

symptoms: the Knee Injury and Osteoarthritis Outcome Score (KOOS)[57] and the International Knee Documentation Committee Subjective Knee Form (IKDC)[58].

3.2.2 Imaging

Participants were scanned standing in a 0.5T upright, open MRI (MROpen, Paramed, Genoa, Italy). All scans were done in the morning, participants were instructed not to do any impact exercise prior to scanning, and participants were seated for 30 minutes prior to scanning, during which time questionnaires were administered. Participants wore compression socks to minimize venous pooling in the lower extremities during standing scans. Participants then stood for 15 minutes prior to acquiring standing scans to ensure a cartilage deformation equilibrium had been reached. Each participant wore a chest harness suspended from an aluminum ceiling track safety-rated to 450 lbs (Handicare, Concord, ON) as a precautionary measure in case the participant fainted during upright scanning. No weight was borne through the bars or the harness. Standing scans of the ACL-injured leg were acquired with the knees in full extension, with the participant instructed to stand comfortably and distribute their weight equally between legs. Three support bars (shins, buttocks, and hands) were placed to help the participant remain still during scanning. We obtained sagittal and coronal images with a double echo steady state T2 sequence (Table 3.1) using a commercial 2-channel knee coil (ParaMed) suspended around the knee. The sequence was optimized to provide excellent cartilage signal quickly enough to minimize the effects of patient movement and fatigue while standing. The data was denoised by an optimized blockwise nonlocal means denoising filter[59], and the component DESS images were subsequently fit to a signal model with a global T1 estimate of 0.5[60].

Table 3.1 Imaging parameters used for UO-MRI scans and for the high-resolution 7T standard

	0.5T UO-MRI	**7T MRI**
Pulse sequence	3D DESS	2D multi-slice RARE
Repetition time (ms)	16	2200
Echo time (ms)	6	8.4
Field of view (cm)	22 x 22 x 16	6 x 6
Acquisition matrix size	256 x 256 x 38	256 x 256, 50 slices
Slice thickness (μm)	250	35.0
Slice gap (μm)	0	0
Voxel dimensions (μm)	85.9 x 85.9 x 250	23.4 x 23.4 x 35.0
Flip angle (°)	30	180
Bandwidth (Hz/pixel)	146.9	318.4
Total scan time (min)	3min 30sec	28min 10sec

Raters identified tibiofemoral contact regions by manually tracing regions with no visible separation between cartilage surfaces on each image slice using the Editor module in 3D Slicer[61] (http://www.slicer.org) in both the coronal and sagittal planes (Figure 3.1.A). Raters selected voxels of cartilage that were in direct contact and did not contain any contribution from other structures (e.g. meniscus or synovial fluid). Volumes were created that represented medial and lateral contact areas, each with a known number of voxels (Figure 3.1.B). We multiplied the number of voxels by their known dimensions to calculate contact areas for the medial and lateral compartments. To account for differences in size between subjects, this measurement was normalized by taking the ratio (%) of the contact area over the maximum axial cross-sectional area of the tibial plateau. The centroid location was the geometric center generated from the contact area segmentations in the medial and lateral compartments (Figure 3.1.B). A validated joint coordinate system was employed to locate contact area centroids within a consistent coordinate frame[41]. Centroid location was

quantified as a percentage on the tibial plateau in the medial (0%) to lateral (100%) and posterior (0%) to anterior (100%) directions to account for differences in size between participants.

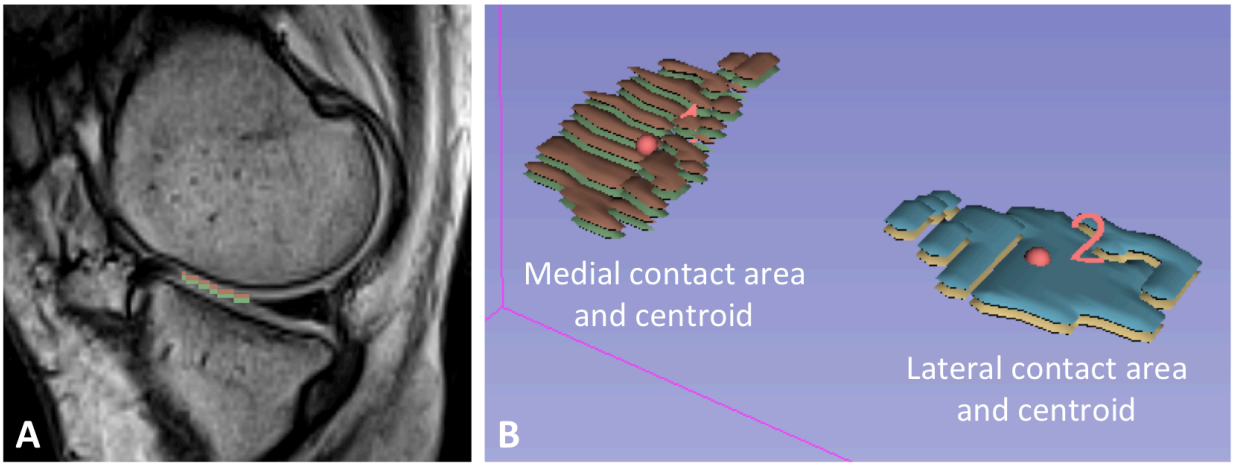

Figure 3.1 A) Representative sagittal slice from the medial compartment of a participant showing the tibial cartilage contact (green) and the femoral cartilage in contact (brown). B) Representative volumes of medial and lateral contact areas and contact centroids.

3.2.3 Accuracy

We assessed the accuracy of contact area measurement by comparing our method in the UO-MRI to reference measurements of contact area made in a 7T MR scanner (Bruker Biospin, Ettlingen, Germany) for two cartilage preparations at two load levels. We created two cartilage contact preparations by dissecting a bovine knee and extracting medial and lateral tibial and femoral blocks using a handsaw. The block dimensions were approximately 30mm by 30mm in the anteroposterior direction and mediolateral direction and were approximately 20mm in the axial (compressive) direction. The bony side of each osteochondral block was affixed to polycarbonate tissue mounts with cyanoacrylate glue.

Care was taken to extract osteochondral blocks in an orientation that approximately matched and were oriented on tissue mounts in a manner that maximized contact of the flattest part of the mating joint surfaces. The preparations were immersed in phosphate-buffered saline and positioned in an MR-compatible compression chamber such that axial compression could be applied by rotating a Delrin plunger (2mm thread) within the capsule of the compression chamber. The samples were positioned such that opposing cartilage surfaces were touching but not compressed, and images were acquired. An axial load was then applied until cartilage compression could be visualized, and the specimen was re-scanned. The displacement of the plunger was marked on the outside of the chamber so that the process could be repeated. On completion, the load was removed and the cartilage given time to equilibrate. The process was performed first on the UO-MRI and then at the 7T MRI with imaging parameters listed in Table 3.1.

3.2.4 Statistics

Inter-rater, test-retest, and intra-rater reliability statistics were calculated for tibiofemoral contact area and centroid location. Inter-rater reliability was obtained for two raters (A. M. S. and D. J. S.) who individually segmented and calculated contact areas for each scan. Test-retest reliability was established by scanning each participant twice, with approximately one month between scans, with one rater (D. J. S.) segmenting both scans. Intra-rater reliability was obtained for one rater (A. M. S.) segmenting the contact areas for each sample 3 times, each 2 weeks apart. We calculated the intra-class correlation coefficient for fixed raters ($ICC_{3,1}$) using the methods described by Shrout and Fleiss[62], the standard error of measurement (SEM), and the smallest detectable change with 95% confidence

(SDC_{95}). ICCs less than 0.5 indicated poor reliability; 0.5 to 0.75 moderate reliability; 0.75 to 0.9 good reliability; and greater than 0.9 excellent reliability. All metrics were obtained for both coronal and sagittal scans.

We assessed contact area accuracy by finding the percent difference for contact areas measured using low-resolution 0.5T UO-MRI and those measured for the same region and load using high-resolution 7T MRI from images obtained in the sagittal plane.

3.3 Results

Descriptive characteristics for the 5 participants included in the reliability analysis are reported in Table 3.2. There were 4 female participants and 1 male; 3 had undergone ACL reconstruction and 2 had not.

Table 3.2 Descriptive characteristics of participants in reliability analysis

	Mean (SD)
Age (years)	23.4 (4.2)
Time since injury (years)	2.9 (1.8)
BMI (kg/m^2)	23.3 (1.1)
IKDC Subjective Score (%)	89.1 (10.2)
KOOS (%)	95.2 (3.2)

Mean absolute contact areas were $452mm^2$ (±103) and $314mm^2$ (±41) for medial and lateral compartments, respectively. Mean normalized contact areas were 13.7% (±2.6) and 9.7% (±1.6) for medial and lateral compartments, respectively.

For scans acquired in the sagittal plane, contact area $ICC_{3,1}$ values (including inter-rater, test-retest, and intra-rater reliability) ranged from 0.94 to 0.99 in the medial compartment, and 0.83 to 0.91 in the lateral compartment (Table 3.3). From the test-retest data, contact area SDC_{95} was 1.28% in the medial compartment and 0.95% in the lateral compartment. Qualitatively, contact regions were very similar between raters (Figure 3.2), and centroid location demonstrated high reliability (Table 3.4). SDC_{95} for medial centroid locations in the X and Y direction were 3.39% and 4.94%, respectively. SDC_{95} for lateral centroid locations in the X and Y direction were 4.41% and 3.85%, respectively.

Table 3.3 Contact area reliability for sagittal UO-MRI scans

	Medial Compartment		Lateral Compartment	
	$ICC_{3,1}$ (95%CI)	SEM (%)	$ICC_{3,1}$ (95%CI)	SEM (%)
Inter-Rater	0.95 (0.59-0.99)	0.39	0.83 (0.06-0.98)	0.44
Test-Retest	0.94 (0.56-0.99)	0.46	0.84 (0.10-0.98)	0.34
Intra-Rater	0.99 (0.94-1.00)	0.21	0.91 (0.64-0.99)	0.31

Table 3.4 Centroid location reliability for sagittal UO-MRI scans

	Medial Compartment			Lateral Compartment		
	$ICC_{3,1}$ (95%CI)	X SEM (%)	Y SEM (%)	$ICC_{3,1}$ (95%CI)	X SEM (%)	Y SEM (%)
Inter-Rater	0.99 (0.97-1.00)	0.71	1.62	0.95 (0.83-0.99)	0.95	2.81
Test-Retest	0.99 (0.95-1.00)	1.22	1.78	0.98 (0.91-0.99)	1.59	1.39
Intra-Rater	0.98 (0.95-1.00)	0.15	2.44	1.00 (0.99-1.00)	0.34	0.57

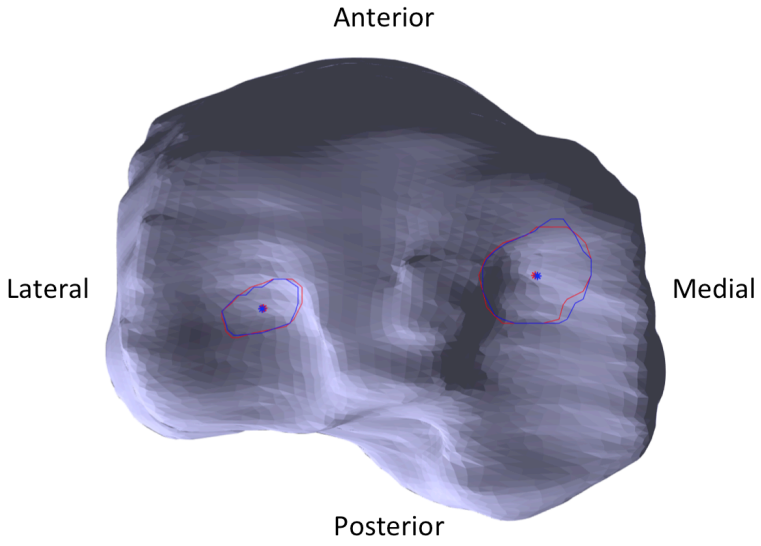

Figure 3.2 Axial view of a standardized tibial plateau with representative cartilage contact areas and centroid locations. Rater one cartilage contact area and centroids are in red and rater two cartilage contact area and centroids are in blue.

For scans acquired in the coronal plane, contact area $ICC_{3,1}$ (including inter-rater, test-retest, and intra-rater reliability) ranged from 0.90 to 0.97 in the medial compartment and 0.76 to 0.94 in the lateral compartment (Table 3.5). From the test-retest data, SDC_{95} was 0.65% in the medial compartment and 1.41% in the lateral compartment. Again, centroid location demonstrated high reliability (Table 3.6). SDC_{95} for medial centroid locations in the X and Y direction were 4.04% and 6.22%, respectively. SDC_{95} for lateral centroid locations in the X and Y direction were 3.38% and 9.83%, respectively.

Table 3.5 Contact area reliability for coronal UO-MRI scans

	Medial Compartment		Lateral Compartment	
	$ICC_{3,1}$ (95%CI)	SEM (%)	$ICC_{3,1}$ (95%CI)	SEM (%)
Inter-Rater	0.90 (0.35-0.99)	0.54	0.87 (0.19-0.99)	0.34
Test-Retest	0.98 (0.86-1.00)	0.23	0.76 (-0.14-0.97)	0.51
Intra-Rater	0.97 (0.85-1.00)	0.35	0.94 (0.74-0.99)	0.23

Table 3.6 Centroid location reliability for coronal UO-MRI scans

	Medial Compartment			Lateral Compartment		
	$ICC_{3,1}$ (95%CI)	X SEM (%)	Y SEM (%)	$ICC_{3,1}$ (95%CI)	X SEM (%)	Y SEM (%)
Inter-Rater	0.99 (0.98-1.00)	0.29	1.50	0.99 (0.95-1.00	0.71	1.43
Test-Retest	0.98 (0.92-0.99)	1.46	2.24	0.93 (0.74-0.98)	1.22	3.55
Intra-Rater	1.00 (1.00-1.00)	0.27	0.54	1.00 (0.99-1.00)	0.23	0.66

In the accuracy analysis, data from one sample was discarded due to a technical error. The remaining areas obtained in the 0.5T UO-MRI for the lateral compartment unloaded, medial compartment loaded, and lateral compartment loaded were: 120mm^2, 271mm^2, and 254mm^2 respectively; areas measured using the 7T MRI were 126mm^2, 258mm^2, and 240mm^2 respectively. This produced a mean measurement error of 4.8%.

3.4 Discussion

We assessed *in vivo* inter-rater, test-retest, and intra-rater reliability of tibiofemoral contact area and centroid location measurements for UO-MRI scans in both sagittal and coronal planes. We evaluated the accuracy of our contact area measurements by comparing measurements made using the UO-MRI to measurements made in a high resolution 7T MRI for a bovine knee model. All measures of contact area reliability, including inter-rater, test-retest, and intra-rater, ranged from good to excellent for coronal and sagittal scans. Qualitatively, there was close correspondence between contact regions identified by different

readers (Figure 3.2). The accuracy analysis found an overall mean error of 4.8% between areas found from 7T MRI and from the UO-MRI. Our results suggest that sagittal or coronal scans are similarly well-suited to evaluate cartilage contact and centroid location in the tibiofemoral joint, with slightly higher repeatability values resulting from sagittal plane acquisition and evaluation.

Our assessment of SDC_{95}, the smallest amount of change that provides 95% confidence that a true change has occurred and is not due to inherent measurement error, may provide useful information for planning research studies that compliments the more widely-used ICC values. For example, our finding of SDC_{95} of 3-5% for changes in contact location (using sagittal plane images) suggests that changes in the anteroposterior direction larger than 2.5mm can be detected (based on a 50mm tibial plateau) using this method. This is smaller than the 4.2mm difference reported between knees with ACL rupture and healthy knees estimated using a biplanar radiography/MRI image registration approach[30], which suggests that our UO-MRI approach can effectively detect differences in centroid location due to ACL deficiency.

Our measures of contact area and centroid location reliability in weightbearing MR are comparable to those from 3T conventional closed-bore scans despite using a lower resolution scanner. For inter-rater reliability, our findings for contact area ICC in the medial compartment of 0.95 and in the lateral compartment of 0.83 are consistent with findings in 3T MRI of 0.90 medially and 0.92 laterally[33]. The inter-rater contact location ICCs (0.99 medially and 0.95 laterally) were also similar those found in 3T (0.99 medially and 0.91 laterally)[33]. For intra-rater reliability our findings for contact area ICC were 0.99 medially

and 0.91 laterally, which was again consistent with 3T MRI findings of 0.97 both medially and laterally[33]. Our intra-rater contact location ICCs (0.99 medially and 0.98 laterally) were similar to those found in 3T (1.00 medially and 0.91 laterally)[33]. No previous study has evaluated the test-retest reliability of contact area and centroid location *in vivo*, although one cadaveric study examined the patellofemoral joint using a 1.5T magnet and found a test-retest ICC value of 0.98, which is comparable to our results[63]. The slightly higher variation in test-retest reliability in the current study is likely due to slight differences in participant posture and positioning between test dates, which may be easier to control in a cadaveric study. The test-retest reliability measures will be of value in experimental design, especially for studies requiring testing on more than one day. Our accuracy results, which found a mean error of 4.8%, suggest higher accuracy for our method than the results from a cadaver study using a silicone casting technique reference standard, which found a standard error of measurement of 14% [40]. This may be due to the substantial differences in the reference method for assessing contact area between the two studies.

The primary strength of this study is that it provides a comprehensive assessment of the role of the intra- and inter-individual differences in raters, and repeated scans, on the reliability of tibiofemoral contact measures. The good to excellent reliability results are supported by a large number of data sets and the inclusion of an accuracy assessment. Incorporation of both sagittal and coronal plane assessment and reporting of SDC_{95} may be useful in protocol development for future studies. Given the clear advantages for ecological validity with the UO-MRI approach for these assessments compared to traditional supine MRI, we feel that our findings have important implications for the study of knee joint mechanics and function.

The findings should be considered in light of some limitations. First, reliability was assessed in ACL-ruptured knees only. The cartilage of these participants may not be representative of cartilage in un-injured knee joints. The effect of this limitation may be that our study underestimated the reliability of our methods, because cartilage contact in healthy knee joints may be easier to identify and segment. Second, the number of samples used in the accuracy assessment was low and the reference method (7T MRI) did not represent a completely independent measure of contact area. We chose 7T MRI as it was the highest resolution possible with which we could ensure similar loads by using the same loading rig. The lengthy scan time and cost of the 7T scanner hindered our ability to process more samples for accuracy assessment; similarly, we were not able to establish the reliability of measuring contact area in the 7T MRI before we used it as the reference standard. Third, our study was limited to two readers, and further assessment might be required for an application where a large number of readers would be involved.

In conclusion, knee contact area and contact centroid location can be assessed in upright weightbearing MRI with good to excellent reliability and accuracy within 5%. The lower field strength used in upright, weightbearing MRI does not compromise the reliability of tibiofemoral contact area and centroid location measures.

Chapter 4: Tibiofemoral Contact and Alignment in Patients with ACL Rupture Treated Conservatively versus Reconstruction: An Upright, Open MRI Study

4.1 Introduction

ACL rupture is one of the most prevalent knee injuries, with an estimated incidence of 69 per 100,000 person-years[7] leading to over 100,000 ACL reconstructions yearly in the United States[8]. 41-51% of individuals who rupture their ACL develop osteoarthritis 10-20 years after their injury[45, 64]. This is an especially devastating outcome for the young and active demographic that typically sustains this injury. While ACL reconstruction reliably improves dynamic instability resulting from ACL rupture, it does not protect the knee from osteoarthritis[3, 9].

Knee osteoarthritis secondary to ACL rupture is widely believed to be associated with changes to joint mechanics caused by the injury. In addition to the chondrocyte damage that occurs at the time of injury[65, 66], kinematic changes result in abnormal cartilage loading that likely has a cumulative effect over time[67]. Alterations in dynamic joint congruency after ACL rupture have been implicated in cartilage degeneration[68], as has excessive tibial rotation during gait[50]. These kinematic changes result in altered cartilage loading patterns, often represented as changes in cartilage-to-cartilage contact points, i.e. contact centroids. In an *in vivo* study using supine MRI with an artificial axial load, the tibial contact centroid in ACL-deficient knees was posterior compared to healthy knees in full extension[35]. Li et al. found contact centroid changes in not just the anteroposterior direction but also in the mediolateral

direction of ACL-deficient knees. They reported a shift in the medial compartment centroid towards the medial tibial spine where degeneration is often observed in patients with chronic ACL injuries[30].

The failure of ACL reconstruction to protect the knee from osteoarthritis may be because the procedure does not restore joint mechanics to normal. Reviews of gait kinematics report that changes in sagittal and frontal plane kinematics persist for years after ACL reconstruction[69, 70]. Joint alignment, represented by the 6 degrees of freedom position of the tibia relative to the femur, also appears to remain abnormal. An *in vivo* study using biplanar fluoroscopy and MRI found that, three months after surgery, the tibiae of ACL-reconstructed knees were 2.9 mm more anterior and 2.7° less externally rotated relative to the femur, than healthy control knees[44]. Cartilage contact behaviour also appears to remain abnormal post-reconstruction, with medial contact centroids remaining posteriorly translated and contact areas remaining smaller than normal knees[33, 36].

Given the arduous post-reconstruction rehabilitation process, evidence of persistent mechanical changes, and no guarantee of a reduced arthritis risk, the decision to undergo ACL reconstruction surgery can be difficult for patients. A randomized trial in 121 young, active patients assigned participants to either rehabilitation plus early reconstruction, or rehabilitation with the option of delayed reconstruction if dynamic instability persisted. The group that was assigned to delayed reconstruction not only demonstrated equivalent functional outcomes at 2 years; 36 out of 59 patients in that group successfully avoided surgery[71]. Individuals treated nonoperatively who are able to resume pre-injury levels of activity without dynamic instability have been termed ACL ‘copers’[47].

The differences in mechanics between ACL ruptures treated nonoperatively, those treated with ACL reconstruction, and healthy knees are unknown. All participants in previously reported *in vivo* studies on the contact mechanics of ACL-deficient knees subsequently went on to surgery[29-31, 33, 35]. This is important because development of osteoarthritis is likely due to persistent, long-term changes in mechanics that might only be evident years after injury. Our research questions were: 1) In a standing, weightbearing posture, are there differences in tibiofemoral contact area, centroid location, and alignment between knees with ACL rupture versus healthy contralateral knees and 2) In a standing, weightbearing posture, are there differences in tibiofemoral contact area, centroid location, and alignment between patients with ACL rupture treated nonoperatively versus those treated with ACL reconstruction?

4.2 Methods

This was an observational cohort study approved by the University of British Columbia Clinical Research Ethics Board (H18-01459). All participants provided informed, written consent (Appendix B).

4.2.1 Participants

We recruited a convenience sample of 18 patients with prior ACL rupture through posted notifications and targeted e-mails (Appendix A). Inclusion criteria for the study were: 1) adult participants between the ages of 18-50 years old; 2) reported unilateral, isolated ACL rupture diagnosed by a physician within the last 5 years; 3) if reconstructed, done within 1

year of injury; 4) intact cartilage (i.e. no full thickness lesions or evidence of arthritis) and confirmation of complete ACL rupture on MRI; and 5) self-reported graduated rehabilitation program culminating with return to sport or recreational activities.

Exclusion criteria were: 1) associated ligament rupture other than the ACL, with the exception of incomplete MCL ruptures; 2) physician-diagnosed knee osteoarthritis; 3) presence of other joint disease; 4) incompletely rehabilitated injury, defined as range of motion less than 0-130 degrees, quadriceps atrophy, or persistent dynamic instability; 5) staple used in securing one end of the ACL graft, if reconstructed; 6) individuals prohibited from undergoing MRI based on the MRI screening form (Appendix C); 7) history of fainting or evidence of change in orthostatic blood pressure prior to scanning; 8) prior or subsequent knee surgery other than diagnostic arthroscopy to the affected knee, or any surgical intervention to the healthy knee; 9) history of corticosteroid injection to either knee; and 10) bilateral ACL rupture or ACL re-rupture.

4.2.2 Outcomes

We collected demographic data from participants including age, height, weight, date of injury, time from injury to surgery (if applicable), and time from injury to study participation. Participants completed two validated outcome questionnaires: the Knee Injury and Osteoarthritis Outcome Score (KOOS)[57] and the International Knee Documentation Committee Subjective Knee Form (IKDC)[58].

All MR scanning was performed in a 0.5T upright open scanner (ParaMed MROpen, Genoa, Italy). We scanned participants in the morning, with instructions not to do any impact exercise prior to scanning. Participants sat for 30 minutes prior to scanning, during which time they completed questionnaires. Participants wore compression socks to minimize venous pooling in the lower extremities during standing scans. We first acquired supine scans with the knees in full extension and the toes taped together to ensure the patellae were pointing directly anterior (Figure 4.1.A). The hip, knee, and ankle of the affected side were scanned first followed by the unaffected side. We used hip and ankle scans, noting the distance between them and the knee, to define three-dimensional coordinate systems in the tibia and femur. Participants then stood for 15 minutes prior to acquiring standing scans to ensure that a cartilage deformation equilibrium had been reached. We acquired standing scans, of the affected leg followed by the unaffected leg, with the knees in full extension and the patellae pointed directly anterior. We instructed participants to stand comfortably, distributing their weight equally between legs. The MRI technician suspended a 2-channel commercial knee coil (Paramed) around the knee, and placed three horizontal support bars (shins, buttocks, and hands) secured to the vertical sides of the scanner to help the participant remain still during scanning. Each participant wore a chest harness suspended from an aluminum ceiling track safety-rated to 450 lbs (Handicare, Concord, ON), as a precautionary measure in case the participant fainted during upright scanning. No weight was borne through the bars or the harness (Figure 4.1.B).

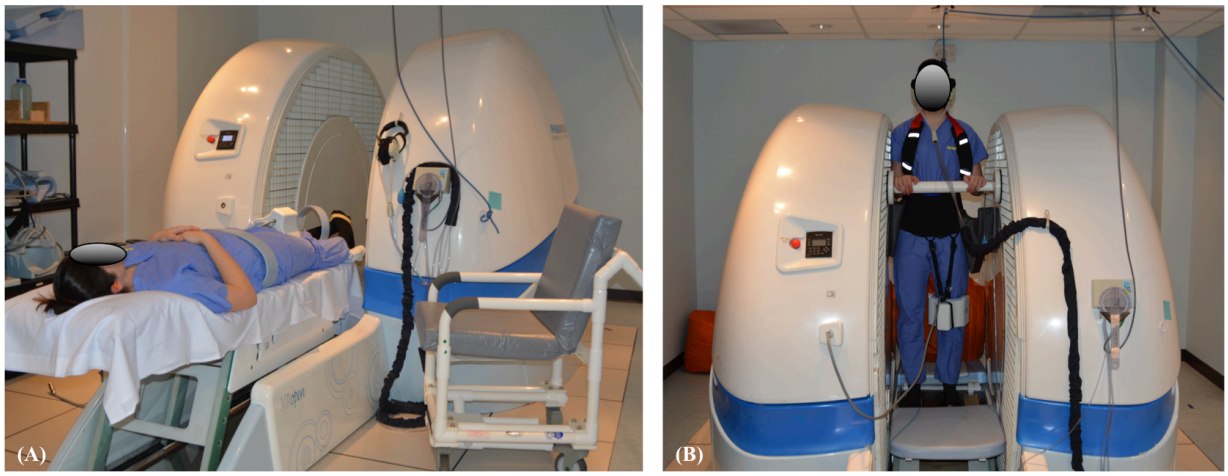

Figure 4.1 A) Supine participant scan setup and B) Standing participant scan setup.

4.2.3 MRI sequence

We obtained sagittal images with a double echo steady state (DESS) T2 sequence (Table 4.1) using a commercial 2-channel knee coil (ParaMed). The sequence was chosen because it provides excellent cartilage signal and can be acquired quickly enough to minimize the effects of patient movement and fatigue while standing.

Table 4.1 T2 double echo steady state sequence parameters in the UO-MRI

0.5T UO-MRI Parameter	Value
Repetition time (ms)	16
Echo time (ms)	6
Field of view (cm)	22 x 22 x 16
Acquisition matrix size	256 x 256 x 38
Slice thickness (μm)	250
Slice gap (μm)	0
Voxel dimensions (μm)	85.9 x 85.9 x 250
Flip angle (°)	30
Bandwidth (Hz/pixel)	146.9
Total scan time (min)	3.5

The T2 data was denoised by an optimized blockwise nonlocal means denoising filter[59] and the component DESS images were subsequently fit to a signal model with a global T1 estimate of 0.5 seconds[60]. The same images were used for contact area definition and joint coordinate system determination.

4.2.4 Contact area

Contact area was defined as the regions of tibiofemoral cartilage in direct contact on cross-sectional imaging. To account for differences in size between subjects, this measure was normalized by taking the ratio (%) of the contact area over the maximum axial cross-sectional area of the tibial plateau. Segmentation of contact area was manually performed using the Editor module in 3D Slicer[61] (http://www.slicer.org) to manually trace contact in a slice-by-slice manner. We selected voxels of cartilage that were visually in direct contact and did not contain any contribution from other structures (meniscus or synovial fluid, for example). The process was similar to the 'delineation' method described by McWalter et al.[39] in the patellofemoral joint. Multiplying the number of voxels by the known dimensions yielded contact areas for the medial and lateral compartments. The centroid location was the geometric center generated from the contact area segmentation in the medial and lateral compartments.

We previously established inter-rater, test-retest, and intra-rater reliability for tibiofemoral contact area using this scanning protocol in the UO-MRI[72]. 5 participants from the present study participated in the analysis. For inter-rater reliability, two raters (A.M.S and D.J.S) independently segmented participants' contact areas; for test-retest reliability, the

same 5 participants returned one month later and repeat scans were taken and processed; for intra-rater reliability, one rater (A.M.S) re-analyzed participants' contact areas 3 times, each 2 weeks apart. ICCs for reliability measures ranged from 0.95 to 0.99 in the medial compartment and 0.83 to 0.91 in the lateral compartment. The SDC_{95} was 1.28% in the medial compartment and 0.95% in the lateral. We also performed an accuracy assessment in which 4 bovine osteochondral blocks were axially loaded and contact areas acquired in 0.5T UO-MRI were compared to high-resolution 7T scans. Our method was accurate to within 4.8% [72].

4.2.5 Alignment and centroid location

We implemented the knee joint coordinate system proposed by Grood and Suntay[41] to describe tibiofemoral alignment using images acquired in the UO-MRI. Right-handed coordinate systems local to the tibia and femur were established based on bony landmarks, allowing for description of the position and orientation of the tibia relative to the femur in three dimensions[73]. Reference bony landmarks were established from supine scans of the hip, knee, and ankle, with the scan position relative to each other noted from the difference in UO-MRI scan table position. Positions and orientations of the coordinate systems in the upright posture were determined by registering supine images of the tibia and femur to corresponding upright images using Analyze 12.0 (AnalyzeDirect, Inc., Overland Park, KS). We calculated the 3 rotations (flexion/extension, abduction/adduction, and internal/external rotation) and 3 translations (anterior/posterior, medial/lateral, and superior/inferior) describing the orientation and position of the tibia segment relative to the femur segment for the standing positions using a custom MATLAB program. This allowed comparison of joint

position changes between ACL-reconstructed and nonreconstructed knees, and between participants' ACL-ruptured knees and their healthy knees.

We implemented a normalized reference frame for centroid location translation by segmenting the tibial plateau and creating bounds mediolaterally and posteroanteriorly based on the minimum and maximum coordinates of the corresponding axes. The result was a 2-dimensional reference frame with the origin at the most posterior and medial point on the tibial plateau. Centroid location translations were calculated in the posteroanterior and mediolateral direction.

In a previous assessment of the reliability of the 6 degrees of freedom alignment analysis using the same Grood and Suntay method in the UO-MRI, test-retest ICCs ranged from 0.95 to 0.99 for the tibiofemoral joint[17]. We performed a reliability analysis for our method of determining centroid location from contact area, using the same participants and methods described in the previous section[72]. Inter-rater, test-retest, and intra-rater ICC ranged from 0.98 to 0.99 in the medial compartment and 0.95 to 1.00 in the lateral compartment. SDC_{95} for medial centroid locations were 3.39% and 4.94% in the mediolateral and posteroanterior directions respectively. SDC_{95} for lateral centroid locations were 4.41% and 3.85% in the mediolateral and posteroanterior directions respectively.

4.2.6 Sample size

We calculated sample size based on data from a supine MRI study[43] that examined *in vivo*, loaded tibiofemoral contact area. We calculated sample size based on the planned

cohort analysis comparing ACL-nonreconstructed knees to reconstructed knees to ensure that we were powered for both the cohort analysis and the case-control analyses. From this study's observed contact area standard deviation of 13.6 mm^2, we calculated that we needed 8 or more knees per group to detect a minimum contact area change of $20mm^2$ with 80% power and an α of 0.05.

4.2.7 Statistical analysis

We used a linear mixed-effects model to test the null hypothesis that there was no effect of ACL rupture on tibiofemoral contact area, controlling for cartilage region (medial or lateral compartment), gender (male or female), posture (supine or standing), age, body mass index, and time from injury, allowing for random intercepts for inter-subject variability. Similar model parameters were used for the cohort analysis, testing the null hypothesis that there was no effect of ACL reconstruction status on contact area. For the secondary analysis examining joint alignment and contact centroids, we used a paired t test to test the null hypothesis that there was no difference between ACL-ruptured knees versus control knees, and the independent t test between ACL reconstruction versus no reconstruction. Tests were two-sided, the level of significance was set at $p<0.05$, and Bonferroni correction was used to account for multiple comparisons. All analyses were performed using R Version 3.5.1 (R Core Team 2018: Vienna, Austria).

4.3 Results

8 participants with nonreconstructed ACL rupture and 10 participants with reconstructed ACL rupture met inclusion criteria and were recruited. Each participant's healthy contralateral knee was included in the control group. The case-control analysis therefore included 18 ACL-ruptured knees and 18 healthy matched control knees; the cohort analysis included 8 ACL-ruptured, nonreconstructed knees (i.e., ACL 'copers') and 10 ACL-ruptured, reconstructed knees. Hamstrings autograft was used in all reconstructed ACLs except one where patellar tendon autograft was used. A single-bundle technique was universally used in the ACL-reconstructed cohort, with tunnels drilled through the standard anatomic ACL insertion sites.

There were no significant differences between subgroups in gender, BMI, and time since injury. The ACL-reconstructed group tended to be slightly younger and have better knee functional outcome scores (Table 4.2).

Table 4.2 Descriptive data for participants

		ACL Rupture		
	Total (N=18)	Reconstructed (N=10)	Nonreconstructed (N=8)	ACL-R vs. ACL-nR
Age; years (SD)	28.4 (7.3)	25.5 (4.6)	32.1 (8.7)	P=0.081
Percent female; % (#)	61.1 (11/18)	60.0 (6/10)	62.5 (5/8)	P=1.000
BMI; kg/m2 (SD)	24.6 (3.7)	24.3 (3.2)	25.0 (4.6)	P=0.710
Time-to-surgery; years (SD)	-	0.53 (0.36)	-	-
Time since injury; years (SD)	2.7 (1.6)	2.6 (1.3)	2.8 (1.9)	P=0.826
IKDC; % (SD)	84.4 (13.5)	89.4 (9.0)	77.3 (16.2)	P=0.108
KOOS; % (SD)	87.9 (14.4)	92.3 (8.4)	81.6 (19.3)	P=0.210

ACL-R: ACL-ruptured, reconstructed

ACL-nR: ACL-ruptured, nonreconstructed

Knees with ACL rupture had 10.4% higher mean contact area (P=0.001) than healthy knees after adjusting for region, posture, gender, age, BMI, and time since injury (Figure 4.2 & Table 4.3). We found no difference (P=0.710) in contact area between knees with and without ACL reconstruction (Table 4.4).

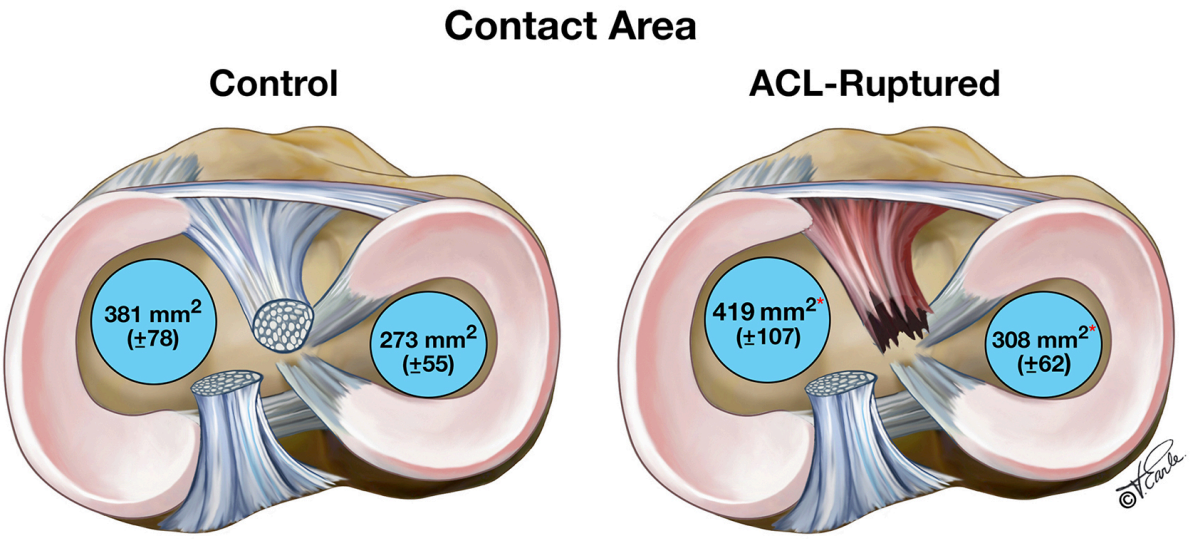

Figure 4.2 Contact area differences between knees with ACL rupture and healthy matched controls. *Significant at P<0.05.

Table 4.3 Adjusted effect of ACL rupture on contact area, controlling for region, posture, gender, age, BMI, and years since injury

The model took the form: Contact area = Presence of ACL rupture [no: 0/ yes: 1] + Region [medial: 0/ lateral: 1] + Posture [supine: 0/ standing: 1] + Gender [male: 0/ female: 1] + Age [continuous] + BMI [continuous] + Years since injury [continuous] + (1|Subject). Model CV=18.2%

	Estimate (mm^2)	95% CI	P Value
Intercept	354.0	229.1 to 479.0	-
ACL rupture	36.7	15.0 to 58.4	0.001*
Region	-109.6	-131.3 to -87.9	<0.001*
Posture	8.0	-13.7 to 29.8	0.472
Gender	-71.7	-111.4 to -32.1	0.007*
Age	-3.1	-5.7 to -0.5	0.056
BMI	6.2	1.0 to 11.3	0.055
Years since injury	1.4	-9.9 to 12.8	0.826

*Significant at P<0.05

Table 4.4 Adjusted effect of ACL reconstruction on contact area, controlling for region, posture, gender, age, BMI, and years since injury

The model took the form: Contact area = ACL reconstruction [no: 0/ yes: 1] + Region [medial: 0/ lateral: 1] + Posture [supine: 0/ standing: 1] + Gender [male: 0/ female: 1] + Age [continuous] + BMI [continuous] + Years since injury [continuous] + (1|Subject). Model CV= 19.3%

	Estimate (mm^2)	95% CI	P Value
Intercept	372.8	189.2 to 556.4	-
ACL reconstruction	11.3	-38.9 to 61.6	0.710
Region	-110.8	-146.8 to -74.8	<0.001*
Posture	2.1	-33.9 to 38.1	0.910
Gender	-68.4	-123.1 to -13.8	0.056
Age	-3.2	-7.2 to 0.8	0.203
BMI	6.5	-0.4 to 13.4	0.140
Years since injury	4.3	-10.9 to 19.5	0.641

*Significant at P<0.05

In ACL-ruptured knees in the standing position, the medial centroid was located 5.2% more posterior (P=0.001, 95% CI 2.4 to 8.0) than in healthy matched control knees (Figure 4.3 & Table 4.5). This is equivalent to a 2.6mm posterior translation on a representative tibia from our population which had a mean posteroanterior width of 49.4mm. We found no differences in centroid location in the mediolateral direction for the medial centroid, or in both mediolateral and posteroanterior directions for the lateral centroid. We found no differences in the location of contact centroids between ACL-ruptured knees with and without reconstruction (Figure 4.3 & Table 4.6).

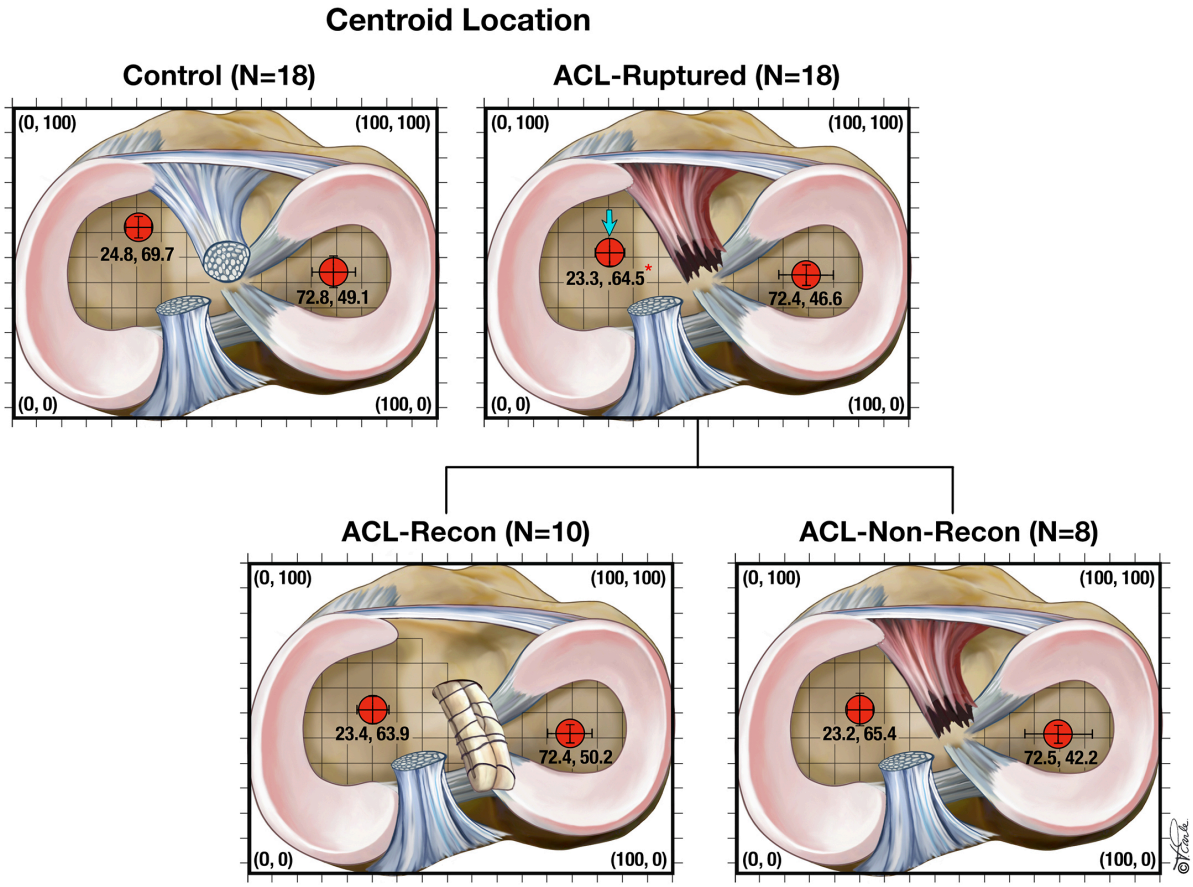

Figure 4.3 Contact centroid locations comparing ACL-ruptured knees versus healthy contralateral control knees, and ACL-reconstructed knees versus nonreconstructed knees. *Significant at P<0.0125 (α/4).

Table 4.5 Centroid position for knees with ACL rupture (N=18) and controls (N=18) in percent mediolateral (X) direction and percent posteroanterior (Y) direction, relative to origin (0,0) in medial, posterior position

	Medial Centroid	**Lateral Centroid**
Healthy Control: X % (SD), Y % (SD)	24.8 (2.5), 69.7 (4.1)	72.8 (3.2), 49.1 (11.1)
ACL Rupture: X % (SD), Y % (SD)	23.3 (3.0), 64.5 (4.3)	72.4 (1.87), 46.6 (9.4)
Difference: X % (P value, 95%CI) Y % (P value, 95%CI)	X: 1.5 (P=0.208, -0.9 to 4.0) Y: 5.2 (P=0.001, 2.4 to 8.0)*	X: 0.4 (P=0.688, -1.7 to 2.5) Y: 2.5 (P=0.432, -4.0 to 9.0)

*Significant at P<0.0125 (α/4)

Table 4.6 Centroid position ACL-reconstructed knee (N=10) and ACL-nonreconstructed knees (N=8) in percent mediolateral (X) direction and percent posteroanterior (Y) direction, relative to origin (0,0) in medial, posterior position

	Medial Centroid	**Lateral Centroid**
ACL-nonreconstructed: X % (SD), Y % (SD)	23.2 (3.3), 65.4 (4.1)	72.5 (1.6), 42.2 (12.0)
ACL-reconstructed: X % (SD), Y % (SD)	23.4 (2.8), 63.9 (4.6)	72.4 (1.6), 50.2 (5.0)
Difference: X % (P value, 95%CI) Y % (P value, 95%CI)	X: -0.2 (P=0.896, -3.4 to 3.0) Y: 1.5 (P=0.465, -2.8 to 5.9)	X: 0.1 (P=0.938, -2.0 to 2.2) Y: -8.0 (P=0.110, -18.2 to 2.2)

In the standing position, the tibiae of knees with ACL rupture were 2.3mm more anterior (P=0.003, 95% CI 0.9 to 3.6) than controls (Figure 4.4 & Table 4.7). We found no significant differences in medial/lateral position or inferior/superior position between knees with ACL rupture versus controls. We found no significant differences in the position of the tibia relative to the femur between ACL-ruptured knees with and without ACL reconstruction (Figure 4.4 & Table 4.8).

In the standing position, knees with ACL rupture were significantly less externally rotated by 2.6° (P=0.010, 95% CI 0.7 to 4.5) than controls (Figure 4.4 & Table 4.9). We found no differences in flexion/extension or abduction/adduction between knees with ACL rupture versus controls. We found no significant differences in tibiofemoral alignment between knees with and without reconstruction (Table 4.10).

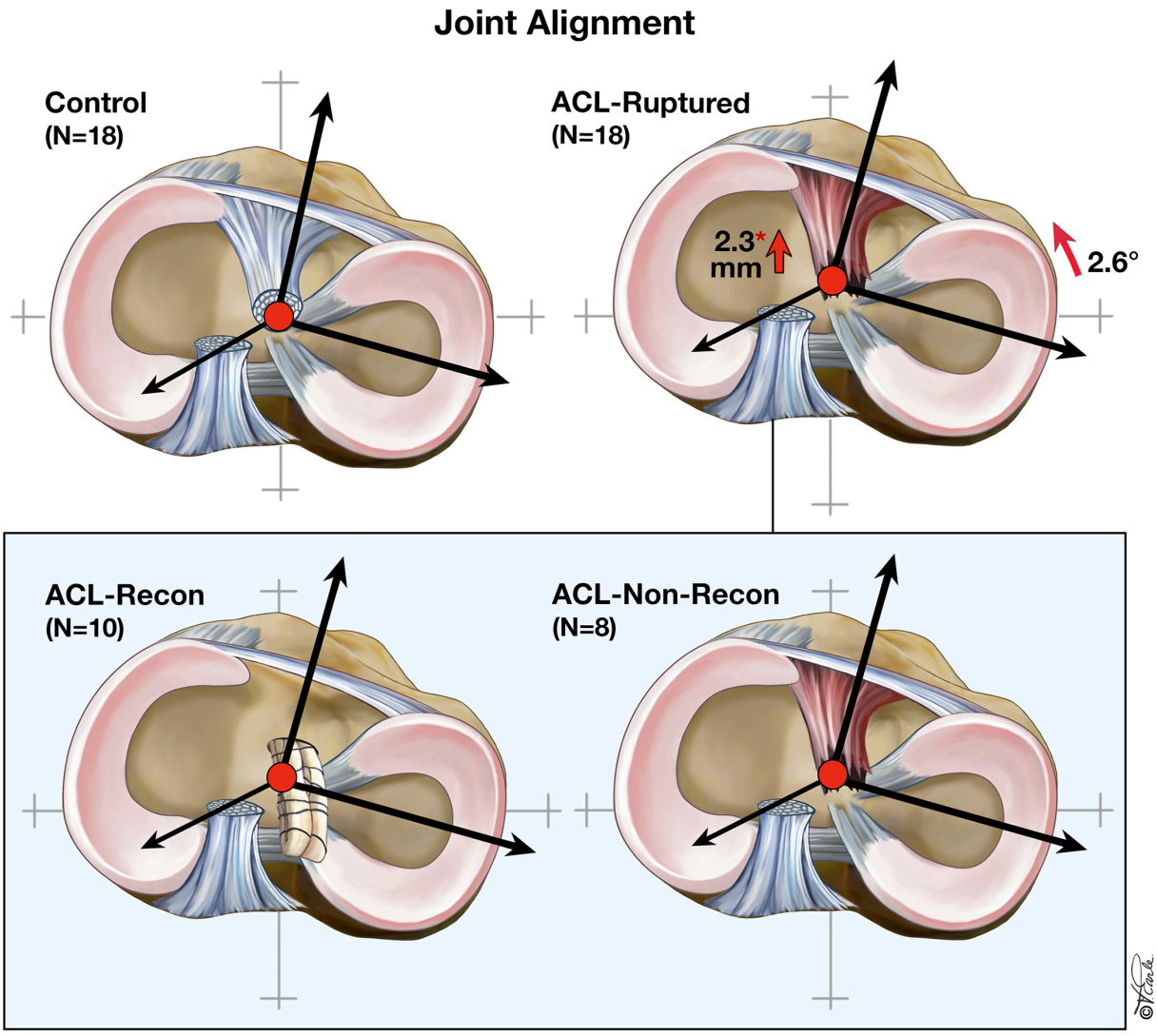

Figure 4.4 Alignment mean differences comparing ACL-ruptured knees versus healthy contralateral control knees, and ACL-reconstructed knees versus nonreconstructed knees. *Significant at P<0.017 (α/3).

Table 4.7 Tibial segment origin relative to femoral segment origin for knees with ACL rupture (N=18) and controls (N=18) in medial/lateral (X) direction, posterior/anterior (Y) direction, and inferior/superior (Z) direction

	X (lateral positive)	**Y (anterior positive)**	**Z (superior positive)**
Healthy Control: mm (SD)	4.7 (1.8)	-0.9 (3.0)	-22.5 (2.6)
ACL Rupture: mm (SD)	5.3 (3.4)	1.4 (3.7)	-22.6 (2.5)
Difference: mm (P value, 95% CI)	0.6 (P=0.505, -1.3 to 2.5)	2.3 (P=0.003, 0.9 to 3.6)*	-0.1 (P=0.861, -1.7 to 1.5)

*Significant at P<0.017 (α/3)

Table 4.8 Tibial segment origin relative to femoral segment origin for ACL-reconstructed knee (N=10) and ACL-nonreconstructed knees (N=8) in medial/lateral (X) direction, posterior/anterior (Y) direction, and inferior/superior (Z) direction

	X (lateral positive)	**Y (anterior positive)**	**Z (superior positive)**
ACL-nonreconstructed: mm (SD)	5.6 (3.9)	0.4 (5.1)	-22.9 (3.4)
ACL-reconstructed: mm (SD)	5.1 (3.2)	2.1 (2.0)	-22.4 (3.1)
Difference: mm (P value, 95% CI)	0.5 (P=0.775, -3.2 to 4.2)	-1.7 (P=0.394, -6.1 to 2.7)	-0.5 (P=0.633, -2.9 to 1.9)

Table 4.9 Tibiofemoral joint position for knees with ACL rupture (N=18) and controls (N=18) in sagittal (flexion/extension), axial (internal/external rotation), and coronal (adduction/abduction) planes

	Flexion	**Internal rotation**	**Varus**
Healthy Control: ° (SD)	-5.5 (4.1)	-10.1 (5.0)	-2.3 (2.7)
ACL Rupture: ° (SD)	-3.9 (4.9)	-7.4 (4.3)	-2.2 (3.0)
Difference: ° (P value, 95% CI)	1.6 (P=0.105, -0.4 to 3.5)	2.6 (P=0.010, 0.7 to 4.5)*	0.1 (P=0.873, -1.1 to 1.2)

*Significant at P<0.017 (α/3)

Note: In sagittal plane flexion is positive; in axial plane internal rotation is positive; in coronal plane varus (tibial adduction) is positive

Table 4.10 Tibiofemoral joint position for ACL-reconstructed knees (N=10) and ACL-nonreconstructed knees (N=8) in sagittal (flexion/extension), axial (internal/external rotation), and coronal (adduction/abduction) planes

	Flexion	**Internal rotation**	**Varus**
ACL-nonreconstructed: ° (SD)	-3.0 (6.3)	-5.7 (4.0)	-3.6 (2.4)
ACL-reconstructed: ° (SD)	-4.7 (3.6)	-8.8 (4.1)	-1.0 (3.1)
Difference: ° (P value, 95% CI)	-1.7 (P=0.515, -3.8 to 7.2)	-3.2 (P=0.120, -0.9 to 7.3)	2.5 (P=0.068, -5.3 to 0.2)

Note: In sagittal plane flexion is positive; in axial plane internal rotation is positive; in coronal plane varus (tibial adduction) is positive

4.4 Discussion

We assessed contact area, centroid location, and alignment in ACL-ruptured knees treated conservatively versus operatively, as well as between ACL-ruptured knees and healthy contralateral knees, to better understand the mechanical changes associated with ACL injury and treatment. We found that knees with ACL rupture had larger contact areas in both medial and lateral compartments, and more posterior contact in the medial compartment, than healthy contralateral knees. We found no difference in contact area or contact centroid position between knees with reconstructed and nonreconstructed ACL ruptures. We found that the tibiae of knees with ACL rupture were 2.3mm more anterior and 2.6° less externally rotated, relative to the femur, than contralateral controls. We found no difference in alignment between reconstructed and nonreconstructed ACL ruptures. These results suggest that ACL reconstruction does not restore joint mechanics to normal in the short term.

Our measurements of tibiofemoral contact area and centroid location are generally consistent with previous literature. The healthy control knees in our analysis had mean contact areas of 381mm^2 and 273mm^2 in the medial and lateral compartments, respectively,

which were slightly higher than those reported by Van de Velde et al. (314mm^2 medially and 193mm^2 laterally at full extension)[31] and Carpenter et al. (298mm^2 medially and 195mm^2 laterally at full extension)[32]. These previous studies used biplanar radiography in their determination of contact area, during a quasi-static lunge task in which the participant paused at varying degrees of flexion for 5 seconds while radiographs were taken. It is possible that our larger values were a result of cartilage creep as our participants maintained the same standing, knee extended position for 15 minutes prior to scanning. Additionally, the lower resolution of our MRI may have partially accounted for this difference. Finally, differences in tibiofemoral contact area in the same knees have been observed depending on the MRI sequence used due to its ability to enhance cartilage signal[43].

Our finding of larger contact area, by a mean 38mm^2 in the medial compartment and 35mm^2 in the lateral compartment, in knees with ACL rupture at a mean 2.7 years after injury, is not consistent with studies done more recently after injury. This difference was well above the smallest detectable change of 1.3% and 1.0% in the medial and lateral compartments, respectively. Previous studies reported that ACL rupture was associated with decreased contact area. Chen et al. reported a smaller contact area by 14.3mm^2 in the medial compartment with non-significant changes in the lateral compartment of ACL-deficient knees[33], and Van de Velde et al. reported a smaller contact area by 94.8mm^2 medially and 56.3mm^2 laterally[31]. In the former study, the decreased contact area persisted in the medial compartment 6 months post-reconstruction[33] while in the latter, the decreased contact area persisted 6 months post-reconstruction in both compartments[36]. These differences may be due to a combination of the time course of the pathology of post-traumatic arthritis and/or due to differences in methods. Moderate arthritis has been associated with a significant

increase in contact area in the medial compartment by 93.1mm^2 [43]. Since our cohorts were scanned a mean 2.7 years from injury while other investigators scanned their participants much closer to the time of injury (for example, a mean 4.4 months post-injury in the paper by Van de Velde et al.[31]), our findings may represent the natural course of disease for post-traumatic arthritis. Interestingly, Chen et al. performed follow up of their ACL-reconstructed cohort two years postoperatively and found that contact area medially was no different from the healthy contralateral side, and that contact area laterally had increased by 24.5mm^2 [33]. Another contributing factor may be the method of contact area determination. The dual modality method relies on matching biplanar radiographic models to high resolution MRI images and determining contact area via projected areas of cartilage overlap. As such, it does not involve a direct determination of contact area and has a demonstrated measurement error of 14%[40]. The present UO-MRI method of direct determination of contact area demonstrated a measurement error of 4.8%.

Our finding that ACL rupture was associated with a posterior translation of the medial centroid by 5.2% (which exceeds the smallest detectable change of 4.9%) was consistent with a prior study whose results are directly comparable to ours given that it used a normalized reference system. In a study of 20 participants in supine MRI, researchers found that the medial contact centroid in healthy control knees was positioned a mean 66.4% of the posteroanterior distance versus a mean 64.4% in ACL-ruptured knees (P=0.012)[74], in full extension. We found the medial centroid in healthy control knees located at 69.7% of the posteroanterior distance versus a mean 64.6% in ACL-ruptured knees (P=0.001), with no difference found in those reconstructed versus not. Other literature more commonly reports absolute translation values, with similar observations. Medial centroid location in ACL-

deficient individuals at full extension has ranged from 1.4mm to 6.3mm more posterior than control knees[30, 31, 33, 35], and in ACL-reconstructed individuals has ranged from 0.9mm to 4.8mm more posterior than control knees[33, 36]. Whereas previous studies reported contact location in ACL-deficient knees that eventually went on to get a reconstruction, the present study demonstrates similar findings in a group of ACL-deficient participants who have been successfully treated conservatively. We however did not detect any medial-lateral shift of the medial centroid, or any shift at all in the lateral centroid. The medial centroid has previously been reported to shift laterally, closer to the tibial spine, by up to 4.7mm[30, 31, 36]. Translation of the lateral centroid has been more variable, with some studies observing posterior and lateral translations there as well[31, 35, 36], and others finding no significant difference[30, 32, 33]. Our study was powered to detect a difference in the contact area, so the lack of significant translation found in the lateral compartment and in the medial compartment mediolateral direction may be a result of Type II error. Additionally, our MRI cuts were taken in the sagittal orientation and with a 2.5mm slice thickness, therefore our MRI sequence was likely more sensitive in detecting posteroanterior translation than mediolateral translation.

Our finding that the tibia was more anteriorly translated (2.3mm) and less externally rotated (2.6°) relative to the femur in ACL-ruptured knees than healthy contralateral knees was consistent with the posterior shift in medial centroid location and consistent with findings in the literature. Our translation results were consistent with previous reports of increased anterior tibial translation in full extension: ACL-deficient knees showed differences from 2.6mm to 3.5mm greater than healthy knees[29, 35], and ACL-reconstructed knees have showed residual anterior tibial translation of 2.9mm greater than healthy controls[44]. The effect of ACL rupture on internal/external tibial rotation is more unclear.

Greater internal rotation[44] has been reported as has greater external rotation[32] compared to control knees. In this respect, we believe that alignment measured using the UO-MRI has the greatest ecological validity as the effect of gravity and postural muscles most closely reproduces everyday weight-bearing.

The primary strength of this study is that we assessed knee joint contact in a weightbearing, standing posture using a single modality. Conventional MRI studies require simulation of physiological weightbearing, and biplanar radiography studies require assessments with two or more scanners followed by substantial analysis. A second strength is that our measures were well validated, with a clear specification of the minimum detectable difference. A final strength of this study was that we were able to recruit an ACL 'coper' cohort that enabled us to compare contact and alignment measures directly between a high functioning, ACL-reconstructed cohort and a similarly high functioning, nonreconstructed cohort. Interestingly, 5 of the 8 participants in the ACL-nonreconstructed group had successfully returned to pivoting sports including ultimate frisbee, hockey, and soccer. 3 returned to strenuous activities but had chosen to adapt their activities to ones that were unidirectional.

One limitation of the study is that we did not evaluate kinematic changes through the range of knee flexion, and chose to focus on the static, terminally extended position. We were partially constrained in this regard by the acquisition time of the MRI sequence. Though this was not a complete representation of physiological activity, this knee position is where differences were most notable in previous studies[30, 44], and it is also the position of the knee in mid-stance of gait during which the ipsilateral leg bears the majority of body weight.

Second, we could not ensure complete homogeneity of the ACL-reconstructed group, and there may have been some differences in placement of graft that may have affected the findings of the ACL-reconstructed cohort[75]. Additionally, due to the resolution of the scanner we could not account for the status of the menisci, which undoubtedly play a role in tibiofemoral kinematics[15, 76]. Finally, while there were no statistically significant differences between cohorts, the ACL-nonreconstructed group tended to be older and have a slightly worse functional outcome score.

The clinical significance of this study is twofold. This is the first study to quantify the mechanical changes present in a cohort of ACL 'copers' that have returned to activity after injury. From the standpoint of joint contact area, centroid location, and alignment, our findings support the recommendation to trial nonoperative management in individuals without dynamic instability. While the long-term clinical outcomes are unclear, the evidence suggests that nonoperative treatment does not put the individual at risk of additional injury and results in equivalent rates of osteoarthritis[3, 77]. Second, we describe an *in vivo* method to directly measure these mechanical outcomes in standing, weightbearing postures. Longer term follow-up and investigation of associated patient, injury, and surgical factors is warranted.

We found that, at a mean of 2.7 years after injury, knees with ACL rupture had larger contact areas in both medial and lateral compartments, and a more posterior contact centroid in the medial compartment, than healthy contralateral knees. We found no difference in contact area or centroid location between knees with reconstructed and nonreconstructed ACL rupture. These findings support the hypothesis that persistently abnormal mechanics

may predispose to cartilage degeneration after ACL rupture. Patients and clinicians can be reassured that nonoperative management of this injury, for the right individuals, results in no detectable differences in the measures used in this study compared to ACL reconstruction.

Chapter 5: Integrated Discussion and Conclusions

5.1 Summary

The aims of this thesis were:

I. To establish the reliability and accuracy of *in vivo* tibiofemoral contact area and centroid location in a fully extended, weightbearing posture in the UO-MRI.

II. To examine differences in contact area, centroid location, and alignment between individuals with ACL rupture who have been treated with reconstruction versus nonreconstruction.

III. To examine differences in contact area, centroid location, and alignment between knees with ACL rupture and healthy control knees.

In addressing Aim I, we assessed *in vivo* inter-rater, test-retest, and intra-rater reliability of tibiofemoral contact area and centroid location measurements for UO-MRI scans in both sagittal and coronal planes, in 5 participants with ACL rupture. We evaluated the accuracy of our contact area measurements by comparing measurements made using the UO-MRI to measurements made in a high resolution 7T MRI for a bovine knee model. All measures of contact area and centroid reliability (including inter-rater, test-retest, and intra-rater reliability) ranged from 0.83 to 1.00 for sagittal scans and from 0.76 to 1.00 for coronal scans. Qualitatively, there was close correspondence between contact regions identified by different readers. The accuracy analysis found an overall measurement error of 4.8% between contact areas found from 7T MRI and from the UO-MRI.

We assessed contact area, centroid location, and alignment in 8 ACL-ruptured knees treated nonoperatively versus 10 treated operatively, as well as between ACL-ruptured knees and healthy contralateral knees, to better understand the mechanical changes associated with ACL injury and treatment. At a mean 2.7 years after injury, we found that knees with ACL rupture had 10.4% larger contact areas in both compartments, and 5.2% more posteriorly located contact in the medial compartment, than healthy contralateral knees. We found that the tibiae of knees with ACL rupture were 2.3mm more anterior and 2.6° less externally rotated, relative to the femur, than contralateral controls. We found no difference in contact area or contact centroid position between knees with reconstructed versus nonreconstructed ACL ruptures. There was also no difference in alignment between reconstructed and nonreconstructed ACL ruptures.

5.2 Strengths and contributions

The primary strength of the study was the development of a method of directly assessing *in vivo* tibiofemoral contact using the UO-MRI that was reliable and accurate. Previous measures employed indirect assessment of cartilage contact and alignment in weightbearing, using supine MRI with axial loading[32] or weightbearing biplanar radiographs matched to supine MRI images[29, 30]. Supine MRI methods rely on simulated weightbearing, axially applied to the participant's feet via an MRI-safe apparatus with pulleys and weights. The loads applied are not physiological in magnitude or direction[11]. Loads applied in previous studies have been 25% body weight[33] or 125N[35]. With the UO-MRI, we were able to assess cartilage biomechanics in physiologic weightbearing, with the affected knee experiencing approximately 50% body weight. The dual modality method combining

biplanar radiography with MRI images involves indirect cartilage contact determination. This may be a factor in the 14% measurement error reported from that technique[40]. The UO-MRI involved direct assessment of cartilage contact and had much better measurement error of 4.8%. Our technique involved only one imaging modality which simplifies the process for participants and researchers.

A second strength was the recruitment and analysis of a cohort of high-functioning participants with ACL rupture who were successfully treated nonoperatively. This is the first report of such a group in the literature. We found that ACL copers (i.e. patients successfully treated nonoperatively) exhibit similar patterns in contact area, centroid location, and alignment as patients treated with ACL reconstruction. Moreover, we observed this at a mean 2.7 years from injury. The longest follow-up that used MR-based methods to date was reported by Chen et al., who longitudinally followed a series of patients after ACL reconstruction[33]. Preoperatively and 6 months postoperatively they observed smaller contact areas in ACL-ruptured knees. However at 2 years, there was no difference in medial contact area and a larger contact area in the lateral compartment. It has also been reported that the contact regions that experience load after ACL rupture have thinner cartilage[31]. Though contact stresses remain the same, local stresses within cartilage may increase in areas of thinner cartilage. Over time, increased cartilage stresses in thinner cartilage regions may lead to cartilage degeneration. Eventually, this may result in increased contact areas which has been observed in osteoarthritis[43]. Taken together, these findings help us better understand a potential pathomechanism that links ACL rupture with post-traumatic osteoarthritis.

Specific contributions include:

- We developed a protocol to image the tibiofemoral joint *in vivo* with participants standing with their knees in full extension. The T2 3D DESS sequence provided excellent cartilage enhancement and took 3 min 30 seconds per scan. Scans of this length were generally well tolerated by participants. The same scans that were used for contact area segmentation were also used for the determination of bony landmarks in the joint coordinate system thus maximizing efficiency. We also developed a robust system to screen for and prevent syncope during scanning (Appendix C), which is a real danger in upright MRI scanning.
- In the 0.5T UO-MRI, we determined that the reliability of tibiofemoral contact area and centroid location assessment is comparable to that obtained with clinical MRI scanners that use 1.5T or 3.0T magnetic fields.
- We estimated the minimal important difference, or smallest detectable change with 95% confidence, for contact area and centroid location in the medial and lateral tibiofemoral compartments. These estimates informed the interpretation of our results from the cohort study, and most importantly, they outline specific effect sizes that can be detected with these methods. In these ways, calculating SDC_{95} estimates were more useful than the classic ICC.
- We found that the accuracy of contact area assessment, with a measurement error of 4.8%, was better than previously reported methods[40]. This lends confidence to the absolute values for contact area that we obtained with our methods. It also means that tibiofemoral contact area assessed in the UO-MRI can accurately be applied to the study of a range of pathologies that affect the knee joint.

- We found that there was no difference in contact area, centroid location, or knee alignment between participants with ACL rupture treated operatively and those treated nonoperatively in well-matched cohorts of high-functioning individuals at a mean 2.7 years after injury. This is novel and important, because previous studies only examined ACL-deficient knees soon after injury, and only in individuals who went on to surgery. This is the first biomechanical study of a group of ACL 'copers' in the literature.
- We found strong evidence that ACL reconstruction does not completely restore native knee mechanics. The persistent alterations in these measures may be a contributing factor in the progression of post-traumatic osteoarthritis. Our findings provide motivation for continued research into technical advances in surgery that might be able to better restore normal tibiofemoral mechanics.
- We found that knees with ACL rupture had a higher mean contact area, a more posteriorly located medial centroid, and a more anteriorly translated and less externally rotated tibia than the healthy contralateral knee, in high-functioning individuals 2.7 years after injury. This is novel and important because most previous studies only examined the effects of ACL rupture and reconstruction soon after injury. Our finding of a larger mean contact area, in contrast to previous findings of lower contact areas post-ACL injury in participants within 1 year of ACL rupture[31, 33, 36], adds to the evidence that knee mechanics change substantially over time. The mechanical changes that we observed may be a part of the early degenerative process that leads to osteoarthritis. Our findings provide impetus for further longitudinal, long-term studies evaluating the mechanics of the knee post-ACL rupture.

5.3 Limitations

Our findings should be considered in light of the following limitations:

- The reliability analysis involved a limited number of raters and participants. In this respect, we were guided by previous literature. For MRI investigations on knee mechanics, reliability studies have used anywhere from 5[78] to 7[74] to 10[33] subjects. In our study, only 5 participants volunteered to return for another scanning session in order to complete the test-retest aspect of reliability analysis. Increasing the number of participants and/or raters may have had the effect of narrowing the confidence intervals of our estimates, and not necessarily changing the estimate value.
- There were limitations to the reference standard method for the accuracy analysis, and only 4 samples were used, one of which had to be discarded. We used a high resolution 7T MRI as a gold standard, though there do exist other standards such as laser scanning[79] or validation with silicon casted models[56]. Our 7T MRI standard required a similar process of segmentation and calculation of contact area as the 0.5T UO-MRI method. The similarity of the methods may have negated accuracy measurement error that we could have detected if we used a non-MRI gold standard. We were constrained by cost and time, and we justified our choice by prioritizing the reliability analysis over the accuracy analysis given that our primary interests were differences in contact areas, not absolute values.
- Our biomechanical assessment was not dynamic. We were able to examine static knee alignment at full extension, but not dynamic knee kinematics through the range of flexion. Further protocol development must occur for this to be possible. Our scans were 3 minutes 30 seconds long, nowhere near the 5 seconds that it takes for biplanar

radiographs to be taken using the dual modality method. Much shorter scan times would need to be implemented, however this may come at the cost of poorer image resolution and artifact.

- The ACL cohort study could be improved with more participants in each group. This would reduce the risk of Type II error, especially with our lack of statistically significant findings in the lateral centroid location, and the medial centroid mediolateral direction. We powered our study based on contact area, but future studies may wish to focus more specifically on contact centroid. The variances and effect sizes noted in our study could contribute to those calculations. For the difference that we observed in the medial centroid in the posteroanterior direction, *post hoc* power analysis shows that we were had a 96% chance of correctly observing the difference that we did (given a pooled standard deviation of 4.2, an effect size of 5.2, a sample size in each group of 18, and an α of 0.05). However, for the medial centroid in the mediolateral direction, in order to observe the 1.5% difference that we did we would have needed 51 patients per group to have 80% power (using a pooled standard deviation from our data of 2.7 and an α of 0.05).
- Our cohorts were reasonably well-matched *a priori* with regards to functional outcome, but we did not factor in functional outcome in our outcome analyses. Such an analysis would require many more patients, but it is critically important that future studies begin to investigate the relationships between the mechanical changes observed, and patient-reported functional outcome. This would help define the minimal clinically important differences in mechanical outcome measures.

- We were not able to account for the presence, location, size, or type of meniscal lesions in our assessments. It is an important co-variable, and has been associated with increased anterior tibial translation at 2 year follow-up[15]. Our inability to control for meniscal lesions was partially due to the low resolution of the 0.5T UO-MRI and the specific T2 sequence that was optimized for hyaline cartilage. Clinically, this is a difficult task due to the heterogeneity in type, location, and size of meniscal injury that can be associated with ACL rupture. Future ACL research should incorporate this variable, but this will likely require large numbers to adequately account for the variation that heterogeneous meniscal lesions introduce.
- Our control group may not have represented a cohort of healthy knees. It could be argued that our control group represented a cohort of knees that had compensated for a contralateral ACL rupture, and therefore may have undergone changes themselves. This limitation was balanced by the fact that the control knees provided a matched comparison for the contralateral, injured knees. This successfully accounted for differences in size, shape, and geometry that would have otherwise introduced significant variation into a small cohort study.
- We could not measure forces or stresses directly; variables which may be most closely related to cartilage degeneration[11]. During protocol development, we attempted to use a quantitative T2 3D DESS sequence with the hope of generating T2 maps. T2, particularly in the superficial zone of cartilage, has been shown to decrease with load[80, 81]. We attempted to generate T2 maps in order to infer how load is experienced in different regions of the knee after ACL injury but unfortunately, the T2 maps were not repeatable. Additionally, the large voxel size resulted in problems

with segmentation and partial volume effect. The non-homogenous, anisotropic nature of cartilage led to difficulty analyzing quantitative T2 MRI data that blended the signal from multiple cartilage layers.

5.4 Biomechanical and clinical implications

Our findings in ACL-ruptured knees were consistent with the known function of the ligament. The ACL functions primarily as a restraint to anterior translation of the tibia relative to the femur, and secondarily as a restraint to internal rotation near full knee extension[19]. Therefore, with this restraint compromised, we observed an anteriorly translated and less externally rotated tibia relative to the femur. We observed similar alignment in the ACL-reconstructed cohort, which supports the hypothesis that persistently abnormal mechanical loading of knee following ACL rupture contributes to the development of post-traumatic osteoarthritis, regardless of repair.

Our findings of tibiofemoral alignment and altered centroid location were consistent with previous literature, but the increase in contact area that we observed was not. Degenerative changes after knee trauma are known to be complex and involve inter-related biological, mechanical, and structural pathways[37]. The mechanical changes that we observed represent state of ACL-reconstructed and nonreconstructed knees at a mean 2.7 years post-injury, which is longer follow-up than previous studies. Contact areas appear to decrease soon after injury but further out from injury, we show that contact areas increase. Important degenerative processes may be implicated in this. Longitudinal biomechanical studies would help clarify the interpretation of our contact area findings in the context of previous literature.

Our findings suggest that technical improvements to ACL reconstruction are necessary if the goal of the surgery is to restore normal knee mechanics. There has been significant interest in an adjunct extra-articular procedure called lateral extra-articular tenodosis (LET), which involves a reconstruction of the anterolateral capsule. Theoretically, the LET procedure may confer the added restraint to internal rotation that the ACL reconstruction in isolation seems to lack[5, 16]. Biomechanically, an added restraint across the anterolateral aspect of the knee may restore a more anterior medial centroid location and further externally rotate the tibia relative to the femur. Direct *in vivo* UO-MRI evaluation of the contact area, centroids, and alignment after ACL reconstruction done with this adjunct LET procedure may provide important information about its efficacy.

5.5 Future directions

The significant results that we showed have the potential to be expanded upon in further investigations.

Testing through the full range of knee flexion may be a worthwhile addition. Multiple kinematic studies have reported results throughout knee flexion[29, 30, 36], and comparison with results achieved with direct tibiofemoral cartilage mechanics measured in the UO-MRI may serve to strengthen or refute other indirect methods.

An emerging discipline in the investigation of ACL injury is quantitative MRI. T2, for example, has been negatively correlated with load[80, 81], and positively correlated with

damage to cartilage extracellular matrix[82]. Therefore, there is great potential to use sequences like T2 to better understand the mechanical role of cartilage in degeneration. An appealing aspect of some these sequences is that the measurements can be done *in vivo* under load. Though we were unsuccessful in including T2 in this study, quantitative MR has great potential in joint biomechanics research. One of the goals of quantitative MRI is to accurately and reliably determine the health of injured cartilage before the clinical signs and symptoms of diseases like osteoarthritis set in[83]. This kind of 'surrogate' marker of cartilage health may allow for early, targeted treatments of lesions, which are notoriously difficult to diagnose in more mild stages of disease[84].

Early in his career, Dr. Cy Frank remarked on the significant controversy surrounding how to optimally reconstruct the ACL. The UO-MRI method of directly measuring cartilage mechanics *in vivo* outlined in this thesis provides a reliable approach to further investigate surgical techniques. For example, these approaches could be applied to investigating the longitudinal study of ACL reconstruction versus nonreconstruction, the optimal drilling approach for the femoral tunnel[75], or the LET procedure as mentioned previously. Finally, there is the opportunity to investigate related ligamentous injuries, to the posterior cruciate, medial collateral, and lateral collateral ligaments.

5.6 Conclusion

This thesis outlines an UO-MRI method for the *in vivo* determination of tibiofemoral contact area, centroid location, and alignment in individuals with ACL rupture under standing, weightbearing conditions. We evaluated inter-rater, test-retest, and intra-rater

reliability, with good to excellent results. In an observational cohort study, we observed no difference in contact area, centroid location, and alignment between knees with ACL rupture that were treated operatively versus nonoperatively, at a mean 2.7 years from injury. Using the contralateral healthy knee as a control, we showed that ACL rupture was associated with posterior translation of the medial centroid, and a more anterior and less externally rotated position of the tibia relative to the femur. We conclude that ACL rupture leads to significant mechanical changes that are not reversed by ACL reconstruction. These findings may partially explain the equivalent risk of post-traumatic osteoarthritis in patients treated operatively and nonoperatively after ACL rupture.

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Appendices

Appendix A: Study advertisement

Have you torn your ACL before?

Would you like to be a part of a research study?

We are looking for participants who wish to undergo an MRI in a new
Upright, Open MRI scanner

We are looking for adult patients age 18-50 years old who have torn their ACL, to be a part of a study that seeks to quantify the cartilage changes that occur after this injury using a new, upright, open MRI scanner (UO-MRI). If you have torn only your ACL (on one side) within the last 10 years, and have fully rehabilitated from your injury, regardless of whether or not you had a surgery to reconstruct the ACL, this study may be of interest to you.

The study involves have a series of MRI scans at the UO-MRI scanner, located in the Blackmore Pavilion at Vancouver General Hospital. These scans are for research purposes only; they are not clinical diagnostic MRI scans. Participation will take up to 3 hours on a single day.

If you are interested, please contact us. We ask that you come in for a short screening session to ensure that you qualify for the study.

Participants will be compensated $100.

If you are interested, or would like more information, please contact:

Dr. David Stockton, on behalf of Principal Investigator Dr. Dave Wilson

[redacted]

Letter of Initial Contact – Upright Open MRI

Title: Quantification of cartilage changes using upright, open Magnetic Resonance Imaging (UO-MRI) after Anterior Cruciate Ligament (ACL) injury

Dear Patient,

We are writing to inform you of a study involving patients who have ruptured their ACL.

Principal Investigator: Dr. Dave Wilson, DPhil, Professor in the Department of Orthopaedics and Co-Director of the Centre for Hip Health and Mobility, UBC

Co-Investigators: Dr. Pierre Guy, MD, MBA, FRCSC, Head of Orthopaedic Trauma at Vancouver General Hospital and Associate Professor in the Department of Orthopaedics, UBC; Dr. Bas Masri, MD, FRCSC, Professor and Head of the Department of Orthopaedics, UBC; Dr. David Stockton, MD; Andrew Yung, MSc; Dr. Jane Desrochers, PhD; Andrew Schmidt, BSc; & Dr. Honglin Zhang, PhD. Contact telephone number (Available 24hrs): [redacted].

Background:
The research team is trying to help better understand the cartilage changes that occur in knee cartilage after an ACL rupture. You are being contacted because you have been identified from the orthopaedic trauma database at VGH as a patient who has sustained a ruptured ACL.

Reason for the Study:
People who have ruptured their ACL are at higher risk of the cartilage in their knees degenerating in the future, that is, developing osteoarthritis. We hope to study whether or not there are early changes in the cartilage properties after an ACL rupture using a special MRI scanner that allows patients to stand up during scans. It has an 'open-to-the-sky' structure and is not a closed tube. Performing MRI scans under weight-bearing conditions gives us potentially a much more realistic understanding of the knee cartilage properties and behaviour.

Who may Participate:
We are looking for participants who are:

- Adult participants between the ages of 18-50 years old, with an ACL rupture of only one knee.
- Male and female participants will be equally represented, and we will also seek equal representation of participants who have had their ACL's reconstructed and those that have not.
- Participants must have intact cartilage and evidence of unilateral complete ACL rupture (either from clinical exam or MRI).
- Intact cartilage (to the best of your knowledge).

- Documented unilateral ACL rupture within the last 10 years, reconstructed within 1 year from injury.
- Must have undergone full rehabilitation program and returned to baseline sport/ recreational activities.

If any of the following are true, you **cannot** not participate.

- If you have torn any ligaments OTHER THAN just your ACL (i.e. multiligamentous knee injury: ACL + PCL, LCL, or complete MCL rupture). ACL + incomplete MCL rupture will NOT be excluded. Associated meniscal tear will NOT be excluded.
- Known knee osteoarthritis
- Other joint disease (inflammatory arthritis, prior septic arthritis, osteonecrosis, dysplasia, fracture, or other disease).
- Incompletely rehabilitated injury, defined as range of motion less than 0-130 degrees, visible quads atrophy, or persistent mechanical symptoms during non-sporting activities.
- Staple used in securing one end of the ACL graft, if reconstructed.
- Individuals who cannot undergo MRI (based on MRI screening form); i.e. patients with a cardiac pacemaker or defibrillator, those with metal in their eye or orbit, or a ferromagnetic aneurysm clip, or who are or may be pregnant.
- History of fainting, or orthostatic blood pressure changes of >20mmHg in systolic blood pressure, 10mmHg diastolic blood pressure, or >30 beats per minute change in pulse (this will be checked prior to your scan).
- Prior or subsequent knee surgery other than diagnostic arthroscopy.
- Intra-articular corticosteroid injection to either knee.
- ACL rupture of BOTH knees.
- Re-ruptured ACL.
- Delayed reconstruction of ACL (>1year from injury).

Voluntary Participation:
Your participation in this study is entirely voluntary and if you choose not to participate you will not be asked to provide any reason for your choice.

Study Procedures:
If you agree to participate, scanning in the UO-MRI will take approximately 3 hours in the morning. The MRI technologist will first complete a detailed MRI Screening Form with you. The scans involve a series of supine (lying down) and upright standing scans.

There is no known or foreseeable risk to your physical health associated with MRI scans. There is a slight risk of claustrophobia (fear associated with confined spaces); however, this is reduced by the open structure of this particular scanner compared to traditional MRI scanners.

There are no direct benefits from participating in this study. You will be able to obtain copies of your scans if you wish, however these scans are for research purposes only and are not clinical scans.

Remuneration/Reimbursement:
As this study requires a significant portion of your time, we will reimburse all expenses incurred as a result of your participation. Please bring original travel receipts with you to your scanning session.
We also offer reimbursement of $100 for your time and as appreciation for your participation.

Contact:
If you have any questions or desire further information about this study before or during participation, please do not hesitate to contact Dr. David Wilson, [redacted]; he or another member of the study team will be more than happy to respond to all of your questions and concerns.

If you have any concerns or complaints about your rights as a research participant and/or your experiences while participating in this study, contact the Research Participant Complaint Line in the University of British Columbia Office of Research Ethics by e-mail at [redacted] or by phone at [redacted] (Toll Free: [redacted]). Please reference the study number (H18-01459) when calling so the Complaint Line staff can better assist you.

Confidentiality:
Your confidentiality will be respected. However, research records and health or other source records identifying you may be inspected in the presence of the Investigator or his or her designate by representatives of the UBC Clinical Research Ethics Board for the purpose of monitoring the research. No information or records that disclose your identity will be released or published without your consent, nor will any information or records that disclose your identity be removed or released without your consent unless required by law. You will be assigned a unique study number as a participant in this study. This number will not include any personal information that could identify you (e.g. it will not include your Personal Health Number, SIN, or your initials, etc.). Only this number will be used on any research-related information collected about you during the course of this study, so that your identity will be kept confidential. Information that contains your identity will remain only with the Principal Investigator and/or designate. The list that matches your name to the unique study number that is used on your research-related information will not be removed or released without your consent unless required by law.

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to ensure that your privacy is respected. You also have the legal right of access to the information about you that has been provided to the sponsor and, if need be, an opportunity to correct any errors in this information. Further details about these laws are available on request to your study doctor.

All of the data collected in this study is confidential. Access to data is restricted to the investigators reported at the opening of this document only. We may also use a completely anonymized and de-identified copy of your MRI scans for educational or promotional purposes, for example: on our website, in a presentation, or in a brochure about our research.

Participation:
This letter will be followed up with a phone call by one of the study team members within three weeks of receiving the letter. Or, if you are sure that you want to participate, please e-mail david.stockton@alumni.ubc.ca to schedule a date for your scan, and to receive an official participant consent form.

If you do NOT want any further contact regarding this study, please contact the study co-ordinator at [redacted] or [redacted].

Efforts have been made to ensure this notification does not reach the families of patients who have passed away. If a grieving family member receives this letter, please accept our heartfelt condolences and our sincere apology.

Sincerely,

Dr. Dave Wilson, DPhil
Professor, Dept. of Orthopaedics, UBC
Co-Director, Centre for Hip Health and Mobility

Dr. Pierre Guy, MD, MBA, FRCSC
Associate Professor and Head of Orthopaedic Trauma, UBC
Co-Director, Centre for Hip Health and Mobility

Dr. Bas Masri, MD, FRCSC
Professor and Head, Dept. of Orthopaedics, UBC
and Vancouver Coastal Health

Dr. David Stockton, MD
PGY-5 Orthopaedic Surgery Resident and UBC Clinician Investigator Program

Appendix B: Participant consent

Participant Information and Consent Form – Upright Open MRI

Title: Quantification of cartilage changes using upright, open Magnetic Resonance Imaging (UO-MRI) after Anterior Cruciate Ligament (ACL) injury

Principal Investigator and contact:
Dr. David R. Wilson, DPhil
[redacted]
Department of Orthopaedics, Centre for Hip Health and Mobility, Vancouver Coastal Health Research Institute and University of British Columbia

Co-Investigators:
Dr. Bas A. Masri, MD, FRCSC
Professor and Head, Department of Orthopaedics, UBC

David J. Stockton, BSc, MD
Centre for Hip Health and Mobility, Department of Orthopaedics, UBC

Andrew Yung, MSc
Centre for Hip Health and Mobility, Department of Physics and Astronomy, UBC

Jane Desrochers, PhD
Centre for Hip Health and Mobility, Department of Orthopaedics, UBC

Andrew Schmidt, BSc
Centre for Hip Health and Mobility, Department of Orthopaedics, UBC

Honglin Zhang, PhD
Centre for Hip Health and Mobility, Department of Orthopaedics, UBC

Invitation:
You have been invited to participate in a research study and undergo a magnetic resonance (MR) scan in an open scanner to help us quantify the changes in knee cartilage after sustaining an ACL injury

Purpose:
The purpose of this work is to use the 0.5 Tesla Paramed UO-MRI research scanner, located in the Radiology Department in the Blackmore Pavilion of Vancouver General Hospital, to investigate differences in cartilage loading patterns after ACL injury. The upright, open MRI scanner differs from a traditional MRI scanner in that it is not a closed tube; rather, it has an “open-to-the-sky” structure. This allows much more flexibility in both the types of subjects that may be imaged and also in the position in which the subjects may be imaged.

Voluntary Participation:
Your participation is entirely voluntary, so it is up to you to decide whether or not to take part in this study. Before you decide, it is important for you to understand what the research involves. This consent form will tell you about the study, why the research is being done, what tests will be performed during the study, and the possible benefits, risks and discomforts.

If you wish to participate, you will be asked to sign this form. If you do decide to take part in this study, you are still free to withdraw at any time and without giving any reasons for your decision.

If you do not wish to participate, you do not have to provide any reason for your decision.

Please take time to read the following information carefully and to discuss it with your family, friends, and doctor before you decide.

Participant INCLUSION Criteria:
We are looking for participants who are:

- Adult participants between the ages of 18-50 years old, with unilateral ACL ruptures.
- Male and female participants will be equally represented, and we will also seek equal representation of participants who have had their ACL's reconstructed and those that have not.
- Participants must have intact cartilage and evidence of unilateral complete ACL rupture (either from clinical exam or MRI).
- Intact cartilage (Kellgren-Lawrence grade 0 or 1).
- Documented unilateral ACL rupture within the last 10 years, reconstructed within 1 year from injury.
- Must have undergone full rehabilitation program and returned to baseline sport/ recreational activities.

Participant EXCLUSION Criteria:
If any of the following are true, you cannot not participate.

- If you have torn any ligaments OTHER THAN just your ACL (i.e. multiligamentous knee injury: ACL + PCL, LCL, or complete MCL rupture). ACL + incomplete MCL rupture will NOT be excluded. Associated meniscal tear will NOT be excluded.
- Known knee osteoarthritis (Kellgren-Lawrence grade >1)
- Other joint disease (inflammatory arthritis, prior septic arthritis, osteonecrosis, dysplasia, fracture, or other disease).
- Incompletely rehabilitated injury, defined as range of motion less than 0-130 degrees, visible quads atrophy, or persistent mechanical symptoms during non-sporting activities.
- Staple used in securing one end of the ACL graft, if reconstructed.
- Individuals who cannot undergo MRI (based on MRI screening form); i.e. patients with a cardiac pacemaker or defibrillator, those with metal in their eye or orbit, or a ferromagnetic aneurysm clip, or who are or may be pregnant.
- History of fainting, or orthostatic blood pressure changes of >20mmHg in systolic blood pressure, 10mmHg diastolic blood pressure, or >30 beats per minute change in pulse (this will be checked prior to your scan).
- Prior or subsequent knee surgery other than diagnostic arthroscopy.
- Intra-articular corticosteroid injection to either knee.
- ACL rupture of BOTH knees.

- Re-ruptured ACL.
- Delayed reconstruction of ACL (>1year from injury).

Depending upon the individual situation, you may not be able to participate if you have any of the following:

- artificial heart valve;
- ear or eye implant;
- brain aneurysm clip;
- implanted drug infusion pump;
- electrical stimulator for nerves or bones;
- coil, catheter, or filter in any blood vessel;
- orthopaedic hardware (artificial joint, plate, screw, rod);
- other metallic prostheses;
- shrapnel, bullets or other metal fragments;
- surgery or tattoos (including tattooed eyeliner) in the last six weeks.

If you have any of the above, your individual case will be reviewed by the hospital MR Technologist and/or Radiologist, and a decision will be made regarding your participation in this study. An operative report may be required to assess the nature of the implants in your body.

Study Procedures:
If you choose to participate in this study you will be asked to complete a detailed MR Screening Form asking about contraindications to MRI. This form will be reviewed with you by the MR Technologist to ensure your safety during the scanning session.

You will be asked to change into hospital scrubs and to remove all metal objects (such as hearing aids, dentures, jewellery, watches, hairpins, and ALL piercings) from your body because these objects interfere with imaging and may be attracted to the scanner magnet, or may heat up, with the potential risk of injury. You will be seated in a chair for at least 30 minutes while the screening form and consents are reviewed, to make sure that your knee cartilage is fully unloaded prior to scanning. You will also be given compression socks to be worn while scanning, to minimize venous pooling in your legs. Finally, we will measure your orthostatic blood pressure (blood pressure lying down vs. standing up) to see if you may be at risk of fainting during the upright scans. If there is any evidence that you may be at risk of fainting, you will unfortunately not be able to participate in the study.

You will then be positioned in the MR scanner. This scanner is different from typical MR scanners where subjects are asked to lie on a table which is then moved into the magnet centre (the “doughnut”). The UO-MRI is a vertically open scanner (two parallel discs oriented on edge, 58 cm apart), which allows for a wide range of positioning. An MRI coil (a specifically designed antenna) will be placed near the part of your body we wish to image. The MRI technician will orient the participant to the scanner and instruct them on positioning for the scans, and also on how to use the call bell which is available should the participant feel claustrophobic or faint during scanning. The uninjured knee will be imaged first (as a control), followed by the affected knee with the ACL rupture. Following each scan, the technician will ensure adequate imaging was captured with minimal artifact or motion. The patient will next stand for at least 15 minutes before obtaining the standing scan to allow for loading of knee cartilage to equilibrate. Then standing scans will be obtained, first the uninjured knee followed by the affected knee. Each scan takes approximately 3 minutes. The first 6 participants will be asked to repeat this process again during the same session,

and then asked to return 2 weeks later for more scanning using the same protocol. This data will be used to test the repeatability of the UO-MRI in quantifying knee cartilage loading. Subsequent participants will only attend for one session. Each session will take no longer than 3 hours.

Possible Risks Involved in Participation:
There is no known or foreseeable risk to your physical health associated with MRI scans. There is a slight risk of claustrophobia (fear associated with confined spaces); however, this is reduced by the open structure of this particular scanner as compared to traditional MR scanners. You will be asked to remain as still as possible for the duration of the scanning procedure. During the scan you will hear acoustic noises (very loud "knocking" sounds) from the magnet. You will be required to wear earplugs to minimize the noise. In this scanner, it is possible to image you while you are standing; there is a risk of fainting. Predisposed individuals will be screened out of participation, and precautionary measures will be taken including compression stockings and placing supports and foam mats during scanning. Lastly, a harness 'vest' will be applied to prior to standing scans, to catch you in the rare event that fainting occurs.

Possible Benefits:
You will not receive any direct benefits from participating in this study. You will be able to obtain copies of your scans if you wish, however these scans are for research purposes only and are not clinical scans.

Incidental Findings:
As this will NOT be a medically indicated examination, there will be no formal review of the scans and no report will be made. This MRI scan is not a substitute for one a doctor would order. It may not show problems that would be picked up by a diagnostic MRI scan. However, if we believe that we have found a medical problem in your MRI scan, we will ask a doctor who is trained in the reading of MRI scans, a radiologist, to help us review the images. If the radiologist thinks that there may be an abnormality in your MRI scan that requires follow-up, we will contact you, and with your permission, contact your family physician and help him or her obtain the appropriate follow-up for you. No information generated in this study will become part of your permanent medical record. However, if the study detects an abnormality in your MRI scan and further follow-up is required, then this information may become part of your record.

Confidentiality:
Your confidentiality will be respected. However, research records and health or other source records identifying you may be inspected in the presence of the Investigator or his or her designate by representatives of the UBC Clinical Research Ethics Board for the purpose of monitoring the research. No information or records that disclose your identity will be released or published without your consent, nor will any information or records that disclose your identity be removed or released without your consent unless required by law. You will be assigned a unique study number as a participant in this study. This number will not include any personal information that could identify you (e.g. it will not include your Personal Health Number, SIN, or your initials, etc.). Only this number will be used on any research-related information collected about you during the course of this study, so that your identity will be kept confidential. Information that contains your identity will remain only with the Principal Investigator and/or designate. The list that matches your name to the unique study number that is used on your research-related information will not be removed or released without your consent unless required by law.

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to ensure that your privacy is respected. You also have the legal right of access to the information about you that has been provided to the sponsor and, if need be, an opportunity to correct any errors in this information. Further details about these laws are available on request to your study doctor.

All of the data collected in this study is confidential. Access to data is restricted to the investigators reported at the opening of this document only. We may also use a completely anonymized and de-identified copy of your MRI scans for educational or promotional purposes, for example: on our website, in a presentation, or in a brochure about our research.

Remuneration/Reimbursement:
As this study requires a significant portion of your time, we will reimburse all expenses incurred as a result of your participation. Please bring original receipts with you to your scanning session.
We also offer reimbursement of $100 for your time and as appreciation for your participation.

Refusal or Withdrawal from Study:
This study is strictly voluntary; it is your choice as to whether or not you wish to participate. You may withdraw from this study at any time without giving reasons. If you choose to enter the study and then decide to withdraw at a later time, all information about you collected up to the point of your withdrawal will be retained for analysis in order to protect the integrity of the research, which may benefit future research participants and patients. However, no further information will be collected.

What Happens if Something Goes Wrong?
By signing this form, you do not give up any of your legal rights and you do not release the study doctor, participating institutions, or anyone else from their legal and professional duties. If you become ill or physically injured as a result of participation in this study, medical treatment will be provided at no additional cost to you. The costs of your medical treatment will be paid by your provincial medical plan.

Questions or Concerns Regarding the Study:
If you have any questions or desire further information about this study before or during participation, please do not hesitate to contact Dr. David Wilson, [redacted]; he or another member of the study team will be more than happy to respond to all of your questions and concerns.

If you have any concerns or complaints about your rights as a research participant and/or your experiences while participating in this study, contact the Research Participant Complaint Line in the University of British Columbia Office of Research Ethics by e-mail at [redacted] or by phone at [redacted] (Toll Free: [redacted]). Please reference the study number (H18-01459) when calling so the Complaint Line staff can better assist you.

Consent:
I have read and understood all of the statements above. I realize that participation in this study is strictly voluntary and that I may refuse to participate or I may withdraw at any time. I recognize that all of the measurements are in addition to my normal health care. I understand that I am not waiving my legal rights by signing this consent form.

I have been told that I will receive a **signed and dated** copy of this document for my personal records.

By signing this document, I consent to participate in this study.

☐ Please check this box if you wish to have your family doctor contacted in the case that there are incidental findings.

Participant _____ Date _____
(please print)

Signature_____

Witness _____ Date _____
(please print)

Signature_____

Investigator_____ Date _____
(please print)

Signature_____

Please provide the following information so that we may contact you in the case that there are incidental findings in your scan. Only include your family doctor's name if you would like them to also be contacted regarding any incidental findings.

PLEASE PRINT

Name_____

Phone:_____

Date of Birth:
(dd/mm/yy)_____

Family Doctor:_____

Appendix C: MRI screening form

Vancouver Coastal Health Authority

☐ LGH ☐ RH ☐ UBCH ☐ VGH

MAGNETIC RESONANCE IMAGING (MRI)
PATIENT SCREENING FORM

STUDY ID: _____

DATE: _____

Every patient scheduled for MRI **MUST** complete the following questionnaire prior to the being scanned. The technologist will be happy to answer any of your questions. **Please answer each question accurately and explain any marked "yes".**

Birth date: _____ Age: _____ Height____ft____in or ____cm Weight:_____kg or _____lbs

Do you have:	**Yes**	**No**	**Unsure**	**If yes, explain**
Cardiac (Heart) Pacemaker or Wires (At any time in your life)				
Artificial Heart Valves				
Brain aneurysm clips				
Metal in your eyes (At any time in your life)				
Implanted Electrodes, Pumps or Catheters				
Neurostimulators				
Shrapnel, Bullets or other metal fragments				
Any Tattoos – including permanent make up				
Ear implants (Cochlear, Stapes) /Hearing Aid				
Orthopedic (Bone) Screws, Pins, Plates, Rods (If yes, state location)				
Breast tissue expander or other implants				
Prosthesis (Eye, Penile, Leg, Arm, Joint, etc.)				
Any Stents, Coils, or Filter in blood vessels				
Dentures, retainer, braces, magnetic implants				
Transdermal medication patches (Examples: Nitroglycerin for heart or Nicotine to stop smoking)				
Body Piercing other than earrings				
Have you ever had surgery or operation on:				
Brain, Eye, or Ear				
Heart				
Neck, Chest, or Back (Spine)				
Abdomen, Pelvis, Hips				
Arms and/or Legs				
Injection into a joint within the last 2 weeks				
Are you:				
Pregnant				
Claustrophobic				

Please remove all your jewelry, watch, credit cards, coins and other metallic items (earrings, hair clips, bobby pins, etc.). A MRI staff member will instruct you about securing your items prior to entry into the examination area. I have read and understand the entire contents of this form. I affirm that the above information is true to the best of my knowledge and I hereby consent to the MRI study

_____ _____
Signature of person completing this form Date

_____ _____ _____
Relationship to patient if form not completed by patient Review Date Patient Initials

_____ _____
Signature of translator Date

MR Technologist Initials/Date

If your MRI exam date occurs after the date the screening form was completed, you must review the screening form and alert the MR technologist of any changes. Please enter the date of review and your initials indicating confirmation of review.

CENTRE for HIP Health and Mobility

How to Prepare for your Upright Open MRI Standing Scan

Standing MRI scans provide a unique way to look at the human body in clinically relevant weight-bearing positions. Some people feel lightheaded or faint during standing scans. To reduce this possibility we ask that you follow these preparation instructions:

Before arriving for your scan:

- **Eat a healthy full meal before coming to your scanning appointment**
- Increase your fluid consumption while limiting the amount of caffeine (compared to your normal routine)
- You may otherwise carry on with your normal routine (e.g. exercise, etc.) but please be cognisant of your body's nutritional and fluid needs
- Plan to have something to drink and eat just prior to your scan, e.g. water or juice, and a piece of fruit, granola bar, or other snack.

What you can expect during your scan:

- You will be given a call bell to squeeze if at any time you feel faint, dizzy, lightheaded or otherwise unwell
- You will be given juice and a granola bar approximately 30 minutes prior to the standing portion of your scan (whenever there is an appropriate pause between scans)
- You will be given a short rest period between standing scans (each scan is typically less than 5 minutes in length), during which we will ask you to flex your legs, squat, or otherwise increase blood flow in your legs
- You will wear fabric compression leggings around your calves that will gently squeeze your calves to increase blood flow to and from your legs
- You will be given bathroom breaks as needed
- During standing scans, it is very important that you DO NOT LOCK YOUR KNEES, but rather keep your legs comfortably straight with a slight bend at the knee as per your normal posture. Locking your knees restricts the return of venous blood to your heart and brain.

When you arrive at the scanner:

In addition to the MRI Safety Screening, we will ask you questions about relevant health history. Please check all that apply and bring this sheet to your appointment:

- ❑ Do you have epilepsy?
- ❑ Have you fainted in the past? If yes, please describe the situation(s)
- ❑ Do you have low blood pressure?
- ❑ Are you hypoglycemic?
- ❑ Are you anemic?
- ❑ In the past week have you donated blood?
- ❑ In the past two weeks have you been ill (cold, flu, etc.)?
- ❑ Do you have circulatory problems in your legs?
- ❑ Is there any other reason that you might be at increased risk of fainting?

We look forward to having you participate in Upright Open MRI Research!