Quantitative Magnetic Resonance Imaging of Knee Articular Cartilage and Effusion-Synovitis: The Structural Response to Changes in Joint Loading

Hayden F. Atkinson, The University of Western Ontario

Supervisor: Birmingham, Trevor B., The University of Western Ontario
A thesis submitted in partial fulfillment of the requirements for the Doctor of Philosophy degree in Health and Rehabilitation Sciences
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ABSTRACT

Knee osteoarthritis (OA) is a progressive degenerative condition that can affect all tissues within the joint. Methods to measure early changes in joint structures and the effect of interventions are required. The purpose of this thesis was to investigate aspects of quantitative magnetic resonance imaging (MRI) as outcome measures in knee OA studies. Specifically, changes in articular cartilage composition and/or effusion-synovitis were examined in people with or at risk for knee OA and healthy controls, and after altering joint loads.

Chapter 2 is a systematic review that studied articular cartilage composition using MRI T2 and T1ρ relaxation in patients at risk for knee OA and healthy controls. We performed meta-analyses to examine the effect of knee OA risk factors on T2 and T1ρ relaxation. The presence of risk factors resulted in lengthened T2 and T1ρ relaxation. These findings support the use of compositional MRI to detect articular cartilage degeneration early in the OA disease process.

Chapter 3 explores the acute response of knee articular cartilage T2 relaxation to a functional loading stimulus in patients at risk for knee OA and healthy controls. T2 relaxation shortened similarly in both groups following the loading stimulus. The loading stimulus evoked consistent changes in articular cartilage composition but did not detect compromised articular cartilage in patients at risk for knee OA.
Chapter 4 evaluates the effect of high tibial osteotomy (HTO), a limb realignment surgery, on T2 relaxation of articular cartilage in patients with knee OA and varus alignment. Shortening of T2 relaxation was observed in the medial compartment, with no change in the lateral or patellar compartments, suggesting HTO can improve articular cartilage composition in the targeted compartment, without harming other compartments.

Chapter 5 studies the effect of knee load on effusion-synovitis, using HTO as a model. The change in knee adduction impulse was associated with the change in effusion-synovitis. The findings suggest that mechano-inflammation is an active pathway in knee OA that can respond to biomechanical intervention.

Overall, this thesis provides evidence that quantitative MRI is sensitive to structural changes of articular cartilage and effusion-synovitis at various stages of knee OA.
**KEYWORDS:** osteoarthritis, knee, articular cartilage, inflammation, effusion-synovitis, quantitative magnetic resonance imaging, high tibial osteotomy
SUMMARY FOR LAY AUDIENCE

Knee osteoarthritis (OA) is a chronic disease that affects the entire joint. Changes throughout the joint contribute to knee OA. Being able to measure change is important to understanding how the joint responds, and which treatments are effective. Quantitative magnetic resonance imaging (MRI) measures specific changes within the knee joint. This thesis uses quantitative MRI to measure changes in articular cartilage and inflammation in knee OA.

Chapter 2 measures how the makeup of articular cartilage differs between patients at risk for knee OA and healthy participants in previously published studies. After evaluating all of the literature, people at risk for knee OA had unfavourable changes in their cartilage compared to healthy controls, well before being diagnosed with OA.

Chapter 3 studies how articular cartilage responds to knee joint load in patients at risk for knee OA and healthy controls. After both groups completed a challenging workout, the cartilage of both groups responded very similarly. This suggests that people at risk for knee OA still have similar cartilage function despite being at greater risk for knee OA.

Chapter 4 evaluates the effect of surgical realignment of the lower limb on the makeup of articular cartilage in patients with knee OA with bowed legs and pain on the inside of the knee. One year after surgery, articular cartilage structure was improved on the inside of the knee, with no changes to the outside of the knee or under the kneecap. This shows that surgical realignment can help the cartilage of patients with knee OA.
Chapter 5 evaluates long term changes in joint load on inflammation within the joint, using surgical realignment as the method to induce changes in joint load. One year after surgery, patients who experienced the greatest reductions in load during walking had substantial decreases in inflammation within the knee joint. This shows that joint load is a major contributor to inflammation, and is treatable by changing the load.

All of these findings were determined using quantitative MRI, an extremely valuable tool to determine how the joint changes over the course of disease, and how it responds to treatment.
CO-AUTHORSHIP STATEMENT
This thesis contains material from one published manuscript (Chapter 2), two manuscripts submitted for publication (Chapters 4 and 5), and one manuscript prepared for submission (Chapter 3). H.F. Atkinson is the primary author of all chapters in this thesis with contributions from the following:

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LIST OF ABBREVIATIONS

In order of appearance

OA Osteoarthritis
MRI Magnetic Resonance Imaging
CT Computed Tomography
RF Radiofrequency
ROI Region of Interest
3D Three Dimensional
HTO High Tibial Osteotomy
SMD Standardized Mean Difference
ACL Anterior Cruciate Ligament
OAI Osteoarthritis Initiative
KL Kellgren & Lawrence
SD Standard Deviation
ROBINS-I Risk of Bias in Nonrandomized Studies of Interventions
95%CI 95% Confidence Interval
ICC Intra-Class Correlation Coefficient
CV Coefficient of Variation
3T 3 Tesla
ANOVA Analysis of Variance
MF Medial Femur
MT Medial Tibia
LF Lateral Femur
LT Lateral Tibia
P Patella
Tr Trochlea
BMI Body Mass Index
MAA Mechanical Axis Angle
PEEK Polyethyletherketone
dGEMRIC Delayed Gadolinium-Enhanced MRI of Cartilage
%Bw•H Percent Bodyweight Times Height
%Bw•H•s Percent Bodyweight Times Height Times Seconds
Hz Hertz
DESS Dual-Echo Steady State
Tx Transmit
Rx Receive
NPRS Numeric Pain Rating Scale
CHAPTER 1 – Introduction: Background and Rationale

Osteoarthritis (OA) currently affects 250 million people worldwide and ranks amongst the highest health burdens globally\textsuperscript{1-3}. The knee is the most common site of OA\textsuperscript{1,2}, typically affecting the articular cartilage of the medial compartment of the tibiofemoral joint, largely because of the high loads borne by the joint during ambulation\textsuperscript{4}. The etiology of knee OA is complex, however, and includes both mechanical and biological processes that affect the entire joint as an organ\textsuperscript{5}.

Advanced imaging techniques provide an opportunity to investigate the potential links between biomechanical and biological processes in knee OA. Termed imaging biomarkers, imaging modalities such as magnetic resonance imaging (MRI) enable the quantification of various disease features in knee OA. For this thesis, two relatively novel MRI biomarkers were studied in their response to changes in knee loading in various conditions: compositional MRI of articular cartilage, and volume of effusion-synovitis.

**Osteoarthritis**

OA is the most common form of arthritis, with the hallmark being articular cartilage degradation in synovial joints, with many other accompanying signs and symptoms, including inflammation of the synovium, lesions of the subchondral bone, degeneration of the surrounding connective tissue, and subsequent deconditioning of the surrounding musculature\textsuperscript{6}. 
The primary symptom of OA is pain in the affected joint\textsuperscript{7}, which typically increases in severity as the disease progresses. Knee OA is responsible for compromised quality of life\textsuperscript{8} due to years lived with pain and functional limitations. OA is a musculoskeletal condition, however it is also an independent risk factor for cardiovascular disease\textsuperscript{9} and all-cause mortality\textsuperscript{10}. Given the increased risk for major medical events, combined with the diminished quality of life and often substantial years lived with disability\textsuperscript{11}, it is of paramount importance to detect OA at the earliest stage to initiate interventions and lifestyle changes to preserve the integrity of the joint and quality of life.

The most prominent risk factors for OA include joint injury, obesity\textsuperscript{12}, limb malalignment\textsuperscript{13,14}, female sex\textsuperscript{15}, increased age\textsuperscript{16}, and family history\textsuperscript{17}. OA incidence can either be primary or secondary. Primary OA occurs idiopathically with no known direct cause. Secondary OA occurs as a result of another disease or injury, such as joint injury resulting in post-traumatic OA, or rheumatoid arthritis leading to OA complications. The burden of OA is tremendous, being the single greatest cause of days lost due to disability in North America\textsuperscript{18}, and a financial health burden over $128 billion in the US alone in 2003\textsuperscript{19}, and between 1-2.5\% of the gross domestic product of developed countries\textsuperscript{20}. Current treatments for knee OA can be separated into operative and non-operative options. Currently the most widely used operative options include arthroscopy, high tibial osteotomy, and joint arthroplasty\textsuperscript{21}. Non-operative treatment options approved by the Osteoarthritis Research Society International include education on self-management, gait retraining, cardiopulmonary and resistance exercise, corticosteroids, and weight management, and anti-inflammatories for patients with inflammation of the joint\textsuperscript{22}. 

Osteoarthritis most commonly affects the knee joint, due to a combination of factors, given its large range of motion, lack of stability relative to other load-bearing joints such as the hip and ankle, and complex articulating structure, given that it is really made up of two joints that function together; the patellofemoral joint and the tibiofemoral joint.

There are two common pathways resulting in the incidence of knee OA, referred to as idiopathic (primary) or post-traumatic (secondary) OA\(^23\). Idiopathic OA does not occur as a result of any obvious cause or modifiable risk factor, and typically occurs later in life. Contributing factors include, but are not limited to genetic factors\(^24\), female sex\(^25\), cell senescence\(^26\), or joint shape\(^27\). Sub-phenotypes and biological disease pathways within idiopathic OA are intensely studied, however they are beyond the scope of this thesis. Post-traumatic OA occurs as a result of an injury to the joint of great enough magnitude to compromise the integrity of one or more of the joint tissues\(^28\), resulting in maladaptive structural and biological changes, driving joint degeneration that typically occurs at a much faster rate than idiopathic OA\(^29\). A large proportion of patients who suffer traumatic knee injuries develop radiographic evidence of knee OA within 10 years or less from the initial injury\(^30,31\).

**The Knee Joint**

The knee joint is a synovial, bicondylar joint that primarily flexes and extends in the sagittal plane, however has some internal and external range of motion in the transverse plane, and some adduction and abduction range of motion in the frontal plane\(^32\). These 6 degrees of freedom allow for greater range of motion of the entire lower limb in open and closed-
chain movements. The knee joint, like all synovial joints, operates truly as an organ as it requires many tissue types to function properly.

The structure of the knee joint is founded by two long bones, the femur and the tibia, and a sesamoid bone, the patella. The fibula is also implicated in the function of the knee joint, as there are several muscles and ligaments that cross the knee joint that insert onto the fibula, however it does not contribute to the articulation of the knee joint. The joint itself is wrapped in a fibrous capsule made of connective tissue that contributes to some of the structural integrity of the joint, but the main purpose is to create a seal between the joint and the external environment. Within the joint are a variety of tissues with specific functions. Ligaments provide tension in specific directions to provide stability to the joint. The articular cartilage provides a frictionless surface on which bones can glide and bear load. The menisci provide congruence and additional load-bearing capacity. The synovium secretes synovial fluid to lubricate the joint. The surrounding muscles contract to move the long bones and enable locomotion and functional activity. Articular cartilage and synovium will be explored in greater depth in this thesis.

**Articular Cartilage**

The articular cartilage is an aneural, avascular, highly specialized tissue that lines the ends of long bones at the articulation of a joint. The purpose of articular cartilage is to reduce friction to allow pain-free range of motion and dissipate loads to reduce impact on the subchondral bone. Articular cartilage can be found in any synovial joint. The primary functional cell in articular cartilage is the chondrocyte, which maintains the extracellular
matrix, which is composed of type II collagen and proteoglycans (Figure 1.1). Collagen acts as the primary support structure of articular cartilage, dispersed in columnar patterns to provide tensile strength and absorb loading stress, and horizontal patterns near the articular surface to best take on shear forces from the cartilage of the underlying bone. Proteoglycans are the primary water-binding structures of articular cartilage, providing the ability to compress when loaded. Although many tissues are implicated in OA, articular cartilage is the primary currency of disease progression. Complete erosion of articular cartilage results in bone-on-bone lesions, exposing sensitive nerve endings, resulting in painful symptoms characteristic of OA.

![Figure 1.1. Laminar organization of articular cartilage and changes associated with progression of knee osteoarthritis](image)

**Synovium**

The synovium is another tissue critical to joint function. It is highly vascularized, and lines the inside layer of the joint capsule. The synovium secretes synovial fluid providing lubrication, nutrients, and a means of waste excretion. The synovium can be highly implicated in OA, and can even be an independent contributor to OA progression\(^3^4\). The inflammation of the synovium, termed “synovitis” contributes to the pain characteristic of OA\(^3^5,3^6\), and results in excessive secretion of synovial fluid, creating an effused, swollen
joint. The primary pathway for synovitis is small fragments of frayed articular cartilage irritating the synovium, inflammation and thickening of the synovial lining, and increased synovial fluid excretion\textsuperscript{37}.

**Imaging of Osteoarthritis**

OA implicates all tissues of the joint, thus there are many imaging modalities that can best represent specific aspects of the joint. The most common imaging modality used to study and assess knee OA are radiographs (x-rays). Radiographs provide a low-cost means to assess the alignment and gross bony changes of the knee joint, such as joint space, and superficial changes, such as osteophytes or attrition\textsuperscript{38,39}. The limitation of radiographs is the ability to capture the knee joint in only one plane, which can sometimes affect the interpretation of the severity of disease\textsuperscript{40,41}. Radiographs also fail to provide any information on the status of soft-tissue integrity, such as articular cartilage, meniscus, synovium, or ligaments\textsuperscript{42}; all strong components of knee joint health and OA status in their own right.

Computed tomography (CT) offers an improvement to radiographs, providing three-dimensional representation of the calcified tissues of the knee joint, with small improvements in soft-tissue representation depending on the intensity of the scan. Unfortunately, CT involves a much higher radiation dose, as it is essentially a multiplanar $360\degree$ radiograph. Given the moderate additional value for the increased health risk, CT is seldom used in knee OA care, and is only used in research when high quality 3D representations of bony structures are of the highest importance.
MRI is an excellent imaging modality for soft tissue contrast to detect morphological changes due to injury, degeneration, or abnormal growth in a tissue\textsuperscript{43}. This soft tissue contrast is extremely beneficial for diagnostic purposes, providing radiologists with a view inside the organ to make a complete assessment. Many current semi-quantitative scoring systems are available which intend to evaluate each individual tissue, as well as providing a total score for the joint, in keeping with the perception that OA is a disease of the entire joint as an organ\textsuperscript{44–47}. Aside from the visually apparent benefits that MRI provides, quantitative outcomes can be obtained from an image set and applied as a means of assessing disease status and progression. Quantitative MRI takes advantage of the measurable properties of MR allowing clinicians and researchers to assess changes in tissues. Quantitative MRI applications in knee OA include thickness and volume of a number of tissues, including cartilage\textsuperscript{48}, meniscus\textsuperscript{49}, and synovium\textsuperscript{50}. Within the scope of quantitative MRI is compositional MRI, which provides a means to measure the biochemical properties of tissues based on physical principles applied in MRI. Specific application of compositional MRI are the measurement of collagen organization, free water concentration, and extracellular matrix integrity in articular cartilage via T2\textsuperscript{51} or T1\textsubscript{ρ}\textsuperscript{52} relaxation time for example. All of these measures provide valuable information on the status of progression of knee OA and are very sensitive to changes that would otherwise be undetectable with other non-invasive assessments. While MRI is an excellent research tool with little to no involved health risks, it is seldom used in knee OA care, as the costs and wait times are much higher than radiographs, and it is often reserved for health conditions with greater imminent threat or more internal in nature.
**Cartilage Relaxometry**

T2 and T1ρ relaxation are physical properties of tissues in the context of MRI. They are both measures of magnetization relaxing in the transverse plane; specifically, the time taken for the magnetization to decay to $1/e$ (or approximately 37% of the original magnetization), thus T2 and T1ρ are exponentially decaying signals. To quantify and analyze these properties for the purpose of relaxometry, T2 or T1ρ maps must be constructed based on an image set acquired in the MR scanner. To acquire T2 maps, the selected slice is excited by a 90° pulse to flip the magnetization into the transverse plane. The magnetization vector precesses about the static magnetic field ($B_0$) while shortening along the transverse plane (spin-spin relaxation, or T2) and lengthening towards the direction of $B_0$ (spin-lattice relaxation, or T1), with 180° pulses over the course of the pulse sequence. The purpose of the 180° pulses is to control for some of the magnetic field inhomogeneities that can disproportionately affect the relaxation. Without these pulses, the relaxation would be known as T2* (T2-star) relaxation, which is always faster and more variable than T2 relaxation. Typically, six or seven 180° pulses are applied, and the signal in the transverse plane is recorded at each spin echo, which are all evenly spaced. An example of a T2 mapping pulse sequence is represented in Figure 1.2. Given that the signal is recorded at several time points over the course of its decay, the relaxation time can be calculated as a function of the exponential decay of the signal over time. When this is applied to every voxel, a T2 “map” can be created that is representative of the range of relaxation times within the image slice.
The main difference between T1ρ and T2 pulse sequences, is that with T1ρ, there are no spin echoes, as it is a gradient echo sequence. Instead, a series of low power, long duration spin-locking RF pulse is applied immediately after the initial 90° radiofrequency (RF) pulse and before the second 90° pulse, essentially blocking the magnetization vector from relaxing towards $B_0$. The decay in the signal between each spin-locking RF pulse is used to calculate the T1ρ relaxation time. As a result, all of the relaxation occurs in the transverse plane, thus measuring T1 relaxation in the rotating frame. An example of a T1ρ mapping sequence is represented in Figure 1.3.

**Figure 1.2.** Example of a fast spin echo multi-echo pulse sequence used for T2 mapping\(^2\). rf = radiofrequency pulse, GSS = slice select gradient, GPE = phase encode gradient, GR = readout (of frequency encode) gradient, ACQ = signal acquisition, ETL = Echo Train Length.
Figure 1.3. Example of a spin-locking single echo pulse sequence used for T1ρ mapping\textsuperscript{53}. rf = radiofrequency pulse, GSS = slice select gradient, GPE = phase encode gradient, GR = readout (of frequency encode) gradient, ACQ = signal acquisition.

T1ρ relaxation measures low-frequency interactions between water molecules, with more interactions yielding lengthened values. T1ρ is inversely correlated with proteoglycan integrity and concentration; meaning lengthened T1ρ relaxation time is indicative of increased severity of extracellular matrix degeneration in articular cartilage\textsuperscript{54}, and T2 is inversely correlated with collagen network organization and structure\textsuperscript{55}, meaning lengthened T2 relaxation represents a more disorganized and compromised collagen network. This is represented well in Figure 1.4. The reason for this is that proteoglycan molecules bind to water tightly, and collagen molecules maintain the structure of the extracellular matrix. Compromised proteoglycans with chains of glycosaminoglycans cleaved off of the molecular structure are unable to bind to water effectively, resulting in a higher frequency of reactions between free hydrogen ions of water molecules, and sodium
ions of the proteoglycan molecules, thus lengthening $T1_\rho$ relaxation values. The same applies to compromised collagen; their uniformity and laminar organization within the extracellular matrix is lost and becomes more heterogeneous, also impacting the ability of collagen to bind water, this lengthening $T2$ relaxation values.

**Figure 1.4.** Example of a T2 map, with segmented tibial and femoral cartilage. Blue pixels represent low T2, while red pixels represent higher T2. Image A is a healthy control, and image B is an obese subject. Notice the higher prevalence of red pixels, in figure B, indicating higher T2 in that cartilage$^{56}$.

**Articular Cartilage T2 Relaxation Response to Disease Progression**

T2 relaxation of articular cartilage tends to lengthen as OA progresses over time. A cross-sectional study identified that T2 relaxation increases in a near-linear fashion from patients with mild OA to patients with moderate-to-severe OA, with a plateau effect in patients with end-stage OA, as it was hypothesized that the limitation at end-stage disease was the insufficient amount of cartilage volume available for analysis$^{57}$. The proposed mechanism for lengthening of T2 relaxation time with disease progression is the degradation of the extracellular matrix, leading to a greater concentration of unbound water molecules, and increased collagen network disorganization over time$^{55,58}$. 
Articular Cartilage T2 Relaxation Response to Acute Load

The acute response of articular cartilage to loading is generally opposite of the response to disease progression. During load, the cartilage is compressed and water effuses out of the cartilage and into the joint cavity. This is a normal mechanism and the water is able to progressively be reimbibed into the articular cartilage over a period of up to one hour if the joint is not in a loaded state\textsuperscript{59}. As water effuses out of the articular cartilage, the concentration of free water molecules decreases, resulting in a shortening of T2 relaxation time with load\textsuperscript{60}. It is hypothesized that articular cartilage of patients with OA responds more poorly to load, and experiences greater changes in T1ρ relaxation due to load\textsuperscript{61}, but there is limited evidence of this phenomenon in patients with knee OA, and no evidence in patients at risk for knee OA. The acute response of articular cartilage to functional joint loading in healthy controls and patients at risk for knee OA is studied in Chapter 3 of this thesis.

Segmentation of Articular Cartilage

Segmentation of articular cartilage is possible in various forms, which mostly fall into three categories; manual, semi-automatic, or automatic. In any case, software is used to segment articular cartilage. Regions of interest (ROI) are specifically selected based on the research question, but the usual ROIs consist of medial and lateral femur, medial and lateral tibia, patella, and trochlea. Certain analyses, such as laminar and sub-segmented analyses are sometimes performed as well. Examples of laminar and sub-segmentation analyses can be found in Figure 1.5. A sub-segmentation analysis consists of separating the previously mentioned ROIs into even smaller ROIs; for example, segmenting the weightbearing or
contact regions of the medial femoral cartilage from non-weightbearing medial femoral cartilage to determine the effect of standing load-bearing on articular cartilage composition. A laminar analysis consists of subdividing the segmented cartilage into a superficial half (the articular surface) and a deep half (portion closest to the bone), or sometimes into thirds. The superficial half of the cartilage often displays higher T2 compared to the deep half, as the collagen is aligned more in parallel to the surface in the superficial half, and more perpendicular to the surface in the deep half of the cartilage. The increased superficial T2 is a result of the anisotropic orientation of collagen in the cartilage, with the deeper layers demonstrating a vertical alignment of the collagen, and the superficial layers being oriented more horizontally along the articulating surface of the cartilage\textsuperscript{62}. The same phenomenon is observed with T1\textsubscript{ρ}, as the laminar differences between superficial and deep layer are a result of a concentration of proteoglycans in the deep half of the cartilage\textsuperscript{63}.

**Figure 1.5.** Sagittal views of the medial compartment of the knee demonstrating laminar and sub-segmentation analyses\textsuperscript{61}. The left image demonstrates a laminar analysis, with the ROI in red representing the superficial layer of the articular cartilage of the medial femur and tibia, and the blue representing the deep layer. The right image demonstrates a sub-segmentation analysis, having divided the articular cartilage of the medial tibia and femur into even smaller regions.
MRI Acquisition & Segmentation of Effusion-Synovitis

Segmentation of the synovium in the knee joint is only reliably feasible with the use of contrast-enhanced imaging\textsuperscript{64}, typically involved a gadolinium contrast agent injected into systemic circulation. Due to high costs, and rare but serious complications in some patients, contrast-enhanced studies of knees are typically avoided, as this subtype of advanced imaging is typically reserved for potentially serious disease and very specific research questions\textsuperscript{65}. Given this drawback, MRI parameters can be adjusted to acquire high contrast images between tissues with high and low concentrations of fluid, with techniques such as water enhancement or fat suppression, or a combination of the two. Examples of contrast-enhanced and noncontrast-enhanced MR images of synovitis are shown in Figure 1.6. Without contrast-enhancement injections, it is impossible to resolve the synovial lining from synovial fluid. In this case, there are two preferred surrogate measures for inflammation within the knee joint, Hoffa-synovitis (inflammation of the infrapatellar fat pad) and effusion-synovitis (the accumulation of synovial fluid and tissue within the suprapatellar pouch), with effusion-synovitis being the more reliable of the two\textsuperscript{66}. Segmentation of effusion synovitis is relatively simple, as inflamed tissue within the synovium appears hyperintense with relatively high contrast due to the high water concentration. The reader segments the hyperintense tissue within the known region of the synovium, and can use signal intensity thresholding tools to filter out any hypointense structures that were included in the ROI.
Figure 1.6. Contrast-enhanced and non contrast-enhanced MR images of knee synovitis. Axial view of the same knee, same slice\textsuperscript{67}. Image A shows a non contrast-enhanced proton density-weighted image suggesting diffuse effusion marked by black arrowheads. Image B shows a contrast-enhanced T1-weighted fat-suppressed contrast-enhanced image, hyperintense tissue marked by full arrows represents thickened synovial tissue, and the actual effusion is represented by the grey hypointense fluid indicated by the arrowheads.

Gait

Gait pattern is a unique expression of locomotion, with certain “normal” ranges and some identifiable pathological features. In knee osteoarthritis, kinematics and kinetics focusing on the knee flexion and adduction angles and moments are of particular interest, and have been shown to be predictors of OA progression\textsuperscript{68}. Deviations from normal gait biomechanics can be multifactorial, including pain-induced antalgic gait, structural changes, or neuromusculoskeletal pathology, affecting the motor pattern of the surrounding muscles\textsuperscript{69}. 
3D Gait Analysis in Knee OA

3D gait analysis is a tool used to assess a variety of pathologies involving a motor component affecting gait. For the purposes of knee OA assessment, forces and angles about the knee joint are measured to assess the load distribution occurring at the knee joint. Measures of interest in gait biomechanical studies of knee OA are primarily the knee adduction moment, and the knee flexion moment. The greater the knee adduction moment, the greater the disparity in the balance of load distribution between the medial and lateral compartment. This imbalance over the course of years creates unfavourable adaptations on the medial aspect of the joint, such as increased subchondral bone mineral density in the medial compartment, straying from the optimal elastic modulus of the bone-cartilage interface, creating excessive load on the articular cartilage, resulting in degeneration.

Changes in knee flexion moment are also characteristic of OA progression, with decreases in flexion moment being associated with higher severity of disease, as patients adopt a stiffening gait strategy in an effort to stabilize the joint. This creates increased pressure on the patellofemoral compartment, eliciting the same changes as described above that occur in the medial compartment. The earliest of these changes are not detectable with the current clinical standards of imaging. Use of MRI and particularly quantitative MRI can help detect and measure these changes.

Alignment

Lower limb malalignment in the frontal plane is a strong contributor to the distribution of loads across the knee joint. In patients with OA presenting with malalignment, majority (58%) present with varus malalignment, resulting in static and
aberrant dynamic loading of the medial compartment. Varus malalignment is an independent risk factor for medial compartment knee osteoarthritis\textsuperscript{13}, creating a cycle of aberrant load on the medial compartment, contributing to degeneration. As the medial compartment progresses in severity, joint space decreases, further shifting the imbalance of load distribution in favour of the medial compartment, accelerating the mechanical component of disease progression\textsuperscript{78}. There are some non-operative treatment options to alleviate patients experiencing pain associated with varus malalignment, such as valgus bracing, or lateral heel wedges, where a valgus force generated by the brace or wedge is intended to reduce the excess loads on the medial compartment\textsuperscript{79}. The only intervention available to permanently alter knee joint loads and restore normal alignment of the lower limb is high tibial osteotomy.

**Figure 1.7.** Full standing hip-knee-ankle radiographs demonstrating varus, neutral, and varus alignment of the lower extremity.
High Tibial Osteotomy

Medial opening wedge high tibial osteotomy (HTO) is an elective surgical procedure indicated for patients with medial joint pain related to lower limb malalignment. Surgery can be beneficial for appropriate patients if performed any time prior to end stage knee OA (total erosion of articular cartilage). The rationale for HTO is to offload the affected medial compartment and to redistribute loads towards the relatively unaffected lateral compartment\cite{80}. The surgical procedure involves creating a wedge from the medial to lateral aspect of the tibia, opening the wedge with an osteotome device, achieving a correction angle that allows for the desired lower limb alignment by manipulating and measuring the size of the opening wedge, and fixing the wedge with plate and screws\cite{81} (Figure 1.8). This surgery has been demonstrated to be successful in reducing the knee adduction moment\cite{82}, approximating more normal gait biomechanics, and alleviating symptoms for patients with medial compartment knee OA for years after surgery\cite{83}. In previous decades, HTO required exceptionally long recovery times, requiring full casting of the lower limb for months, completely immobilizing the knee joint, bringing about additional complications due to deconditioning of the muscle, bone density changes, and weakening of connective tissue. Now, with the use of internal fixation plates, and more reasonable correction angles, patients can resume weightbearing within 4 to 8 weeks of surgery, allowing for much faster rehabilitation times and return to previous activities\cite{84}. Other controversy surrounding HTO involves the shift in loads, arguing that the new loads borne by the lateral compartment will place those tissues at increased risk of OA progression\cite{85,86}.  

Figure 1.8. Fluoroscopy images depicting surgical technique for medial opening wedge high tibial osteotomy. A) an osteotomy guide pin is drilled through the medial tibia. B) an oscillating bone saw is used to cut the wedge in the tibia. C) An osteotome is inserted to open the wedge. D/E) A locking plate is inserted and fixed with screws to maintain the desired correction.

Purpose

In clinical practice, a combination of radiographic assessment, symptoms, patient history, and clinical exam findings are used to diagnose and assess the progression of knee OA, often resulting in treatment being initiated much later than the original disease onset. Some treatments have shown promise in alleviating symptoms of knee OA, however current clinical measures aren’t sensitive enough to measure structural changes related to treatment. The ability to recognize small but important structural changes in knee OA is required to provide evidence for the efficacy of interventions to obtain approval for their implementation and funding on a wide scale. Quantitative MRI can help identify these changes.
The overall purpose of this thesis was to investigate the role of quantitative MRI in measuring the response of articular cartilage and effusion-synovitis to changes in load within the knee joint at various stages of disease in OA. Specifically, we were interested in
1) the biochemical composition of knee articular cartilage in patients at risk for knee OA compared to healthy controls, 2) the acute response of knee articular cartilage to dynamic, functional load in patients at risk for knee OA compared to healthy controls, 3) the long-term response of knee articular cartilage composition after realignment of the lower limb, and 4) the inflammation response within the knee joint to long-term changes in dynamic load after realignment of the lower limb.

The following four hypotheses were tested using four different studies

1) Knee articular cartilage composition, measured using MRI T2 and T1ρ relaxation, will be significantly lengthened in patients with risk factors for knee OA compared to healthy controls.

2) Knee articular cartilage response to dynamic functional loading, as measured by the change in MRI T2 relaxation time, will be larger in patients with risk factors for knee OA versus asymptomatic healthy controls.

3) Knee articular cartilage composition, measured using MRI T2 relaxation time, will shorten after lower limb realignment surgery in patients with varus malalignment and medial compartment knee OA.
4) Knee inflammation, quantified as MRI effusion-synovitis volume, will decrease after lower limb realignment surgery, and the change in effusion-synovitis will be associated with the change in surrogate measures of medial compartment load.
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CHAPTER 2 – MRI T2 and T1ρ relaxation in patients at risk for knee osteoarthritis: a systematic review and meta-analysis

SUMMARY: Magnetic resonance imaging (MRI) T2 and T1ρ relaxation are increasingly being proposed as imaging biomarkers potentially capable of detecting biochemical changes in articular cartilage before structural changes are evident. We aimed to: 1) summarize MRI methods of published studies investigating T2 and T1ρ relaxation time in participants at risk for but without radiographic knee OA; and 2) compare T2 and T1ρ relaxation between participants at-risk for knee OA and healthy controls. We conducted a systematic review of studies reporting T2 and T1ρ relaxation data that included both participants at risk for knee OA and healthy controls. Participant characteristics, MRI methodology, and T1ρ and T2 relaxation data were extracted. Standardized mean differences (SMDs) were calculated within each study. Pooled effect sizes were then calculated for six commonly segmented knee compartments. 55 articles met eligibility criteria. There was considerable variability between scanners, coils, software, scanning protocols, pulse sequences, and post-processing. Moderate risk of bias due to lack of blinding was common. Pooled effect sizes indicated participants at risk for knee OA had lengthened T2 relaxation time in all compartments (SMDs from 0.33 to 0.74; p<0.01) and lengthened T1ρ relaxation time in the femoral compartments (SMD from 0.35 to 0.40; p<0.001). T2 and T1ρ relaxation distinguish between participants at risk for knee OA from healthy controls. Greater standardization of MRI methods is both warranted and required for progress towards biomarker validation.
INTRODUCTION

Magnetic resonance imaging (MRI) is commonly used to study knee osteoarthritis (OA), largely because of its ability to visually detect morphological changes in soft tissues\textsuperscript{1-6}. However, in addition to visualizing structures within a joint, the measurable characteristics of MRI enable the quantification of tissue biochemistry, often termed compositional MRI.

Although several types of compositional MRI techniques exist, the vast majority of research in OA focuses on knee articular cartilage T2 and T1\textsubscript{ρ} relaxation times as these are suggested to show considerable promise and be clinically feasible\textsuperscript{7-10}. Although the reported strengths of the correlations are variable, T2 and T1\textsubscript{ρ} relaxation times are associated with the composition of the extracellular matrix. T2 relaxation is inversely correlated with collagen network organization and structure, and is directly correlated with free water content\textsuperscript{7}. Changes in T1\textsubscript{ρ} relaxation appear to be less specific, yet are also sensitive to changes in the extracellular matrix\textsuperscript{8-14}. When the extracellular matrix of articular cartilage is compromised, characteristic of early biochemical processes in OA, water moves more freely within the cartilage, prolonging both MRI T2 and T1\textsubscript{ρ} relaxation times\textsuperscript{13,15,16}.

T2 and T1\textsubscript{ρ} relaxation have engendered considerable interest as a potential biomarkers for knee OA\textsuperscript{17}, especially given their proposed ability to detect biochemical changes in articular cartilage before structural changes are evident\textsuperscript{15,18,19}. If these measures can detect compromised articular cartilage prior to radiographic evidence of OA, they may have the potential to serve as an outcome measure in early intervention studies targeting at-risk
populations, such as people with knee anterior cruciate ligament (ACL) rupture\textsuperscript{20–22}, meniscal injuries\textsuperscript{23,24}, or obesity\textsuperscript{25,26}. While this may be true of other compositional MRI measures (such as sodium, gagCEST, dGEMRIC\textsuperscript{27}), T2 and T1\textsubscript{ρ} relaxation are perhaps the most clinically feasible, do not require a contrast agent, and are the focus of numerous studies that may enable meta-analysis when investigating their potential use as a biomarker.

Previous systematic reviews are encouraging in that they suggest T2 and T1\textsubscript{ρ} measures can be highly reliable when similar testing methods are used\textsuperscript{27}, and can distinguish between articular cartilage of healthy controls and patients with established radiographic OA\textsuperscript{27,28}. There are established criteria, however, for biomarker validation and qualification\textsuperscript{29–31}. These include the ability to consistently measure the biomarker across testing sites\textsuperscript{32,33}. The extent to which previous studies investigating compositional MRI have used similar collection and analysis methods is presently unclear, and has been recently called into question\textsuperscript{34}. Moreover, the potential utility of a biomarker to detect changes in the composition of knee articular cartilage relies on its ability to do so early in the disease process, before degenerative joint changes are evident on x-ray. Although there is abundant evidence suggesting T2 and T1\textsubscript{ρ} relaxation times are higher in knees with established radiographic OA compared to healthy knees\textsuperscript{27,28}, the ability to detect changes between knees at risk for OA and healthy knees is less clear.

Therefore, purposes of this systematic review and meta-analysis were to: 1) summarize the MRI methods of published studies investigating T2 and T1\textsubscript{ρ} relaxation times in participants
at risk for but without radiographic knee OA; and 2) compare T2 and T1\(\rho\) relaxation values between participants at-risk for knee OA and healthy controls.

**METHODS**

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines\(^\text{35}\) (PROSPERO ID: CRD42018088352).

**Literature Search**

We sought the assistance of a research librarian to develop the search strategy. We searched the following electronic databases from their inception to June 2018: MEDLINE, EMBASE, Scopus, CINAHL, SPORTDiscus, and Web of Science, in addition to hand searching reference lists of included articles. Combined and truncated keywords and subject headings included “magnetic resonance imaging OR compositional magnetic resonance imaging” AND “T2 mapping OR T1rho mapping OR T2 relaxation OR T1rho relaxation” AND “osteoarthritis OR articular cartilage” AND “knee OR tibiofemoral OR patellofemoral”.

**Eligibility Criteria**

Eligible studies included those published in English that reported T2 and/or T1\(\rho\) relaxation time in knee articular cartilage in at least two groups of participants including one group with any of the criteria commonly accepted for being at risk for knee OA, and a control group without any of those criteria. All study designs were considered. We used the Osteoarthritis Initiative (OAI) Incidence cohort criteria\(^\text{36}\) to define a list of criteria for
participants at risk for knee OA. These criteria include native knee symptoms in the past 12 months, overweight or obesity, history of knee injury which would cause difficulty walking for at least a week, history of knee surgery, family history of OA, lifestyle factors such as occupational risk (i.e. repetitive knee bending, squatting, lifting, etc.), age 70 years or older, and Kellgren & Lawrence (KL) radiographic grading of 0 or 1. Studies that included at-risk knees and contralateral healthy knees within the same participant were also included. We excluded patients with KL grade 2 or higher. For studies with multiple follow-up time points, only the baseline T2 and/or T1ρ relaxation data were used in our meta-analyses. Two reviewers independently assessed the eligibility of each article in two stages. Two reviewers independently assessed all titles and abstracts identified by the search. Articles meeting the inclusion criteria were obtained as full-text manuscripts for further review. Articles meeting the inclusion criteria after full-text review were accepted in the review. Reviewers discussed any conflicts at all stages and a consensus was achieved.

Data Extraction

Two reviewers independently extracted T2 and T1ρ relaxation time of knee articular cartilage in six primary compartments: medial femoral condyle, medial tibial plateau, lateral femoral condyle, lateral tibial plateau, patellar cartilage, and trochlear groove cartilage. If authors presented laminar differences (superficial and deep cartilage as separate regions of interest) the data from both regions were pooled. Given the variability in defining anterior, central, and posterior subregions in the most load-bearing aspect of the femur and tibia across studies, we pooled the identified subregions (where necessary) to best analyze the entirety of the load-bearing regions of the femoral condyles (generally
in the region of the anterior horn of the meniscus to the posterior horn of the meniscus). For the patella and trochlea, we pooled all subregions (where necessary) to obtain a single value for the patella or trochlea. Reviewers discussed any conflicts and achieved consensus in all cases. Reviewers independently extracted relaxation time means and standard deviations (SD) for each participant group. The same reviewers also extracted the following information from each article: sample size, participant demographics, risk factors for OA, MRI hardware, pulse sequences, and parameters. Authors were contacted when sufficient data were not reported. If data were not provided or unclear, we contacted the original authors using provided e-mail addresses. In the case of no reply from the authors, we extracted data from figures when available. We used Covidence systematic review and meta-analysis software (www.covidence.org) to extract data.

**Quality Assessment**

Two reviewers independently evaluated the methodological quality of each study using the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) tool\(^3\), consisting of seven items to assess the internal validity of each study (confounding, participant selection, intervention classification, deviation from intervention, missing data, outcome measurement, and outcome selection). Each item was evaluated as a low, moderate, serious, or critical risk of bias. Disagreements between reviewers were resolved by consensus after initial independent evaluation.

**Data Analyses**

We assessed agreement between reviewers using the kappa (κ) statistic. We compared compositional MRI data by calculating pooled estimates with 95% confidence intervals
(95%CIs) for standardized mean differences (SMDs) using random-effects models. When calculating pooled effect sizes, we weighted all SMDs based on the sample size of the respective study. For both $T_2$ and $T_1$ relaxation time, the SMD was calculated using the difference between healthy controls and participants at risk for knee OA, divided by the pooled SD. If a study had multiple groups at risk for knee OA, only the group with the lowest risk was included in the calculation of the overall pooled effect size, based on reported measures of disease severity (KL Grade, ICRS grade, Outerbridge Score, WORMS Grade, etc.). All meta-analyses were performed using the Comprehensive Meta-Analysis software program (V3, Biostat; https://www.meta-analysis.com). We interpreted the magnitude of the SMD using Cohen’s $d$ as small (<0.2), moderate (0.2-0.8) and large (>0.8) and positive values representing prolonged relaxation times in participants at risk for OA. We assessed publication bias using the Egger’s Regression test, and if present, further analyses were planned to explore treatment effects adjusted for selective reporting. We assessed the proportion of variability associated with heterogeneity using the $I^2$ statistic and $Q$ statistic. We interpreted the size of $I^2$ as low (25%), moderate (50%) or high (75%) heterogeneity.

**Sensitivity Analyses**

We repeated the primary analyses after excluding all but one study (with the greatest sample size) that included OAI participants to ensure we included data from the same knee only once. We also repeated the analyses after excluding studies that used both limbs from the same participant.
In the event of substantial heterogeneity, we planned three subgroup analyses. These groups included participants with a history of ACL injury (based on physical exam, imaging, or surgical confirmation), participants at risk for patellofemoral OA (based on the OAI Incidence cohort criteria)\textsuperscript{36}, and participants with articular cartilage injuries based on MR imaging, arthroscopic International Cartilage Repair Society grades, or Outerbridge scores\textsuperscript{43,44}.

**RESULTS**

**Study Selection & Article Screening**

We performed the initial search August 1\textsuperscript{st}, 2018 and updated the search March 7\textsuperscript{th}, 2019. We identified 6,417 articles by the database search. After removing duplicates, we reviewed 3,071 articles by title and abstract with excellent inter-rater agreement ($\kappa=0.96$) and 53 disagreements (1.7\%) between reviewers. Disagreements were discussed, and after consensus, 386 articles were deemed eligible for full-text review (Figure 2.1). After full text reviews, inter-rater agreement was excellent ($\kappa=0.95$), with 12 disagreements between reviewers. Disagreements were discussed, and after consensus, 55 articles met our inclusion criteria (Figure 2.1)\textsuperscript{15,16,20,23,24,45–94}, with a total of 3,676 participants. Forty-seven studies were included in the meta-analysis, including data from 3,079 participants. Articles included in the systematic review but excluded from the meta-analysis either examined incomparable regions of interest (ROI), or had insufficient data to be included in the meta-analyses\textsuperscript{54,66,68,69,77,85,89,90}. 
Figure 2.1. PRISMA flowchart quantifying studies accepted and rejected with reasons at different phases of review.

Study Characteristics

Characteristics of all studies included in the systematic review are described in Table 2.1\textsuperscript{15,16,20,23,24,45–94}. T2 relaxation was included as an outcome measure in 38 studies, T1ρ relaxation was an outcome measure in 24 studies, and 8 of those studies evaluated both T2 and T1ρ relaxation. Studies varied considerably in terms of compositional MRI data acquisition and post-processing. Two different magnet strengths, four different manufacturers, 12 different magnet models, 16 different reported knee coils, 17 reported
pulse sequences, and a wide variety of parameters were used to acquire compositional MRI data.

**Quality Assessment**

Agreement between reviewers for all seven items in the ROBINS-I tool was moderate (κ=0.54, 95%CI=0.48-0.61), with disagreements being primarily on the subjective severity of bias rather than the presence or absence of bias. Forty-five studies presented with a moderate overall risk of bias, seven presented with a serious risk of bias, and three presented with a low risk of bias. The most common sources of risk for bias was lack of blinding, or reporting of blinding, of the outcome assessors, as well as risk of bias in participant selection. No studies were excluded based on quality assessment.

**Descriptive Analyses**

Forty-seven out of 55 studies observed a significant increase in compositional MRI values in one or more regions of interest in the at-risk group compared to the healthy control group. Specifically, 31 of 38 studies assessing T2 relaxation time reported significant lengthening in the at-risk group, and 21 of 24 studies assessing T1ρ relaxation time reported significant lengthening in the at-risk group.
Table 2.1. Description of studies included in the systematic review

<table>
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<tr>
<th>Authors</th>
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<th>Age</th>
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<th>Coil</th>
<th>T1c Sequence (resolution)</th>
<th>T2l (ms/SL Frequency (Hz))</th>
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<td>Control 19 (13)</td>
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<td>Imuvo 8-Ch Tx/Rx</td>
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<td></td>
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<td>3D FSE (0.5x0.5x3.0) [3 slices/SL]</td>
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<td>3T GE</td>
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<td>Sag 3D MIP/SS (0.3x0.3x1.5)</td>
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<td>15-Ch Tx/Rx</td>
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<td>1.5T Philips</td>
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Table 2.1. Description of studies included in the systematic review (continued)

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Table 2.1. Description of studies included in the systematic review (continued)
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<td>0, 10, 40, 80/500</td>
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Table 2.1. Description of studies included in the systematic review

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<tr>
<th>Authors</th>
<th>Participants</th>
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<th>Age (y)</th>
<th>Scanner</th>
<th>Coil</th>
<th>T1\rho Sequence (resolution)</th>
<th>TSL (MHz/SL Frequency (Hz))</th>
<th>T2 Sequence (resolution)</th>
<th>TR/TE</th>
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<td>Tao et al. (2018)</td>
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<td>3T</td>
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<td></td>
<td>ACL Rupture</td>
<td>23 (5)</td>
<td>32 ±10</td>
<td>Siemens</td>
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<td>Teng et al. (2017)</td>
<td>Healthy</td>
<td>12 (8)</td>
<td>32 ±6</td>
<td>GE</td>
<td>3T</td>
<td>Invivo B-Ch, Tu/Rx</td>
<td>Sag 3D MAPSS (0.5x1.1x4.0)</td>
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<td>0.14, 27,</td>
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<td></td>
<td>ACL Rupture</td>
<td>33 (20)</td>
<td>31 ±9</td>
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<td>Wang et al. (2018)</td>
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<td>3T</td>
<td>Siemens B-Ch</td>
<td>Sag 2D MESE (0.4x0.4x30)</td>
<td>1200/14, 28, 41, 55, 69</td>
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<tr>
<td></td>
<td>ACL Rupture</td>
<td>28 (17)</td>
<td>30 ±6</td>
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<tr>
<td>Collins et al. (2018)</td>
<td>Normal BMI</td>
<td>8 (5)</td>
<td>30 ±7</td>
<td>Siemens</td>
<td>3T</td>
<td>Invivo B-Ch, Tu/Rx</td>
<td>Sag 3D FISP (1.3x0.5x3.0)</td>
<td>3500/5.5, 10.0</td>
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<td>Obese BMI</td>
<td>7 (3)</td>
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ms millseconds, SL spin lock, TR Repetition time, TE echo time, ACL anterior cruciate ligament, ACUR ACL reconstruction, GE General Electric, MAPSS magnetization-prepared spoiled gradient echo, SP subregion, PF patellofemoral, PPF patellofemoral pain, FFE fast field echo, FSE fast spin echo, RFSR spoiled gradient refocused echo, MRI Magnetic Resonance Imaging, ART accelerated resolution recovery, T2 Relaxation time, T1\rho T1rho relaxation time, T2 Relaxation time, ROI region of interest, a indicates post-processing methods that could be used in any dataset.

Meta-Analyses

We were able to pool data for T2 and/or T1\rho relaxation time for cartilage ROIs in the medial and lateral femur, medial and lateral tibia, patellar, and trochlear cartilage. Forest plots, including individual and pooled SMDs are presented in Figures 2.2-2.4.

At-risk knees had significantly prolonged T2 relaxation times for all compartments, small-to-moderate effect sizes (SMD=0.33-0.74; p<0.001; Figures 2.2-2.4). At-risk knees had significantly prolonged T1\rho relaxation times for the medial femur and lateral femur with small effect sizes (SMD=0.35-0.40; p<0.001; Figures 2.2a, 2.3a). There were no significant differences in T1\rho relaxation between groups for the medial tibia, lateral tibia, patella, or trochlear compartments (SMD=0.04-0.19, p>0.05-0.76; Figures 2.2b, 2.3b-2.4b).
### MEDICAL THERA

#### Table 2: Risk Factors for Knee OA

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<tr>
<th>Risk Factor</th>
<th>Odds Ratio (95% CI)</th>
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<tr>
<td>Obesity</td>
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<tr>
<td>Smoking</td>
<td>1.21 (1.04-1.40)</td>
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<tr>
<td>Physical Activity</td>
<td>0.82 (0.69-0.97)</td>
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#### Table 3: Risk Factors for Knee OA

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<th>Risk Factor</th>
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<td>Age</td>
<td>1.05 (1.02-1.07)</td>
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<tr>
<td>Obesity</td>
<td>1.32 (1.13-1.53)</td>
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<tr>
<td>Smoking</td>
<td>1.24 (1.06-1.45)</td>
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<tr>
<td>Physical Activity</td>
<td>0.80 (0.68-0.94)</td>
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### MEDICAL THERA

#### Table 4: Risk Factors for Knee OA

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<th>Risk Factor</th>
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<td>Age</td>
<td>1.04 (1.01-1.06)</td>
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<tr>
<td>Obesity</td>
<td>1.28 (1.07-1.54)</td>
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<td>Smoking</td>
<td>1.18 (1.02-1.36)</td>
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<tr>
<td>Physical Activity</td>
<td>0.85 (0.71-1.01)</td>
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#### Table 5: Risk Factors for Knee OA

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<td>Age</td>
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<td>Physical Activity</td>
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### MEDICAL THERA

#### Table 6: Risk Factors for Knee OA

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<td>Physical Activity</td>
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#### Table 7: Risk Factors for Knee OA

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<td>Physical Activity</td>
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</table>
**Figure 2.2.** (see figure on previous page) Forest plots illustrating individual and pooled SMD for differences in $T_1^\rho$ and $T_2$ relaxation time of medial femoral (a) medial tibial (b) articular cartilage and between healthy controls and participants at risk for knee OA. SMD = standardized mean difference, 95%CI = 95% confidence interval, ACL = anterior cruciate ligament, PCL = posterior cruciate ligament, ICRS = International Cartilage Repair Society, OAI = Osteoarthritis Initiative, OA = osteoarthritis, GE = General Electric, T = Tesla

**Publication Bias and Heterogeneity**

Egger’s regression test for publication bias was not significant for any meta-analysis assessing pooled SMD of $T_2$ relaxation time. For $T_1^\rho$ relaxation time, meta-analyses of the medial femur and lateral tibial compartments showed significant evidence of publication bias ($p<0.01$). After using Duval & Tweedie’s trim and fill method to correct for publication bias, $T_1^\rho$ relaxation time of the medial femur was not significantly different in participants at risk for knee OA (SMD=0.16[95%CI:-0.07;0.40]; $p=0.17$). After adjustment for publication bias, $T_1^\rho$ relaxation time of the lateral tibia remained non-significant (SMD=0.17[95%CI:-0.38;0.71]; $p=0.54$).

For meta-analyses assessing $T_2$ relaxation time, heterogeneity was significant for all analyzed compartments ($I^2=77-87%$; $p<0.01$) except for the trochlear compartment ($I^2=31%$; $p=0.19$). Four studies consistently contributed to the heterogeneity of $T_2$ relaxation SMD, including two studies fitting in the cartilage injury subgroup. Removal of these studies resulted in non-significant heterogeneity in the medial femoral and patellar compartments ($I^2=19-23%$; $p>0.2$); however, heterogeneity remained high after removal of outliers in the medial tibial and lateral femoral compartments ($I^2=66-70%$, $p>0.01$). After removal of outliers, $T_2$ relaxation time remained significantly prolonged for those at risk for knee OA. For meta-analyses assessing $T_1^\rho$ relaxation time, heterogeneity was
Figure 2.3. Forest plots illustrating individual and pooled SMD for differences in T1\(^\rho\) and T2 relaxation time of lateral femoral (a) lateral tibial (b) articular cartilage and between healthy controls and participants at risk for knee OA. SMD = standardized mean difference, 95%CI = 95% confidence interval, ACL = anterior cruciate ligament, PCL = posterior cruciate ligament, ICRS = International Cartilage Repair Society, OAI = Osteoarthritis Initiative, OA = osteoarthritis, GE = General Electric, T = Tesla.
Figure 2.4. Forest plots illustrating individual and pooled SMD for differences in T1ρ and T2 relaxation time of patellar (a) trochlear (b) articular cartilage and between healthy controls and participants at risk for knee OA. SMD = standardized mean difference, 95%CI = 95% confidence interval, ACL = anterior cruciate ligament, PCL = posterior cruciate ligament, ICRS = International Cartilage Repair Society, OAI = Osteoarthritis Initiative, OA = osteoarthritis, GE = General Electric, T = Tesla

### a. Patella

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<td>Ho et al. (2013)</td>
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<td>Patellar Cartilage</td>
<td>GE</td>
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<td>GE</td>
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### b. Trochlea

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<td>GE</td>
<td>3/0</td>
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<td>GE</td>
<td>3/0</td>
<td>-0.04 (0.06, 0.77); 0.83</td>
<td>4.94</td>
<td></td>
</tr>
</tbody>
</table>

Note: The trim & fill method is limited in its ability to identify publication bias in heterogeneous datasets.

Significant for the medial femoral and lateral tibial compartments (I²=44-87%; p<0.01), and non-significant for all other compartments (I²=0-28%; p=0.15-0.94).
where no true bias exists\textsuperscript{95}. Thus there may be no significant publication bias for the heterogeneous SMD’s of T1\textsubscript{ρ} in the MF and LT compartments.

**Sensitivity Analyses**

We performed two sensitivity analyses. The first analysis excluded all but one study (6 articles excluded) using OAI data to ensure no subjects in the meta-analyses were used more than once. Effect sizes remained moderate and significant in all compartments (SMD=0.38-0.73; p<0.02). The second analysis excluded all studies which used within-patient comparisons (healthy knee versus at-risk knee). Following exclusion of articles (6 articles for T2, 6 for T1\textsubscript{ρ}), effect sizes remained moderate-to-large for T2 (all compartments: SMD=0.42-0.83; p<0.1), and remained moderate for some T1\textsubscript{ρ} compartments (MF, MT, LF: SMD=0.27-0.37; p<0.02) and remained small and non-significant for others (LT, P, Tro: SMD=0.13-0.14; p>0.29.

**Subgroup Analyses**

We performed three subgroup analyses to determine respective effect sizes for patients with ACL injury, risk for patellofemoral OA, and articular cartilage lesions. Results of the subgroup analyses suggested that SMDs controls were small-to-moderate for the ACL-injury subgroup compared to controls (14 articles for T2: SMD=0.13-0.56; p=0.002-0.27. 14 articles for T1\textsubscript{ρ}: SMD=0.11-0.30; p=0.001-0.8). We obtained similar small-to-moderate effect sizes for the patellofemoral OA risk subgroup (8 articles for T2: SMD=0.06-0.20; p=0.004-0.78. 3 articles for T1\textsubscript{ρ}: SMD=0.13-0.28; p=0.06-0.89). These
effect sizes were generally smaller compared to the remainder of the sample in the primary analysis. The articular cartilage injury subgroup demonstrated large effect sizes (4 articles for T2: SMD=1.29-2.88; p=0.001-0.38) which were larger in comparison to the remainder of the sample in the primary analysis.

DISCUSSION

The present pooled within-study effect sizes that combine data from 47 studies involving 3,661 participants suggest T2 and T1ρ relaxation times distinguish between healthy participants and participants at risk for knee OA. The present results are consistent with the only other published systematic review we are aware of23, yet extends its findings by focusing on persons at-risk for but without radiographic knee OA, and by providing a thorough summary of the variable T2 and T1ρ collection, processing, and analysis methods. Strengths of the present study include adherence to well-established guidelines for conducting systematic reviews and meta-analyses35. These include multiple reviewers reaching consensus at each step of the literature search, study selection and data extraction; assessment of study quality; assessment and adjustment for publication bias; and pre-planned meta-analyses including sensitivity analyses based on a priori hypotheses in the event of substantial heterogeneity. Limitations of the present meta-analyses may include pooling participants at risk, as there are likely several different phenotypes for the development of OA90. Our subgroup analyses suggest that T2 and T1ρ values of articular cartilage are slightly different across participants with various risk factors, and future research should explore those differences further. A common methodological limitation in the studies included in this review is the lack of blinding and/or reporting of blinding
procedures. Other limitations include those inherent to cross-sectional versus prospective designs that measure change in patient status over time.

Importantly, there was considerable variability between MRI methods, including scanners, coils, software, scanning protocols, pulse sequences, and post-processing, which can all influence T2 or T1ρ relaxation. For example, knee articular cartilage T2 relaxation time is inversely proportional to magnetic field strength\(^96\), and can differ significantly when using different brands of scanners of the same advertised field strength\(^97\). In this review alone, four brands of scanners, and two magnet strengths were identified across studies (Table 2.1). T2 relaxation time is significantly prolonged when using a phased-array knee coil compared to a quadrature transmit receive knee coil\(^98\). Sixteen different knee coils were used in studies in this review (Table 2.1), with a wide variety of phased-array and quadrature coils. Choice of pulse sequence can also significantly affect relaxation time, with a difference of as much as 10 ms observed across commonly used sequences\(^99,100\).

Knowledge of the context and collection methods is important when comparing compositional MRI values across the literature, as a 1.8 ms increase in T2 relaxation time is representative of a 1% increase in free water content when comparing within the same participant\(^101,102\). Seventeen different pulse sequences were used to collect the data presented in this review (Table 2.1). Pre-scan unloading protocol is an important consideration that varies across studies, as T2 relaxation time increases with unloading time due to water reuptake into the cartilage\(^93\). Post-processing and segmentation can also affect T2 and T1ρ values, such as how the assessor defines the ROI, ROI variance between studies, number of slices included in the ROI\(^103\), proximity of borders to other tissues, and
Continued use of proposed standardized nomenclature and ROI definition will improve comparability of ROI’s across studies and sites. Taken together, these findings identify substantial differences in methods across testing sites, suggest considerable caution should be adopted when making comparisons across studies, and highlight the limitation in the current state of T2 or T1ρ relaxation as imaging biomarkers.

These findings suggest future use of compositional MRI measures as potential biomarkers would benefit considerably from a greater understanding of the effects of different testing methods and greater standardization of data collection and analysis measures. The importance of greater standardization across testing sites is underscored by the variability in results of studies evaluating the test-retest reliability of compositional MRI measures, even when the exact same methods are used. For example, studies evaluating test-retest reliability using the same testing conditions report intra-class correlation coefficients (ICC) ranging from 0 to 0.98, and coefficients of variation (CV) ranging from 1.7 to 22. Fewer studies evaluating test-retest reliability using similar methods but different scanner manufacturers suggest ICCs ranging from 0.2 to 0.93, and CVs ranging from 2.3 to 6.3. Arguably, the most important consideration regarding improved reliability of compositional MRI as an imaging biomarker is comparability of values across scanners and centers. The present findings therefore support current international efforts from researchers and vendors to improve sequences, calibration, and standardization, such as the Radiological Society of North America Quantitative Imaging Biomarker Alliance, and multicenter studies such as the OAI. In addition to these...
efforts, another approach may be the use of calibration phantoms\textsuperscript{119} to develop correction functions to account for varying hardware and software used by different centers\textsuperscript{17}.

By pooling within-study comparisons, the present primary analysis indicates that T2 and T1\textsubscript{ρ} relaxation times in articular cartilage are significantly prolonged in knees at risk for developing OA, especially in the more commonly affected compartments. T2 relaxation time was significantly prolonged in participants at risk for knee OA in all analyzed compartments with effect sizes ranging from small-to-moderate (SMD=0.33-0.74; p<0.001), suggesting T2 is sensitive to early changes in collagen orientation and structural integrity\textsuperscript{120}, as well as water content in these at-risk participants\textsuperscript{13,15,16}. These findings add support to the use of T2 relaxation time for early detection of OA, before substantial radiographic changes are evident, and support further efforts towards compositional MRI biomarker validation and qualification.

Interestingly, effect sizes for T1\textsubscript{ρ} relaxation time were small, and lower for each analyzed compartment in comparison to effect sizes for T2 relaxation time, (SMD=0.04-0.40; p=0.001-0.76), and only the medial and lateral femoral compartments demonstrated significantly prolonged T1\textsubscript{ρ} relaxation time compared to healthy controls (SMD=0.35-0.40; p<0.001). However, there were fewer studies that included T1\textsubscript{ρ} as an outcome measure with generally smaller sample sizes. More research comparing T2 and T1\textsubscript{ρ} relaxation times for participants at various stages of knee OA is required.
In all knee compartments, there was significant heterogeneity associated with the overall pooled effect sizes for T2 relaxation time (Figures 2.2-2.4). Sensitivity analysis suggested that the high effect sizes of the cartilage injury subgroups are responsible for this heterogeneity (SMD=1.29-2.88; p=0.001-0.38), and after removal from the analyses, heterogeneity was no longer significant in the medial femoral and patellar compartments ($I^2=19-23\%$; $p>0.2$) but remained moderate in the medial tibial and lateral femoral compartments ($I^2=66-70$, $p>0.01$). There were no articles assessing T1ρ relaxation time of participants with cartilage injury, which may explain the lack of heterogeneity in the T1ρ meta-analyses. The large effect sizes observed in these studies including patients with cartilage injury may be due to the different mechanopathology as a result of focal defects in comparison to other participants in this systematic review. Alternatively, we must acknowledge the substantial difference in age between this at-risk subgroup and controls. Publication bias was also significant in three compartments for T1ρ relaxation time, which may be due to the relative novelty of such measures in comparison to T2 relaxation time. There was no publication bias observed in any meta-analyses assessing T2 relaxation time.

**CONCLUSIONS**

Based on these results, T2 and T1ρ relaxometry of articular cartilage show substantial promise in their ability to identify pathological cartilage in participants at risk for knee OA. The present results are consistent with cross-sectional studies reporting known risk factors, such as increased age, body mass, and knee malalignment, and their association with significantly prolonged articular cartilage T2 relaxation times. The present study also highlights the wide variety of methods currently used to collect, process, and analyze T2
and T1ρ mapping. Overall, the present results emphasize both the potential, as well as the need for greater standardization of methods across sites for T2 and T1ρ data collection and processing procedures to make greater gains toward potential biomarker validation.
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106. Li X, Pedoia V, Kumar D, et al. Cartilage T1ρ and T2 relaxation times:


120. Xia Y, Moody JB, Burton-Wurster N, Lust G. Quantitative in situ correlation between microscopic MRI and polarized light microscopy studies of articular
CHAPTER 3 - Acute compositional MRI response of articular cartilage to functional load in patients at-risk for knee osteoarthritis and healthy controls

SUMMARY: Quantitative magnetic resonance imaging (MRI) provides a means to assess knee articular cartilage biochemical composition and can detect early changes in people with knee injuries at risk for osteoarthritis (OA). However, the effects of functional loading on the biochemical composition of knee articular cartilage, and potential differences in the loading response between at-risk and healthy knees, are less clear. The purposes of this study were to 1) evaluate the effect of a standardized functional loading stimulus on knee articular cartilage compositional MRI, and 2) compare the response in patients at risk for knee OA and healthy controls. We recruited 16 patients with risk factors for knee OA, and 16 asymptomatic healthy controls. Participants completed 3T MRI scans including a T2 mapping pulse sequence immediately before and after completing a standardized dynamic functional loading stimulus consisting of 25 minutes of challenged walking under a variety of conditions. The superficial and deep layers of the load-bearing regions of tibiofemoral, patellar, and trochlear cartilage were segmented by a single reader blinded to group (patients vs. controls) and time (before and after loading). T2 relaxation time was analysed using two-factor group by time analysis of variance. There was a statistically significant main effect for time in the superficial layer of all regions (p<0.01), except the trochlea (p=0.07), indicating T2 relaxation time decreased in both groups. The main effect for group, and the group by time interaction, were not statistically significant. When quantified using MRI T2 relation time, the present functional loading stimulus caused immediate changes in knee articular cartilage biochemical composition. Changes were not statistically significantly different in this sample of patients at risk for knee OA and healthy controls.
INTRODUCTION

Articular cartilage is a highly specialized tissue present at the articulating surfaces of synovial joints that is designed to dissipate loads and create near-frictionless surfaces on which bones can move freely. Under normal conditions, cyclic loading is essential to articular cartilage health as it assists metabolic by-products exit and nutrients from the surrounding synovial fluid enter the cartilage\(^1\). However, aberrant loading can contribute to acute and long-term damage to articular cartilage, as well as other synovial joint structures, and the gradual degradation of articular cartilage is considered the hallmark of osteoarthritis (OA)\(^2-3\). Moreover, damage to articular cartilage compromises its ability to dissipate loads, which contributes to further cartilage damage. The ability to identify compromised articular cartilage early in the OA disease process would improve our understanding of this vicious cycle and may provide opportunities to intervene.

Magnetic resonance imaging (MRI) enables knee articular cartilage to be visualized and certain features quantified. Termed compositional MRI, various measures such as T2 relaxation time provide non-invasive surrogates for articular cartilage integrity and can detect differences between patients with knee OA\(^4\), people with risk factors for knee OA, and healthy controls\(^5\). Changes in T2 relaxation time occur prior to radiographic features of OA and are associated with the onset and progression of such features\(^6,7\). The knee articular cartilage in patients with risk factors for knee OA displays prolonged T2 relaxation time, which indicates higher levels of collagen disorganization, increased free water concentration, and compromised extracellular matrix\(^8\). These changes in the extracellular matrix are hypothesized to be a precursor to articular cartilage thinning\(^9\).
More recently, researchers have used compositional MRI measures to evaluate the response of articular cartilage to acute loads applied to the joint in vivo. This includes studies that use devices to apply highly controlled loads in the scanner\textsuperscript{10–12}, and studies that scan the knee immediately after less controlled yet more functional loading, such as walking\textsuperscript{13}, running\textsuperscript{14,15}, squatting\textsuperscript{16}, and cycling\textsuperscript{17}. These studies have assessed healthy controls, or patients with established radiographic knee OA. The results suggest acute shortening of T2 relaxation of articular cartilage in the compartments typically bearing greater loads (i.e. medial femoral and tibial cartilage), and the more permeable superficial layer of the cartilage. There is also some evidence to suggest greater shortening of T2 relaxation time (i.e. an increased loading response) in patients with radiographic knee OA compared to controls\textsuperscript{11}.

To our knowledge, there have been no studies evaluating the compositional MRI response of articular cartilage to loading in patients who are at risk for developing knee OA. This is an important omission as people with risk factors for knee OA, such as knee injury\textsuperscript{18–21}, obesity\textsuperscript{22}, malalignment\textsuperscript{23} and various genetic factors\textsuperscript{24}, may be more responsive to early intervention and would observe the greatest long-term benefit from successful treatment\textsuperscript{25}. Moreover, compared to people with established knee OA, people at risk for knee OA more commonly participate in loading activities that may be harmful. A common hypothesis is that load-bearing exercise induces microtrauma, and the long-term accumulation of this load leads to OA\textsuperscript{26}. Although the knee articular cartilage of people at risk for knee OA may
exhibit a different response to dynamic, functional loading similar to that during exercise, this response has not been previously investigated.

Therefore, the purposes of this study were to 1) evaluate the effect of a standardized functional loading stimulus on knee articular cartilage compositional MRI, and 2) compare the response in patients at risk for knee OA and healthy controls. We hypothesized that 1) T2 relaxation time would decrease following functional loading, and 2) that patients with risk factors for knee OA would demonstrate greater shortening of T2 relaxation time compared to healthy controls.

**METHODS**

**Participants**

We recruited 16 patients with risk factors for knee OA and 16 healthy controls. Patients at risk for knee OA were recruited from the Fowler Kennedy Sport Medicine Clinic. Eligibility criteria were based on the Osteoarthritis Initiative (OAI) Incidence Cohort criteria, which include any one of the following: i) knee symptoms (pain, aching, stiffness) in the past 12 months, ii) history of knee injury affecting gait for two weeks or more, and iii) history of knee surgery. For healthy control group, eligibility criteria were based on the OAI control cohort, which includes: i) free of symptoms such as pain, aching, stiffness in the past year, and ii) no history of knee surgery, or injury that would have affected ability to walk normally for more than two weeks. For the controls, we matched the sex and body mass index (BMI) of the patients, but opted to recruit skeletally mature participants ≤30 years of age to limit potentially confounding effects of age-related changes of articular
cartilage. All participants completed the Knee injury and Osteoarthritis Outcome Score (KOOS), where higher scores indicated greater function and decreased pain\textsuperscript{28}. All participants provided written informed consent to participate in the study. We did not perform any sample size calculation as the purpose of this study was exploratory, and there is no agreed-upon value for important change in T2 relaxation time as a result of acute loading. The present study is the largest sample size we are aware of used to assess changes in T2 relaxation due to acute loading. The study was approved by the institution’s Research Ethics Board for Health Science Research Involving Human Subjects.

**Testing Protocol**

Participants completed a 3T MRI scan including a T2 mapping pulse sequence immediately (within 10 minutes) before and after completing a standardized dynamic functional loading stimulus consisting of 25 minutes of challenged walking under a variety of conditions (Figure 3.1). Testing was performed in the morning to minimize the potential effects of load incurred throughout the day. Participants agreed to avoid high-impact and high-intensity activities for two days prior to the test date. Following the pre-loading scan, participants completed the functional loading stimulus in a biomechanics laboratory and returned immediately to the MRI scanner for the post-loading scan. The distance between the MRI scanner and biomechanics laboratory is 780 m, and all patients took the same route and walked at their preferred pace between sites, accompanied by the tester.
Imaging

We scanned the affected knees of all at-risk patients, and the right knee of all healthy controls, using a 3T Siemens Magnetom Trio magnet and a 15-channel Siemens PRISMA knee coil, located in the Centre for Functional and Metabolic Mapping, Robarts Research Institute. Pulse sequences included 3D Dual Echo Steady State and Multi-Echo Spin Echo.

Figure 3.1. Testing protocol for the study. Participants started with a baseline scan including 3D DESS and T2 mapping sequences, followed by the loading stimulus, and returned to the scanner for the post-loading sequence, using the same scanning protocol in reverse order.

T2 Mapping (TR 2700 ms/TE 11.1-77.7 ms, ETL 7). Participants were seated 30 minutes prior to the pre-loading scan to reduce effect of loading incurred earlier in the morning. For the pre-loading scan, the T2 Mapping sequence was performed last, again to reduce the effect of prior loading on articular cartilage, and for the post-loading scan, the T2 Mapping sequence was performed first to avoid dissipation of the effect of the functional loading stimulus on articular cartilage.

Image Processing

We generated T2 relaxation maps using software developed in-house by fitting image intensities of the T2 weighted images pixel-by-pixel to the equation \( S(TE) \propto \exp(-TE/T2) \) using a Levenberg-Marquardt mono-exponential fitting algorithm implemented using Insight Toolkit. The first echo was eliminated from the decay curve to eliminate the effect.
of stimulated echoes on the computed T2 relaxation time\textsuperscript{29}. One reader was blinded to group and scan order by using re-coded identifications for all scans by a third party. We used the T2-weighted image from the first echo of the T2 mapping sequence for segmentation. The reader manually segmented articular cartilage in three consecutive slices for each load-bearing region of the medial femur (MF), medial tibia (MT), and lateral femur (LF), and lateral tibia (LT) using a standardized anatomical atlas, as well as the patellar (P) and trochlear (Tr) articular cartilage using 3D Slicer software\textsuperscript{30} (http://www.slicer.org). Segmentations were divided into equal sized superficial and deep layers (laminae) based on each pixel’s minimum Euclidean distance to the articular surface and bone cartilage interface.

**Functional Loading Stimulus**

Following the baseline scan, all participants completed the same standardized loading stimulus in the Wolf Orthopaedic Biomechanics Lab, Fowler Kennedy Sport Medicine Clinic. The loading stimulus consisted of 25 minutes of challenged walking on the Gait Real-time Analysis Interactive Laboratory, a computerized treadmill capable of moving with 6 degrees of freedom within a virtual reality environment (Motekforce Link, Amsterdam, NL). The functional loading stimulus was pre-programmed and exactly repeatable between participants. We subjected participants to changes in speed (110-120% self-selected speed), inclines and declines (±10°), lateral sways (1 m/s, 15 cm left/right), and random pre-specified perturbations in the form of rapid belt slips, sagittal plane pitches, and frontal plane sways. A full timeline of the functional loading stimulus is provided in Appendix A.
**Statistical Analysis**

For the primary analysis, a composite measure for T2 relaxation time in the entirety of the superficial layer of the knee articular cartilage was derived using the mean of the segmented load-bearing regions in the MF, MT, LF, LT, P and Tr. The same process was used to calculate a composite measure for T2 relaxation time in the entirety of the deep layer of the knee articular cartilage (Figure 3.2a). T2 relaxation time in patients and controls was compared before and after the loading stimulus using two separate two-factor group by time analysis of variance (ANOVA) tests. For the secondary analysis, we repeated the ANOVAs using the T2 relaxation time for each laminar layer of each segmented region.

**Figure 3.2.** Representation of the segmentation technique for the laminar analysis (a) and the regional analysis (b). The combined ROI for the superficial articular cartilage in throughout the knee is represented in red, and in blue for the deep articular cartilage in image a. The twelve separate ROI’s for the regional analysis (MF, MT, LF, LT, P, Tr; superficial and deep for each) are represented by the various colours in image b. The 3D reconstruction of the bone has been made translucent to allow for visualization of all ROIs.
(Figure 3.2b). All analyses were performed using SPSS 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp).

RESULTS

Participants

Participant characteristics are summarized in Table 3.1. Patients at risk for knee OA had a variety of risk factors, including anterior cruciate ligament (ACL) rupture (n=7), frequent symptoms (n=6), meniscal tear (n=2), and articular cartilage lesion (n=1). All participants completed the study without incident.

<table>
<thead>
<tr>
<th></th>
<th>Healthy Controls (n=16)</th>
<th>At Risk for OA (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>25±3 years</td>
<td>38±12 years</td>
</tr>
<tr>
<td>Sex</td>
<td>13M/3F</td>
<td>13M/3F</td>
</tr>
<tr>
<td>BMI</td>
<td>24±3 kg/m²</td>
<td>26±3 kg/m²</td>
</tr>
<tr>
<td>KOOS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>98.4±2.7</td>
<td>80.0±12.8</td>
</tr>
<tr>
<td>Symptoms</td>
<td>96.5±4.2</td>
<td>78.2±9.6</td>
</tr>
<tr>
<td>ADL</td>
<td>99.6±0.8</td>
<td>89.9±12.5</td>
</tr>
<tr>
<td>Sport &amp; Rec</td>
<td>96.9±4.8</td>
<td>70.0±21.5</td>
</tr>
<tr>
<td>QoL</td>
<td>98.5±2.7</td>
<td>58.3±17.7</td>
</tr>
</tbody>
</table>

KOOS = Knee Injury and Osteoarthritis Outcome Score, ADL = activities of daily living, QoL = quality of life

T2 relaxation response

Primary Analysis

T2 relaxation times for the composite measures of the superficial and deep layers of knee articular cartilage for patients at risk for knee OA and healthy controls before and after loading are illustrated in Figure 3.3. For the superficial layer, there was a statistically significant main effect for time (p<0.001), but no statistically significant main effect for
group (p=0.8) and no statistically significant group by time interaction (p=0.8), indicating T2 relaxation time decreased similarly in both groups after the functional loading stimulus. The mean (95% confidence interval (CI)) change in T2 relaxation time of the superficial layer was -3.1 ms (-3.9; -2.3 ms) for patients at risk for knee OA and was -3.2 ms (-4.3; -2.2 ms) for healthy controls. Results were similar for the composite measure of the deep layer of knee articular cartilage, although decreases after loading were more variable and not as large. The change in T2 relaxation time was -0.4 ms (-1.1; 0.2 ms) for patients at risk for OA and -1.0 ms (-2.5; 0.6 ms) for healthy controls.

**Figure 3.3.** Changes in composite superficial (top) and composite deep (bottom) articular cartilage T2 relaxation time in patients at risk for knee OA (red) and healthy controls (green). Error bars represent 95% confidence intervals for the group mean.
Secondary Analysis

Results were consistent when the ANOVAs were repeated for each superficial layer of each segmented region of articular cartilage. Except for the superficial trochlear compartment (p>0.07), there were statistically significant main effects for time for all regions, indicating T2 relaxation decreased following the functional loading stimulus in both groups (p<0.01), but there were no statistically significant main effects for group (p>0.09) and no statistically significant group by time interactions (p>0.3). For the deep layers of the

Table 3.2. Changes from pre to post loading in patients at risk for knee OA and healthy controls. Means and 95% confidence intervals (CI) are shown.

<table>
<thead>
<tr>
<th></th>
<th>Group</th>
<th>Superficial T2 change (mean [95%CI])</th>
<th>Deep T2 change (mean [95%CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medial Femur</td>
<td>Healthy Controls</td>
<td>-4.3 ms [-2.9; -5.8 ms]</td>
<td>-2.2 ms [-4.8; 0.4 ms]</td>
</tr>
<tr>
<td></td>
<td>At-Risk for OA</td>
<td>-5.4 ms [-3.1; -7.8 ms]</td>
<td>-1.6 ms [-0.4; -2.9 ms]</td>
</tr>
<tr>
<td></td>
<td>Between-Group Δ</td>
<td>-1.1 ms [-3.8; 1.5 ms]</td>
<td>0.6 ms [-2.2; 3.4 ms]</td>
</tr>
<tr>
<td>Medial Tibia</td>
<td>Healthy Controls</td>
<td>-5.0 ms [-3.8; -6.2 ms]</td>
<td>1.0 ms [-0.9; 2.8 ms]</td>
</tr>
<tr>
<td></td>
<td>At-Risk for OA</td>
<td>-5.2 ms [-3.4; -6.9 ms]</td>
<td>0.2 ms [-1.1; 1.4 ms]</td>
</tr>
<tr>
<td></td>
<td>Between-Group Δ</td>
<td>-0.1 ms [-2.2; 1.9 ms]</td>
<td>0.8 ms [-1.3; 2.9 ms]</td>
</tr>
<tr>
<td>Lateral Femur</td>
<td>Healthy Controls</td>
<td>-3.3 ms [-2.1; -4.6 ms]</td>
<td>1.0 ms [-0.9; 2.9 ms]</td>
</tr>
<tr>
<td></td>
<td>At-Risk for OA</td>
<td>-2.6 ms [-1.9; -3.2 ms]</td>
<td>0.9 ms [-0.3; 2.0 ms]</td>
</tr>
<tr>
<td></td>
<td>Between-Group Δ</td>
<td>0.8 ms [-0.6; 2.2 ms]</td>
<td>0.2 ms [-2.0; 2.3 ms]</td>
</tr>
<tr>
<td>Lateral Tibia</td>
<td>Healthy Controls</td>
<td>-2.9 ms [-1.6; -4.1 ms]</td>
<td>0.3 ms [-1.4; 1.9 ms]</td>
</tr>
<tr>
<td></td>
<td>At-Risk for OA</td>
<td>-2.1 ms [-1.1; -3.0 ms]</td>
<td>-0.7 ms [-2.1; 0.7 ms]</td>
</tr>
<tr>
<td></td>
<td>Between-Group Δ</td>
<td>0.8 ms [-0.7; 2.3 ms]</td>
<td>0.9 ms [-1.1; 3.0 ms]</td>
</tr>
<tr>
<td>Patella</td>
<td>Healthy Controls</td>
<td>-2.2 ms [-0.1; -4.3 ms]</td>
<td>0.6 ms [-1.5; 2.7 ms]</td>
</tr>
<tr>
<td></td>
<td>At-Risk for OA</td>
<td>-2.9 ms [-1.1; -4.6 ms]</td>
<td>0.0 ms [-1.3; 1.3 ms]</td>
</tr>
<tr>
<td></td>
<td>Between-Group Δ</td>
<td>-0.7 ms [-3.3; 1.9 ms]</td>
<td>0.7 ms [-1.7; 3.0 ms]</td>
</tr>
<tr>
<td>Trochlea</td>
<td>Healthy Controls</td>
<td>-1.8 ms [0.2; -3.7 ms]</td>
<td>0.7 ms [-1.0; 2.4 ms]</td>
</tr>
<tr>
<td></td>
<td>At-Risk for OA</td>
<td>0.5 ms [-1.1; 2.1 ms]</td>
<td>0.6 ms [-0.5; 1.8 ms]</td>
</tr>
<tr>
<td></td>
<td>Between-Group Δ</td>
<td>1.3 ms [-1.1; 3.7 ms]</td>
<td>0.0 ms [-1.9; 2.0 ms]</td>
</tr>
</tbody>
</table>
articul ar cartilage, there was a statistically significant main effect for time for the medial femur only (p=0.007). There were no main effects for group (p>0.1), with the exception of the medial femur, with the direction indicating increased shortening of T2 in the healthy controls (p=0.01). There were no statistically significant group by time interactions (p>0.09). Results for the superficial layer of each region are summarized in Table 3.2.

DISCUSSION
Consistent with our hypothesis, we observed a decrease in T2 relaxation time in the knee articular cartilage after the loading stimulus. To our knowledge this is the first study to use a standardized, functional loading stimulus that challenges the participants considerably, through sudden changes in speed, inclinations and perturbations, and allows for exact replication of the test within and between participants. This functional loading stimulus produced changes in the superficial layers of all of the weight-bearing regions of the articular cartilage segmented, and in the deep layer of articular cartilage of the medial femur. Consistent with previous studies11,13,14, the superficial compartments experienced a greater response to the load compared to the deep compartment, presumable because there is the greater potential for permeation at the articular surface of the cartilage. The deep compartment of the medial femur was the only deep ROI to experience a significant change, which could be explained by the medial compartment being the most loaded during ambulation, even in normally aligned healthy controls31.

Contrary to our hypothesis, we observed a similar response in the articular cartilage of patients at risk for knee OA and the healthy controls. This was also consistent for each of
the subregions of cartilage segmented. We hypothesized that the knee articular cartilage of patients seeking treatment for knee injuries and/or knee pain, and who had identifiable risk factors for knee OA, would experience a greater response to loading compared to the healthy controls because previous reports suggest compositional MRI has detected changes within months after knee trauma, such as ACL rupture\textsuperscript{32,33}. Notably, we also did not observe baseline differences in T2 relaxation time between the patients at risk for knee OA and the healthy controls. This may be due to the variability in specific risk factors for knee OA, which included ACL rupture, meniscal tear, cartilage lesions, and frequent pain. Strictly recruiting patients with ACL rupture may have resulted in baseline differences in T2 relaxation time between groups, and perhaps differences in the response to the loading stimulus.

Although contrary to our hypotheses, the lack of differences between the present patients and controls might be interpreted as encouraging, as it suggests that patients with risk factors for knee OA are safe to pursue moderate intensity recreational exercise without immediate changes indicative of microtrauma to the cartilage. This finding is somewhat consistent with a systematic review of randomized trials that suggests completing exercise interventions for people with or at risk of knee OA does not result in greater articular cartilage damage\textsuperscript{34}.

Strengths of this study include the use of a repeatable, standardized loading stimulus, and the first comparison of the effects of loading on compositional MRI in participants with risk factors for knee OA to healthy controls. The present functional loading stimulus
provides a realistic loading environment for the knee joint that mimics physiological movements and loads incurred on the knee throughout the day, rather than a simulation of static load in a compromised position, such as lying supine in a scanner. Loading the joint under multiple conditions, negotiating inclined and declined walking, perturbations and lateral sways, better represents daily demands of the joint compared to level walking or running. The ability to repeat the loading stimulus exactly for each participant is also an important strength. While a variety of activities may apply similar functional loading stimuli, variability in terrain, weather, etc. would be difficult to control.

A limitation of this study was the potential effects of the time between scans and the loading stimulus, which was typically <10 minutes. The delay was necessary given the distance between the biomechanics laboratory and the MRI scanner. The time delay may have attenuated the effects of loading, and may have created additional variability among participants. We limited this possibility by having all participants take the same route to the scanner and be scanned immediately upon arrival, spending no time resting between T2 mapping scans other than the time required to run localizer sequences (<2 minutes). Another potential limitation is the use of different risk factors for knee OA to create our at-risk group of patients. Although we used the criteria supported by the OAI incident cohort, they may have been too variable for the present purpose. Future research should focus on more specific risk factors that may create more acute responses than others, as well as determining what mechanical factors are responsible for potential differences in load response (e.g.: BMI, malalignment, excessive co-contraction, increased age, injury, etc.).
Such knowledge may also help to further personalize exercise recommendations for patients with risk factors for knee OA to provide more informed prevention strategies.
REFERENCES


CHAPTER 4 – Improvements in knee articular cartilage composition 1 year after high tibial osteotomy

SUMMARY: The aim of medial opening wedge high tibial osteotomy (HTO) is to limit osteoarthritis progression in the medial compartment of the varus aligned knee, yet HTO may have unintended effects on other knee compartments. The purposes of this study were to 1) test the hypothesis that medial opening wedge HTO improves medial tibiofemoral articular cartilage composition without adversely affecting the lateral compartment and patella, and 2) to explore the associations between changes in radiographic measures of joint alignment and magnetic resonance imaging (MRI) measures of cartilage composition. 34 patients were scanned using 3T MRI before and 1 year after HTO. Weight-bearing regions of articular cartilage in the tibiofemoral joint and patella were manually segmented from T2 relaxation maps. Mechanical axis angle (MAA), posterior tibial slope, and patellar height were measured from radiographs. T2 relaxation and radiographic measures before and after surgery were compared using dependent samples t-tests. Associations between radiographic measures and T2 relaxation were assessed using Pearson correlation coefficients (r). The mean (SD) MAA before and after HTO were $-6.5^\circ$ (2.4) and $0.6^\circ$ (3.0) respectively. There was a significant shortening (mean [95%CI]) of T2 relaxation in the medial femur ($-2.6$ ms [-4.3; -1.0], p<0.003) and medial tibia ($-2.3$ ms [-3.4; -1.2], p<0.001), and no significant changes in the lateral femur ($-0.6$ ms [-1.6; 0.5], p=0.3), lateral tibia (0.6 ms [-0.6; 1.8], p=0.3), or patella (1.3 ms [-0.3; 2.9], p=0.1). Associations between changes in radiographic measures of alignment and T2 relaxation measures were low. HTO can improve articular cartilage composition in the medial compartment without compromising the lateral compartment or patella.
INTRODUCTION

The burden of osteoarthritis (OA) is tremendous and growing\textsuperscript{1,2}. There is currently no cure for OA and no interventions widely accepted to modify the course of disease\textsuperscript{3,4}. Although OA is now known to affect the entire joint\textsuperscript{5}, articular cartilage damage is considered the hallmark of the disease\textsuperscript{6}. The knee is the most commonly affected joint and typically involves the medial tibiofemoral compartment due to ambulatory biomechanics that load the medial tibiofemoral compartment more than the lateral\textsuperscript{7}. Varus malalignment is a strong risk factor for the incidence and progression of articular cartilage damage in the medial knee\textsuperscript{8,9} because it exaggerates the disproportionate loads borne by the medial compartment.

An aim of high tibial osteotomy (HTO) is to limit OA progression in patients with medial tibiofemoral OA by correcting varus malalignment\textsuperscript{10,11}. Although not unequivocal, there is preliminary evidence based on second-look arthroscopy and magnetic resonance imaging (MRI) to suggest HTO may enable regeneration of damaged articular cartilage in the medial compartment\textsuperscript{12,13}. HTO may be also be associated with undesirable changes in the lateral compartment and/or patella due to the lateral shift in load and potential alterations in posterior tibial slope and patellar height; inadvertent changes that may be higher when performing larger corrections\textsuperscript{14–16}. To our knowledge, no studies have used MRI to investigate changes in articular cartilage of both tibiofemoral compartments and the patella, or their associations with changes in knee joint alignment, following HTO.

Compositional MRI consists of advanced imaging techniques that quantify physical properties of tissues of interest to deduce their biochemical composition. T2 relaxometry
is a common compositional MRI technique that is sensitive to changes in free water content and collagen orientation within the cartilage\textsuperscript{17–19}, with lengthened values indicating collagen disorganization and higher concentrations of free water molecules\textsuperscript{20}. T2 relaxation is capable of distinguishing between healthy controls and patients with and at-risk for knee OA\textsuperscript{21,22}, and is sensitive to differences in radiographic severity of disease\textsuperscript{23}. This makes T2 relaxation an appropriate tool to measure \textit{in vivo} changes in articular cartilage biochemistry that would not otherwise be detectable\textsuperscript{24}.

The purposes of this study were to: 1) test the hypothesis that medial opening wedge HTO will improve medial tibiofemoral articular cartilage composition, measured as shortening of T2 relaxation time, without adversely affecting the lateral tibiofemoral compartment and the patella, and 2) explore the associations between radiographic measures of joint alignment and changes in MRI measures of articular cartilage composition.

**METHODS**

**Study design**

A subgroup of patients participating in an interventional cohort study of medial opening wedge HTO for medial tibiofemoral compartment knee OA agreed to undergo additional MRI testing. We evaluated knee articular cartilage composition using T2 relaxation times measured from 3T MRI scans obtained before and 1 year after surgery. We included the first 34 participants at 1-year follow-up based on 80\% power to detect a statistically significant (p<0.05) within-patient change of moderate effect size (d=0.45) with $\alpha=0.05$\textsuperscript{25}. 
All participants provided informed consent. The study was approved by the institution’s Research Ethics Board for Health Science Research Involving Human Subjects.

**Participants**

We recruited patients who were referred to an orthopaedic surgeon for consultation regarding treatment options for medial compartment knee OA. Patients underwent subjective, physical and radiographic assessments completed by an orthopaedic surgeon. Inclusion criteria were clinical diagnosis of knee OA, which involves meeting three of the following American College of Rheumatology criteria\textsuperscript{26}: age > 50 years, morning stiffness <30 minutes, crepitus, bony tenderness, bony enlargement, and no palpable warmth, varus alignment of the lower limb (identified from full limb standing anteroposterior radiographs), and with both symptoms and radiographic features of OA primarily confined to the medial tibiofemoral compartment. Specifically, patients who had radiographic features of OA in the lateral tibiofemoral or patellofemoral compartments were eligible as long as the medial tibiofemoral compartment was the most severely affected.

**High Tibial Osteotomy**

Medial opening wedge HTO was completed using methods similar to previously described techniques\textsuperscript{27,28}. The angle of correction was determined preoperatively from full-limb standing anteroposterior radiographs using custom software\textsuperscript{29}. The extent of correction aimed to shift the weight-bearing line (hip joint center to ankle joint center) laterally, typically to a maximum of 62.5% of the tibial width, and ideally passing through the tibial spine. The exact angle of correction was determined at the surgeon’s discretion considering
the extent of preoperative deformity and severity of OA in other compartments. The medial opening wedge was fixed proximally and distally using either a polyethyletherketone (PEEK) plate and PEEK screws, or a metal fixation plate and cortical and cancellous screws and confirmed by fluoroscopy. If a titanium fixation plate and screws were used, they were removed within 1 year after surgery and postoperative imaging was delayed at least 6 weeks after its removal. Cancellous bone allograft was packed into the opening wedge to accelerate fracture union. Early postoperative management included the use of a hinge brace and crutches while patients ambulated with feather weight-bearing. Weight-bearing was gradually increased based on clinical and radiographic evidence of healing of the osteotomy, with patients scheduled to return to partial weight-bearing with a single crutch by 6 weeks postoperatively, and full weightbearing by approximately 12 weeks postoperatively. Patients received a standardized postoperative rehabilitation protocol with exercise progressions and typical milestones, reviewed on postoperative day 1, and 2-, 6-, and 12-week follow-up visits.

**Outcome Measures**

Consistent with our hypothesis, the primary outcome measure was T2 relaxation time of weight-bearing articular cartilage in the medial compartment of the tibiofemoral joint. Secondary outcome measures were T2 relaxation of articular cartilage in the lateral tibiofemoral joint and patella, and radiographic measures including mechanical axis angle (MAA), posterior tibial slope, and patellar height ratio (Insall-Salvati ratio) (Figure 4.1).
Figure 4.1. Radiographic measures of joint alignment. Figure 4.1a illustrates the mechanical axis angle, measured using the angle created by the intersection of the line between the centre of the femoral head to the centre of the knee, and the line between the centre of the ankle to the centre of the knee joint. Figure 4.1b illustrates the posterior tibial slope, measured by the angle created between the posterior cortex of the tibia, and the tibial plateau. Figure 4.1c illustrates the Insall-Salvati ratio, the length of the patellar ligament divided by the length of the patella.

Magnetic Resonance Imaging

A Siemens Magnetom Trio 3.0 Tesla magnet and dedicated 15-channel Tx/Rx PRISMA knee coil was used for all participants. The T2 mapping sequence was a sagittal multi-slice multi-echo spin echo sequence with seven echoes (TE = 10, 20, 30, 40, 50, 60, 70 ms), repetition time of 2700 ms, and a total acquisition time of 10.6 minutes. T2 relaxation values were calculated using Siemens MapIt software (Siemens Medical Solutions, Erlangen, Germany).
One rater, trained by a musculoskeletal radiologist, was blinded to timepoint (i.e. pre or post HTO) by masking the proximal tibia using a technique similar to the validated method previously described\textsuperscript{31}. The same blinding mask was applied to both pre and postoperative images. The rater manually segmented articular cartilage of the medial femur and tibia, lateral femur and tibia, and patella, using the menisci as landmarks for boundaries of weight-bearing regions of articular cartilage. Based on anatomical landmarks, five subregions were created for the medial femoral condyle (MFC 1-5), and lateral femoral condyle (LFC 1-5), three subregions for the medial tibia (MT 1-3) and lateral tibia (LT 1-3), and one for the patella (PAT). Segmentation of subregions is represented in Figure 4.2. Segmentation was performed using 3D Slicer\textsuperscript{32} (http://www.slicer.org). To evaluate reliability, the same rater repeated segmentation of each knee approximately 30 days later with all images being assigned new identification labels to ensure repeatability.

\textbf{Figure 4.2.} Sagittal views of the first echo of the multi-echo spin echo mapping sequence used for T2 mapping and segmentation. Pre-defined subregions are represented in the medial and lateral compartments. Medial femoral condyle (MFC) subregions 2-5, and medial tibial (MT) subregions 1-3 are visible in 2a, lateral femoral condyle (LFC) subregions 1-5, and lateral tibial (LT) subregions 1-3 are visible in 2b, and the patellar subregion (PAT) is visible in 2c. MFC 1 is not in the image, but would consist of the medial femoral articular cartilage that is superior and anterior to the anterior horn of the meniscus.
**Radiographic Assessment**

Weight-bearing hip-to-ankle anteroposterior digital radiographs were used to measure MAA\(^2\). Patellar height and posterior tibial slope were measured from standing lateral views. Kellgren and Lawrence grades and the Osteoarthritis Research Society International (OARSI) Atlas joint space narrowing grades for the tibiofemoral joint were measured from semi-flexed posteroanterior views. Radiographs were measured using the same software used for operative planning\(^2\) (TheHTO Pro; Fowler Kennedy Sport Medicine Clinic, London, Ontario, Canada). Baseline and 1-year postoperative MAA, and posterior tibial slope, and patellar height ratio were measured by one rater. Mechanical axis angle was measured using the angle created by a straight line from the center of the femoral head to the center of the knee joint, and a straight line between the center of the tibiotalar joint and the center of the knee joint, with negative values representing varus alignment and positive values representing valgus alignment\(^\)\(^2\)\(^8\). Posterior tibial slope was measured using the angle created by the proximal medial tibial plateau and a perpendicular line drawn through the axis of the tibial shaft\(^3\)\(^3\). Patellar height was measured using the Insall-Salvati ratio, which is the length of the patellar ligament divided by the length of the patella in the sagittal plane\(^3\)\(^0\).

**Statistical Analysis**

Intra-rater reliability of T2 relaxation time was assessed using intraclass correlation coefficients (ICC\(_{2,1}\)). Changes from preoperative to 1-year postoperative T2 relaxation values and radiographic measures were compared using dependent samples t-tests. Within-patient change scores were calculated as the 1-year follow-up value minus the preoperative
value. Associations between the 1-year changes in T2 relaxation and the change in radiographic measures (change in MAA, posterior tibial slope), and postoperative radiographic alignment (1-year MAA, 1-year posterior tibial slope) were assessed using Pearson’s correlation coefficients (r). The effect of correction angle was also explored by comparing T2 relaxation changes between subgroups derived from lowest and highest tertiles for postoperative MAA using an independent samples t-test. The statistical analysis was performed using SPSS 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp).

RESULTS
Baseline demographic and clinical characteristics are reported in Table 4.1. Consistent with previous research in HTO, patients were typically middle-aged males, overweight or obese and had varus alignment with OA primarily affecting the medial tibiofemoral compartment. Two patients were excluded at the 1-year follow-up timepoint after they were found to have loss of varus alignment correction, resulting in a return to baseline alignment.

Intra-rater reliability for T2 relaxation time measures was excellent pre and postoperatively; preoperative ICC: 0.86 [95% confidence interval (95%CI): 0.81; 0.91], postoperative ICC: 0.88 [0.84; 0.92]. Baseline, 1-year and change in MRI measures are reported in Table 4.2 and demonstrate statistically significant shortening of T2 relaxation time in the medial femur and medial tibia, with no statistically significant changes in the lateral femur, lateral tibia, or patella. Results are consistent with improved articular
### Table 4.1. Baseline demographic and clinical characteristics (n=34)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y), mean (SD)</td>
<td>53 (6)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>7 (19.4%)</td>
</tr>
<tr>
<td>BMI (kg/m²), mean (SD)</td>
<td>29.8 (4.2)</td>
</tr>
<tr>
<td>OARSI Tibiofemoral Joint Space</td>
<td></td>
</tr>
<tr>
<td>Narrowing Grade</td>
<td></td>
</tr>
<tr>
<td>Medial Compartment</td>
<td></td>
</tr>
<tr>
<td>Grade 0</td>
<td>--</td>
</tr>
<tr>
<td>Grade 1</td>
<td>11 (32.4%)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>11 (32.4%)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>12 (35.3%)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>--</td>
</tr>
<tr>
<td>Lateral Compartment</td>
<td></td>
</tr>
<tr>
<td>Grade 0</td>
<td>--</td>
</tr>
<tr>
<td>Grade 1</td>
<td>27 (79.4%)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>7 (20.5%)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>--</td>
</tr>
<tr>
<td>Grade 4</td>
<td>--</td>
</tr>
<tr>
<td>Kellgren &amp; Lawrence Grade</td>
<td></td>
</tr>
<tr>
<td>Grade 0</td>
<td>--</td>
</tr>
<tr>
<td>Grade 1</td>
<td>4 (11.8%)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>10 (29.4%)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>20 (58.8%)</td>
</tr>
<tr>
<td>Mechanical Axis Angle (°)</td>
<td>-6.5 (2.4)</td>
</tr>
<tr>
<td>Posterior Tibial Slope (°)</td>
<td>5.5 (3.3)</td>
</tr>
<tr>
<td>Patellar Height (Insall-Salvati Ratio)</td>
<td>1.07 (0.21)</td>
</tr>
</tbody>
</table>

*BMI = body mass index*

cartilage composition in the medial compartment and no harmful effects to the lateral compartment or patella 1 year after HTO. Changes in MAA, posterior tibial slope, and patellar height ratio are reported in Table 4.3. The mean value indicates frontal plane
malalignment was corrected to approximately neutral. There were no statistically significant changes in posterior tibial slope and patellar height.

| Table 4.2. T2 relaxation time before and 1 year after medial opening wedge HTO |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Baseline T2 (ms) | 1-year T2 (ms)  | Change (ms)     | p-value         |
| (mean ± SD)      | (mean ± SD)     | (mean [95%CI])  |                 |
| Medial Femur     | 51.8 ± 6.1      | 49.2 ± 6.4      | -2.6 [-4.3; -1.0] | 0.003           |
| Medial Tibia     | 43.7 ± 4.2      | 41.4 ± 3.2      | -2.3 [-3.4; -1.2] | <0.001          |
| Lateral Femur    | 50.8 ± 5.1      | 50.2 ± 5.3      | -0.6 [-1.6; 0.5] | 0.3             |
| Lateral Tibia    | 40.1 ± 4.7      | 40.7 ± 4.4      | 0.6 [-0.6; 1.8]  | 0.3             |
| Patella          | 48.0 ± 5.7      | 49.3 ± 4.9      | 1.3 [-0.3; 2.9]  | 0.1             |

Correlation coefficients for the associations between radiographic measures and changes in T2 relaxation are reported in Table 4.4. All associations were very low (r<0.32) with the exception of the association between the postoperative posterior tibial slope and the change in T2 relaxation time in the lateral femur (r = 0.48, p = 0.006, Figure 4.3). Subgroup analyses comparing the most varus (n = 11) and most valgus (n = 11) subgroups suggested no statistically significant difference in articular cartilage T2 relaxation change in any of the tibiofemoral compartments (p>0.14). Results of the subgroup analysis are summarized in Table 4.5.

**DISCUSSION**

In this sample of 34 patients undergoing HTO, we observed a shortening of T2 relaxation time 1 year after surgery with no apparent changes in the lateral compartment or the patella.
<table>
<thead>
<tr>
<th>Table 4.3. Radiographic measures before and 1 year after HTO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanical Axis Angle (°)</strong></td>
</tr>
<tr>
<td>-6.5 ± 2.4</td>
</tr>
<tr>
<td><strong>Posterior Tibial Slope (°)</strong></td>
</tr>
<tr>
<td><strong>Patellar Height (Insall-Salvati Ratio)</strong></td>
</tr>
</tbody>
</table>

**Figure 4.3.** Association between posterior tibial slope 1 year after HTO and change in lateral femur T2 relaxation time (n=34). The line of best fit is represented in the middle, surrounded by the 95% confidence intervals.
This finding suggests an improvement in articular cartilage composition in the medial tibiofemoral compartment and is consistent with HTO being a disease modifying intervention.

We used T2 relaxation time as our primary outcome measure as it is a non-invasive imaging biomarker sensitive to changes in collagen organization and free water content, both of which are important to the integrity of articular cartilage and are precursors to joint space narrowing. T2 relaxation is a measurable time constant in MRI that lengthens proportionately with the severity of knee OA. Patients in this study experienced a mean [95%CI] shortening of T2 relaxation of -2.8 ms [-4.2; -1.3] in the medial femoral articular cartilage, and -2.2 ms [-3.3; -1.0] in the medial tibial articular cartilage. Shortened T2 relaxation of articular cartilage over time suggests either collagen fibril recovery, or increased bound water content, or a combination of the two, due to improved articular cartilage integrity. We are not aware of any intervention for OA that has shortened T2 relaxation time of articular cartilage over a relatively long-term (1 year) follow-up.

The present results are generally consistent with previous studies on samples of 10 to 20 patients assessed with second-look arthroscopy, delayed gadolinium enhanced MRI and T2 relaxation time to investigate potential changes in medial tibiofemoral cartilage after HTO. Kanamiya et al reported fibrocartilaginous regeneration in 32/58 knees in the medial compartment, using the modified Noyes classification for arthroscopic grading.
Table 4.4. Association between changes in T2 relaxation and changes in radiographic measures. Pearson product moment correlations (r) and 95%CI are shown.

<table>
<thead>
<tr>
<th>Change in alignment</th>
<th>Postoperative Alignment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mechanical Axis Angle Δ</td>
</tr>
<tr>
<td>Medial Tibia T2 Δ</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>[-0.29; 0.38]</td>
</tr>
<tr>
<td>Medial Femur T2 Δ</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>[-0.22; 0.44]</td>
</tr>
<tr>
<td>Lateral Tibia T2 Δ</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>[-0.20; 0.47]</td>
</tr>
<tr>
<td>Lateral Femur T2 Δ</td>
<td>-0.03</td>
</tr>
<tr>
<td></td>
<td>[-0.36; 0.31]</td>
</tr>
<tr>
<td>Patellar T2 Δ</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td>[-0.02; 0.59]</td>
</tr>
</tbody>
</table>

A positive correlation indicates an association between a concurrent increase in T2 and increase in the respective radiographic measure.

*p=0.006

Rutgers et al\textsuperscript{36}, and Parker et al\textsuperscript{13} used delayed gadolinium-enhanced MRI of cartilage (dGEMRIC), a contrast-enhanced imaging technique sensitive to glycosaminoglycan (GAG) composition of cartilage, to evaluate the articular cartilage response of 10 patients, 2 years after HTO. They found no significant changes in dGEMRIC, with changes trending towards a worsening of articular cartilage composition. Although our results do not agree with those findings, differences may be attributable to smaller in sample size in the Parker et al\textsuperscript{13} study (n = 10 vs. n = 34) and the reliability of dGEMRIC compared to T2 relaxation techniques\textsuperscript{21,39}. Our results are also consistent with a study by Nishioka et al\textsuperscript{37}, who observed a statistically significant shortening in T2 relaxation time after medial opening.
wedge HTO. They reported a mean (SD) shortening from 50.7 ms (4.2) preoperatively to 46.5 ms (4.1) in the medial femoral cartilage, and from 45.2 ms (2.4) to 43.1 ms (2.6) in the medial tibial cartilage, 1 year after HTO. The magnitude of T2 relaxation time shortening is similar to the present results (Table 4.2). The authors did not measure the T2 relaxation in the lateral tibiofemoral compartment or the patella.

Importantly, the present results were achieved with a relatively conservative approach to surgical correction of varus malalignment, where postoperative alignment (MAA) was approximately 1° valgus (Table 4.3). The present approach uses a considerably smaller correction compared to postoperative angles reported by Kanamiya et al12 (approximately 13° of valgus) and by Nishioka et al37 (6.3° of valgus). Although the present results suggest corrections to approximately neutral alignment can improve medial compartment articular cartilage composition without compromising the lateral compartment or patella at 1-year postoperative, longer term results are required.

In the present sample, the size of HTO correction angle was not associated with changes in T2 relaxation, and the observed shortening of T2 relaxation time was not statistically significantly different between subgroups of patients with the highest and lowest corrections. As indicated above, the size of corrections in this sample should be considered when interpreting this finding. The intent to restore the MAA to approximately neutral, rather than overcorrecting to an excessive valgus angle, appears enough to provide a regenerative stimulus to the articular cartilage of the medial compartment without compromising the lateral compartment or patella.
We observed very small changes in posterior tibial slope and patellar height that did not reach statistical significance and were not associated with changes in T2 relaxation in any knee compartment. Interestingly, there was a positive association between the postoperative posterior tibial slope and the increase in articular cartilage T2 relaxation of the lateral femoral compartment ($r = 0.48$, $p = 0.006$). That single association may be interpreted as decreasing lateral femur articular cartilage integrity after HTO in patients with steeper posterior tibial slope (Figure 4.3), and is consistent with attempts to minimize an increase in posterior tibial slope during medial opening wedge HTO\textsuperscript{15}. However, that finding must be interpreted with caution, as posterior tibial slope measures varied considerably and there were few patients with large postoperative values.

Strengths of the present study include the prospective assessment of articular cartilage composition in multiple knee compartments using a valid and reliable imaging measure that is predictive of OA progression\textsuperscript{40}. The T2 mapping sequence and segmentation of articular cartilage were performed using a widely accepted sequence. Post-processing was carried out using blinded scans, and repeated segmentations demonstrated high intra-rater reliability. Limitations in this study include the lack of a non-operative control group to allow comparisons to natural progression, or other treatments. It is possible that the change in T2 relaxation time was observed because of reasons other than surgical realignment, such as decreased in loading and activity during healing after surgery, or regression to the mean. Another limitation is only 1 year of follow-up and relatively small sample size.
A negative value indicates a shortening of T2 relaxation time. There were no statistically significant differences in the changes in T2 relaxation between subgroups.

<table>
<thead>
<tr>
<th>Difference</th>
<th>Mechanical Axis Angle &gt;2.2°</th>
<th>Mechanical Axis Angle &lt;0.3°</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correction angle</td>
<td>[mean (SD)]</td>
<td>[mean (95%CI)]</td>
</tr>
<tr>
<td>Lateral Femur T2</td>
<td>-2.0 [-5.8; 1.8]</td>
<td>-0.8 [-4.3; 2.6]</td>
</tr>
<tr>
<td>Lateral Tibia</td>
<td>0.3 [-1.2; 1.8]</td>
<td>0.7 [-4.4; 0.4]</td>
</tr>
<tr>
<td>Medial Femur T2</td>
<td>1.3 [-3.0; 5.6]</td>
<td>-1.4 [-3.9; 1.2]</td>
</tr>
<tr>
<td>Medial Tibia</td>
<td>-3.0 [-6.4; 3.9]</td>
<td>-1.4 [-3.9; 1.2]</td>
</tr>
<tr>
<td>Patella</td>
<td>-0.8 [-3.5; 1.9]</td>
<td>-0.8 [-3.5; 1.9]</td>
</tr>
</tbody>
</table>

**Table 4.5.** Correction angle subgroup comparisons for changes in T2 relaxation after HTO.
Although sample size was adequate for our primary objective, we lacked power to more confidently investigate subgroups of patients. We focused on articular cartilage composition as its degeneration is considered a hallmark of OA; however, several other structures are affected by the disease and could be influenced by HTO. For example, the menisci, bone marrow lesions, bone density, synovitis and bone shape have all been implicated in disease progression and should be investigated after HTO.

In conclusion, the present study suggests that in patients with medial compartment knee OA and varus malalignment, HTO improves medial compartment articular cartilage composition 1 year postoperatively, without altering the lateral compartment or patella. These findings are consistent with HTO being a disease modifying intervention for knee OA.
REFERENCES


CHAPTER 5 – Association between changes in knee load and effusion-synovitis: evidence of mechano-inflammation in knee osteoarthritis using high tibial osteotomy as a model

SUMMARY: Although mechanically-induced inflammation is an appealing explanation linking different etiologic factors in osteoarthritis (OA), clinical research investigating changes in both biomechanics and joint inflammation is limited. The purpose of this study was to evaluate the association between change in knee load and change in knee effusion-synovitis in patients with medial compartment knee OA undergoing high tibial osteotomy (HTO). Thirty-six patients with medial compartment knee OA and varus alignment underwent 3D gait analysis and 3T magnetic resonance imaging (MRI) preoperatively and 1 year after medial opening wedge HTO. Primary outcome measures were the change in knee adduction impulse and change in knee suprapatellar effusion-synovitis volume. Baseline means ± SD for knee adduction moment impulse and knee effusion-synovitis volume were 1.50 ± 0.33 and 8976.7 ± 8016.9 mm³, respectively. The changes [mean reductions (95%CI)] in knee adduction moment impulse [-0.65 %Bw•Ht•s (-0.81, -0.50)] and knee effusion-synovitis volume [-1856 mm³ (-3830, 117)] were positively associated [r = 0.61 (0.35, 0.78)]. Simple linear regression suggested an approximate 4000 mm³ reduction in knee effusion-synovitis volume for each 0.5-unit (%Bw•Ht•s) reduction in knee adduction moment impulse [unstandardized beta = 7983 mm³ (4389, 11577)]. Change in knee adduction moment impulse accounted for 36% (R² = 0.36) of the variance in change in knee effusion-synovitis volume. Reduction in medial knee load is positively associated with reduction in knee inflammation after HTO, demonstrating the phenomenon of mechano-inflammation in patients with knee OA.
INTRODUCTION

The etiology of osteoarthritis (OA) is complex and includes mechanical, biological and immune processes that affect the health of the entire joint-organ system. The high loads borne by the knee during ambulation make it particularly vulnerable to OA, and the knee joint is the most common site of the disease. Although OA is not an autoimmune disease, it frequently manifests signs of inflammation, including synovitis in early and later stages of disease. At the tissue level, synovitis manifests in OA as synovial hyperplasia with or without fibrosis, increased vascularity, inflammatory cell infiltration and joint effusion. Synovial membrane thickening and effusion identified on magnetic resonance imaging (MRI) is termed effusion-synovitis; it is readily demonstrated in the supra-patellar and para-patellar regions and is distinct from MRI signs of inflammation in the infra-patellar (Hoffa’s) fat pad (“Hoffa-synovitis”). Longitudinal cohort studies suggest knee effusion-synovitis is associated with the onset and progression of structural OA joint changes, including cartilage damage and bone marrow lesions. Longitudinal studies also suggest knee synovitis is associated with pain and pain sensitization in patients with knee OA. Moreover, limited evidence suggests change in knee synovitis in knee OA following corticosteroid injection is associated with change in pain and function.

Although mechanopathology can manifest variably in OA, aberrant loading at the knee due to lower limb frontal plane malalignment is common and is strongly associated with future structural damage and symptom progression. Medial compartment tibiofemoral OA is frequently observed in neutral and varus alignment because the knee adduction moment during walking distributes greater load medially, creating a feed-forward cycle of increased...
medial loading, medial joint damage and further varus alignment. The external knee moments derived from 3D gait analysis are independently associated with medial knee OA progression and increased pain after walking. There is also limited evidence suggesting change in gait biomechanics is associated with clinically important change in symptoms.

Medial opening wedge high tibial osteotomy (HTO) is a lower limb realignment surgery for patients with symptomatic OA primarily affecting the medial tibiofemoral compartment and varus alignment. The procedure aims to correct malalignment and thereby improve distribution of the dynamic loads on the knee. Conceptually, HTO is a biomechanical intervention that targets the underlying mechanical etiology in knee OA. Although the commonly proposed rationale for biomechanical interventions is that changing joint loads alters structural tissues including cartilage and bone, we propose there may also be effects on joint inflammation that are not well understood.

Defining the association between aberrant mechanics and local inflammation (mechano-inflammation) would be a key milestone in improving our overall understanding of the etiology of knee OA. As gait biomechanics and knee synovitis are both modifiable, an association between these measures would be highly relevant to the development and delivery of clinical interventions for OA. This could include the opportunity to define biological mechanisms of mechano-inflammation, which may inform the discovery of new treatment targets. Although mechano-inflammation is an appealing explanation linking etiological factors, we are unaware of any human studies directly investigating the
association of change in knee loading with change in knee inflammation in patients with OA. Therefore, the purpose of this study was to compare measures of dynamic knee loading and knee inflammation before and 1 year after medial opening wedge HTO and evaluate the association between the changes. Specifically, we aimed to test the hypothesis that a reduction in the knee adduction moment impulse measured during walking is positively associated with a reduction in knee effusion-synovitis volume measured on MRI.

METHODS

Study design
A subgroup of patients participating in an ongoing prospective cohort study investigating medial opening wedge HTO agreed to additional testing, including gait analyses and MRI (completed on the same day) preoperatively and 1-year postoperatively. Participants also agreed to the use of an osteotomy fixation plate that did not create metal artifact on MRI, or to have a more commonly used titanium plate removed before the postoperative visit. The first 36 patients with preoperative and 1-year postoperative gait and MRI data were analyzed based on 80% power to detect an association between change in knee load and change in knee effusion-synovitis as low as $r = 0.45$ with $\alpha = 0.05$. All participants provided informed consent. The study was approved by the institution’s Research Ethics Board for Health Science Research Involving Human Subjects.

Participants
We recruited patients referred to a tertiary care clinic for consultation with an orthopaedic surgeon regarding unresolved knee pain and/or decreased function. All patients met the
American College of Rheumatology clinical classification criteria for knee OA. Additionally, patients had varus alignment of the lower limb, with radiographic signs and symptoms of knee OA primarily affecting the medial tibiofemoral compartment. Patients with concomitant radiographic signs of OA in the lateral tibiofemoral and/or patellofemoral compartments were considered suitable candidates for HTO as long as radiographic joint space narrowing and pain were greatest in the medial tibiofemoral compartment. Patients who met all above criteria but were unwilling to undergo additional MRI scanning or remove metal fixation plates prior to 1-year follow-up were not considered for participation in the study.

**Intervention**

Participants underwent medial opening wedge HTO with internal fixation completed by one of five surgeons. The operative technique aimed to correct varus alignment to approximately neutral to very slight valgus alignment using methods similar to those previously described. The tibial osteotomy wedge was fixed using either a polyethyletherketone insert and screws, which did not produce artifact on MRI, or a titanium locking plate and cortical and cancellous screws. If a titanium fixation plate and screws were used, they were removed within 1 year after surgery and postoperative imaging was delayed at least 6 weeks after its removal. Early postoperative management included the use of a hinged brace and feather weight-bearing with crutches. Patients gradually increased weight-bearing based on clinical and radiographic evidence of healing of the osteotomy, typically progressing to one crutch within 6 weeks, full weight-bearing within 12 weeks, and resuming high-demand activities by 6 months. Patients completed a
rehabilitation protocol with exercise progressions and milestones reviewed on postoperative day 1, and 2-, 6-, and 12-week follow-up visits.

Gait Analysis

All participants completed 3D gait analysis using a 10-camera motion capture system (Motion Analysis Corporation, Santa Rosa, CA, USA), a modified Helen-Hayes reflective marker set, and floor-mounted force platforms (AMTI, Watertown, MA, USA), using valid and reliable methods sensitive to change after HTO\textsuperscript{30,31}. Patients walked barefoot across the laboratory while kinematic data (sampled at 60 Hz) and kinetic data (sampled at 600 Hz) were recorded for five trials of each limb. We calculated external moments about the knee in the frontal, sagittal and transverse planes, and peak moments in all respective planes, using an inverse dynamics model (Orthotrak 6.6.1; Motion Analysis Corporation, Santa Rosa, CA, USA) with a fixed tibia coordinate system (Cortex-64 5.0, Motion Analysis Corporation, Santa Rosa, CA, USA). Knee moments were normalized to bodyweight and height (%Bw•Ht) and normalized to 100% of stance phase, with the exception of the knee adduction moment impulse; a time-dependent outcome measure. For the knee adduction moment impulse, we calculated the integral (area under the curve) of the knee adduction moment waveform plotted over the time (%Bw•Ht•sec). We calculated the mean of five trials for each patient. Given its association with pain\textsuperscript{22} and disease progression\textsuperscript{20}, and its reduction after HTO\textsuperscript{24}, the knee adduction moment impulse was determined \textit{a priori} as the primary gait outcome measure.
Magnetic Resonance Imaging

All participants were scanned using a Siemens Magnetom Trio 3.0 Tesla magnet with a dedicated 15-channel Tx/Rx PRISMA knee coil. We used the 3D Dual-Echo Steady State (DESS) pulse sequence with fat suppression and water excitation, which enabled excellent contrast to identify effusion-synovitis. The 3D DESS sequence consists of 160 slices, with a slice thickness of 0.7 mm and 0.37×0.46 mm in-plane resolution (acquisition time 10.6 minutes). Example sagittal and axial slices obtained from the present dataset are presented in Figure 5.1.

![Figure 5.1](image)

**Figure 5.1.** Sagittal (a) and axial (b) views of 3D DESS sequences with white arrows indicating effusion-synovitis (hyperintense tissue posterior and superior and lateral to the patella).

One reader trained by a musculoskeletal radiologist and a rheumatologist measured suprapatellar effusion-synovitis volume by manual segmentation (3D Slicer, http://www.slicer.org)\(^{32}\). Using effusion-synovitis as a surrogate for synovial inflammation, we followed recommendations from previous investigators reporting repeatability and validity of the method\(^{33,34}\). We studied the suprapatellar pouch, as it is the most responsive synovial region of interest in the knee joint\(^{13}\). The reader segmented
borders of effusion-synovitis in the suprapatellar pouch of all knees in the sagittal view, then applied a signal intensity threshold for each image to eliminate hypointense tissue within the synovial volume. Upon completing segmentation in the sagittal view, the imaging plane was converted to the axial view to verify multiplanar accuracy of effusion-synovitis segmentation. Examples of sagittal and axial views of effusion-synovitis are presented in Figure 5.1. The reader carried out segmentations on paired images while blinded to timepoint. A separate investigator masked the evidence of HTO surgery on the tibia of both the preoperative and postoperative images and randomized the order of the paired images26.

To assess intra-rater reliability, the reader repeated segmentation of each preoperative and postoperative knee approximately 30 days after the first reading, in random order with all images being assigned new identification labels. To assess inter-rater reliability, a second rater segmented 10 pre-operative and 10 post-operative knees, selected at random.

**Statistical Analyses**

Baseline demographic and clinical characteristics for the sample were described using means and standard deviations for continuous data and frequencies and percentages for categorical data. We assessed the intra-rater and inter-rater reliability of the effusion-synovitis measurements by calculating separate intraclass correlation coefficients (ICC\(_{2,1}\)) for the preoperative and postoperative images. We calculated mean changes and 95% confidence intervals (95%CI) for all biomechanical variables and for effusion-synovitis. We plotted individual patient 1-year change scores (postoperative minus preoperative
value) for knee adduction moment impulse versus knee effusion-synovitis volume, including the linear line of best fit with mean 95% CIs. Given the proposed effects of changing knee load on changes in knee inflammation, simple linear regression of the change scores was then used to evaluate the association between the change in surrogate measures of knee load (predictor) and the change in knee effusion-synovitis volume (outcome) from baseline to 1-year after HTO. Given the gait data were normalized to body weight and height, we did not adjust for body mass index in the model. To test model assumptions, we visually inspected component-plus-residual plots for linearity, residual plots (e.g. Kernel density plot) for normality and residual-versus-predictor plots for homoscedasticity. Data were linear with normally distributed and homoscedastic residuals. We used Stata 16 statistical software (StataCorp LLC, College Station, TX).

**RESULTS**

Intra-rater and inter-rater reliability of effusion-synovitis measurements were excellent for both preoperative and postoperative knees (lower ends of all ICC 95% CI > 0.80) and was consistent with a previous study\(^{34}\). The participants’ baseline characteristics are reported in Table 5.1. Consistent with previous research in HTO, the majority of recruited patients were middle-aged males, overweight or obese, with varus alignment. Most patients had Kellgren and Lawrence grades 2 or 3.

The mean time (standard deviation) from preoperative to postoperative assessments was 13.3 (1.2) months. Mean changes for all measures are reported in Table 5.2. Mean knee effusion-synovitis volume, knee adduction moment impulse, first peak, and second peak
Table 5.1. Baseline characteristics (n = 36)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>53.6 (6.1)</td>
</tr>
<tr>
<td>Sex, no. (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>29 (80.6)</td>
</tr>
<tr>
<td>Female</td>
<td>7 (19.4)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>29.8 (4.2)</td>
</tr>
<tr>
<td>Mechanical axis angle, degrees a</td>
<td>-6.5 (2.4)</td>
</tr>
<tr>
<td>Kellgren &amp; Lawrence Grade, no. (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>1</td>
<td>4 (11.1)</td>
</tr>
<tr>
<td>2</td>
<td>11 (30.6)</td>
</tr>
<tr>
<td>3</td>
<td>21 (58.3)</td>
</tr>
<tr>
<td>4</td>
<td>--</td>
</tr>
<tr>
<td>OARSI Tibiofemoral Joint Space Narrowing Grade, no. (%)</td>
<td></td>
</tr>
<tr>
<td>Medial Compartment</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>1</td>
<td>11 (30.6)</td>
</tr>
<tr>
<td>2</td>
<td>13 (36.1)</td>
</tr>
<tr>
<td>3</td>
<td>12 (33.3)</td>
</tr>
<tr>
<td>Lateral Compartment</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>29 (80.6)</td>
</tr>
<tr>
<td>1</td>
<td>7 (19.4)</td>
</tr>
<tr>
<td>2</td>
<td>--</td>
</tr>
<tr>
<td>3</td>
<td>--</td>
</tr>
</tbody>
</table>

*Values are reported as means with standard deviations unless otherwise specified
a A negative mechanical axis value indicates varus alignment

Knee adduction moments decreased from baseline to 1 year after HTO. Individual patient changes in knee adduction moment impulse and knee effusion-volume are plotted in Figure 5.2. Change in knee adduction moment impulse was positively associated with change in knee effusion-synovitis volume \( r = 0.61 (0.35, 0.78) \) (Table 5.3). Simple linear regression suggested an approximate 4000 mm\(^3\) (95%CI: 2100, 5800) reduction in knee effusion-synovitis volume for each 0.5-unit (%Bw\*Ht\*s) reduction in knee adduction moment impulse (Table 5.3). The change in knee adduction moment impulse explained 37% of the
Figure 5.2. The association between 1-year changes in knee load (adduction moment impulse) and knee inflammation (effusion-synovitis volume). The line of best fit is black with mean 95% confidence intervals in grey.

Variance in change in knee effusion-synovitis volume over time ($R^2 = 0.37$). Reductions in 1<sup>st</sup> peak knee adduction moment and 2<sup>nd</sup> peak knee adduction moment were also associated with a reduction in knee effusion-synovitis volume, explaining 31% and 24% of the variance in change in knee effusion-synovitis volume, respectively (Table 5.3). Changes in flexion, extension, internal rotation, or external rotation were not significantly associated with changes in effusion-synovitis volume (Table 5.3). 
Table 5.2. Changes in knee effusion-synovitis volume, gait biomechanics and mechanical axis angle from baseline to 1-year after HTO (n = 36).

<table>
<thead>
<tr>
<th></th>
<th>Baseline (mean ± SD)</th>
<th>1-year (mean ± SD)</th>
<th>Mean change (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee Effusion-Synovitis Volume (mm³)</td>
<td>8976.7 ± 8016.9</td>
<td>7120.5 ± 6968.2</td>
<td>-1856.1 (-3829.5, 117.3)</td>
</tr>
<tr>
<td>Adduction Moment Impulse (%Bw·Ht·s)</td>
<td>1.50 ± 0.33</td>
<td>0.86 ± 0.35</td>
<td>-0.65 (-0.80, -0.50)</td>
</tr>
<tr>
<td>1st Peak Adduction Moment (%Bw·Ht)</td>
<td>3.00 ± 0.71</td>
<td>1.65 ± 0.65</td>
<td>-1.34 (-1.61, -1.07)</td>
</tr>
<tr>
<td>2nd Peak Adduction Moment (%Bw·Ht)</td>
<td>3.01 ± 0.66</td>
<td>1.94 ± 0.88</td>
<td>-1.07 (-1.39, -0.74)</td>
</tr>
<tr>
<td>Peak Flexion Moment (%Bw·Ht)</td>
<td>1.08 ± 1.23</td>
<td>1.44 ± 1.00</td>
<td>0.36 (0.04, 0.68)</td>
</tr>
<tr>
<td>Peak Extension Moment (%Bw·Ht)</td>
<td>-2.39 ± 1.14</td>
<td>-2.37 ± 1.04</td>
<td>0.02 (-0.41, 0.45)</td>
</tr>
<tr>
<td>Peak External Rotation Moment (%Bw·Ht)</td>
<td>0.01 ± 0.05</td>
<td>0.03 ± 0.05</td>
<td>0.02 (0.00, 0.04)</td>
</tr>
<tr>
<td>Peak Internal Rotation Moment (%Bw·Ht)</td>
<td>-1.20 ± 0.29</td>
<td>-0.81 ± 0.29</td>
<td>0.39 (0.29, 0.49)</td>
</tr>
<tr>
<td>Mechanical Axis Angle (°)</td>
<td>-6.51 ± 2.5</td>
<td>0.62 ± 3.0</td>
<td>7.13 (5.90, 8.47)</td>
</tr>
</tbody>
</table>

Abbreviations: Bw = bodyweight, Ht = height, SD = standard deviation, CI = confidence intervals
Table 5.3. Association between change in surrogate measures of medial knee load and change in knee effusion-synovitis volume. Results from simple linear regression analyses are shown (n = 36).

<table>
<thead>
<tr>
<th>Predictors:</th>
<th>Outcome: Knee effusion-synovitis volume (mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unstandardized β (95% CI)</td>
</tr>
<tr>
<td></td>
<td>Pearson Correlation Coefficient (95%CI)</td>
</tr>
<tr>
<td>Adduction moment impulse (%Bw•Ht•s)</td>
<td>7983 (4389, 11577)</td>
</tr>
<tr>
<td></td>
<td>0.61 (0.35, 0.78)</td>
</tr>
<tr>
<td>1st Peak Adduction Moment (%Bw•Ht)</td>
<td>4046 (1932, 6160)</td>
</tr>
<tr>
<td></td>
<td>0.56 (0.28, 0.75)</td>
</tr>
<tr>
<td>2nd Peak Adduction Moment (%Bw•Ht)</td>
<td>3055 (1094, 5107)</td>
</tr>
<tr>
<td></td>
<td>0.49 (0.19, 0.70)</td>
</tr>
<tr>
<td>Peak Flexion Moment (%Bw•Ht)</td>
<td>-478 (-2703, 1746)</td>
</tr>
<tr>
<td></td>
<td>-0.08 (-0.40, 0.26)</td>
</tr>
<tr>
<td>Peak Extension Moment (%Bw•Ht)</td>
<td>-60 (-1743, 1623)</td>
</tr>
<tr>
<td></td>
<td>-0.01 (-0.34, 0.32)</td>
</tr>
<tr>
<td>Peak External Rotation Moment (%Bw•Ht)</td>
<td>22135 (-15111, 59381)</td>
</tr>
<tr>
<td></td>
<td>0.21 (-0.12, 0.50)</td>
</tr>
<tr>
<td>Peak Internal Rotation Moment (%Bw•Ht)</td>
<td>-6036 (-12943, 871)</td>
</tr>
<tr>
<td></td>
<td>-0.30 (-0.57, 0.03)</td>
</tr>
<tr>
<td>Mechanical Axis Angle (degrees)</td>
<td>-434 (-924, 56)</td>
</tr>
<tr>
<td></td>
<td>-0.30 (-0.57, 0.03)</td>
</tr>
</tbody>
</table>

Abbreviations: Bw = bodyweight, Ht = height

DISCUSSION

The present findings suggest a substantial association exists between the change in medial knee load and the change in knee effusion-synovitis in patients with medial knee OA 1 year after undergoing HTO. These results provide evidence supporting the existence of a
dynamic process of mechano-inflammation in knee OA. The findings also support the need for future work investigating inflammation as a potential mediator between mechanopathology and OA progression, as well as a potential mediator between biomechanical interventions and treatment outcomes.

It is important to emphasize that while the present results provide evidence of mechano-inflammation, we cannot be certain that the changes were caused by HTO. As there was no control group, the changes in load and inflammation may be attributable to episodic changes in disease status, regression to the mean or unknown sources of change over time. Regardless of their cause, however, the present results strongly suggest a substantial association exists between changes in joint load and changes in joint inflammation. Our regression analysis suggested 37% of the variance in change in knee effusion-synovitis was explained by the change in knee adduction moment impulse; for each 1-unit reduction in knee adduction moment impulse there was a 7983mm³ reduction in knee effusion-synovitis. The regression analyses were also consistent when replacing the knee adduction moment impulse with other surrogate measures of medial compartment load during walking (i.e. first and second peak knee adduction moment; Table 5.3).

The observed magnitudes of change in these surrogate measures of knee load and inflammation should be considered carefully. As the knee adduction moment impulse was normalized to bodyweight and height, a 1-unit (%Bw•Ht•s) reduction in this measure of medial knee load represents a very large change. Describing the reduction in synovitis for
each half-unit (0.5 %Bw•Ht•s) or quarter-unit (0.25 %Bw•Ht•s) reduction in knee adduction moment impulse is prudent and still suggests a large change (approximately 4000 mm$^3$ and 2000 mm$^3$, respectively). Notably, the mean reductions in knee adduction moment impulse (-0.6 %Bw•Ht•s) and effusion-synovitis (-1856 mm$^3$) were large, yet the individual patient responses varied considerably (Figure 5.2). The causes of variability in the observed changes should be a focus of future research, including the effects of baseline disease activity and distinct OA phenotypes. Also, as the change in knee adduction moment impulse explained 36% of the variation in change in effusion-synovitis, there is clearly a need and opportunity to identify additional factors influencing the observed change in this form of inflammation.

Most studies investigating knee inflammation as a treatment target have evaluated the change in synovitis as a result of pharmacological interventions. For example, the mean decrease in synovial tissue volume was 1071 mm$^3$, and mean decrease in synovial fluid volume was 853 mm$^3$, 3 weeks after knee intra-articular corticosteroid injection, measured using contrast-enhanced MRI$^{15}$. Importantly, patients classified as responders according to the OARSI criteria experienced changes in synovial tissue volume of -1474 mm$^3$ and synovial fluid volume of -1045 mm$^3$ and provide some indication of what a clinically meaningful change in synovitis may be. We observed a large mean reduction in effusion-synovitis (1856 mm$^3$) 1 year after an intervention intended to improve knee biomechanics rather than directly targeting inflammation. However, we did not investigate the association of change in effusion-synovitis with symptoms. Although our data suggest the load-altering effects of HTO may provide benefits in part through a reduction in mechano-inflammation,
larger studies are needed to assess the clinical importance and potential mechanisms related to the present findings.

Previous studies that assessed knee synovitis on MRI using semi-quantitative measures after weight change are also relevant. In patients with knee OA having lost $\geq 20\%$ of their bodyweight with either bariatric surgery or dietary intervention, no difference was observed in synovitis between baseline and 1-year follow-up\textsuperscript{35}. Similarly, no difference in synovitis was observed between women with knee OA who’s bodyweight either remained stable, or decreased by 10 kg over the course of a year, with a group that gained 10 kg experiencing an increase in synovitis\textsuperscript{36}. Also, in patients with knee OA having lost $>5\%$ bodyweight over 8 weeks, there was no association between weight loss and changes in synovitis\textsuperscript{37}. As weight-loss lessens load on the knee and improves symptoms, it is unclear why changes in synovitis were not observed. Differences in synovitis measurement methods, patient characteristics and the interventions may all contribute to the different results.

To our knowledge, this is the first study to directly investigate the association between measured changes in joint loading and joint inflammation in patients with OA. The present results are consistent, however, with changes in synovial fluid markers of inflammation observed after 6 weeks of knee joint distraction surgery\textsuperscript{38}. Both studies observed changes in knee inflammation after interventions that alter knee joint loads and both studies contribute to our understanding of mechano-inflammation in OA. Knee inflammation is likely stimulated in part by mechanical and enzymatic disruption of articular cartilage, releasing cartilage matrix degradation products including enzymatic cleavage fragments.
into the joint space\textsuperscript{39,40}. Matrix degradation products may trigger a cascade of inflammation (e.g. binding to Toll-like receptors on synovial macrophages and fibroblasts), recruitment of inflammatory cells from the periphery, and production of additional inflammatory cytokines and proteases that may perpetuate cartilage degradation\textsuperscript{11,41}. Studies that demonstrate reductions in knee inflammation after mechanical interventions suggest these mechano-inflammatory processes can be modified and may help to inform the development and delivery of clinical interventions for OA. This could include the opportunity to define biological mechanisms of mechano-inflammation along with the discovery of new, more specific treatment targets\textsuperscript{25}.

Limitations in this study include the lack of other MRI markers of knee inflammation, such as bone marrow lesions and other regions of interest such as the infra-patellar fat pad ("Hoffa-synovitis"). Contrast-enhanced MRI methods may have provided additional information with respect to synovial thickening and vascularization, which may have provided an even better assessment of the inflammatory state of synovial tissue\textsuperscript{42} and its association with joint loading. Repeated manual segmentation of MRI features is the current gold standard for quantitative MRI assessment in knee joints but can be subject to reader biases and measurement error. The validated MRI blinding method\textsuperscript{26} and very high intra-rater and inter-rater reliability coefficients suggest we limited those possibilities. The external knee moments during walking are surrogate measures of the actual loads on the joint and may not detect the true extent of biomechanical changes. Consideration of those limitations should be weighed against the substantial association observed between the present reliable and valid surrogate measures of knee load and knee inflammation. The
present sample included mostly males with medial compartment knee OA; it is unclear whether the observed association differs between males and females or with other forms of OA. While the present results provide compelling evidence supporting the existence of mechano-inflammation in patients with knee OA, and that this may be a modifiable process, the clinical importance of the observed association between changes in knee loading and effusion-synovitis requires future research.
REFERENCES


CHAPTER 6 – Thesis summary and general discussion

The purpose of this discussion chapter is to summarize the results of each study in the thesis and provide an understanding of its overall findings. New knowledge gained from each study is discussed and interrelated, and the findings and limitations of the overall thesis are described with the intent to improve future research. Strengths and limitations are reviewed, and suggestions about how imaging might be used as a research tool and as a component of clinical care in OA are suggested. This discussion aims to help clarify how quantitative MRI may be used to improve the assessment of progression for patients with or at risk for knee OA, and ultimately improve treatment outcomes.

Thesis Overview

This thesis had four distinct but related objectives: 1) identify if differences in biochemical composition of knee articular cartilage exist in patients at risk for knee OA compared to healthy controls, 2) explore the acute response of knee articular cartilage to dynamic, functional load in patients at risk for knee OA compared to healthy controls, 3) evaluate the long-term response of knee articular cartilage composition after surgical realignment of the lower limb, and 4) understand the inflammation response within the knee joint to long-term changes in dynamic load after realignment of the lower limb. Overall, the common theme was to understand how quantitative MRI can be used to assess interventions and treatments and their effects on structural progression of knee OA at various stages of disease.
Chapter 2 (Study 1): This systematic review and meta-analysis demonstrated that significant differences exist in cartilage composition in patients presenting with risk factors for knee OA prior to any radiographic evidence when compared to healthy asymptomatic controls. Using effect sizes allowed us to compare healthy and at-risk populations across studies despite differences in MRI scanning, processing, and analysis protocols across the literature. Clarifying that differences in cartilage composition exist at such an early stage of disease (arguably prior to disease depending on which definition is used) strengthens the case for compositional MRI measures like T2 and T1ρ relaxation as potential diagnostic and prognostic imaging biomarkers in knee OA. This work may encourage more standardized imaging methods to allow for clinical comparisons between patients, or working towards a “t-score” of articular cartilage composition T2 or T1ρ, much like what is used in osteoporosis; providing age-adjusted bone mineral density t-scores to assess risk for osteoporotic fractures, used alongside other predictors and risk factors to calculate the risk of osteoporotic fracture.

Chapter 3 (Study 2): This study assessed the acute T2 relaxation response of articular cartilage to acute loading in patients with risk factors for knee OA and healthy controls, adding another dimension to the previous study, now assessing the functional performance of articular cartilage. Among this “at-risk” sample were patients who had suffered ACL rupture, meniscal tears, articular cartilage lesions, or had frequent pain without radiographic progression. This novel, standardized functional loading stimulus evoked consistent, demonstrable changes in compositional MRI measures of knee articular cartilage. However, we found that compared to asymptomatic healthy controls, there was
no difference in articular cartilage response to this acute 25 minute bout of loading. This may suggest that the function of articular cartilage at this stage of disease has yet to be compromised, and that moderate intensity exercise is safe to pursue (i.e. poses no additional risk to the articular cartilage function) in these patients. This finding supports that patients with risk factors for knee OA follow regular exercise guidelines, which is at minimum, to achieve 150 minutes per week of moderate-to-vigorous physical activity per week to reduce the risk of health complications\(^1\). More research should focus on the response of other tissues within the knee joint to acute loading, as the at-risk patients did experience a significant increase in pain, suggesting that other mechanisms are involved, and that articular cartilage isn’t the only important tissue in patients at risk for knee OA.

Chapter 4 (Study 3): This prospective cohort study evaluated changes in articular cartilage composition in the medial and lateral tibiofemoral compartments and the patella before, and 1 year after HTO, to determine the longitudinal articular cartilage response to lower limb realignment. We evaluated if correcting varus alignment to shift loads laterally caused favourable changes in the medial tibiofemoral compartment, yet unfavourable changes in the lateral tibiofemoral compartment and/or the patella. We found that T2 relaxation in the medial tibia and femur were significantly shortened at 1 year compared to baseline, indicating improved cartilage composition, with no significant change in the lateral compartment or patella. Further, we explored if the size of alignment correction influenced the articular cartilage response by comparing the groups with the largest corrections and smallest corrections. We found no difference. Overall, the findings suggest that HTO improves knee joint tissue integrity on a biochemical level in the targeted treatment
compartment, without compromising the rest of the joint. Further research should focus on longer-term follow up and the functional response of the articular cartilage much like what was performed in Study 2 of this thesis.

Chapter 5 (Study 4): This prospective cohort study explored the relationship between changes in effusion-synovitis and changes in load distribution in the knee during gait, using HTO as a model to induce changes in load. Effusion-synovitis was reliably measured using MRI, and knee loads were measured using the external knee adduction moment impulse to act as a surrogate for medial compartment knee loads throughout stance. We found a significant positive relationship between changes in knee load and changes in effusion-synovitis over the course of the year, indicating that there is a relationship between the loading environment and local inflammation within the joint, with greater changes in load resulting in proportionate changes in effusion-synovitis. This study provided evidence for the first time in humans that mechano-inflammation is a real phenomenon and also that it can be treated with biomechanical intervention. Future research should focus on evaluating longer term changes, and studying other means of altering loads such as valgus bracing, lateral heel wedges, gait retraining and exercise.

**Role of quantitative MRI in research and practice**

The chapters in this thesis all use aspects of quantitative MRI as research tools to evaluate the effect of interventions on structural outcomes. Research may be the best current use for quantitative MRI, but hopefully efforts like the present thesis will encourage the eventual clinical use of these measures. The reason quantitative MRI is so highly used in knee OA
research is because it is more sensitive to changes in disease status and structural progression compared to radiographs. This may be the case at all stages of disease, but is especially true at the earlier stages, where most changes occur in soft tissues like articular cartilage, synovium, meniscus, or subchondral bone, and where radiographs would fail to identify these disease features\(^2\). Quantitative MRI is therefore required for studies evaluating the effect of potential disease modifying interventions (eg, drugs, surgery, or exercise), that would take several years to complete if the primary outcome was change in disease status measured by radiographs\(^3\).

**Future Applications of quantitative MRI in knee OA**

The future of quantitative MRI in both clinical and research settings remains to be established. In clinical radiology, specific quantitative measures are often reduced to subjective scales, as the application of segmentation to every image that had the potential for quantitative applications would cost excessive time and money. With the advent of artificial intelligence and machine learning, specific quantitative measures will soon be feasible and rapidly available. Time will tell how long it will take for these measures to be adopted in clinic, and it will also depend on the progress made by scientists in determining the measurement properties of quantitative MRI outcomes in knee OA. The synovitis measure used in Chapter 5 is an example that could be readily used in clinical practice with the aid of machine learning. This and other measures could be quickly adopted in-clinic once they are automated, as they are a simple volume of fluid that can be computed based on the geometry of the scan and the signal intensity of the effusion-synovitis with no reason to be unreliable between scanners or patients.
Compositional MRI has some challenges to overcome prior to its potential for clinical adoption. Firstly, there is no clinically important change or threshold that has been identified using T2, T1ρ relaxation, or otherwise, and the test-retest reliability of two separate scans on the same knee is unknown. The expectation for the clinical application is to have a similar approach to osteoporosis care, where patients are scanned and a t-score of their bone mineral density compared to their age-matched database is presented, and that t-score is considered along with other measures to determine the patient’s risk of osteoporotic fracture, and treatment decisions are made based on the overall risk². Another application is the inclusion of compositional MRI measures of articular cartilage in routine knee MRI exams, as the inclusion of a T2 mapping scan increases the sensitivity and specificity of radiologists ability to detect cartilage lesions⁵.

Before any of these advancements can happen, cross-comparability of a variety of imaging parameters need to be addressed. The effect of magnet strength⁶, manufacturer⁷, radiofrequency coil⁸, pulse sequence⁹, software upgrades¹⁰, and segmentation technique¹¹ all impact the end product of relaxation time of articular cartilage, often by a greater amount than what is deemed a significant difference between at-risk and healthy control patients, rendering the comparison of one dataset to another challenging at best, especially without a reference standard of healthy control participants. This was demonstrated in Chapter 2 of this thesis; without the inclusion of studies involving healthy control groups, that meta-analysis would not have been possible, and comparisons between studies would have been futile.
Ongoing efforts on this front include the use of calibration phantoms, which allow the scanner to be calibrated such that the scanner will have the intended relaxation time output for various tissues or solutions within the phantom\textsuperscript{12}. This is an acceptable solution in theory, however technical radiology teams are far too busy to be calibrating scanners for every patient receiving a knee MRI. A more efficient solution would be to compare known groups between two or more scanner setups, keeping all parameters in mind, and calculating the offset between them to allow for an automated workflow of post-scan corrections to allow for direct comparison between scanners and coils\textsuperscript{13}. Ideally the segmentation would be performed by a highly reliable algorithm developed through machine learning to eliminate inconsistencies in human error, and of course to save time. The final product would be an algorithm with many variables included in the model, such as magnet strength, manufacturer, radiofrequency coil, pulse sequence, etc. to simply compute a correction factor to bring the relaxometry data to be comparable with some gold standard. This will require several contributory studies from research imaging centres across the globe, however the benefit will be that all future and past cartilage relaxometry data will be comparable, whereas the use of calibration phantoms only allows the comparison of studies that used a calibration phantom.

**Strengths & Limitations**

This thesis includes strengths and limitations in the design and execution of all included studies. Strengths of Chapter 2 include the comparison of differences in T2 and T1\(\rho\) relaxation across studies using meta-analysis and standardized mean differences, establishing effect sizes that can be used as standardized references for region-specific
differences in T2 and T1ρ relaxation between patients and healthy controls. Strengths of Chapter 3 include the use of a standardized functional loading stimulus and peri-scanning protocol to limit confounding variables on the effect of load on articular cartilage composition, as well as being the first study to compare the acute response of articular cartilage in healthy controls and patients at risk for knee OA. Strengths of Chapter 4 include the analysis of all potentially implicated compartments in the knee joint due to lower limb realignment. Strengths of Chapter 5 include the use of HTO as a model, a technique known to effectively change joint loads, as a model to study interaction between long-term changes in load and local joint inflammation. Overall strengths of the study include the use of valid, non-invasive imaging measures to study in vivo changes in composition and volume of soft tissues related to load and risk factors in in patients with and at risk for knee OA.

Limitations of Chapter 2, and of the entire field of study of compositional MRI of articular cartilage, include the lack of a standardized threshold or minimal clinically important difference in T2 or T1ρ relaxation time that can be used to interpret the effect of interventions. Future studies with large databases should study the associations between changes in T2 relaxation time with the presence of symptoms, risk factors, or other structural changes within the knee joint. Limitations of Chapter 3 include the heterogeneity of the at-risk group, having recruited participants with a variety of risk factors rather than one specific risk factor for knee OA, as well as the possibility that some patients may have actually presented with radiographic knee OA, but were included based on clinical symptomatic criteria that were below the threshold to be diagnosed with knee OA. Another limitation in Chapter 3 was that patients in the at-risk group did not present with
significantly longer T2 relaxation time at baseline as Chapter 2 would suggest they should. Perhaps an increased response to knee loading would have been observed if differences between groups existed at baseline. Limitations of Chapters 4 and 5 include a lack of a nonoperative or naturally progressing control group, limiting our ability to explain the effect of realignment and changes in load when comparing to no intervention, and leaving open the possibility that the results observed may have been due to confounding factors or regression towards the mean. Another general limitation is the greater proportion of male participants in Chapters 3, 4, and 5. Although it is expected that a greater proportion of males elect to receive HTO surgery, as varus alignment is more common in men, women with varus alignment still undergo HTO for medial compartment knee OA. It would be ideal if they were better represented in the sample to allow for the analysis of sex differences in the inflammatory and cartilage composition response to changes in load and alignment.

Finally, as a general limitation to the thesis, we only evaluated changes in cartilage composition and synovitis, leaving several other tissues to be studied, including bone, meniscus, ligaments, and musculature, each playing an important role in the progression and prevention of knee OA. Future studies should take these limitations into account to improve the internal and external validity of imaging studies in knee OA. As discussed, OA is a disease of the entire joint, and structural changes related to disease progression and treatment are likely not isolated to a single tissue. As we gain knowledge of individual tissue responses to progression and treatment with increasing detail and understanding, we
should begin to study the interactions between these tissue types to improve our ability to treat the joint as an organ.

**Conclusions**

This thesis used quantitative MRI measures of articular cartilage relaxometry and effusion-synovitis volume to investigate the effect of various loading stimuli on soft-tissues within the knee. New knowledge was gained surrounding the differences between patients at risk for knee OA and healthy controls. Under static conditions, patients at risk for knee OA have increased T2 and T1ρ relaxation time, meaning relaxometry could be used to identify features of disease at very early stages, allowing for earlier intervention. Under dynamic loading conditions, there were no differences in cartilage response in patients at-risk for knee OA and healthy controls, suggesting there is no increased risk to the articular cartilage with moderate exercise for patients at-risk for knee OA. Looking more at longer-term changes in load using HTO, significant improvements were observed in articular cartilage in the most affected compartment with joint realignment, with no additional risk to the unaffected knee compartments. Finally, with the same intervention, a significant positive relationship was identified between the change in load on the medial compartment of the knee and the change in local inflammation, meaning that load is a contributor to inflammation, and that treating aberrant loading can alter the inflammatory pathway. Without quantitative MRI, none of these findings would have come to light. With this new knowledge, we can move forward with advancing quantitative MRI applications, and make efforts to one day have the ability to directly compare data across the globe to assess knee OA risk and progression. For now, quantitative MRI will continue to serve as an excellent
research tool to evaluate the effect of interventions and study the mechanopathology of knee OA.
REFERENCES


APPENDICES

Appendix A. Pre-programmed protocol (in minutes) for the dynamic functional loading stimulus. Any gaps between times (e.g.: between 6:00 and 6:10) are filled with level walking at the participant’s self-selected gait speed.

-6:00-0:00 Acclimation period, finding self-selected speed (level walking)
0:00-1:00 level walking preferred speed
1:00-1:30 level walking 110% preferred speed
1:30-3:00 treadmill side-to-side sway
3:10-3:12 left belt acceleration perturbation (intensity 2)
3:20-3:22 right belt deceleration perturbation (intensity 2)
3:30-3:32 sway left perturbation (intensity 2)
3:40-3:42 sway right perturbation (intensity 2)
3:50-3:52 pitch forward perturbation (intensity 2)
4:00-4:02 pitch backward perturbation (intensity 2)
4:10-4:12 right belt acceleration perturbation (intensity 2)
4:20-4:22 left belt deceleration perturbation (intensity 2)
4:30-6:00 incline walking
6:10-7:40 decline walking
7:50-9:00 front-to-back sway
9:30-10:30 level walking 120% preferred speed
10:30-12:00 treadmill side-to-side sway
12:10-12:12 right belt acceleration perturbation (intensity 4)
12:20-12:22 pitch backward perturbation (intensity 4)
12:30-12:32 sway right perturbation (intensity 4)
12:40-12:42 left belt deceleration perturbation (intensity 4)
12:50-12:52 pitch forward perturbation (intensity 4)
13:00-13:02 sway left perturbation (intensity 4)
13:10-13:12 left belt acceleration perturbation (intensity 4)
13:20-13:22 pitch backward perturbation (intensity 4)
13:30-15:00 incline walking
15:10-16:40 decline walking
16:50-18:00 front-to-back sway
18:20-19:00 level walking at preferred speed
Appendix B. Ethics Approval

Western Research

Date: 3 June 2020

Ten: Trevor Cunningham
Project ID: 109126

Study Title: The qMRI Response of Knee Articular Cartilage to a Functional Gut Knee-Loading Stimulus

Application Type: Continuing Ethics Review (CER) Form

Review Type: Delegated

REB Meeting Date: 16/Jan/2020
Date Approval Issued: 05/Jan/2020
REB Approval Expiry Date: 09/Jan/2021

Dear Trevor Cunningham,

The Western University Research Ethics Board has reviewed the application. This study, including all currently approved documents, has been re-approved until the expiry date noted above.

REB members involved in the research project do not participate in the review, discussion or decision.

Western University REB operates in compliance with, and is constituted in accordance with, the requirements of the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonization Good Clinical Practice Consolidated Guidelines (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPPA 2004) and its applicable regulations. The REB is registered with the U.S. Department of Health & Human Services under the REB registration number REB 00000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,

Daniel Wysoki, Research Ethics Coordinator, on behalf of Dr. Joseph Gilbert, HSERB Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).
HAYDEN F. ATKINSON

EDUCATION

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PEER-REVIEWED JOURNAL ARTICLES


PEER-REVIEWED ABSTRACTS


**ORAL PRESENTATIONS**

Atkinson, H. F. T2 relaxation response of knee articular cartilage to a challenging dynamic loading stimulus in patients at risk for OA and healthy controls. *International Workshop for Osteoarthritis Imaging, Charlottetown, PE, 2019*

Atkinson, H. F. Acute compositional MRI response of medial tibiofemoral articular cartilage to challenged walking. *Canadian Society for Biomechanics, Halifax, NS, 2018*


**POSTER PRESENTATIONS**

Atkinson, H. F. Effect of high tibial osteotomy on knee articular cartilage composition and effusion synovitis. *Osteoarthritis Research Society International World Congress, Vienna, Austria, 2020 (Canceled due to COVID-19).*


FUNDING

2020-2021. Transdisciplinary Bone & Joint Postdoctoral Training Award: $10,000.
2019-2020. Ontario Graduate Scholarship: $15,000.
2018-2019. Ontario Graduate Scholarship: $15,000.
2017-2018. Ontario Graduate Scholarship: $15,000.
2016-2020: Transdisciplinary Bone & Joint Training Award: $10,000/annum.
2015: Science Undergraduate Research Award. Funds Awarded: $4250.
2015: CIHR Health Professional Student Research Award. Declined.

ONGOING RESEARCH


RESEARCH HISTORY

2015-2020 Doctor of Philosophy
Wolf Orthopaedic Biomechanics Laboratory, Western University

Apr-Aug 2015 Undergraduate Research Assistant
Faculty of Applied Humans Sciences, University of PEI

TEACHING

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