BIOMECHANICAL AND CLINICAL FACTORS INVOLVED IN KNEE OSTEOARTHRITIS PROGRESSION

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BIOMECHANICAL AND CLINICAL FACTORS INVOLVED IN THE PROGRESSION OF KNEE OSTEOARTHRITIS

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LAY ABSTRACT

Knee osteoarthritis is a multifactorial disease whose progression involves worsening joint structure, symptoms, and mobility. Various factors are linked to the progression of this disease, including biomechanical, patient-reported outcome and mobility measures. This thesis provides important information on how these factors, separately and collectively, are involved in worsening disease over time, as well as benchmarks that are useful to clinicians and researchers in interpreting results from interventional or longitudinal research. First, we examined how different elements of knee loading were associated with changes in knee cartilage quantity over time in persons with knee osteoarthritis. Second, we examined how different elements of knee muscle capacity and patient-reported outcomes were related to changes in mobility over time in persons with knee osteoarthritis. Third, we examined the stability over time of various biomechanical risk factors for the progression of knee osteoarthritis. Novel results from this thesis showed that: (1) larger knee loads predicted cartilage loss over 2.5 years in obese individuals with knee osteoarthritis but not in persons of normal weight or overweight; (2) among women with knee osteoarthritis with lower self-efficacy (or confidence), lesser knee muscle capacity (strength, power) was an important predictor of declining stair-climbing performance over 2 years; and (3) clinical interventions that can positively alter knee biomechanics include weight loss, knee muscle strengthening, as well as specific knee surgery and alterations during walking to reduce knee loads. Interventions for knee osteoarthritis should target biomechanical and clinical outcomes simultaneously.

ABSTRACT

Background: Knee osteoarthritis is a degenerative disease characterized by damaged joint tissues (e.g., cartilage) that leads to joint pain, and reduced mobility and quality of life. Various factors are involved in disease progression, including biomechanical, patient-reported outcome and mobility measures. This thesis provides important longitudinal data on the role of these factors in disease progression, and the trajectory of biomechanical factors in persons with knee osteoarthritis.

Objectives: (1) Determine the extent to which changes over 2.5 years in knee cartilage thickness and volume in persons with knee osteoarthritis were predicted by the knee adduction and flexion moment peaks, and knee adduction moment impulse and loading frequency. (2) Determine the extent to which changes over 2 years in walking and stair-climbing mobility in women with knee osteoarthritis were predicted by quadriceps strength and power, pain and self-efficacy. (3) Estimate the relative and absolute test-retest reliabilities of biomechanical risk factors for knee osteoarthritis progression.

Methods: Data were collected at 3-month intervals during a longitudinal (3-year), observational study of persons with clinical knee osteoarthritis (n=64). Magnetic resonance imaging of the study knee was acquired at the first and last assessments, and used to determine cartilage thickness and volume. Accelerometry and dynamometry data were acquired every 3 months, and used to determine knee loading frequency and knee muscle strength and power, respectively. Walking and stair-climbing mobility, as well as pain and self-efficacy data, were also collected every 3 months. Gait analyses were performed every 6 months, and used to calculate lower-extremity kinematics and kinetics.

Results: (1) The knee adduction moment peak and impulse each interacted with body mass index to predict loss of medial tibial cartilage volume over 2.5 years. These interactions suggested that larger joint loads in those with a higher body mass index were associated with greater loss of cartilage volume. (2) In women, lower baseline self-efficacy predicted decreased walking and stair ascent performances over 2 years. Higher baseline pain intensity/frequency also predicted decreased walking performance. Quadriceps strength and power each interacted with self-efficacy to predict worsening stair ascent times. These interactions suggested that the impact of lesser quadriceps strength and power on worsening stair ascent performance was more important among women with lower self-efficacy. (3) Relative reliabilities were high for the knee adduction moment peak and impulse, quadriceps strength and power, and body mass index (i.e., intraclass correlation coefficients >0.80). Absolute reliabilities were high for quadriceps strength and body mass index (standard errors of measurement <15% of the mean). Data supported the use of interventions effective in reducing the knee adduction moment and body mass index, and increasing quadriceps strength, in persons with knee osteoarthritis.

Conclusion: Findings from this thesis suggest that biomechanical factors play a modest independent role in the progression of knee osteoarthritis. However, in the presence of other circumstances (e.g., obesity, low self-efficacy, high pain intensity/frequency), biomechanical factors can vastly worsen the disease. Strategies aiming to curb structural progression and improve clinical outcomes in knee osteoarthritis should target biomechanical and clinical outcomes simultaneously.

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had reviewed them with a critical eye. Dr. Potvin, I can truly say that you were my favourite Biomechanics teacher. You have an unmatchable teaching style that captivated and inspired me. You not only taught important and complex biomechanical concepts in a way that was easily assimilable but you created an enjoyable learning environment that facilitated fruitful discussions and always ensured that I correctly grasped each concept. I will never forget your flip-it-and-reverse-it nivtopj T-Rex arms.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
6MWT	Six Minute Walk Test
ASES	Arthritis Self-Efficacy Scale
BLOKS	Boston Leeds Osteoarthritis Knee Score
BMI	Body Mass Index
dGEMRIC	Delayed Gadolinium Enhanced Magnetic Resonance Imaging of Cartilage
ICC	Intraclass Correlation Coefficient
ICOAP	Intermittent and Constant Osteoarthritis Pain Measure
K-L	Kellgren-Lawrence
KAM	Knee Adduction Moment
KFM	Knee Flexion Moment
KOOS	Knee Injury and Osteoarthritis Outcome Score
MDC95	Minimal Detectable Change at the 95% Confidence Level
MOAKS	MRI Osteoarthritis Knee Score
MRI	Magnetic Resonance Imaging
MVIC	Maximum Voluntary Isometric Contraction
OA	Osteoarthritis
PRO	Patient-Reported Outcome
SD	Standard Deviation
SEM	Standard Error of Measurement
SPGR	Spoiled Gradient Recalled
WOMAC	Western Ontario and McMaster Universitites Osteoarthritis Index
WORMS	Whole-Organ Magnetic Resonance Imaging Score

DECLARATION OF ACADEMIC ACHIEVEMENT

This thesis is the original work of Nicholas M. Brisson, Doctor of Philosophy Candidate in the School of Rehabilitation Science at McMaster University. Data enclosed in this thesis were collected from 2012–2016 during a longitudinal, observational study of one convenience sample of individuals with clinical knee osteoarthritis. Study participants (n=64) were recruited from local rheumatology and orthopaedic surgery offices. This prospective cohort was followed for approximately three years. Over this duration, data were collected at 3-month intervals for each participant. Magnetic resonance imaging scans of the study knee were acquired at the first and last assessments. Accelerometry and dynamometry data, as well as performance-based measures and patient-reported outcomes were collected every 3 months. Gait data were collected every 6 months.

This thesis is comprised of five chapters, the contents of which are described below. Mr. Brisson is the primary author of this document, including the three distinct manuscripts contained within. Mr. Brisson was part of a team responsible for executing this longitudinal research, and his specific contributions included: development of research questions and literature reviews for each distinct manuscript; data acquisition; data processing/reduction; data analysis and interpretation; and preparation of manuscripts.

The first chapter of this thesis is an introductory chapter that presents, in an integrated fashion, the overall context, key topics and relevant literature, as well as the rationales and objectives of this work.

The second chapter of this thesis (first manuscript) describes a study that examined the link between joint mechanics and longitudinal changes in cartilage morphology in knee OA. This manuscript has been published in the *Journal of Orthopaedic Research*. The full reference is as follows: **Brisson, N. M.**, Wiebenga, E. G., Stratford, P. W., Beattie, K. A., Totterman, S., Tamez-Peña, J. G., Callaghan, J.P., Adachi, J.D., Maly, M. R. (2017). Baseline knee adduction moment interacts with body mass index to predict loss of medial tibial cartilage volume over 2.5 years in knee osteoarthritis. *Journal of Orthopaedic Research*, 1–8. doi.org/10.1002/jor.23564

The third chapter of this thesis (second manuscript) describes a study that examined the association between each of muscle capacity, pain and self-efficacy with longitudinal changes in mobility performance in knee OA. This manuscript is intended for future publication, and is currently formatted for submission to *Clinical Rheumatology*.

The fourth chapter of this thesis (third manuscript) describes a study that estimated test-retest reliabilities of biomechanical factors associated with knee OA progression. This manuscript is currently undergoing review in *Osteoarthritis and Cartilage*. Submission information is as follows: **(Under review) Brisson, N. M.**, Stratford, P. W., Maly, M. R. (2017). Relative and absolute test-retest reliabilities of biomechanical risk factors for knee osteoarthritis progression: benchmark for meaningful change. *Osteoarthritis and Cartilage*; 30 pages. Manuscript number OAC8132.

The fifth chapter of this thesis is a discussion and conclusion chapter that summarizes the main findings and draws out the overall implications of the research, acknowledges study limitations and identifies potential future directions of research.

The following individuals were important contributors to this thesis work. Dr. Monica R. Maly was the thesis Supervisor and Principal Investigator who acquired funding for this research; lead study conception and design; advised on all research questions; was involved in the acquisition, analysis and interpretation of data; and critically revised all three manuscripts prior to publication. Professor Paul W. Stratford was a PhD Supervisory Committee Member who provided expertise in knee osteoarthritis research and guidance in statistical methods; contributed to the study conception and design; advised on all research questions; supported the analysis and interpretation of data; and critically revised all three manuscripts prior to publication. Dr. Karen A. Beattie was a PhD Supervisory Committee Member who provided expertise in knee osteoarthritis research and guidance in musculoskeletal imaging; contributed to the study conception and design, and data acquisition; and critically revised all three manuscripts prior to publication. Dr. Jim R. Potvin was a PhD Supervisory Committee Member who provided expertise and guidance in musculoskeletal modelling, and biomechanics concepts and methodologies; and contributed to the interpretation of data. Dr. Saara Totterman and Dr. José G. Tamez-Peña were collaborators from Qmetrics Technologies who contributed to the analysis and interpretation of radiographic and magnetic resonance imaging data; and critically revised the first manuscript prior to publication. Dr. Jonathan D. Adachi was a collaborator who provided access to patients and imaging equipment

required to carry out the research project; contributed to the study conception and design; and critically revised the first manuscript prior to publication. Dr. Jack P. Callaghan contributed to the study conception and design; and critically revised the first manuscript prior to publication. Emily G. Wiebenga, Christine Dibblee, Neha Arora and Dr. Kristina M. Calder helped with participant scheduling, equipment setup, data collection and data management required for this longitudinal research. Anthony Gatti and Brittany Bulbrook helped with processing of motion capture and dynamometry data.

CHAPTER 1

INTRODUCTION

This thesis focused on osteoarthritis (OA) of the knee, a complex disease mainly due to its multifactorial nature. The progression of knee OA can be characterized according to any one of its elements: be it changes in joint structures, symptoms or mobility; where each element reflects a different disease process. What further complicates our understanding of OA progression is that there exist various disease trajectories: some patients may experience worsening, no change, or improvements over time in diverse aspects of the disease. The overarching objective of this thesis was to investigate the role of various factors involved in the progression of knee OA, as well as the different consequences of the disease. Of particular interest were biomechanical, patient-reported, performance-based, and structural outcomes. By examining these different outcomes, we hoped to acquire a more comprehensive understanding of how knee OA evolves over time. The research purposes, specific to knee OA, were to advance the present body of knowledge concerning: (1) the association between mechanical joint loading and in vivo longitudinal changes in cartilage morphology; (2) the relationship of muscle capacity and patient-reported outcomes (PROs) with longitudinal changes in mobility performance; and (3) the reliability (or stability) of biomechanical measurements over longer time intervals. This introductory chapter reviews the socioeconomic burden of OA, knee OA pathology, methods of measuring and characterizing knee OA progression, as well as risk factors for and biomechanical factors implicated in the progression of knee OA. Further,

the gaps in the literature (for which detailed reviews of literature are provided in the distinct manuscripts (Chapters 2–4)) and corresponding research questions addressed in this thesis are summarized.

Osteoarthritis & Socioeconomic Burden

Osteoarthritis is a progressive degenerative disease of tissues (e.g., cartilage, bone, muscle) within and around synovial joints that leads to joint pain, stiffness, swelling, restricted mobility and ultimately, functional disability (Guccione, 1994). Osteoarthritis is the most debilitating musculoskeletal condition amongst older adults (Badley, 2005). Compared to the general population, individuals with OA have higher rates of comorbidities (e.g., cardiovascular, respiratory and gastrointestinal diseases; cancer; dementia), resulting in a higher risk of mortality (Nuesch et al., 2011). It was estimated that more than 50% of individuals over 65 years of age, and approximately 80% over 75 years old, have evidence of radiographic OA (Arden & Nevitt, 2006). In 2010, an estimated 4.4 million (or 1 in 8) Canadians were living with OA. As a result, the total economic burden of OA on the Canadian economy was approximately $27.5 billion, with direct costs (e.g., hospitalizations, visits to healthcare professionals, diagnostic tests, drugs) exceeding $10 billion, and indirect costs (e.g., lost productivity, informal care by family members) surpassing $17 billion (Bombardier et al., 2011). The number of Canadians with OA was projected to nearly double between 2010 and 2031 (Sharif et al., 2012). Rising prevalence rates of OA are, in large part, attributable to an aging population and increasing rates of obesity (Bombardier et al., 2011).

Pathology – Knee Osteoarthritis

Osteoarthritis most commonly affects the knee joint due to its weight-bearing role (Felson, 2004). Knee OA is more prevalent and more severe in women than in men (Felson, 2004; Nuesch et al., 2011). Symptomatic knee OA affects ~13–16% of women and ~10–12% of men over 60 years of age (Turkiewicz et al., 2014; Zhang & Jordan, 2010). This disease is multifactorial, involving joint structure, symptoms, and mobility (Lane et al., 2011). While relationships do exist between structural breakdown and symptoms (Kaukinen et al., 2016; Oak et al., 2013), these do not necessarily overlap (Fukui et al., 2010; Hunter et al., 2013; Neogi & Zhang, 2013).

Degenerative changes implicated in OA affect the whole joint (Arden & Nevitt, 2006; Felson, 2006). Hallmarks of structural OA include loss of articular cartilage, associated changes to the underlying bone, as well as the formation of cysts and osteophytes and thickening of the joint capsule (Felson, 2006; Goldring & Goldring, 2010). Degenerative changes can also occur in muscles, ligaments, and the synovium (Felson, 2006; Sun, 2010). Deleterious changes to chondral structures are of paramount importance in knee OA. The clinical impact of cartilage loss is likely most significant in contributing to, or perpetuating, malalignment of the joint, necessitating surgical realignment in many cases. Articular cartilage is a specialized (hyaline) tissue that lines the ends of bones within joints, for instance, the femur and tibia of the knee joint. This cartilage improves the congruency of the load-bearing surface and provides a frictionless surface to facilitate joint motion (Buckwalter et al., 2005; Lu & Mow, 2008). Cartilage also attenuates and distributes forces between articulating bones within a joint

(Buckwalter et al., 2005; Lu & Mow, 2008). Cartilage response to mechanical loads depends on loading magnitude, duration, frequency and rate (e.g., impact) (Chen et al., 1999; Jones et al., 2003; Lu & Mow, 2008; Qi & Changlin, 2006). The integrity of articular cartilage depends on its ability to maintain a balance between degenerative and synthesizing processes, including the maintenance of collagen and proteoglycans (Andriacchi et al., 2004; Buckwalter et al., 2005; Sun, 2010). Once mature articular cartilage is damaged, it has a poor ability for repair because it is devoid of nerves and blood vessels (Buckwalter et al., 2005; Sun, 2010). Cartilage damage and consequent impaired function may lead to abnormal joint mechanics, in turn promoting the deterioration of other joint tissues (Andriacchi et al., 2004; Buckwalter et al., 2005; Sun, 2010).

Knee OA is the leading cause of pain, restricted mobility and disability amongst older adults (Litwic et al., 2013). Clinical knee OA is diagnosed based on patient history and physical examination criteria. Clinical diagnosis is typically performed according to the specifications established by the American College of Rheumatology (Altman et al., 1986). These criteria include having knee pain on most days of the month and at least three of the following six criteria: 50 years of age or older, morning stiffness lasting less than 30 minutes, crepitus on active motion, bony enlargement, bony tenderness, and no palpable warmth of synovium (Altman et al., 1986).

Knee OA is a complex disease that involves degradation of joint structure, symptoms including pain, and mobility limitations; each element reflects different disease processes (Lane et al., 2011). The progression of knee OA can be characterized

according to changes observed in any one of these diverse aspects. Importantly, there exist various disease trajectories in knee OA. Some patients may experience worsening, no change, or improvements over time in diverse aspects of the disease (Bartlett et al., 2011; Bastick et al., 2016; Collins et al., 2014; Oiestad et al., 2016; White et al., 2016). To acquire a comprehensive understanding of knee OA evolution, clinical biomechanics research must consider the multiple factors implicated in disease progression.

Methods of Measuring Knee Osteoarthritis Progression

The progression of structural knee OA can be evaluated with musculoskeletal imaging (e.g., radiography, magnetic resonance imaging (MRI)), whereas the progression of clinical knee OA can be characterized using PROs and performance-based measures. The relationship between radiographic and clinical measurements is not particularly strong (Bedson & Croft, 2008; Kinds et al., 2011). For instance, radiographic changes in knee OA were an imprecise marker of knee pain (Bedson & Croft, 2008), a finding confirmed by a systematic review of studies examining the association between radiographic and clinical OA features (Kinds et al., 2011). Results from this critical appraisal showed that, of the 39 studies included, only 10% noted the presence of an association, while 18% noted no association and 72% reported inconsistent relationships (Kinds et al., 2011). Therefore, a combination of each type of measure is likely required to gain in-depth insight regarding knee OA progression.

Characterizing Structural Knee Osteoarthritis Progression

Radiography

Radiographs, or x-rays, allow for excellent visualization of bone contours, including osteophytes and joint space width, the latter being an indirect measure of articular cartilage thickness (Braun & Gold, 2012). Typically, the knee joint is evaluated using standing extended or fixed-flexion knee anteroposterior (or posteroanterior) radiographs (Braun & Gold, 2012). Extended knee x-rays are advantageous in that they allow quantification of lower-limb alignment (hip-knee-ankle), a critical measurement in patients undergoing knee replacements or osteotomies. However, knees in the fixed-flexion view showed higher reproducibility with respect to joint repositioning and joint space width measurements compared to extended knee radiographs (Buckland-Wright et al., 1999). In addition, fixed-flexion radiographs were more sensitive to joint space narrowing than extended knee x-rays, an important attribute in longitudinal assessments of knee OA (Niinimäki et al., 2010). The work described in this thesis utilized coronal weight-bearing knee radiographs acquired in a standardized fixed-flexion position (Figure 1-1) (Kothari et al., 2004). This particular positioning frame, which places the feet and knees in approximately 5° of external rotation and 20° of flexion, respectively, showed excellent short-term reproducibility (intraclass correlation coefficient (ICC)=0.94) for the medial compartment in individuals with knee OA (Kothari et al., 2004).

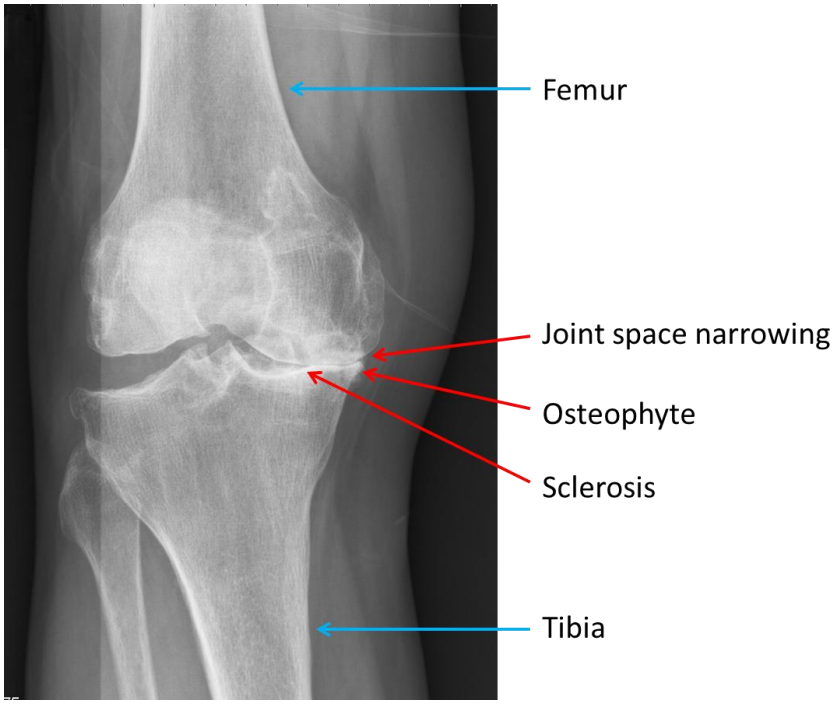

Figure 1-1. Example of a coronal weight-bearing knee radiograph acquired in a standardized fixed-flexion position, with the feet and knees in approximately 5° of external rotation and 20° of flexion, respectively. This x-ray depicts a knee with severe medial compartment dominant OA (KL-4). Joint space narrowing, osteophytes (and bone contour deformity) and sclerosis (i.e., hardening) are visible in the medial knee.

Two common radiographic measures exist to assess the severity of structural knee OA: the Kellgren-Lawrence (K-L) classification and the Osteoarthritis Research International grading scale (Bauer et al., 2006). The K-L system is currently the most widely used grading scheme and an established "gold standard" test for characterizing radiographic OA severity in clinical research (Bauer et al., 2006). This classification uses five grades (0–4) to classify the radiographic severity of OA for the whole knee joint based primarily on the absence/presence and severity of joint space narrowing and osteophytes (Table 1-1) (Kellgren & Lawrence, 1957; Kessler et al., 1998).

Table 1-1. Kellgren-Lawrence classification system of radiographic knee osteoarthritis

Grade	Description
0	no radiographic features of OA are present
1	doubtful joint space narrowing and possible osteophyte lipping
2	definite osteophytes and possible joint space narrowing
3	multiple osteophytes, definite joint space narrowing, some sclerosis, and possible bone contour deformity
4	large osteophytes, marked joint space narrowing, severe sclerosis, and definite bone contour deformity

(Kellgren & Lawrence, 1957)

The K-L classification has been criticized for overemphasizing the importance of osteophytes relative to joint space narrowing, and characterizing disease progression as linear (Altman & Gold, 2007; Roemer et al., 2011; Spector & Hochberg, 1994). Nonetheless, these limitations likely do not affect the ability of the K-L classification to distinguish between mild and severe disease.

The Osteoarthritis Research International grading scale, a more recently developed tool, rates from 0–3+ the severity of joint space narrowing and osteophytes separately. Contrary to the K-L classification, both features are equally weighted (Altman & Gold, 2007). This scale also assesses the presence or absence of sclerosis and attrition, and is compartment-specific which allows the separate assessment of the medial and lateral compartments (Table 1-2) (Altman & Gold, 2007). Consequently, this scale yields distinct scores for each feature but no composite score, which can make treating the data challenging. Further, at the start of this thesis work, this classification was

relatively new and not as widely used in knee OA research as the K-L grading scheme. For these reasons, the K-L classification was used to enable easier comparisons between our data and those from other studies.

Table 1-2. Osteoarthritis Research International grading scale of radiographic knee (tibiofemoral) osteoarthritis.

Description	Scoring
Marginal osteophytes	
Medial femoral condyle	(0-3+)
Medial tibial plateau	(0-3+)
Lateral femoral condyle	(0-3+)
Lateral tibial plateau	(0-3+)
Joint space narrowing	
Medial compartment	(0-3+)
Lateral compartment	(0-3+)
Other	
Medial tibial attrition	(absent/present)
Medial tibial sclerosis	(absent/present)
Lateral femoral sclerosis	(absent/present)

(R. D. Altman & Gold, 2007)

Radiographic assessment is useful for assessment of bone contour and joint space width; however, it does not provide direct information about joint soft tissues. Because radiographs only visualize bone, evidence suggests they are less sensitive to detecting early and progressive signs of structural changes (Amin et al., 2005). For instance, patients demonstrated cartilage loss on MRI without displaying joint space narrowing or

other signs of progression on x-rays (Amin et al., 2005). Accordingly, it is not surprising that disease severity and progression scored from x-rays and MRI scans were only weakly-to-moderately correlated (Bruyere et al., 2007; Cicuttini et al., 2005; Kijowski et al., 2006; Raynauld et al., 2004). Other musculoskeletal imaging modalities such as MRI are therefore important for obtaining direct soft tissue visualization allowing for quantification of tissues to be made and, thus, permitting a more comprehensive evaluation of disease progression.

Magnetic Resonance Imaging

MRI is an imaging modality that allows visualization of different joint tissues through manipulation of image contrast (Braun & Gold, 2012). The human body is mostly comprised of water whose molecules contain hydrogen nuclei (i.e., protons) that become aligned in a magnetic field. An MRI scanner applies a strong magnetic field to the body, which aligns the proton spins. The scanner also generates a radio frequency current that creates a varying magnetic field. The energy from the variable magnetic field is absorbed by the protons, causing their spin to flip. When the field is turned off, the protons gradually return to their natural spin – a process called precession – which produces a radio signal that can be measured by scanner receivers and converted into an image. Since protons in different body tissues return to their natural spins at different rates, different techniques and strategies employed during MRI allow the scanner to distinguish amongst, and produce contrasts between, different tissues. Accordingly, MRI allows detailed visualization of changes in subchondral bone indicative of disease progression,

including bone marrow lesions, subchondral cysts, and subchondral bone attrition. Importantly, MRI scans also enable the morphological assessment of soft tissues, such as cartilage, which provides information about tissue size and structural integrity (Braun & Gold, 2012).

A common protocol for visualizing cartilage is three-dimensional spoiled gradient recalled echo imaging (SPGR) with fat suppression (Cicuttini et al., 2000; Eckstein et al., 2001). The work described in this thesis employed this technique to acquire coronal knee scans. In three-dimensional SPGR, the transverse steady state is spoiled with semi-random radio frequency phase alterations, yielding contrast similar to T1-weighted sequences (Braun & Gold, 2012). Fat saturation is required to provide a sufficient dynamic range to the image contrast to delineate the cartilage, and also eliminate chemical shift artefacts that occur at the bone-cartilage interface (Crema et al., 2011). The voxels acquired with SPGR are nearly isotropic, creating excellent resolution images with high signal from cartilage and low signal from neighbouring joint fluid (Braun & Gold, 2012; Crema et al., 2011). This technique produces images on which cancellous bone, fat and liquid appear dark while cartilage appears bright (Figure 1-2). Specialized software programs (e.g., atlas-based protocol) can then be applied to these images to segment cartilage and yield morphological measurements (Figure 1-3).

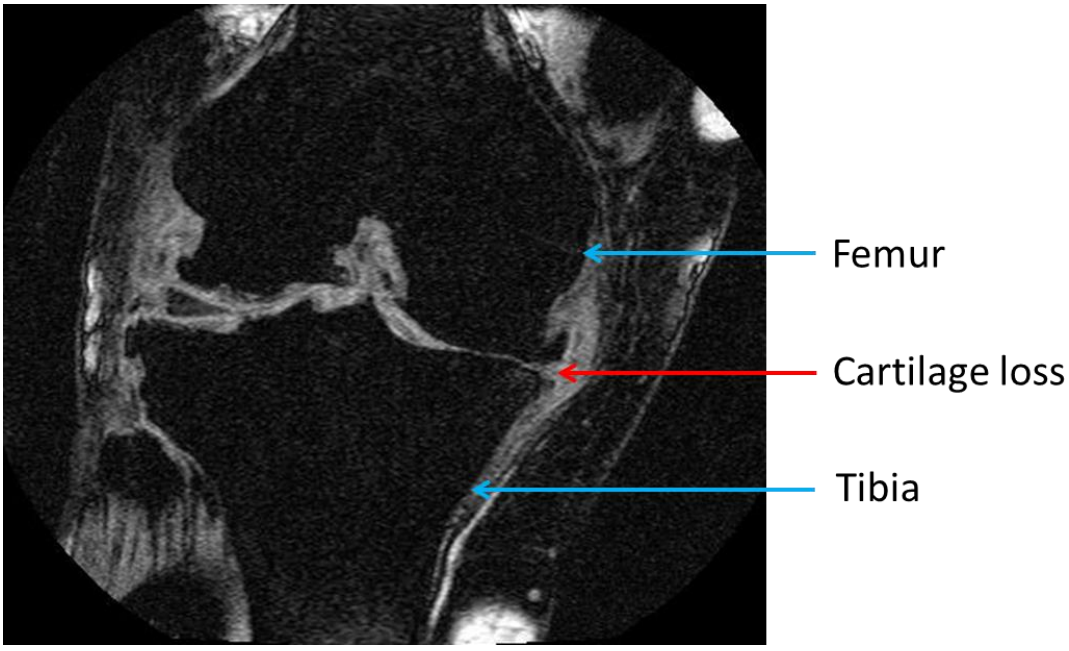

Figure 1-2. Example of a knee MRI coronal scan acquired with a 1.0 Tesla peripheral scanner using three-dimensional SPGR with fat suppression. Cartilage appears bright; whereas cancellous bone, fat and liquid appear dark. This MRI scan depicts a knee with severe radiographic medial compartment dominant OA (KL-4). Cartilage loss can be seen in the medial knee.

Several semi-quantitative MRI scoring systems have been developed for detailed multi-feature assessment of knee OA. Popular semi-quantitative tools that provide whole-organ assessment include the Whole-Organ Magnetic Resonance Imaging Score (WORMS) (Peterfy et al., 2004), the Knee Osteoarthritis Scoring System (KOSS) (Kornaat et al., 2005), the Boston Leeds Osteoarthritis Knee Score (BLOKS) (Hunter et al., 2008), and the MRI Osteoarthritis Knee Score (MOAKS) (Hunter et al., 2011). These tools score, semi-quantitatively, various features that are relevant to the functional integrity of the knee and/or are linked to the pathophysiology of OA. Features include articular cartilage morphology, subchondral bone marrow lesions and cysts, osteophytes,

menisci, ligaments, synovitis, joint effusion, bone attrition, intraarticular loose bodies, and periarticular cysts/bursitis. Each instrument produces data with acceptable reliability, specificity and sensitivity (Hunter et al., 2008, 2011; Kornaat et al., 2005; Peterfy et al., 2004).

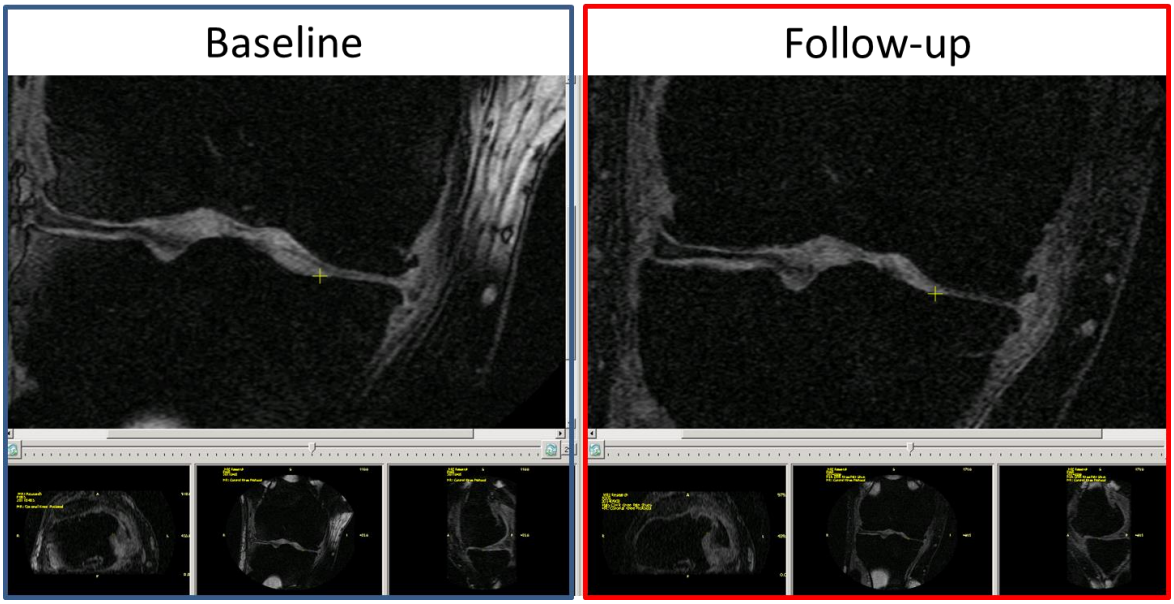

Figure 1-3. Example of knee MRI scans used for cartilage segmentation using specialized software (i.e., atlas-based protocol) [left = baseline; right = ~3.5 year follow-up]. The larger images at the top depict coronal knee scans used for cartilage segmentation and measurement of medial knee cartilage thickness and volume. The smaller images at the bottom depict scout scans in the transverse, coronal and sagittal planes, respectively, used to ensure proper joint positioning in the scanner.

Cartilage morphology/morphometry can also be assessed as continuous variables with quantitative MRI measurements, such as volume and thickness. Cartilage volume is computed by numerically integrating all voxels attributed to cartilage. Cartilage volume is a function of cartilage thickness and cartilage surface area. Therefore, changes in cartilage volume can result from a change in either of these variables (Eckstein et al.,

2006). Cartilage thickness may or may not include denuded areas, depending on the segmentation protocol. These measurements adjust for subchondral bone area and do not include osteophyte cartilage (Eckstein et al., 2006). Various measures of cartilage thickness can be determined, such as the maximum, minimum, mean and standard deviation. It should be noted, however, that the mean thickness for an entire cartilage plate may be relatively insensitive to focal/regional changes that affect only small parts of the surface (Eckstein & Glaser, 2004). As a result, regional cartilage thickness analyses may be required to detect site-specific cartilage thickness changes, particularly in biomechanical analyses of knee OA where regional variations in thickness may be related to joint loading patterns (Koo & Andriacchi, 2007).

The quantitative approach is advantageous in that it is less dependent on the observers and more objective than semi-quantitative scoring methods. Furthermore, relatively small changes over time in cartilage morphology that occur over larger areas may be detected, even though they are not apparent to the naked eye. Conversely, disadvantages of quantitative measurement include the need for specialized software and the time-intensive nature of analyses. Quantitative measurements are also less sensitive to focal lesions, which are more easily identified by expert assessors. Nonetheless, most knee joint features measured using quantitative and semi-quantitative methods are strongly correlated (Guermazi et al., 2015). Ideally, semi- and quantitative approaches should be used conjointly to complement one another.

Characterizing Clinical Knee Osteoarthritis Progression

Patient-Reported Outcomes

Patient-reported outcomes are health outcomes directly reported by the patient who experienced them. These outcome measures can comprise many domains, but pain and disability/physical function are of utmost importance in the assessment of knee OA as they provide valuable information about the severity of symptoms, which is used in determining an appropriate course of treatment (Dougados, 2004).

The Knee Injury and Osteoarthritis Outcomes Score (KOOS) is a common and recommended instrument for the evaluation of pain in knee OA (Juhl et al., 2012; Wang et al., 2010). The KOOS is a standardized, patient-administered questionnaire used to assess patients' perceptions about their knee and associated problems (Roos & Lohmander, 2003). The pain subscale of the KOOS is composed of nine questions about pain intensity/frequency over the previous week. Standardized answer options are given (5 Likert boxes) and each question is assigned a score from 0 to 4. A normalized mean score is calculated, where 100 indicates no symptoms and 0 indicates extreme symptoms (Roos & Lohmander, 2003). Data from the KOOS pain subscale demonstrated adequate internal consistency (pooled Cronbach's α=0.84), test-retest reliability (pooled ICC=0.90) and convergent construct validity with other pain measures (pooled r=0.54) in knee OA patients (Collins et al., 2016). In this thesis, pain was evaluated with the KOOS pain subscale.

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is another widely used tool for assessing pain in knee OA (Bellamy et al., 1988). The

WOMAC pain subscale, which comprises five items, is incorporated in its entirety in the KOOS pain subscale and is scored in a similar fashion. Other versions of the WOMAC are available where items are rated on a 100 mm visual analogue scale. Data from the WOMAC pain subscale showed acceptable internal consistency (Cronbach's α=0.82–0.89), test-retest reliability (ICC=0.65–0.90), and convergent construct validity with other pain measures in persons with knee OA (McConnell et al., 2001; Robbins et al., 2014).

The pain subscales of the KOOS and WOMAC have been criticized. The pain items require patients to rate their pain during functional activities (e.g., "walking on a flat surface"). Therefore, pain scores may not be able to adequately discriminate between changes in pain and physical function (Stratford & Kennedy, 2004). Actually, the pain and physical function subscales of the WOMAC were highly correlated and overlapped on the same factors, indicating that they are measuring the same construct (Faucher et al., 2002; Stratford & Kennedy, 2004). Consequently, these pain subscales might be capturing both pain and physical function statuses. To overcome this shortcoming, other pain measures have been recommended for knee OA.

The Intermittent and Constant Osteoarthritis Pain (ICOAP) measure is a disease-specific instrument that examines intermittent and constant pain domains distinctly (Hawker et al., 2008). The ICOAP is an 11-item measure with two subscales measuring constant pain (5 items) and intermittent pain (6 items) on a 5-point scale (0="not at all"/"never"; 4="very often"). The majority of items ask participants to rate the intensity (or frequency) of symptoms, how pain affects activities (e.g., sleep), and how pain affects emotions. Scores for each ICOAP subscale are obtained by tallying up the items and

normalizing the score out of 100, with higher values representing more extreme pain (Hawker et al., 2008). In knee OA patients, internal consistencies and test-retest reliabilities for the ICOAP were as follows: constant pain (Cronbach's α=0.97; ICC=0.77); intermittent pain (Cronbach's α=0.93; ICC=0.61); total (Cronbach's α=0.93; ICC=0.73) (Robbins et al., 2014). The KOOS, WOMAC and ICOAP pain measures are moderately-to-strongly related and display similar psychometric properties (Hawker et al., 2008; Robbins et al., 2014). It should be noted that the ICOAP questionnaire was fairly new and not yet commonly utilized in knee OA research (compared to the KOOS) at the time this thesis work began, thus explaining why it was not administered.

Patient-reported outcomes can also be used for measuring physical function (or disability) in knee OA. The function in daily living subscale of the KOOS and the function subscale of the WOMAC, which are made up of the same items, have been recommended for use in knee OA studies (Juhl et al., 2012). These subscales are composed of 17 questions about physical functioning during everyday activities over the previous week. Answer options and item scoring are the same as those described above for the pain subscales (Bellamy et al., 1988; Roos & Lohmander, 2003). These subscales have produced data that show adequate internal consistency (pooled Cronbach's α=0.92), test-retest reliability (pooled ICC=0.89) and convergent construct validity with other physical function measures (pooled r=0.65) in individuals with knee OA (Collins et al., 2016). It should be noted that other PROs with varying psychometric properties exist for measuring knee function in OA (Bennell et al., 2011a). For instance, the 36- 12- and 8-Item Short Form Health Surveys are questionnaires that assess various health concepts

(Ware & Sherbourne, 1992; Ware et al., 1996). The physical function subscales from the Short Form Health Surveys, KOOS and WOMAC are strongly correlated (Collins et al., 2016; Ware et al., 1996; Webster & Feller, 2016), and amongst the most responsive in knee OA (Juhl et al., 2012). However, the Short Form Health Surveys are not disease-specific, an important distinction from the KOOS and WOMAC. Accordingly, these general surveys may not appropriately characterize physical function in patients (e.g., knee OA) that experience a unique set of symptoms and mobility challenges.

Other than pain and physical function, PROs capturing self-efficacy may provide valuable information in the assessment of knee OA. Self-efficacy is the belief that one has the capabilities to execute the actions required to satisfy specific situational demands (Bandura, 1998). Self-efficacy is a strong determinant of physical performance in individuals with knee OA (Harrison, 2004). In fact, Social Cognitive Theory suggests that self-efficacy is more important to physical performance than actual physical capacity (Bandura, 1998). The Arthritis Self-Efficacy Scale (ASES) is a standardized, patient-administered questionnaire that assesses how certain patients are that they can perform specific tasks or achieve a result (Lorig et al., 1989). This 20-item instrument is made up of three subscales: self-efficacy for managing pain (5 items), physical function (9 items), and controlling other symptoms (6 items). Participants rate on a 10 cm visual analogue scale their level of certainty that they can perform each task. Each subscale is scored individually by taking the normalized mean score of the items. Higher scores indicate greater confidence or self-efficacy (Lorig et al., 1989). All three subscales of the ASES produce data with adequate internal consistencies (Cronbach's 0.76–0.89) and test-retest

reliabilities (ICC=0.85–0.90), and were correlated with theoretically relevant health outcomes in knee OA (Brady, 2011).

While PROs allow researchers to collect large amounts of data quickly and inexpensively, these tools can be subject to certain biases, including social desirability and cognitive demands of recall (Sallis & Saelens, 2000). The former refers to participants responding in a way that would be seen as socially acceptable, especially when the topic is sensitive; the latter refers to mental fatigue, memory burden or confusion when responding. Participants may also inadvertently under/over report when responding to certain items, for example physical activity habits (Sallis & Saelens, 2000). In addition, self-report scores do not necessarily correlate strongly with or reflect observed scores. This is often the case in the evaluation of physical function in knee OA. Self-reported measures of physical function represent participants' perceived performance. To measure the actual physical capabilities of participants, performance-based measures are required. Performance-based outcomes and PROs are distinct and only moderately related (Maly et al., 2006; Stratford et al., 2006). Thus, it has been recommended to use both types of measures to acquire complementary information about physical functioning in knee OA (Stratford et al., 2006).

Performance-Based Measures

Performance-based tests of physical function usually involve repetition counts, timing or distance measurements, which are observed by assessors (Dobson et al., 2013). While a multitude of performance-based measures exist to evaluate physical function (Bennell et

al., 2011a; Dobson et al., 2012, 2013), the five following tests are recommended in the assessment of knee OA: the Six Minute Walk Test (6MWT), a stair-climbing test, the 30-second chair-stand time, the timed up-and-go test, and the 40 m fast-paced walk (Dobson et al., 2013). Important determinants of physical function in individuals with knee OA include muscle strength, pain and self-efficacy (Dekker et al., 2009). Limited evidence suggests that these aforementioned factors also interact with one another in predicting mobility performance (Miller et al., 2001; Rejeski et al., 2001). It is important to investigate mobility performance for a wide range of activities (e.g., walking, stair-climbing, chair-standing) because these reflect distinct biomechanical challenges and place different demands on the knee (Costigan et al., 2002; McFadyen & Winter, 1988; Protopapadaki et al., 2007). In this thesis, performance-based mobility was assessed with the 6MWT and a stair-climbing task. It should be noted that the abovementioned recommendations were established after the start of this longitudinal work.

The 6MWT is a submaximal test that evaluates walking capacity over long distances (Bennell et al., 2011a; Du et al., 2009). This test is performed on a flat, hard, indoor surface. Participants are asked to walk at a self-selected speed for 6 minutes with the goal of travelling the maximum distance. Standardized verbal encouragement can be provided at 1-minute intervals, and rest as well as adaptive aids are permitted as necessary. The total distance walked, in meters, is recorded (Bennell et al., 2011a; Du et al., 2009). Data from the 6MWT demonstrated high test-retest reliability (ICC=0.94; standard error of measurement (SEM)=26.3 meters) in end-stage knee OA (Kennedy et al., 2005). Though unknown in knee OA, convergent construct validity was demonstrated

by its moderate correlations (r=0.71–0.82) with treadmill performance in older adults (Dobson et al., 2012; Rikli & Jones, 1998).

The stair-climbing test evaluates the ability to ascend and descent a staircase with standard rise and run (Bennell et al., 2011a). Several test variations have been developed in terms of number of steps, whether ascent and descent are assessed conjointly or separately, and whether the goal is as many steps as possible over a given amount of time or as time required to climbing a given number of steps. Five-step and 9-step tests have been described for knee OA, where use of handrails and aids may or may not be permitted (Bennell et al., 2011a). Data from the 9-step stair-climbing test performed in one continuous bout showed high test-retest reliability (ICC=0.90; SEM=2.35 seconds) in end-stage knee OA (Kennedy et al., 2005). While no validity data exist for knee OA, the 11-step stair-climbing test (single bout) demonstrated converging construct validity by its moderate correlations (r=0.59–0.68) with other performance-based measures of physical function in persons with total knee arthroplasty (Almeida et al., 2010).

Risk Factors for Radiographic Knee Osteoarthritis

Knee OA is a multifactorial disease with various potential risk factors. These can be classified as person-level and joint-level factors, which act collectively to cause the onset of OA. Person-level factors are believed to act at a systemic level on relevant joints or are a characteristic of the individual; joint-level factors are joint-specific.

Person-level risk factors include older age, female sex, race/ethnicity, obesity, and genetics (Litwic et al., 2013; Neogi & Zhang, 2013). Older age is one of the strongest

risk factors for OA, though the precise mechanism is unknown. Alterations in the capacity of joint tissues to adapt to biomechanical demands, combined with natural accumulation of various risk factors over years, are likely predominantly involved (Litwic et al., 2013; Neogi & Zhang, 2013). Female sex is associated with greater disease prevalence and severity (Felson et al., 1997; Neogi & Zhang, 2013; Srikanth et al., 2005). The role of hormones in OA, especially estrogen, has been identified as a possibility, though results are conflicting (Hanna et al., 2004; Litwic et al., 2013; Neogi & Zhang, 2013). It has been speculated that the hormonal changes associated with menopause may amplify the effects of aging, further reducing the ability of cartilage to adapt and repair (Andriacchi et al., 2004; Hanna et al., 2004). Different ethnicities and race have a varying prevalence of OA and patterns of joint involvement (Neogi & Zhang, 2013). Obesity (or overweightness) acts on OA through a combination of mechanical and systemic effects (Griffin & Guilak, 2005; Neogi & Zhang, 2013). Obesity results in a greater total accumulation of load borne by weight-bearing joints that may cause tissue overload/damage (Griffin & Guilak, 2005; Harding et al., 2016), as well as reduced tissue tolerance due to exposure to inflammation (Ding et al., 2008; Stannus et al., 2010). The attribution of knee OA to genetics is estimated to be ~40-45%; several susceptibility loci have been linked with OA (Neogi & Zhang, 2013; Spector & MacGregor, 2004). Data supporting the role of other potential risk factors for OA, including bone mineral density and nutrition, remain inconsistent (Johnson & Hunter, 2014; Litwic et al., 2013; Neogi & Zhang, 2013).

Joint-level factors associated with OA reflect mechanisms related to abnormal joint loading, including excessive joint use, knee injury, reduced or unbalanced muscle strength, joint malalignment, and morphology of joint structures (Litwic et al., 2013; Neogi & Zhang, 2013). Excessive knee loading through specific physical and occupational activities (e.g., prolonged and/or repeated exposure to squatting or kneeling) can predispose to OA, particularly if other factors have already augmented joint vulnerability (Litwic et al., 2013; Neogi & Zhang, 2013). Exposure to previous traumatic knee injuries, such as bone fractures and meniscal and cruciate ligament tears, is a strong risk factor for OA development (Litwic et al., 2013; Neogi & Zhang, 2013). Such injuries directly damage joint tissues and may also disrupt the normal stability and load distribution within the joint, further increasing the risk of OA (Andriacchi et al., 2004; Litwic et al., 2013; Neogi & Zhang, 2013). Muscle weakness (particularly of the quadriceps) could contribute to altered joint loading and an increased risk of OA, for example, by not adequately stabilizing the joint or absorbing forces across the knee (Bennell et al., 2013). It is theorized that muscle weakness can be caused by OA-related arthrogenic inhibition and/or disuse atrophy as a result of load-bearing avoidance due to pain (Neogi & Zhang, 2013; Rice & McNair, 2010). Knee malalignment during dynamic weight-bearing activities can modulate the load distribution across the articular surfaces. Abnormal increases in compartmental loading are believed to increase the demands on articular cartilage and other joint tissues, thereby leading to degenerative changes (Litwic et al., 2013; Neogi & Zhang, 2013; Tanamas et al., 2009). Finally, joint tissue morphology and congruency may influence the distribution of biomechanical loads

through the knee since this depends in part on the shape over which load is distributed, in addition to the material properties of the tissues being loaded (Neogi & Zhang, 2013).

Biomechanics in Knee Osteoarthritis Progression

Biomechanical factors are implicated in knee OA progression. Healthy knee joint tissues, such as cartilage, have the ability to adapt to in vivo loads. In osteoarthritic knees, cartilage is damaged and has lost its ability to appropriately attenuate and distribute forces between articulating bones (Buckwalter et al., 2005; Lu & Mow, 2008; Sun, 2010). This impaired function can lead to altered (i.e., abnormal) joint motion and loading, which in turn, promote further cartilage deterioration as well as the degradation of other joint tissues (Andriacchi et al., 2004; Buckwalter et al., 2005; Sun, 2010).

Various biomechanical factors have been associated with knee OA progression. Factors of prime importance include the knee adduction moment (KAM) (Bennell et al., 2011b; Chang et al., 2015; Chehab et al., 2014; Miyazaki et al., 2002), knee flexion moment (KFM) (Chehab et al., 2014; Erhart-Hledik et al., 2015), knee loading frequency (Doré et al., 2013; Lin et al., 2013; Vignon et al., 2006; Wang et al., 2011), obesity (or body mass index (BMI)) (Lee & Kean, 2012; Mezhov et al., 2014), and muscle strength and power (Foley et al., 2007; Mikesky et al., 2006; Segal et al., 2010; Sun, 2010). These factors were examined in this thesis and touched upon within the three manuscripts (Chapters 2–4). All of these biomechanical factors have the ability to modulate forces across the knee and thus represent a means for altered joint loads in knee OA (Creaby,

2015; Moyer et al., 2014; Sun, 2010). Accordingly, these factors may represent important targets for clinical intervention.

Population-specific test-retest reliability and error estimates are required to ascertain whether these biomechanical factors are stable over time and can be used to characterize disease progression and/or evaluate the outcome of therapeutic interventions. While such estimates have been established previously, these have been either in healthy populations (Berkson et al., 2013; Callaghan et al., 2000; Leatherdale & Laxer, 2013; Maffiuletti et al., 2007; Robbins et al., 2009; Wilken et al., 2012) or in knee OA over short periods (i.e., days or weeks) (Birmingham et al., 2007; Carpenter et al., 2006; Kean et al., 2010; Robbins et al., 2013; Villadsen et al., 2012; Wessel, 1996). No known research has estimated the test-retest reliabilities of biomechanical variables over longer periods in knee OA to match work performed for mobility measures and PROs (e.g., pain, physical function) (Pisters et al., 2012; Van Dijk et al., 2006).

Knee Adduction Moment

The external KAM is an indicator of the mechanical load distribution between the medial and lateral compartments of the knee (Meyer et al., 2013; Moyer et al., 2014). During the stance phase of gait, the frontal plane ground reaction force vector passes medially to the knee joint centre, which creates a moment in the frontal plane (i.e., KAM) that tends to adduct the knee (Schipplein & Andriacchi, 1991). The two primary determinants of the KAM are the frontal plane ground reaction force vector and the knee moment arm length (Hunt et al., 2006) (Figure 1-4).

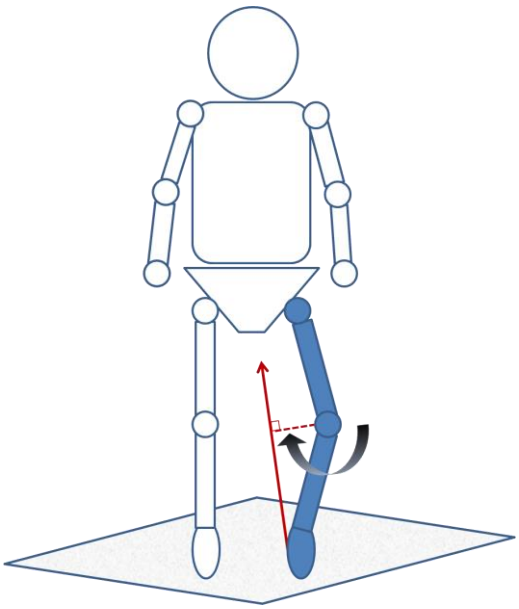

Figure 1-4. Frontal plane depiction of the determinants of the KAM: the frontal plane ground reaction force vector (red arrow) and the knee moment arm length (red dotted line). The KAM describes the tendency to rotate the tibia inward on the femur (black curved arrow) during weight-bearing. A KAM is produced during the stance phase of gait when the ground reaction force vector passes medially to the knee joint centre.

The KAM peak reflects a single maximum at one instance during stance. The KAM impulse, computed as the area under the KAM curve, incorporates both the magnitude and duration of load during stance (Thorp et al., 2006) (Figure 1-5).

The mechanism by which a higher KAM is thought to relate to cartilage loss is theorized to be through its role in increasing the compressive forces across the medial compartment of the knee, the most commonly affected compartment in knee OA. During walking, 60–70% of weight-bearing forces pass through the medial knee compartment (Andriacchi, 1994). It is important to recognize that the KAM represents the medial-to-lateral distribution of loads across the knee, not the actual force on the medial

compartment (Meyer et al., 2013). Nonetheless, the KAM has demonstrated potential in inferring knee loads during gait (Kutzner et al., 2013; Meyer et al., 2013; Trepczynski et al., 2014; Walter et al., 2010; Zhao et al., 2007). For instance, the KAM peak was an independent predictor of the peak medial contact force, accounting for about 63% of the variance (Manal et al., 2015). Importantly, the KAM is only a good indicator of medial knee contact force when the total force remains constant (Moyer et al., 2014).

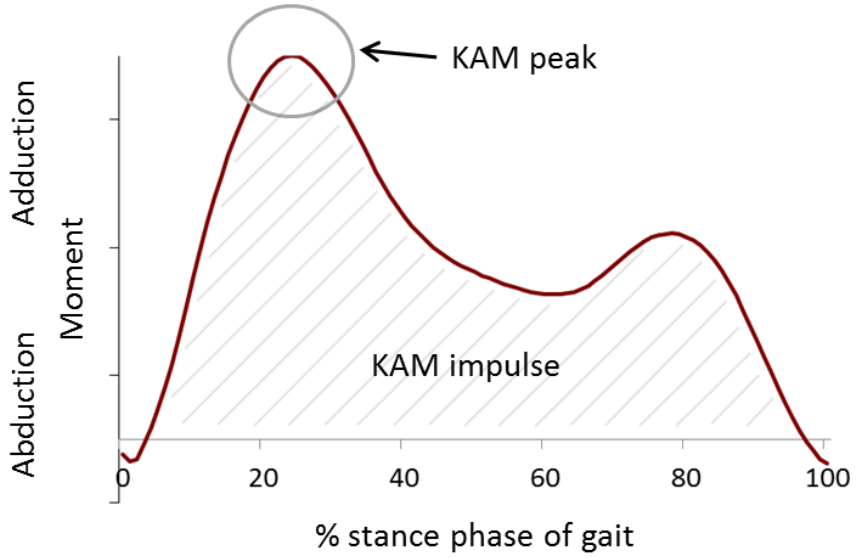

Figure 1-5. Example of a typical bimodal external KAM waveform during the stance phase of gait. The KAM is an indicator of the distribution of mechanical loads between the medial and lateral knee compartments. The KAM peak represents a single maximum at one instance during stance. Usually, the first peak is larger than the second peak, and occurs during weight acceptance (between 20–40% of stance phase) prior to the contralateral foot leaving the ground (i.e., toe-off). The KAM impulse is calculated as the integrated area under the KAM curve (shaded area), and reflects the overall magnitude and duration of frontal plane loading during stance.

Individuals with knee OA often have higher KAM peaks and impulses compared to their healthy counterparts (Baliunas et al., 2002; Kumar et al., 2013; Maly et al., 2013).

Surprisingly, there is very little research linking knee joint loading and the initiation of OA. In 80 older adults with no knee pain at baseline, seven developed new chronic knee pain 3 to 4 years later. Compared to those who did not develop knee pain, those who developed new chronic pain had higher baseline KAM peaks (by 8–39%) for all tested activities (i.e., standing, walking, rising from a chair, and descending stairs) (Amin et al., 2004). A case study analysis showed that, in 28 individuals with no clinical symptoms of OA at baseline, two developed both symptomatic and radiographic evidence of OA over 5 to 10 years (Lynn et al., 2007). Interestingly, the participant who exhibited the highest KAM peak at baseline developed medial knee OA, while the participant with the lowest KAM peak at baseline developed lateral knee OA (Lynn et al., 2007). Finally, an increased KAM during fast-paced walking at baseline was associated with the onset or deterioration of medial knee cartilage defects over 2 years in 70 individuals having undergone arthroscopic partial meniscectomy, a surgery used to manage symptoms associated with medial meniscal lesions but that is also associated with higher risks of developing radiographic knee OA (Hall et al., 2015). While these data appear to implicate the KAM in the initiation of OA, it is important to note that prospective studies with larger samples are required to provide compelling evidence.

There is a larger body of work examining the relationship of the KAM with knee OA severity and progression. In cross-sectional work, the KAM peak and impulse were associated with the severity of medial knee cartilage defects (Creaby et al., 2010), radiographic severity (Kean et al., 2012; Sharma et al., 1998; Thorp et al., 2006), and cartilage morphology (Maly et al., 2015) in knee OA. Furthermore, larger KAMs during

gait predicted the progression of structural knee OA (Bennell et al., 2011b; Chang et al., 2015; Chehab et al., 2014; Miyazaki et al., 2002). Precisely, the KAM peak predicted joint space narrowing at 6-year follow-up on X-ray (Miyazaki et al., 2002). In MRI studies, a higher KAM peak at baseline predicted greater loss of medial knee cartilage thickness over 2–5 years (Chang et al., 2015; Chehab et al., 2014), while a higher KAM impulse at baseline predicted larger reductions in medial knee cartilage volume and thickness over 1 and 2 years, respectively (Bennell et al., 2011b; Chang et al., 2015).

The mechanical basis for reducing the KAM is shown in surgical treatments (i.e., high tibial osteotomy) to realign (from varus to neutral) the lower limb in persons with medial knee OA. For instance, high tibial osteotomy reduced the KAM peak immediately following surgery and 3.2 years postoperatively in 21 patients, regardless of KAM magnitude preoperatively (Prodromos et al., 1985). However, those who had lower KAMs preoperatively had better postoperative clinical results (composite score of pain, function and deformity), lower KAMs and less recurrence of varus deformity (Prodromos et al., 1985). A follow-up study, based on the same sample (n=24) and with longer follow-up times (~3–9 years), confirmed these relationships (Wang et al., 1990). More recent work has yielded similar results, where patients with medial knee OA and varus alignment displayed marked mechanical (i.e., knee alignment, reduction in KAM) and clinical (i.e., patient-reported pain and function) improvements after staged medial opening wedge high tibial osteotomy, with results persisting 3 to 4 years later (Sischek et al., 2014).

Knee Flexion Moment

The external KFM during gait is an indicator of mechanical loading in the sagittal plane. The KFM is principally determined by the sagittal plane ground reaction force vector and moment arm that flexes the knee (Hall et al., 2015) (Figure 1-6). During the stance phase of gait, the quadriceps contract to produce an internal knee extension moment to counterbalance the external KFM, which together contribute to a compressive force within the tibiofemoral joint (Creaby, 2015). The KFM peak represents a single maximum at one instance during stance, and is indicative of an equal but opposite net internal moment that is mostly produced by the quadriceps (Figure 1-7).

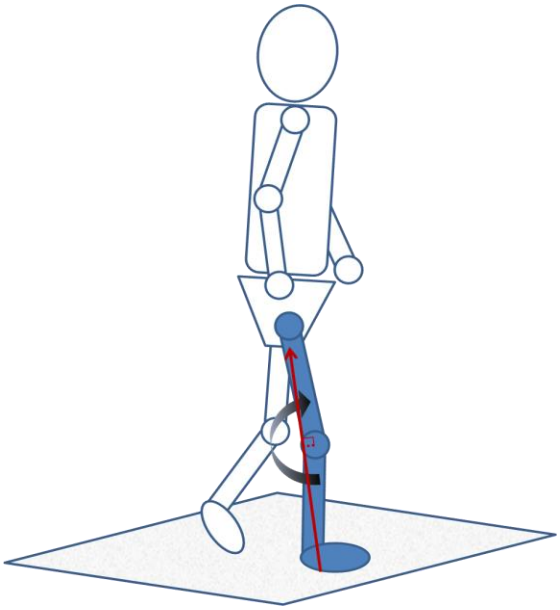

Figure 1-6. Sagittal plane depiction of the determinants of the KFM: the sagittal plane ground reaction force vector (red arrow) and the knee moment arm length (red dotted line). A KFM (black curved arrow) is produced during the stance phase of gait, which is counterbalanced by an internal knee extension moment mostly created by the quadriceps.

The KFM and KAM are speculated to act collectively to modulate contact forces and overall loading environment at the knee (Chehab et al., 2014; Creaby, 2015; Manal et al., 2015; Walter et al., 2010). Limited evidence suggests that individuals with knee OA exhibit a lower KFM peak during gait compared to their healthy counterparts (Kaufman et al., 2001; Mills et al., 2013; Weidow et al., 2006). These lower KFM values may be indicative of abnormal sagittal plane loading patterns, for instance a sustained extension moment as a result of quadriceps-avoidance gait to minimize pain (Astephen et al., 2008a; Kaufman et al., 2001)

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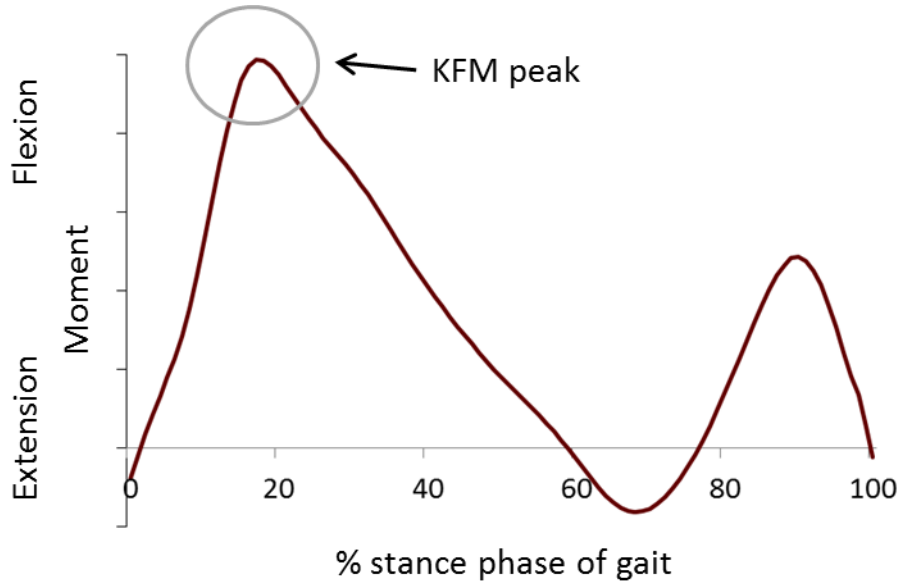

Figure 1-7. Example of a typical bimodal external KFM waveform during the stance phase of gait. The KFM peak represents a single maximum at one instance during stance. Usually, the first peak is larger than the second peak, and occurs during weight acceptance (~15–30% of stance phase) prior to the contralateral foot leaving the ground (i.e., toe-off). The net external KFM peak is indicative of an equal but opposite net internal extension moment mostly produced by the quadriceps.

While individuals with knee OA may exhibit lower KFM peaks (compared to healthy controls), higher KFM values within this patient population may be clinically important. For example, in individuals with moderate-to-severe knee OA, those with moderate-to-severe knee pain displayed a higher KFM peak (by ~1/3) compared to those with mild-to-no pain (O'Connell et al., 2016). The KFM may also be involved in structural knee OA progression; however, previous findings are inconsistent (Chang et al., 2015; Chehab et al., 2014; Erhart-Hledik et al., 2015). A higher KFM peak at baseline was associated with reduced medial tibial cartilage thickness and medial-to-lateral tibial cartilage thickness ratio over 5 years in 16 participants with knee OA (Chehab et al., 2014). In contrast, the KFM peak at baseline was not associated with changes in medial tibial or femoral cartilage thickness over 2 years in 385 knees (Chang et al., 2015).

Loading Frequency

The frequency of mechanical loading can influence the integrity of joint tissues such as articular cartilage (Jones et al., 2003; Qi & Changlin, 2006). In healthy joints, cartilage has the ability to adapt to in vivo mechanical loads (Buckwalter et al., 2005). A moderate level of mechanical loading is thought to be paramount in maintaining the integrity of articular cartilage (Roos & Dahlberg, 2005; Sun, 2010). Joint overuse (i.e., excessive loading frequency) can result in cartilage degeneration; conversely, underuse or disuse (i.e., low loading frequency) may have a similar effect as a result of cartilage under-conditioning (Roos & Dahlberg, 2005; Sun, 2010). Few studies have investigated the association between physical activity levels (i.e. in vivo knee loading frequency) and

cartilage breakdown in adults. Some data support a curvilinear dose-response relationship, where knee loading frequency that is too low or too high is associated with joint tissue degradation (Doré et al., 2013; Lin et al., 2013; Vignon et al., 2006; Wang et al., 2011). Interestingly, some evidence suggests that higher levels of mechanical loading may in fact be protective against cartilage breakdown in non-pathological joints (Hanna et al., 2007; Newton et al., 1997). Further, in community-dwelling adults, higher knee loading frequency (>10,000 steps/day) was protective against cartilage volume loss over 2.7 years – but only in those with more volume at baseline. This higher loading frequency was associated with reduced cartilage volume in those with low baseline volume (Doré et al., 2013). It may be that cartilage quantity (e.g., volume) at baseline mediates the relationship between higher loading repetition and cartilage loss. In knees with OA, however, cartilage function is impaired, resulting in a diminished ability to adapt to mechanical loads (Andriacchi et al., 2004; Buckwalter et al., 2005; Sun, 2010). Only one known study has investigated the link between knee loading frequency and cartilage breakdown in persons with knee OA (Oiestad et al., 2015b). No association was noted between loading frequency and knee cartilage loss over 2 years in adults with mild radiographic knee OA (i.e., K-L≤2) (Oiestad et al., 2015b).

Cumulative Knee Adductor Load

The measure of "cumulative knee adductor load" incorporates the KAM impulse (i.e., magnitude and duration of load) and loading frequency (i.e., # steps/day). This concept may better reflect a mechanism of joint degradation from the overall accumulation of

medial knee loads compared to individual measurements (i.e., KAM, loading frequency) (Robbins et al., 2009). Cumulative load was higher in individuals with knee OA compared to healthy controls, and had a superior ability to discriminate between these groups than the KAM peak (Maly et al., 2013). No known study has evaluated whether the measure of cumulative load is valuable in linking joint mechanics with cartilage degradation longitudinally in knee OA.

Obesity

Obesity is often characterized by a BMI $\geq$30 kg/m^2 (World Health Organization, 2006). A higher BMI is one of the most important risk factors for both the incidence and progression of knee OA (Bastick et al., 2015; Silverwood et al., 2015). Obesity is linked to OA via two main mechanisms: biomechanical factors, as well as metabolic and inflammatory factors (Iannone & Lapadula, 2010; Issa & Griffin, 2012). It can be speculated that these two mechanisms are implicated in the pathogenesis and progression of knee OA due to either abnormal loading acting on normal physiology, or normal loading acting in the presence of abnormal physiology (Guilak, 2011).

First, obesity represents increased body weight, which is directly associated with increased joint loading (Harding et al., 2016). Obesity plays a crucial role in knee OA by overloading and altering the knee joint loading environment. The greater loads imparted by adipose tissue appear to directly alter dynamic knee motion and increase metabolic demands during gait (Browning, 2006; Browning & Kram, 2007; Segal et al., 2009). Obese individuals often display modified spatiotemporal parameters during gait at a self-

selected speed (e.g., shorter and wider steps, slower walking speed, longer stance duration) compared to non-obese persons (Runhaar et al., 2011). These alterations are speculated to represent adaptive strategies to diminish the metabolic cost of walking (Russell et al., 2010) and/or compensatory mechanisms to reduce muscle forces and knee joint loads (Mundermann et al., 2004; Zeni & Higginson, 2009). Compared to their non-obese counterparts, obese individuals also exhibit altered gait kinematics, including smaller peak knee flexion angles (DeVita & Hortobágyi, 2003) and differences in peak knee adduction angles during stance (Freedman Silvernail et al., 2013; Lai et al., 2008). The latter finding is conflicted as obese persons have displayed both larger and smaller knee adduction angles. Further, there is limited evidence suggesting that, in individuals with knee OA of similar severity, those who are obese have decreased peak knee extension angles during stance compared to those who are non-obese (Messier et al., 1996). These aforementioned alterations in spatiotemporal and kinematic parameters may cause or perpetuate abnormal motion or imbalanced loading across the knee (Messier et al., 2014), features theorized to cause a spatial shift in the load-bearing contact location of the joint to an area that is not conditioned to bear loads (i.e., unconditioned cartilage). Such alterations in load-bearing site could potentially damage knee joint tissues (Andriacchi et al., 2004), especially in obese persons who likely have reduced overall joint health and under-conditioned cartilage as a result of sedentary lifestyles.

In addition to spatiotemporal and kinematic alterations, obesity alters gait kinetics in knee OA. Obese individuals with OA exhibited lower KFM peaks compared to non-obese persons with OA, perhaps attributable to slower gait speeds (Harding et al., 2016;

Kaufman et al., 2001; Messier et al., 1996). Obesity was also associated with prolonged activation of quadriceps and gastrocnemii during stance in persons with moderate knee OA, a feature thought to prolong joint contact loading (Amiri et al., 2015). Finally, higher BMI was associated with greater knee shear and compressive peak forces in radiographic knee OA (Harding et al., 2016; Messier et al., 2014). More specifically, absolute tibiofemoral compression and shear forces, as well as absolute forces produced by the major force-generating muscle groups acting at the knee were all higher with increasing BMI, regardless of the presence or absence of moderate knee OA (Harding et al., 2016). These differences may contribute to accelerated joint damage in obese individuals. Importantly, however, osteoarthritic knees may be less able to accommodate the high same level of joint contact forces as asymptomatic joints, without experiencing further disease progression (Andriacchi et al., 2004, 2009; Harding et al., 2016).

Second, the metabolic and inflammatory environment resulting from excessive adipose tissue in obesity is associated with OA (Sowers & Karvonen-Gutierrez, 2010). In obesity, there is an increase in levels of pro-inflammatory cytokines (e.g., leptin, interleukin-1, -6, tumour necrosis factor alpha), which induces low-grade inflammation and is believed to regulate both the synthesis and degeneration of the cartilage matrix (Gomez et al., 2011; Iannone & Lapadula, 2010; Issa & Griffin, 2012). The upregulation of inflammatory responses observed in obese individuals are distinct from those due to "inflammaging", a similar process that occurs with advancing age. Increased levels of serum leptin were noted in overweight and obese individuals with knee OA (Iannone & Lapadula, 2010). Interestingly, serum leptin levels explained about half of the association

between higher BMI and the greater prevalence of knee OA, and may play a key role in cartilage loss as it mediates the association between obesity and cartilage thickness (Fowler-Brown et al., 2015; Stannus et al., 2015). Pro-inflammatory cytokines associated with adipose tissue (i.e., adipokines) have a strong influence on cartilage biology, suggesting that the link between obesity and OA may not be solely biomechanical, but may in fact reflect the biomechanical, metabolic and psychosocial factors on the joint in the presence of systemic inflammation (Guilak, 2011). The mechanisms by which mechanical loading alters the physiology or pathophysiology of joint tissues likely involve complex interactions with molecular and genetic factors – particularly local or systemic inflammation due to injury or obesity – which may detrimentally influence the normal mechanical regulation of chondrocyte activity (Guilak, 2011).

Quadriceps Strength & Power

The role of muscle in knee OA is controversial: muscle may be involved in causal pathway and/or be a consequence of OA. The function of knee muscles is to produce movement, absorb lower-limb loads and provide dynamic joint stability (Bennell et al., 2008). Muscle forces are a major determinant of how loads are distributed across a joint surface (Sowers & Karvonen-Gutierrez, 2010). To achieve equilibrium of motion and joint stability, external forces acting on a joint must be counteracted by internal forces equal in magnitude but opposite in direction (Andriacchi & Mikosz, 1984). Muscles that cross the knee joint (e.g., quadriceps, hamstring) are capable of generating enough force to produce the majority of the internal balancing load; however, other soft tissue

structures (e.g., ligaments, subchondral bone, cartilage) are still required to sustain load (Schipplein & Andriacchi, 1991; Shelburne et al., 2006).

Reduced quadriceps capacity (i.e., muscle weakness) is a common finding in knee OA (Callahan et al., 2015; Hafez et al., 2014; Valtonen et al., 2015). Muscle capacity is commonly characterized by measures of strength and power. Strength is the ability to produce force, while power denotes the ability to produce as much force as possible, as quickly as possible (Sayers, 2007). Some evidence suggests that muscle power may be a more important determinant of mobility than strength in persons with knee OA (Reid & Fielding, 2012). Yet, no known work has examined the association between quadriceps power and longitudinal changes in mobility in knee OA. Primary deficits in muscle capacity are likely associated with muscle fibre atrophy and/or reduced ability to activate muscle fibres (Fink et al., 2007; Ikeda et al., 2005; O'Reilly et al., 1998; Petterson et al., 2008). Muscle weakness observed in knee OA may also be partially due to obesity, which results in reduced strength relative to increased body mass (Bennell et al., 2013).

Muscle weakness, particularly of the quadriceps, may be implicated in the pathogenesis of knee OA. This disease is thought to be caused by joint loading acting within the context of systemic and local susceptibility (Andriacchi et al., 2004; Lee & Kean, 2012; Sun, 2010). A reduction in muscle forces that act about the knee could ultimately alter loading conditions. Failure by the quadriceps to adequately absorb knee forces and provide joint stability during weight-bearing activities can result in greater dynamic loads transmitted to soft tissues such as articular cartilage, resulting in degeneration (Bennell et al., 2013). Alternatively, muscle weakness may be a

consequence of pathology. In the presence of OA, quadriceps weakness may be caused by disuse atrophy resulting from load-bearing avoidance due to disease-related joint pain and/or arthrogenic inhibition (Neogi & Zhang, 2013; Rice & McNair, 2010). Muscle weakness may also be involved in OA progression by perpetuating the effects of existing abnormal joint loads on cartilage breakdown (Segal et al., 2010). Other aspects of muscle function, such as abnormal activation patterns (e.g., increased co-contraction) and proprioception, may also predispose to, or be a consequence of, OA through altered control of movement (Astephen et al,, 2008b; Rutherford et al., 2011; Schmitt & Rudolph, 2007; Sharma & Pai, 1997; Steultjens et al., 2006). Interestingly, quadriceps weakness is a risk factor for both the incidence (symptomatic) and progression (symptomatic and structural) of knee OA (Culvenor et al., 2016; Mikesky et al., 2006; Oiestad et al., 2015a; Segal & Glass, 2011).

Gaps in the Literature

Biomechanical factors are involved in the progression of knee OA. More research is required to elucidate the complex relationships between knee biomechanics and the multifactorial consequences of OA, including damaged joint structure, symptoms and reduced mobility. Longitudinal research linking biomechanics and knee OA progression is scarce. Longitudinal data are more likely to provide information on the timing of disease exposure – and thus an opportunity to identify predictors of OA incidence and progression – than cross-sectional studies, and are required to observe disease-related changes at both the individual and group level.

Chapter 2 describes a study that examined the link between joint mechanics and longitudinal changes in cartilage morphology in knee OA. This study sought to address the following gaps:

1) While the KAM peak and impulse are associated with structural knee OA progression, particularly cartilage loss, these relationships are not very strong. Mechanics other than the KAM may contribute to disease progression. The KFM is a potential candidate; however, further investigation is warranted since evidence supporting its role in worsening OA remains unclear.
2) Cartilage response to mechanical loading depends on load magnitude, duration and frequency (repetition). While the KAM and KFM reflect magnitudes and duration of joint loading, these measures do not capture load repetition. Assessing knee loading frequency may improve our understanding of the association between mechanics and knee OA progression.
3) Examining the KAM, KFM or loading frequency individually may not provide a comprehensive picture of the mechanical elements linked to cartilage breakdown. "Cumulative knee adductor load" incorporates the magnitude and duration of load (i.e., KAM impulse) as well as loading frequency (i.e., # steps/day). This concept may better reflect a mechanism of joint breakdown from overall accumulated exposure to medial knee loads. No study has assessed whether cumulative load is valuable in understanding cartilage loss over time in knee OA.

Chapter 3 describes a study that examined the association between each of muscle capacity (strength, power), pain and self-efficacy with longitudinal changes in mobility performance in knee OA. This study sought to address the following gaps:

1) Muscle strength, pain and self-efficacy are known determinants of mobility in older adults with knee OA. Cross-sectional data suggest that muscle power may be a more critical determinant of mobility than strength. Nonetheless, no known study has investigated this link between power and mobility performance longitudinally in knee OA.
2) While ample evidence supports a negative association between knee pain intensity/frequency and self-reported physical function, the relationship between pain intensity/frequency and performance-based mobility remains unclear. Thus, further work is required to clarify the longitudinal relationship between pain intensity/frequency and mobility performance in knee OA.
3) Some studies have reported interaction effects between muscle capacity and each of pain and self-efficacy on mobility performance in knee OA, though such research is scarce and based on a single mobility outcome. Considering the multifactorial nature of OA, it is logical to investigate whether different elements of the disease act together in worsening mobility over time. Also, it is important to investigate the determinants of performance for various activities as they likely vary in biomechanical demands.

Chapter 4 describes a study that estimated test-retest reliabilities of biomechanical factors associated with knee OA progression. This study sought to address the following gaps:

1) Test-retest reliability estimates for some biomechanical factors have been established previously in healthy populations or in knee OA over short periods. It is important to determine population-specific estimates over longer intervals to capture variability occurring in these measures over time due to the natural course of disease, and to match similar work conducted in PROs and mobility measures.
2) It is important to estimate the magnitude of measurement error for these biomechanical factors to determine whether they are stable over time and can be used appropriately to characterize disease progression and evaluate the outcome of therapeutic interventions.

Research Objectives

To address the aforementioned gaps in the literature, this thesis had the following research objectives:

- Study 1 – To determine the extent to which changes over 2.5 years in medial knee cartilage thickness and volume in individuals with clinical knee OA could be predicted by: (1) KAM peak and KFM peak; and (2) KAM impulse and loading frequency (representing cumulative load exposure) after adjusting for age, sex, BMI and baseline cartilage measurement.

- Study 2 – To determine the extent to which baseline measures of (1) quadriceps capacity (strength, power) and (2) PROs (pain, self-efficacy for functional tasks) predicted change in mobility performance (walking, stair ascent, stair descent) over 2 years in women with knee OA. We also examined whether baseline quadriceps strength and power interacted with pain and self-efficacy in predicting 2-year change in mobility performance.

- Study 3 – To estimate both the relative and absolute test-retest reliabilities of biomechanical risk factors for progression of knee OA. The biomechanical risk factors of interest included the KAM peak and impulse, KFM peak, quadriceps muscle strength and power, physical activity level, and BMI. The results will inform readers whether an observed change within a patient over time falls within the limits of measurement error or if it represents true change.

Significance & Clinical Relevance

This thesis advances knee OA research with regards to our understanding of the longitudinal relationships between in vivo joint mechanics and changes in knee cartilage morphology, as well as the associations of muscle capacity and PROs with changes in mobility. Furthermore, this work provides reliability estimates for various biomechanical risk factors for the progression of structural knee OA, which may help clinicians and researchers establish cut-off values for patients at risk of disease progression, and interpret findings from interventional or longitudinal research. Finally, data from this

thesis emphasize the notion that biomechanical factors do not work in isolation. On their own, biomechanical factors seem relatively stable and modestly implicated in OA progression; however, in the presence of other circumstances, they can vastly exacerbate the disease. Ultimately, results from this work will aid in the development of prevention, management and treatment strategies to curb the progression of knee OA.

**Note: This Introduction chapter identified the context, and key topics and literature concerning the overall thesis. This thesis does not contain a distinct Methods chapter describing the general methodologies used to carry out the various studies. Rather, each manuscript (Chapters 2–4) includes detailed Introduction/Background and Methods sections pertinent to its specific topics and analyses.*

CHAPTER 2

GAIT MECHANICS & OBESITY PREDICT THE PROGRESSION OF STRUCTURAL KNEE OSTEOARTHRITIS

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Baseline Knee Adduction Moment Interacts with Body Mass Index to Predict Loss of Medial Tibial Cartilage Volume over 2.5 Years in Knee Osteoarthritis

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Abstract

This study aimed to determine the extent to which changes over 2.5 years in medial knee cartilage thickness and volume were predicted by: (1) peak values of the knee adduction (KAM) and flexion moments; and (2) KAM impulse and loading frequency, representing cumulative load, after controlling for age, sex and body mass index (BMI). Adults with clinical knee osteoarthritis participated. At baseline and approximately 2.5 years follow-up, cartilage thickness and volume of the medial tibia and femur were segmented from magnetic resonance imaging scans. Gait kinematics and kinetics, and daily knee loading frequency were also collected at baseline. Multiple linear regressions predicted changes in cartilage morphology from baseline gait mechanics. Data were collected from 52 participants (41 women) [age 61.0 (6.9) y; BMI 28.5 (5.7) kg/m^2] over 2.56 (0.51) years. There were significant KAM peak-by-BMI ($p=0.023$) and KAM impulse-by-BMI ($p=0.034$) interactions, which revealed that larger joint loads in those with higher BMIs were associated with greater loss of medial tibial cartilage volume. In conclusion, with adjustments for age, sex, and cartilage measurement at baseline, large magnitude KAM peak and KAM impulse each interacted with BMI to predict loss of cartilage volume of the medial tibia over 2.5 years among individuals with knee osteoarthritis. These data suggest that, in clinical knee osteoarthritis, exposure to large KAMs may be detrimental to cartilage in those with larger BMIs.

Keywords: Degenerative Arthritis; Cartilage; Locomotion; Magnetic Resonance Imaging; Obesity

Introduction

Mechanical loading is implicated in worsening structural or tissue damage inside the knee. Osteoarthritis (OA) is a complex disease that involves degradation of joint structure, symptoms including pain, and mobility limitations; each element reflects different disease processes[1]. "Progression" in this study was characterized as cartilage loss, a hallmark feature of knee OA. Cartilage loss (or its surrogate of joint space narrowing) sometimes relates with pain and contributes to joint malalignment that may require joint replacement[2]. Cartilage loss is also linked with the knee adduction moment (KAM). The KAM reflects the distribution of load between medial and lateral knee compartments[3]. The KAM peak predicted progression of knee OA at 6-year follow-up on X-ray[4]. In magnetic resonance imaging (MRI) studies of knee OA, a higher KAM peak at baseline predicted greater loss of medial knee cartilage thickness, but not volume, over 2–5 years [5,6]; while a higher KAM impulse at baseline predicted larger reductions in medial knee cartilage volume and thickness over 1 and 2 years, respectively[5,7]. It is important to note the strength of these relationships was weak. A KAM impulse greater by 1.0 percent body weight × height × seconds (%BW×HT×s) was associated with a 2-year reduction of only 3.38% in medial tibial cartilage thickness, after adjusting for covariates, in 385 knees with radiographic OA (n=203)[5]. Mechanics other than the KAM may also contribute to knee OA progression, notably the knee flexion moment (KFM)[6,8] and knee loading frequency[9–12].

The KFM may be involved in OA progression; though there is a lack of consensus in the literature[5,8]. Greater KFM peak at baseline was associated with reduced tibial

medial-to-lateral cartilage thickness ratio, and with medial tibial cartilage thickness loss over 5 years in 16 participants[6]. In contrast, the KFM peak at baseline was not related with changes in medial tibial or femoral cartilage thickness over 2 years in 385 knees[5]. Since the role of the KFM in predicting cartilage breakdown remains unclear, further investigation is warranted.

Assessing knee loading frequency in conjunction with measures of joint loading magnitude and duration may improve our understanding of the association between mechanics and knee OA progression. The KAM and KFM peaks do not reflect the accumulated load applied to knee tissues during daily activity. Cartilage response to mechanical loading depends not only on load magnitude and duration, but also load frequency[13,14]. Some evidence supports a dose-response, curvilinear relationship between loading frequency and the incidence and progression of knee OA[9–11]. In 405 community-dwelling older adults, greater steps/day (>10,000) increased cartilage volume loss over 2.7 years in those with low cartilage volume at baseline[12]. Conversely, no association was found between loading frequency and knee cartilage loss (scored semi-quantitatively) over 2 years in 779 knees with mild radiographic OA[15]. Loading frequency alone may not provide a comprehensive picture of the mechanical elements linked to cartilage breakdown. "Cumulative knee adductor load" incorporates the magnitude and duration of load (i.e., KAM impulse) as well as loading frequency (i.e., # steps/day). This concept may better reflect a mechanism of joint breakdown from overall accumulated exposure to medial knee loads[16]. Cumulative load was greater in individuals with knee OA compared to their healthy counterparts, and performed better than the KAM peak at distinguishing

between groups[17]. The total accumulated load on joint tissues is also reflected in obesity, often characterized by a body mass index (BMI) ≥30 kg/m^2. Obesity represents excessive body mass and is a well-established modifiable risk factor for knee OA[18]. While the association between higher BMI and tissue breakdown can be attributed to a greater total accumulation of load, other factors such as altered loading patterns[19], increased compressive and shear contact forces and dynamic loads during gait[20–22], and reduced tissue tolerance due to exposure to inflammation[23,24] are likely also involved. To-date, no study has assessed whether cumulative load is valuable in understanding cartilage loss over time in knee OA.

The purpose of this study was to determine the extent to which changes over 2.5 years in medial knee cartilage thickness and volume in individuals with clinical knee OA could be predicted by: (1) KAM peak and KFM peak; and (2) KAM impulse and loading frequency (representing cumulative load exposure) after adjusting for age, sex, BMI and baseline cartilage measurement. Our hypotheses were based on findings from previous literature[5–7,12]. Due to the inverse relationship between the KAM peak at baseline and tibial cartilage thickness (change over 2–5 years)[5,6], we hypothesized that a higher KAM peak at baseline would be associated with reduced cartilage thickness. In light of conflicting findings in the literature regarding the KFM[5,6], we anticipated that studies utilizing the largest samples reflected the true association between variables. Due to the lack of association between the KFM peak at baseline and changes in medial knee cartilage thickness and volume over 2 years[5], we hypothesized that the KFM peak at baseline would not be predictive of cartilage morphology changes. Due to the inverse

relationship between the KAM impulse at baseline and each of tibial cartilage thickness and volume (change over 1–2 years)[5,7], we hypothesized that a higher KAM impulse at baseline would be associated with reduced cartilage thickness and volume. Finally, our hypothesis regarding loading frequency was based on the only study that examined the link between objectively measured loading frequency and changes in quantitative measurements of cartilage morphology[12]. Due to the inverse relationship between loading frequency at baseline and knee cartilage volume (change over 2.7 years)[12], we hypothesized that a higher loading frequency at baseline would be associated with reduced cartilage volume.

Methods

This longitudinal, observational study was approved by the Hamilton Integrated Research Ethics Board at McMaster University, Canada (prospective cohort study; level of evidence II). We previously reported on cross-sectional relationships using baseline data from the same cohort[25].

Participants

A sample of consecutive individuals fulfilling the eligibility criteria were recruited from local rheumatology and orthopaedic surgery offices. Inclusion criteria included being 40–70 years old and diagnosed with clinical knee OA according to the American College of Rheumatology specifications[26]. Exclusion criteria included other types of arthritis; prior lower-limb joint injury/surgery; ipsilateral hip or ankle conditions; habitual use of an adaptive walking aid; lower-limb trauma or use of intra-articular therapies within the past

3 months; or contraindication to MRI. In total, 64 participants satisfied the inclusion/exclusion criteria and were enrolled. Participants provided written, informed consent.

Descriptives recorded at baseline included the Knee Injury and Osteoarthritis Outcome Score (KOOS)[27], which produces reliable and valid data in knee OA[28]. Baseline Kellgren-Lawrence (K-L) scores were determined from coronal weight-bearing knee radiographs acquired in a standardized fixed-flexion position using a Synaflexer™ (Acrylic Art, Inc., Emeryville, CA, USA). Each digital radiograph was assessed by an experienced radiologist (ST) to yield a K-L score[29].

Cartilage Morphology

At baseline and approximately 2.5 years follow-up, participants underwent MRI of the study knee. To minimize diurnal variations in measurements of cartilage morphology, participants were scanned in the morning and instructed to minimize weight-bearing activity prior to the MRI acquisitions. However, there were 8 instances across baseline and follow-up where imaging was scheduled later in the day to accommodate participant availability. Both MRI scans were acquired with the same 1.0 Tesla peripheral MRI scanner (General Electric Healthcare, USA) using a coronal T1-weighted fat-saturated spoiled gradient recalled acquisition in the steady-state (SPGR), and the following parameters: repetition time (TR) 60 ms; echo time (TE) 12.4 ms (or minimum); flip angle 40°; bandwidth 30 kHz; matrix 512 x 256 (frequency x phase); 1 excitation; field of view 150 mm; slice thickness 1.5 mm; and 56-64 partitions. Cartilage from the medial tibia

and femur were segmented from the MRI scans using a highly-automated protocol based on eight atlases (Qmetrics, Rochester, NY, USA)[30]. An experienced radiologist (ST) reviewed all segmentations for quality assurance. Test-retest precision errors (coefficients of variation) for cartilage measures obtained with a 1.0 Tesla scanner were as follows: medial tibia (volume 3.6%; thickness 2.9%) and central medial femur (volume 5.5%; thickness 4.1%)[31]. No statistical differences were found between the precision of cartilage thickness or volume from 1.0 Tesla and 1.5 Tesla MRI scanners[31]. The following cartilage measures were calculated for each of the medial tibia and femur: volume (mm^3), mean thickness (mm), and 5^{th} percentile thickness (mm) (i.e., thinnest region). Change in each measure was calculated as the mean value at follow-up minus the mean value at baseline, divided by the number of days between time points.

Biomechanical Assessment

Within one week of baseline MRI, motion analyses were performed. Participant setup, instrumentation and gait analysis protocol have been described previously[25]. Briefly, three-dimensional kinematics and kinetics were collected during barefoot walking trials at a self-selected pace for five successful trials.

Gait data were processed using commercial software (Visual 3D, C-Motion, Inc., Germantown, MD, USA). Marker and force plate data were filtered using a second-order low-pass Butterworth bidirectional filter with 6 Hz cut-off. External knee moments were calculated in a three-dimensional floating axis coordinate system[32]. The KAM peak, KFM peak and KAM impulse during stance were determined for five gait cycles, then

averaged. The KAM impulse was calculated using trapezoidal integration (Version 7.0.1, Matlab, MathWorks Inc., Natick, MA, USA). Only positive values from stance were integrated (i.e., adduction) to represent loading experienced by the medial knee. The KAM and KFM peaks were normalized to body mass (Nm/kg); KAM impulse was expressed in non-normalized units (Nm•s). Non-normalized KAM impulse and KAM impulse normalized to %BW×HT are strongly correlated and yield similar patterns in sensitivity analyses[5].

Loading Frequency

Loading frequency was the average number of steps taken daily by the study leg over five days. At baseline, participants wore an accelerometer (GT3X+, ActiGraph Corp., Pensacola, FL, USA) for seven consecutive days during waking hours, except for water activities. The accelerometer, attached to an adjustable belt, was worn around the waist and aligned with the anterolateral aspect of the study leg. Wear time and number of steps per day were calculated (ActiLife 6, ActiGraph Corp., FL, USA) and subjectively corroborated with activity logbooks. Days with wear time ≥10 hours were retained for further analysis[33]. The number of steps/day for five full days (selected chronologically) was averaged, then divided by two to reflect loading frequency of only the study knee.

Statistical Analysis

Descriptive statistics were calculated. Each baseline and follow-up measure of cartilage morphology was compared with two-tailed paired *t*-tests. We constructed linear

regression models that expressed the relationship between knee mechanics and changes in medial knee cartilage morphology over 2.5 years. Six measures of normalized change in medial knee cartilage morphology over 2.5 years were dependent variables: volume, mean thickness, and 5th percentile thickness for each of the tibia and femur. Two combinations (models) of independent variables were investigated for each dependent variable. Model 1 included KAM and KFM peaks at baseline as independent variables, reflecting a theoretical model based on peak knee moments during gait. Model 2 comprised the KAM impulse and knee loading frequency at baseline as independent variables, reflecting the concept of cumulative load. Each of these two models was created in two steps. In the first step, the covariates age, sex, BMI, and cartilage measurement at baseline were simultaneously entered in each model. Evidence suggests that older age, female sex and higher BMI are associated with cartilage loss[34,35]. In the second step, the independent variables were entered collectively and separately with interaction terms between predictors and BMI in all models (and an additional interaction term in model 2 between KAM impulse and loading frequency to reflect cumulative load) to examine the extent to which they explained variance in the dependent variable over and above the covariates. BMI was the only covariate for which we examined the interaction terms with predictors because this is the only modifiable covariate[18]. Non-significant interaction terms were removed.

Regression diagnostics were performed to identify potential outliers. Leverage versus normalized residuals squared plots were utilized to examine the overall influence of observations. The data were tested for homoscedasticity, multicollinearity and

linearity to ensure the appropriateness of the linear regression analyses. All tests were two-tailed and significance was set at $p<0.05$. Analyses were performed using Stata (Version 13.1, StataCorp LP, College Station, TX, USA).

Results

From the 64 participants who enrolled, 53 completed the follow-up visit. Reasons for not completing included unrelated injury (n=1), medical issues (n=2), personal issues (n=2), study commitment (n=3), or unreachable (n=3). Data from one participant were excluded due to MRI motion artifact. The final sample used for analysis (n=52) (Table 2-1) was comprised of 41 women (78.8%), and the following K-L scores: grade 1=2 (3.8%), grade 2=18 (34.6%); grade 3=18 (34.6%); grade 4=14 (26.9%). In addition to presenting with clinical symptoms, >95% of participants had radiographic knee OA (K-L≥2). Of these participants, 48 had medial dominant OA and 2 had lateral dominant OA. Non-completers were not different from the remaining sample in baseline descriptives ($p>0.05$). However, there was a strong suggestion of worse knee pain amongst non-completers (between-group difference of 11 points; $p=0.06$).

The mean (standard deviation) follow-up time was 2.56 (0.51) years, over which the mean medial tibial cartilage volume was reduced by 6.4 (11.6)% ($p<0.001$) and the mean 5^{th} percentile of femoral thickness was reduced by 3.8 (11.4)% ($p=0.016$). All other cartilage morphology measures were unchanged ($p>0.05$). Mean cartilage measures for the medial knee at follow-up were as follows: tibial cartilage volume 1562 (385) mm^3; tibial cartilage mean thickness 1.8 (0.2) mm; tibial cartilage 5^{th} percentile thickness 0.8

(0.1) mm; femoral cartilage volume 1812 (499) mm^3; femoral cartilage mean thickness 1.8 (0.2) mm; and femoral cartilage 5^{th} percentile thickness 0.8 (0.1) mm. No evidence of a ceiling effect on further cartilage change was observed in participants with K-L=4 at baseline, as this subgroup experienced significant reductions in cartilage thickness and volume over 2.5 years.

Our regression analyses focused on medial tibial cartilage volume because, of the two dependent variables that changed significantly over 2.5 years, only this one displayed a change larger than the precision error of the measurement. For this dependent variable, regression diagnostics revealed three outliers with high residuals (values exceeding ±2.25) that were not clustered together. Data from these persons were removed. Thus, the final analyses were performed on n=49. Robust error estimates were used owing to heterogeneity of residuals. To satisfy the assumption of noncollinearity, data were centered for independent variables that displayed large variance inflation factors (>10), by subtracting the means from the respective terms of interest. Significant results are summarized in Table 2-2.

Model 1: Knee Adduction and Flexion Moment Peaks

For change in medial tibial cartilage volume, the covariate model containing age, sex, BMI and medial tibial cartilage volume at baseline yielded an R^2=0.44 (95% Confidence Limits (CL): 0.18, 0.61; p<0.001). The enhanced model including the KAM peak displayed a KAM peak-by-BMI interaction (p=0.023), and increase in R^2 to 0.59 (95% CL: 0.36, 0.69; p<0.001) compared to the covariate model. Neither the simultaneous

addition of the KAM peak, KFM peak and interactions, nor the discrete addition of the KFM peak and interactions increased the variance explaining change in medial tibial cartilage volume ($p>0.05$).

The addition of the KAM peak and KFM peak, separately or collectively, and of interaction terms, did not explain additional variance beyond covariates for any other dependent variable ($p>0.05$).

Model 2: Cumulative Knee Adductor Load

The model containing the KAM impulse exhibited a KAM impulse-by-BMI interaction ($p=0.034$), and explained an additional 15% of the variability in the change in medial tibial cartilage volume ($R^2=0.59$; 95% CL: 0.41, 0.66; $p=0.018$) compared to the covariate model. The model containing both the KAM impulse and loading frequency did not explain more variance. The model containing only loading frequency and interactions did not increase the predictive ability of the model ($p>0.05$).

The addition of the KAM impulse and loading frequency, separately or collectively, and of interaction terms, did not increase the ability of the models to predict change in any other dependent variable beyond covariates ($p>0.05$).

To provide a two-dimensional graphical illustration of the KAM-by-BMI interactions, we performed a secondary analysis that dichotomized BMI at 30.0 kg/m^2 (Figure 2-1). These analyses included the same aforementioned covariates. In these secondary analyses, the interactions remained significant between KAM peak and BMI ($F(1,45) = 21.48$, $p<0.001$) and between KAM impulse and BMI ($F(1,45) = 26.68$,

$p<0.001$). Over 2.5 years, mean medial tibial cartilage volume was reduced by 3.4 (6.0)% for normal/overweight participants ($p=0.026$) and 14.1 (11.6)% for obese participants ($p<0.001$).

Discussion

Greater KAM peak and KAM impulse during gait were each associated with 2.5-year reductions in cartilage volume of the medial tibia in obese individuals with clinical knee OA. In normal weight and overweight individuals (i.e., BMI 18.5–29.9 kg/m^2), the KAM was of little importance in predicting medial tibial cartilage volume change. Reducing body mass for obese individuals may modulate the deleterious effects of knee mechanics on knee OA progression.

The interactions of the KAM peak and KAM impulse with BMI as predictors of change in medial tibial cartilage volume over 2.5 years were striking. In our sample, the magnitudes of the KAM peak [0.36 (0.18) Nm/kg; or 2.27 (1.14) %BW×HT)] and KAM impulse [9.86 (7.25) Nm•s; or 0.80 (0.53) %BW×HT×s] were within the range of previously reported values from large cohort studies [KAM peak range: 1.7–5.3 %BW×HT[4,5,7,8,36]; KAM impulse range: 0.60–1.58 %BW×HT×s[5,7,36]]. To the best of our knowledge, no previous study examined the effect of interactions between these predictors on outcomes. In knee OA, the effect of the KAM on cartilage change depends on BMI. The negative beta coefficients for the KAM-by-BMI interactions imply that the higher the KAM, the greater the effect of BMI on cartilage volume loss.

Consistent evidence supports the detrimental relationships between obesity and cartilage defects[37]. However, the relationship between obesity and changes in knee cartilage morphology is more obscure[37]. Obesity increases dynamic knee loads during gait[20,21]. Excessive body mass contributed to increased compressive mechanical loads as well as altered movement and loading patterns at the knee[19]. Further, higher BMI was associated with greater knee shear and compressive peak force estimates during gait in radiographic knee OA[22,38]. Obesity was also associated with prolonged activation of quadriceps and gastrocnemii during stance, a feature thought to prolong joint contact loading[39]. Interestingly, obesity eliminated the positive relationship between knee cartilage thickness and the KAM peak during gait in healthy individuals[40]. A cross-sectional investigation of 40 individuals with mild-to-moderate clinical knee OA showed that the KAM and BMI better explained the variability in structural disease severity than either factor alone[41]. Obesity-related metabolic factors also contribute to OA. Adipokines are elevated in obesity and related to reduced knee cartilage volume, independent of BMI[23,24]. A combination of mechanics and metabolic factors likely contribute to obesity-related OA progression.

Previous work implicated the KAM in knee cartilage degradation. Cartilage volume is achieved by integration of all voxels attributed to cartilage. In the present study, mean medial tibial cartilage volume for the whole sample was reduced by 6.4 (11.6) % over 2.5 years ($p<0.001$); obese participants experienced a greater loss of 14.1 (11.6) % ($p<0.001$). This change was greater than the precision error for volume measures at the medial tibia (3.6%)[31]. Assuming a linear relationship between cartilage

loss and time based on findings from Wluka et al.[42], participants lost on average 2.5% of cartilage volume annually. This magnitude of volume change falls within the range of previously reported values. For instance, medial tibial cartilage volume was lost at an average annual rate of 4.7 (6.5) % over 2 years (n=123)[43] and 3.7 (4.7) % over 4.5 years (n=78)[42] in knee OA. Conversely, others have reported little to no changes over 1–3 years[44,45]. Discrepancies across studies are likely due to heterogeneity of structural severity and other participant characteristics (i.e., age, sex, BMI, pain). Higher baseline KAM impulse (but not peak) during gait predicted greater reductions in medial tibial cartilage volume over 1 year in clinical and radiographic knee OA[7].

In comparison to volume, mean cartilage thickness measures may or may not include denuded areas, depending on the segmentation protocol[46]. Cartilage thickness measurements adjust for subchondral bone area and do not include osteophyte cartilage. In contrast to some reports[5,6], the present study found no association of the KAM peak or impulse with changes in medial tibial or femoral cartilage thickness. No mean change in femoral cartilage mean thickness was seen across all K-L subgroups. Conversely, mean medial tibial cartilage mean thickness loss over 2.5 years was observed for subgroups K-L=2 and K-L=4, but not K-L=3. A lack of mean change in cartilage mean thickness in the K-L=3 subgroup (~1/3 of the sample) likely contributed to detecting no change in the whole sample. Further, use of mean thickness across the articular surface likely washed out regional variations in cartilage thickness, which may be related to loading patterns during gait[47].

A loss of 3.8% was observed over 2.5 years in the mean 5th percentile of femoral cartilage thickness. This measure, which represents the average thickness of the thinnest region of cartilage, likely equates with other categorizations of cartilage defects[7]. In cross-sectional analyses on the same sample at baseline, the KAM peak was inversely related with the mean 5th percentile of femoral cartilage thickness[25]. Yet, in the current longitudinal analysis, no association was found between the KAM and change in mean 5th percentile of femoral cartilage thickness over 2.5 years. Previous reports demonstrated that the KAM peak was most related to cartilage changes in the medial central region of the femur[5,6], which is subject to greatest loss of cartilage in knee OA[48]. It may be that, over this time, relatively little change occurred in the 5th percentile of femoral cartilage thickness. This point reflects that the amount of change observed was similar to the precision error of cartilage thickness measurements at the femur[31]. It should be noted that this measure does not capture changes in the width of a cartilage defect. Therefore, enlargements of cartilage defects signalling OA progression would not be reflected in the 5th percentile thickness. Previous studies showed relatively weak relationships between the KAM and subsequent cartilage loss[5–7]. We use data from the largest published sample and relatively long follow-up period to illustrate this point[5]. The mean (standard deviation) baseline KAM impulse was 0.60 (0.44) %BW×HT×s. A KAM impulse larger by 1.0 %BW×HT×s was associated with a reduction of only 3.38% in medial tibial cartilage thickness over 2 years in knee OA, after adjusting for various covariates[5]. Given the mean KAM impulse for the sample, a 1-unit difference in the KAM impulse is very large.

The notion that the KFM peak during gait plays an important role in disease progression has gained popularity, though longitudinal evidence supporting this hypothesis is inconsistent. The KFM is thought to work alongside the KAM to modulate the loading environment at the knee[6,49,50]: a reduction in KAM does not guarantee an equivalent decrease in medial knee contact force probably due to a concurrent increase in KFM[49]. In previous work, greater baseline KFM peak during gait was associated with reduced medial tibial cartilage thickness and medial-to-lateral tibial cartilage thickness ratio over 5 years (n=16)[6]. In contrast, in the current study, and among 385 knees over 2 years[5], the KFM peak alone was not associated with changes in cartilage morphology. The interplay between the KAM and KFM on the loading environment may depend on OA severity[8]. The influence of the KFM may be greater in early disease when symptoms are less severe[8]. More than half (56.3%) the sample in the work by Chehab et al.[6] had mild disease (K-L≤2), whereas the majority (61.5%) of the current sample had more advanced disease (K-L≥3). Consequently, the differences in disease severity between samples may partly explain why the KFM was associated with cartilage loss in the study by Chehab et al. but not in the current investigation.

Cartilage response is theoretically influenced by loading frequency[13,14]. The present study was the first to incorporate loading frequency with external knee loads to explore the association between the KAM and cartilage loss. Contrary to our hypothesis, higher loading frequency did not predict cartilage loss in the medial knee. Similarly, no association was noted between loading frequency and cartilage loss in 779 knees (K-L≤2) from older adults over 2 years[15]. In contrast, in 405 older community-dwelling adults,

high loading frequency (>10,000 steps/day) was protective against cartilage volume loss in individuals with more baseline volume, but deleterious in those with low baseline volume over 2.7 years[12]. The samples from the current study [3893 (1938) steps/day for the study leg; or 7786 (3876) steps/day for both legs] and Oiestad et al.[15] [7185 (2565) steps/day] had lower activity levels compared to the sample where an association was observed between activity and cartilage loss [8895 (3345) steps/day][12]. Participants in this study may not have been active enough to induce further cartilage loss.

This study was not without limitations. While the analyses performed were sufficiently statistically powered, a larger sample would have allowed adjustments for additional covariates. Our sample comprised mostly older, overweight women; thus, generalisability to other populations is unknown. Large individual variability in change in cartilage measures may have limited the ability to detect mean cartilage loss over time. Accelerometry data were not adjusted for variability in physical activity habits associated with different days of the week or seasons.

In conclusion, BMI interacts with the KAM to predict cartilage volume loss in the medial tibia over time in individuals with clinical knee OA. Among obese participants, large magnitude KAM peak and KAM impulse at baseline predicted cartilage volume loss over 2.5 years; whereas KAM was of little importance in predicting cartilage volume loss in individuals with a healthy/overweight BMI. The KFM peak and loading frequency at baseline did not predict change in medial knee cartilage morphology. Treatment strategies should aim to shift BMI from obesity to normal/overweight categories to curb structural disease progression associated with mechanical loading.

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Table 2-1. Descriptive statistics of participants at baseline (n=52).

Variable	Mean (Standard Deviation)
Age (y)	61.0 (6.9)
Body mass (kg)	76.0 (16.1)
Height (m)	1.63 (0.09)
Body mass index (kg/m^2)	28.5 (5.7)
Pain (0-100) †	76.6 (16.0)
Other symptoms (0-100) †	75.9 (14.4)
Function in daily living (0-100) †	82.7 (15.8)
Function in sports and recreation (0-100) †	67.7 (24.4)
Knee related quality of life (0-100) †	64.7 (18.6)
Gait speed (m/s)	1.18 (0.21)
Knee adduction moment peak (Nm/kg)	0.36 (0.18)
Knee flexion moment peak (Nm/kg)	0.57 (0.21)
Knee adduction moment impulse (Nm•s)	9.86 (7.25)
Loading frequency (steps/day) ϕ	3893 (1938)
Tibial cartilage volume (mm^3)	1669 (399)
Tibial cartilage mean thickness (mm)	1.8 (0.2)
Tibial cartilage 5th percentile thickness (mm)	0.8 (0.1)
Femoral cartilage volume (mm^3)	1782 (444)
Femoral cartilage mean thickness (mm)	1.8 (0.2)
Femoral cartilage 5th percentile thickness (mm)	0.8 (0.1)

† Pain, other symptoms, function in daily living, function in sports and recreation, and knee related quality of life were measured with the Knee Injury and Osteoarthritis Outcome Score. Scores range between 0 and 100, where lower scores reflect worse symptoms and function[27].

ϕ Steps/day reflects loading frequency for the study leg only.

Note: All cartilage measures are for the medial knee only.

Table 2-2. Statistically significant associations between baseline variables and longitudinal changes in cartilage morphology (n=49). The dependent variable is change in medial tibial cartilage volume (mm^3/day) over 2.5 years. Baseline covariates are age, sex, BMI, and baseline medial tibial cartilage volume. Predictors are KAM peak and KFM peak for model 1, and KAM impulse and loading frequency for model 2. Regression models used centered data, with robust error estimates. Statistically significant values are presented in bold.

Predictors	**Unstandardized β Coefficient**	**95% CI**	**R^2**	**P-value**
Covariates only			0.44	**<0.001**
Age	-0.0016	-0.0091, 0.0060		
Sex	0.1937	0.0534, 0.3340		
BMI	-0.0144	-0.0232, -0.0057		
Medial tibial cartilage volume	-0.0003	-0.0005, -0.0002		
Model 1: Covariates + KAM peak			0.59	**<0.001**
Age	0.0023	-0.0050, 0.0095		0.531
Sex	0.1669	0.0332, 0.3007		**0.016**
BMI	-0.0176	-0.0265, -0.0088		**<0.001**
Medial tibial cartilage volume	-0.0003	-0.0004, -0.0001		**0.001**
KAM peak	-0.0736	-0.3176, 0.1704		0.546
KAM peak x BMI	-0.0762	-0.1410, -0.0113		**0.023**
Model 2: Covariates + KAM impulse			0.59	**0.018**
Age	0.0010	-0.0060, 0.0081		0.770
Sex	0.1448	0.0217, 0.2680		**0.022**
BMI	-0.0135	-0.0217, -0.0054		**0.002**
Medial tibial cartilage volume	-0.0002	-0.0004, -0.0001		**0.008**
KAM impulse	-0.0012	-0.0089, 0.0066		0.761
KAM impulse x BMI	-0.0018	-0.0034, -0.0001		**0.034**

Note: BMI = body mass index; KAM = knee adduction moment.

Figures

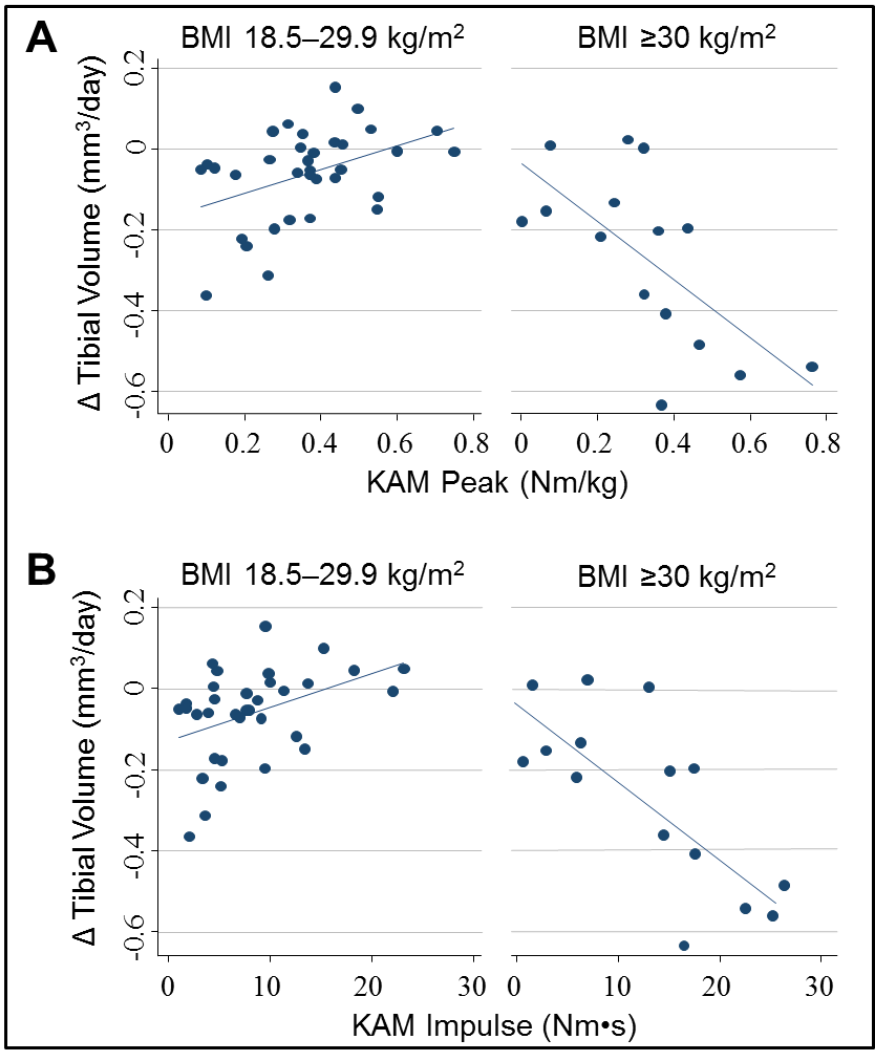

Figure 2-1. Relationships of the KAM peak (A) and KAM impulse (B) with change in medial tibial cartilage volume over 2.5 years, with BMI dichotomized at 30.0 kg/m^2. A BMI between 18.5–29.9 kg/m^2 reflected normal/overweight individuals (n=34); whereas a BMI ≥30.0 kg/m^2 represented obese individuals (n=15). KAM = knee adduction moment; BMI = body mass index.

CHAPTER 3

MUSCLE CAPACITY & PATIENT-REPORTED OUTCOMES PREDICT MOBILITY CHANGES IN KNEE OSTEOARTHRITIS

Prepared for *Clinical Rheumatology*

Self-efficacy, pain and quadriceps capacity at baseline predict changes in mobility performance over 2 years in women with knee osteoarthritis

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Abstract

Introduction: This study examined the extent to which baseline measures of quadriceps strength, quadriceps power, knee pain and self-efficacy for functional tasks, and their interactions, predicted 2-year changes in mobility performance (walking, stair ascent, stair descent) in women with knee osteoarthritis. We hypothesized that lesser strength, power and self-efficacy, and higher pain at baseline would each be independently associated with reduced mobility over 2 years; and each of pain and self-efficacy would interact with strength and power in predicting 2-year change in stair-climbing performance.

Method: This was a longitudinal, observational study of women with clinical knee osteoarthritis. At baseline and follow-up, mobility was assessed with the Six Minute Walk Test, and stair ascent and descent tasks. Quadriceps strength and power, knee pain and self-efficacy for functional tasks were also collected at baseline. Multiple linear regression examined the extent to which 2-year changes in mobility performances were predicted by baseline strength, power, pain and self-efficacy, after adjusting for covariates.

Results: Data were analyzed for 37 women with knee osteoarthritis over 2 years. Lower baseline self-efficacy predicted decreased walking (β=1.783; p=0.030) and stair ascent (β=-0.054; p<0.001) performances over 2 years. Higher baseline pain intensity/frequency predicted decreased walking performance (β=1.526; p=0.002). Lower quadriceps strength (β=0.051; p=0.015) and power (β=0.022; p=0.022) interacted with lesser self-efficacy to predict worsening stair ascent performance.

Conclusions: Strategies to sustain or improve mobility in women with knee osteoarthritis must focus on controlling pain and boosting self-efficacy. In those with worse self-efficacy, developing knee muscle capacity is an important target.

Keywords: Osteoarthritis, Knee; Walking; Stair Climbing; Muscle Strength; Muscle Power; Patient Reported Outcomes

Introduction

Declines in mobility due to knee osteoarthritis (OA) can be explained by worse knee muscle capacity and patient-reported outcomes (i.e., pain and self-efficacy) [1]. Muscle capacity can be characterized by strength, the ability to generate force, and power, the ability to generate as much force as possible, as quickly as possible [2]. Baseline quadriceps strength predicted 30-month change in stair-climbing time in adults with knee pain [3], and chair sitting-and-standing mobility over 3 years in knee OA [4]. Moreover, 2-year change in quadriceps strength was inversely associated with change in stair-climbing time in knee OA [5]. Muscle power may be a more critical determinant of mobility than strength [6]. Quadriceps power was positively related with walking and stair-climbing performances in knee OA [7,8]. No known study has investigated this link between power and mobility performance longitudinally.

The impact of pain on mobility in knee OA is complex. Longitudinal work supports a negative association between knee pain intensity and self-reported physical function [4,9–11]. The relationship between pain intensity and performance-based mobility is less clear [3,4,10–12]. Baseline pain intensity did not predict 30-month change in stair-climbing performance [3], a finding confirmed for chair-stands performance at 3-year follow-up [4] and walking at 2-year follow-up in people with knee OA [10]. In contrast, change in constant pain was positively associated with change in chair-stands time over 2 years in women with knee OA [10]. Further work is required to clarify the longitudinal relationship between pain and mobility performance in knee OA.

Self-efficacy, an influential determinant of mobility in knee OA, is the belief that one has the capabilities to execute the actions required to satisfy specific situational demands [13]. Baseline self-efficacy predicted 30-month change in stair-climbing time in adults with knee pain [3]. Moreover, higher baseline self-efficacy protected against poor chair sitting-and-standing performance 3 years later in knee OA [4]. Social Cognitive Theory suggests that self-efficacy is more important to mobility performance than actual physical capacity, such as muscle strength/power [13].

Pain and self-efficacy likely interact with muscle capacity to affect mobility in knee OA. For example, the effects of greater strength on reducing the odds for poor chair-stands outcome over 3 years was partially mediated by each of pain intensity and self-efficacy [4]. Similarly, baseline quadriceps strength interacted with each of pain and self-efficacy in predicting 30-month change in car transfer and stair-climbing performances, respectively, in adults with knee pain [3,14]. Nonetheless, large gaps exist in understanding how muscle capacity interacts with pain and self-efficacy. First, previous findings of these interactions were based on a single mobility outcome. It is important to investigate the determinants of performance for various activities such as walking, stair ascent and stair descent since these tasks vary in biomechanical demands [15–18]. Stair-climbing is biomechanically more challenging than walking [15], where ascending and descending stairs place different physical demands on the knee [16,17]. Second, muscle power, a capacity measure likely more predictive of mobility than strength, remains unexamined longitudinally.

This study aimed to determine the extent to which baseline measures of (1) quadriceps capacity (strength, power) and (2) patient-reported outcomes (pain, self-efficacy for functional tasks) predicted change in mobility performance (walking, stair ascent, stair descent) over 2 years in women with knee OA. We also examined whether baseline quadriceps strength and power interacted with pain and self-efficacy in predicting 2-year change in mobility performance. Our hypotheses were based on findings from previous literature. Due to the positive relationships of quadriceps strength with stair-climbing and sitting-and-standing performances over 2 to 3 years in persons with knee pain and/or OA [3–5], we hypothesized that lesser quadriceps strength at baseline would be independently associated with reduced mobility over 2 years. Due to the positive relationships of quadriceps power with walking and stair-climbing performances in cross-sectional studies of knee OA [7–8], we hypothesized that lesser quadriceps power at baseline would be independently associated with reduced mobility over 2 years. In light of conflicting findings in the literature regarding the association between pain and mobility in persons with knee pain and/or OA [3–4,10], we based our hypothesis on the only study that examined women with knee OA separately [10]. Due to the inverse relationship between constant pain and chair sitting-and-standing mobility over 2 years [10], we hypothesized that higher pain intensity/frequency at baseline would be independently associated with reduced mobility over 2 years. Due to the positive relationships of self-efficacy with stair-climbing and chair sitting-and-standing performances over 2.5 to 3 years in persons with knee pain and/or OA [3–4], we hypothesized that lesser self-efficacy at baseline would be independently associated with

reduced mobility over 2 years. Finally, due to the interactions of pain and self-efficacy with muscle capacity on chair-stands, car transfer and stair-climbing mobility over 2.5 to 3 years in adults with knee pain and/or OA [3–4,14], we hypothesized that each of pain and self-efficacy would interact with quadriceps strength and power in predicting 2-year change in mobility performance.

Materials and Methods

This longitudinal, observational study was approved by the institutional human research ethics board.

Participants

A convenience sample of women 45-70 years of age with clinical knee OA was recruited from orthopaedic surgery and rheumatology offices. Women were studied because knee OA affects women more frequently [19], with a greater impact on physical function compared to men [20]. Clinical disease was characterized by the American College of Rheumatology criteria [21].

Exclusion criteria at baseline comprised other forms of arthritis; past lower-limb injury and/or surgery; ipsilateral ankle or hip conditions; use of adaptive walking aids, intra-articular therapies or lower-limb trauma within the past 3 months; and inability to ascend/descend a 9-step staircase twice. Participants provided written, informed consent prior to their inclusion in the study.

Descriptive statistics including age, body mass and height were recorded at baseline. The Kellgren-Lawrence score, which characterized radiographic severity at baseline, was determined from anterior-posterior weight-bearing knee X-rays acquired in a standardized fixed-flexion position [22]. An experienced radiologist evaluated each digital radiograph to determine Kellgren-Lawrence scores.

Quadriceps capacity

Quadriceps strength and power were assessed at baseline using a dynamometer (System 3 Pro, Biodex Medical Systems, Inc., Shirley, USA). Participants were positioned on the dynamometer with the knee joint center of rotation aligned with the dynamometer axis of rotation. Straps secured the chest, waist, mid-thigh and lower-shank. The summative weight of the lower-limb and dynamometer attachment was recorded to correct torque data for gravity. Then, participants flexed and extended their knee several times under minimal resistance to familiarize themselves with the apparatus and protocol. To measure strength, participants performed five repetitions of a 5-second maximum voluntary isometric contraction (MVIC) of the quadriceps, with the knee in 60° of flexion (full extension defined as 0° flexion). Five seconds of rest was provided between contractions. Participants were instructed to "kick as hard as possible". To measure power, participants executed 10 consecutive knee extension-flexion cycles between 0-90° of flexion, across an arc of motion of at least 70°. Participants were instructed to "kick and bend their knee as fast and as hard as possible". During these isotonic contractions, resistance was set to 25% of MVIC peak quadriceps torque to ensure most participants

could complete 10 consecutive trials [8]. For dynamometry assessments, participants were permitted to brace themselves using the stabilization straps or handles, and were provided verbal encouragement and visual feedback to maximize volitional efforts [23].

Raw time, torque, and velocity data were extracted for each trial. Such measurements produced by this type of dynamometer demonstrated excellent between-trial reliability (intraclass correlation coefficient (ICC)=0.99) and validity (ICC=0.99; measurement error 1–3%) [24]. Quadriceps strength was defined as the mean of the three highest peak torque values recorded during MVICs. Velocities were converted from degrees/second to radians/second and multiplied by torques (Nm) to generate measurements of power (W). Quadriceps power was defined as the mean of the three highest peak power values achieved during the quadriceps isotonic contractions. Strength (Nm/kg) and power (W/kg) values were normalized to body mass.

Patient-reported outcomes

Pain and self-efficacy were recorded at baseline. The pain subscale of the Knee Injury and Osteoarthritis Outcome Score (KOOS-Pain) was used [25]. KOOS-Pain is composed of nine questions, scored from 0–4, about pain intensity/frequency over the previous week. KOOS-Pain was reported as the normalized mean score, where 100 indicated no pain and 0 indicated extreme pain. Data from this subscale demonstrated high internal consistency (Cronbach's α=0.84) and test-retest reliability (ICC=0.90) in knee OA [26].

The physical function subscale of the Arthritis Self-Efficacy Scale (ASES-FSE) was used to measure arthritis-specific self-efficacy for physical function tasks [27]. The

ASES-FSE consists of 9 items about distinct physical tasks, rated on a 10 cm visual analogue scale. It was scored by taking the normalized mean score, where 0 indicated "very uncertain" (low self-efficacy) and 100 indicated "very certain" (high self-efficacy). Data from the ASES-FSE showed high internal consistency (Cronbach's α=0.89) and test-retest reliability (ICC=0.85) in knee OA [28].

Mobility performance

At baseline and follow-up, mobility performance was assessed with the Six Minute Walk Test (6MWT) and stair-climbing tasks. The 6MWT is a submaximal test of walking capacity [29]. This test was performed on a 50-meter unobstructed, hard-tiled, rectangular circuit. Participants walked at a self-selected speed for 6 minutes with the goal of travelling the maximum distance. Jogging and running were not allowed but slowing down, stopping or sitting was permitted, with time continuing to elapse. Standardized verbal encouragement was provided at 1-minute intervals [29]. The 6MWT score corresponded to the total distance (m) walked. Data from the 6MWT demonstrated high test-retest reliability (ICC=0.94; standard error of measurement (SEM)=26.3 meters), and a minimum detectable change at 90% confidence of 61.3 meters in end-stage knee OA [30].

A stair-climbing task is recommended in the evaluation of physical function in knee OA [31]. Stair-climbing was performed on a 9-step staircase with a standard rise and run, and handrails on each side. In separate bouts, participants ascended and descended the staircase as rapidly as possible without running, jogging or skipping a step.

This test was completed twice. Participants could use handrails if desired. Ascent and descent times were registered with a stopwatch, from the time the lead foot left the floor until the moment both feet were planted on the final step. The mean duration (s) of each task was used as the test score. Since ascending and descending stairs place different biomechanical demands on the knee, these tasks were evaluated separately. Although no reliability data are available for stair ascent and descent tasks independently, such data exist for the 9-step stair-climbing test performed in one continuous bout. This test showed high test-retest reliability (ICC=0.90; SEM=2.35 seconds), and a minimum detectable change at 90% confidence of 5.5 seconds in end-stage knee OA [30].

Statistical analysis

Descriptive statistics were computed as means and standard deviations (SD) for continuous data, and counts for categorical data. Baseline and follow-up mobility scores were compared with two-tailed paired *t*-tests. Multiple linear regression was used to examine the extent to which changes in walking and stair-climbing performances over 2 years were predicted by baseline measures of quadriceps capacity and patient-reported outcomes. The dependent variables were the 2-year change scores for each of the 6MWT, stair ascent, and stair descent tasks. Change scores were calculated as the mean at follow-up minus the mean at baseline. Potential predictors were baseline quadriceps strength, quadriceps power, KOOS-Pain, and ASES-FSE. Covariates were age, BMI and corresponding mobility score at baseline. Older age and higher BMI are determinants of

poorer functional task performance in knee OA [4,32]. Baseline mobility scores were used to control for the status of participants at the start of the study.

To answer both research questions, eight models were investigated for each dependent variable. Each model was created in two steps. First, the covariates were concurrently entered. Covariates were selected based on evidence and remained in the regression models whether or not they were unique contributors. The second step differed between models aiming to answer the first and second research questions. To address the first research question, each of the four independent variables was added separately to examine the extent to which it explained variance in the dependent variable over and above the covariates. To address the second research question, four additional models were run, which included a muscle capacity measure (either strength or power) and a patient-reported outcome (either pain or self-efficacy), as well as their interaction term.

Linear regression analyses were scrutinized for requisite assumptions. Outliers were examined using leverage versus normalized residuals squared plots. All analyses were two-tailed with statistical significance set at $p<0.05$, and conducted using Stata software (version 13.1, StataCorp LP, College Station, USA).

Results

Forty-five women met the inclusion/exclusion criteria and were enrolled. Among these participants, 38 completed the follow-up visit. Reasons for not finishing the study included medical issues (n=1), personal issues (n=2), study commitment issues (n=1), or

unreachable (n=3). Quadriceps capacity data were lost for one participant due to equipment failure. Therefore, the final sample used for analysis comprised 37 women (Table 3-1), with the following Kellgren-Lawrence scores: grade 1=1, grade 2=13; grade 3=16; grade 4=7. Participants with incomplete data (n=8) had lower self-efficacy compared to those who completed the study (-11.5 points; p=0.021). No other baseline descriptive statistics differed between groups (p>0.05), though there was strong suggestion of lesser quadriceps strength among non-completers (-0.35 Nm/kg; p=0.06).

The mean (SD) follow-up time was 2.23 (0.34) years, and varied from 1.05 to 2.76 years. At follow-up, mean mobility scores were as follows: 6MWT = 549.5 (85.0) meters, stair ascent = 4.3 (1.6) seconds, stair descent = 4.1 (1.8) seconds. The mean (SD) 6MWT score at follow-up was greater than that at baseline [+23.2 (52.0) meters; p=0.010]; whereas mean stair ascent [-0.13 (0.85) seconds; p=0.36] and descent [+0.03 (0.83); p=0.81] times were unchanged.

Regression diagnostics revealed no outliers that were not clinically plausible, thus data from all 37 participants were used. In regression models that displayed variance heterogeneity, robust error estimates were applied. To satisfy the assumption of noncollinearity, data for independent variables that displayed a large variance inflation factor (>10) were centered by subtracting the means from the respective terms of interest. No evidence of nonlinearity was noted on plots of standardized residuals versus each independent variable in the regression models.

Six Minute Walk Test

For change in 6MWT score, the covariate model yielded a R^2=0.31 (p=0.006) (Table 3-2). The separate addition of pain (p=0.002) increased the predictive ability of the model (R^2=0.49; p<0.001). The discrete addition of self-efficacy (p=0.030) also increased the predictive ability of the model (R^2=0.40; p=0.002). The separate addition of quadriceps strength (p=0.06) and power (p=0.43) did not explain additional variance.

No interaction was observed between measures of knee muscle capacity and patient-reported outcomes: strength and pain (p=0.90); strength and self-efficacy (p=0.94); power and pain (p=0.52); power and self-efficacy (p=0.57).

Stair ascent

For change in stair ascent time, the covariate model yielded a R^2=0.10 (p=0.30) (Table 3-3). The discrete addition of self-efficacy (p<0.001) increased the predictive ability (R^2=0.40; p=0.002). While pain was a significant predictor (p=0.025), it did not significantly increase the predictive ability of the model (R^2=0.24; p=0.065). The separate addition of quadriceps strength (p=0.53) and quadriceps power (p=0.54) did not explain additional variance.

There was a strength-by-self-efficacy interaction (p=0.015), with an increase in R^2 to 0.52 (p=0.001) (Figure 3-1). Also, a power-by-self-efficacy interaction was revealed (p=0.022), with an increase in R^2 to 0.50 (p=0.001) (Figure 3-2). No interaction was observed between strength and pain (p=0.053), and power and pain (p=0.18).

Stair descent

For change in stair descent time, the covariate model yielded a R^2=0.11 (p=0.78). Neither measures of quadriceps capacity (strength, p=0.24; power, p=0.89), nor patient-reported outcomes (pain, p=0.52; self-efficacy, p=0.44) explained additional variability.

No interaction was observed between measures of quadriceps capacity and patient-reported outcomes: strength and pain (p=0.39); strength and self-efficacy (p=0.20); power and pain (p=0.16); power and self-efficacy (p=0.17).

Discussion

Higher pain intensity/frequency and lower self-efficacy for functional tasks at baseline predicted decreased walking performance over 2 years in women with clinical knee OA. Lower baseline self-efficacy also predicted decreased stair ascent performance. While neither quadriceps strength nor power at baseline independently predicted mobility changes, lower muscle capacity (either quadriceps strength or power) interacted with poorer self-efficacy in predicting worsening stair ascent time over 2 years. These findings suggest that strategies aiming to sustain or improve mobility in women with knee OA must focus on controlling pain and boosting self-efficacy. In women with lower self-efficacy, developing knee muscle capacity remains an important target.

Over 2 years, the mean 6MWT score increased by 23.2 m; whereas stair ascent and descent scores were unchanged. The greater mean walking distance at follow-up, however, was smaller than the minimum detectable change (i.e., measurement error) for knee OA, and likely not clinically significant [30,33]. Little-to-no mean change in

performance-based measures over time is not surprising, as previous studies also reported no mean change in various mobility measures longitudinally in knee OA [5,34,35]. Nonetheless, a lack of mean change in mobility scores (at the group level) does not preclude the detection of statistically significant predictors of change in mobility, as was the case for change in stair ascent time. The large variability around the mean change score over 2 years, where SDs are multiples of the mean, emphasize that some individuals likely improved or worsened over that period. This notion aligns with previous work identifying different trajectories in knee OA, where some individuals remained stable, worsened or improved in different aspects of the disease over time [12,36,37].

Pain and self-efficacy for functional tasks were independently associated with 2-year change in mobility scores; contrary to our hypotheses, quadriceps strength and power were not. Previous investigations identified pain, self-efficacy, and quadriceps strength to be determinants of mobility in knee OA [1]. Results from this study corroborate the importance of pain and self-efficacy in predicting future mobility in this population. No such evidence was found for quadriceps strength, though a trend toward statistical significance was observed for change in walking performance. The latter may be due to some discrepancies across studies. For example, quadriceps strength was recorded during MVICs in this investigation; other studies assessed strength concentrically at constant speeds [3–5]. Nonetheless, moderate-to-high relationships exist between isometric and isokinetic strength measurements [38]. Interpretation of the literature may also be obscured because some prior studies analyzed women and men

conjointly [3,5], although reduced quadriceps capacity impacts knee OA progression differently across sexes (e.g., joint space narrowing, worsening pain) [39,40].

There is growing interest in muscle power as a critical determinant of mobility in knee OA [6–8]. The velocity component of muscle power may make this variable a better target of intervention since it can influence joint mechanics and loading during dynamic tasks commonly encountered in daily life [41]. The investigation of quadriceps power was a novel contribution of the current work.

Unique to previous studies, the current study observed interactions between each of quadriceps strength and power with self-efficacy in predicting change in stair ascent performance in women with knee OA. Previous reports indicated positive associations of baseline self-efficacy with change in stair-climbing performance over 2.5 years in 324 adults with knee pain [3], and chair sitting and standing mobility 3 years later in 236 adults with knee OA [4]. We advance this prior work by showing that among women with lower self-efficacy for functional tasks at baseline (compared to those with high self-efficacy), the impact of quadriceps strength and power on the change in stair ascent performance was more important. It appears that women with knee OA must perceive their muscular capacity in a positive light to influence a favorable outcome in terms of mobility. A similar interaction was noted between baseline quadriceps strength and self-efficacy in predicting change in stair-climbing performance over 2.5 years in adults with knee pain [3]. However, in that report, self-efficacy was specific to stair-climbing (ascent and descent evaluated conjointly), and reflected participants' level of certainty that they could perform the task 2, 4, 6, 8, and 10 times without stopping [3]. This hierarchical

measurement technique was consistent with the standard method developed by Bandura to measure task-specific self-efficacy [42]; nonetheless, it may not capture realistic situational demands encountered by most older adults with knee OA. A novel finding from the current analysis was the interaction between quadriceps power and self-efficacy in predicting change in stair ascent performance longitudinally. This interaction was similar to that of quadriceps strength with self-efficacy. This was the only instance when quadriceps power contributed to a significant model, suggesting that it may not actually be more important than quadriceps strength in predicting walking and stair-climbing mobility in women with knee OA.

Self-efficacy is a central component of self-management. Self-management education programs are complementary to and more effective in improving self-efficacy in OA than traditional patient education. Self-management education teaches problem-solving skills; traditional patient education typically offers information and technical skills [43]. Task-specific self-efficacy can also be enhanced by: (1) identifying and reinforcing patients' past/present successful accomplishments; (2) directing patients to observe successful behaviors of others; (3) providing positive feedback for patients' efforts; and (4) ensuring patients interpret their feelings correctly [13]. Accordingly, treatments to improve mobility may need to consider patients' disease manifestation and focus on advancing self-efficacy not only with self-management education but also by focusing patients on consciously acknowledging their muscle capacity.

While ample work supports an inverse relationship between knee pain intensity and self-reported physical function [4,9–11], the link between pain and performance-

based mobility in knee OA remains unclear [3,4,9–11]. Results from the present study suggest a modest, negative association between baseline knee pain and longitudinal change in mobility in women with knee OA. A similar finding was noted previously, where increased constant pain predicted decreased chair-stands performance over 2 years in women (n=133), but not men (n=189), with knee OA [10]. In contrast, baseline pain intensity did not predict change in stair-climbing performance over 2.5 years in 324 adults with knee pain [3], and in 20-meter timed walking at 2-year follow-up (n=322) [10] and chair sitting-and-standing mobility at 3-year follow-up (n=236) in knee OA [4]. Longitudinal evidence reporting on the link between pain and performance-based mobility in knee OA may be confounded by various factors. Some studies assessed pain using instruments that were not specific to OA, and did not analyze women and men separately [3,4], though each sex typically tends to experience/report pain differently [44]. Further, only one known study examined the relationship of different pain types (i.e., intermittent, constant) with mobility [10]. It may be that one type of pain (and not the other) is associated with mobility performance.

A trend toward statistical significance was observed for the interaction between pain and quadriceps strength in predicting change in stair ascent time. Of interest, Miller and colleagues [14] noted an interaction between baseline quadriceps strength and knee pain intensity in predicting 30-month change in car transfer performance in women and men with knee pain (n=317), only about half of whom had established OA [14]. While not entirely comparable, these results are important in characterizing various mobility limitations due to compromised knee joint health. Pain and muscle capacity likely

interact on mobility performance in various ways. Pain may play a role in arthrogenic inhibition of the quadriceps; that is, neural inhibition preventing the central nervous system from fully activating the muscle [45]. Also, weakness and atrophy of the quadriceps can result from disuse [46].

It is interesting that self-efficacy (and statistical trend for pain) interacted with muscle capacity only for the stair ascent task. Participants may attribute more importance to their self-efficacy (and pain) levels during stair ascent, a task more biomechanically demanding than walking or descending stairs. Ascending stairs requires greater knee and hip sagittal plane range of motion, moments and powers [16,17,47]. The quadriceps play a dominant role in progressing from step to step during stair ascent [17]. This task mainly involves concentric contractions of quadriceps and calf muscles, resulting in the generation of considerable internal energy (i.e., positive power). The knee generates the most energy during the "pull-up" phase, mostly due to quadriceps activity [17]. Conversely, in stair descent, the quadriceps contract eccentrically and are involved in significant energy absorption. Compared to walking and stair descent, greater muscle activity is thus required for stair ascent due to antigravity activity, type of muscle contractions and differences in loads imposed by various body positions. Muscle activity during concentric work would be expected to exceed that for equal eccentric work, and the body is less optimally positioned with the center of mass further from the point of support in stair ascent [17].

This study had limitations. The small variability around mean mobility scores and lack of mean change over 2 years in these measurements across the sample may have

limited the detection of significant associations between predictor and outcome variables. Medication use and comorbidities were not controlled for in the analyses, which may have modulated relationships between predictors (e.g., pain) and mobility. Selection bias due to the use of a convenience sample may have also affected the results (e.g., non-completers displayed lower self-efficacy). Generalisability of results to men or other populations is unknown.

In conclusion, in older women with clinical knee OA, lower self-efficacy for functional tasks at baseline predicted decreased performance over 2 years during walking and stair ascent. Higher baseline pain intensity/frequency also predicted decreased walking performance. Interactions were observed between baseline self-efficacy and each of knee extensor strength and power in predicting 2-year change in stair ascent performance. These findings support the use of strategies for bolstering self-efficacy and reducing pain to sustain or improve mobility over time in women with knee OA. Interestingly, future work could explore the impact of targeting knee extensor capacity in those with lower self-efficacy, and possibly greater pain, during biomechanically challenging tasks.

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Conflict of interest

The authors have no financial relationship with the organizations that sponsored the research. The authors have full control of all primary data and agree to allow the journal to review their data if requested.

Ethical standards

This longitudinal, observational study was approved by the institutional human research ethics board. Participants provided written, informed consent prior to their inclusion in the study.

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Table 3-1. Descriptive statistics of the sample at baseline (n=37 women).

Variable	Mean (Standard Deviation)	Minimum–Maximum
Age (y)	62.2 (5.5)	45–69
Body mass (kg)	72.5 (13.6)	52.6–104.8
Height (m)	1.61 (0.06)	1.45–1.74
Body mass index (kg/m^2)	28.1 (5.2)	20.1–41.8
Quadriceps strength (Nm/kg)	1.59 (0.49)	0.33–2.22
Quadriceps power (W/kg)	3.45 (1.41)	0.52–6.44
Pain (0-100) †	77.6 (15.3)	44.4–100
Self-efficacy (0-100) ϕ	91.2 (9.8)	64.0–100
Six Minute Walk Test (m)	526.2 (87.0)	317–747
Stair ascent (s)	4.4 (1.4)	1.7–8.5
Stair descent (s)	4.0 (1.4)	2.3–9.5

† Pain was measured with the Pain subscale of the Knee Injury and Osteoarthritis Outcome Score. Scores range from 0 (extreme pain) to 100 (no pain) [25].

ϕ Self-efficacy was measured with the Physical Function subscale of the Arthritis Self-Efficacy Scale. Scores range from 0 (very uncertain/unconfident) to 100 (very certain/confident) [27].

Table 3-2. Relationships of baseline covariates (age, body mass index, mobility score) and statistically significant predictors [and trends] (pain, self-efficacy, quadriceps strength) with the dependent variable *2-year change in Six Minute Walk Test score* (n=37).

Predictors	**Unstandardized β Coefficient**	**95% CI**	**R^2**	**P-value**
Covariates Only			0.309	**0.006***
Age	-1.4066	-4.3255, 1.5123		
Body mass index	-4.9601	-8.3391, -1.5812		
Six Minute Walk Test	-0.3664	-0.5758, -0.1570		
Covariates + Strength			0.381	**0.003***
Age	-0.8753	-3.7396, 1.9889		0.538
Body mass index	-3.6114	-7.1610, -0.0618		**0.046***
Six Minute Walk Test	-0.4280	-0.6397, -0.2163		**<0.001***
Strength	37.0398	-2.0633, 76.1430		0.063
Covariates + Pain			0.486	**<0.001***
Age	-1.5520	-4.1139, 1.0098		0.226
Body mass index	-3.6375	-6.7108, -0.5642		**0.022***
Six Minute Walk Test	-0.3985	-0.5832, -0.2138		**<0.001***
Pain	1.5259	0.5884, 2.4634		**0.002***
Covariates + Self-efficacy			0.405	**0.002***
Age	-1.1275	-3.8941, 1.6391		0.413
Body mass index	-4.2653	-7.5154, -1.0152		**0.012***
Six Minute Walk Test	-0.4133	-0.6154, -0.2112		**<0.001***
Self-efficacy	1.7834	0.1790, 3.3879		**0.030***

Note: Pain was measured with the Pain subscale of the Knee Injury and Osteoarthritis Outcome Score [25]. Self-efficacy was measured with the Physical Function subscale of the Arthritis Self-Efficacy Scale [27].

* Statistically significant at $p<0.05$.

Table 3-3. Relationships of baseline covariates (age, body mass index, mobility score) and statistically significant predictors [and trends], (pain, self-efficacy, quadriceps strength, quadriceps power) with the dependent variable *2-year change in stair ascent score* (n=37). Regression models used centered data for terms included in the interactions.

Predictors	**Unstandardized β Coefficient**	**95% CI**	**R^2**	**P-value**
Covariates Only			0.103	0.303
Age	0.0263	-0.0281, 0.0806		
Body mass index	0.0550	-0.0095, 0.1196		
Stair ascent	-0.1804	-0.4318, 0.0711		
Research Question 1				
Covariates + Pain			0.236	0.065
Age	0.0317	-0.0195, 0.0829		0.216
Body mass index	0.0426	-0.0189, 0.1042		0.168
Stair ascent	-0.2587	-0.5041, -0.0132		**0.040***
Pain	-0.0223	-0.0415, -0.0030		**0.025***
Covariates + Self-efficacy			0.404	**0.002***
Age	0.0227	-0.0224, 0.0677		0.313
Body mass index	0.0445	-0.0092, 0.0983		0.101
Stair ascent	-0.3411	-0.5647, -0.1174		**0.004***
Self-efficacy	-0.0542	-0.0816, -0.0267		**<0.001***
Research Question 2				
Covariates + Strength & Pain			0.333	**0.045***
Age	0.0406	-0.0106, 0.0917		0.116
Body mass index	0.0316	-0.0306, 0.0939		0.308
Stair ascent	-0.3525	-0.6428, -0.0623		**0.019***
Strength	0.0874	-0.7685, 0.9433		0.836
Pain	-0.0277	-0.0472, -0.0081		**0.007***
Strength*Pain	0.0423	-0.0006, 0.0852		0.053
Covariates + Strength & Self-efficacy			0.524	**0.001***
Age	0.0280	-0.0145, 0.0705		0.188
Body mass index	0.0362	-0.0158, 0.0882		0.165
Stair ascent	-0.4626	-0.7160, -0.2092		**0.001***
Strength	-0.1694	-0.8533, 0.5144		0.617

Self-efficacy	-0.0514	-0.0769, -0.0259		**<0.001***
Strength*Self-efficacy	0.0514	0.0108, 0.0920		**0.015***
Covariates + Power & Self-efficacy			0.501	**0.001***
Age	0.0278	-0.0152, 0.0709		0.197
Body mass index	0.0356	-0.0160, 0.0871		0.169
Stair ascent	-0.4367	-0.7135, -0.1599		**0.003***
Power	-0.0579	-0.2794, 0.1636		0.597
Self-efficacy	-0.0518	-0.0785, -0.0251		**<0.001***
Power*Self-efficacy	0.0218	0.0033, 0.0404		**0.022***

Note: Pain was measured with the Pain subscale of the Knee Injury and Osteoarthritis Outcome Score [25]. Self-efficacy was measured with the Physical Function subscale of the Arthritis Self-Efficacy Scale [27].

* Statistically significant at $p<0.05$.

Figures

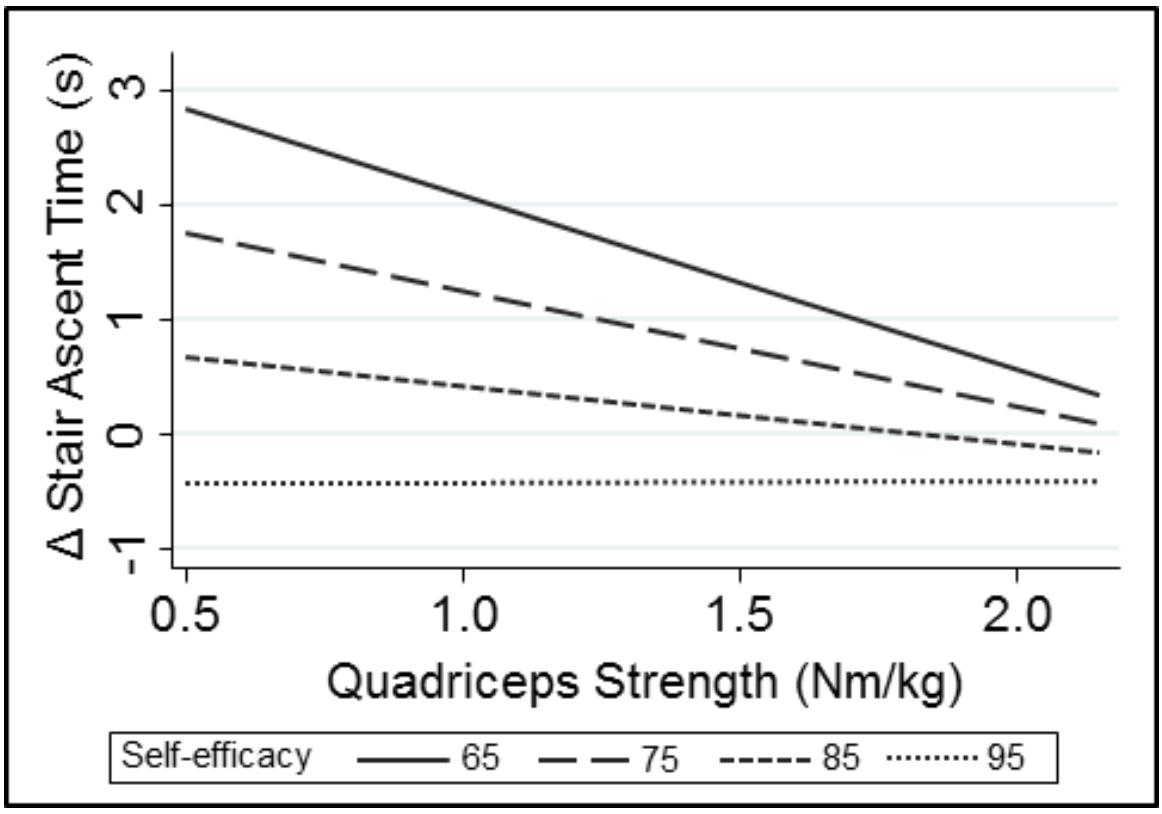

Figure 3-1. Interaction between baseline quadriceps strength and self-efficacy for functional tasks, after adjusting for baseline covariates (age, body mass index, mobility score), in predicting change in stair ascent time over 2 years in women (n=37) with knee osteoarthritis. Lower scores indicate lower self-efficacy. The impact of strength on change in stair ascent time is greater in those with lower self-efficacy.

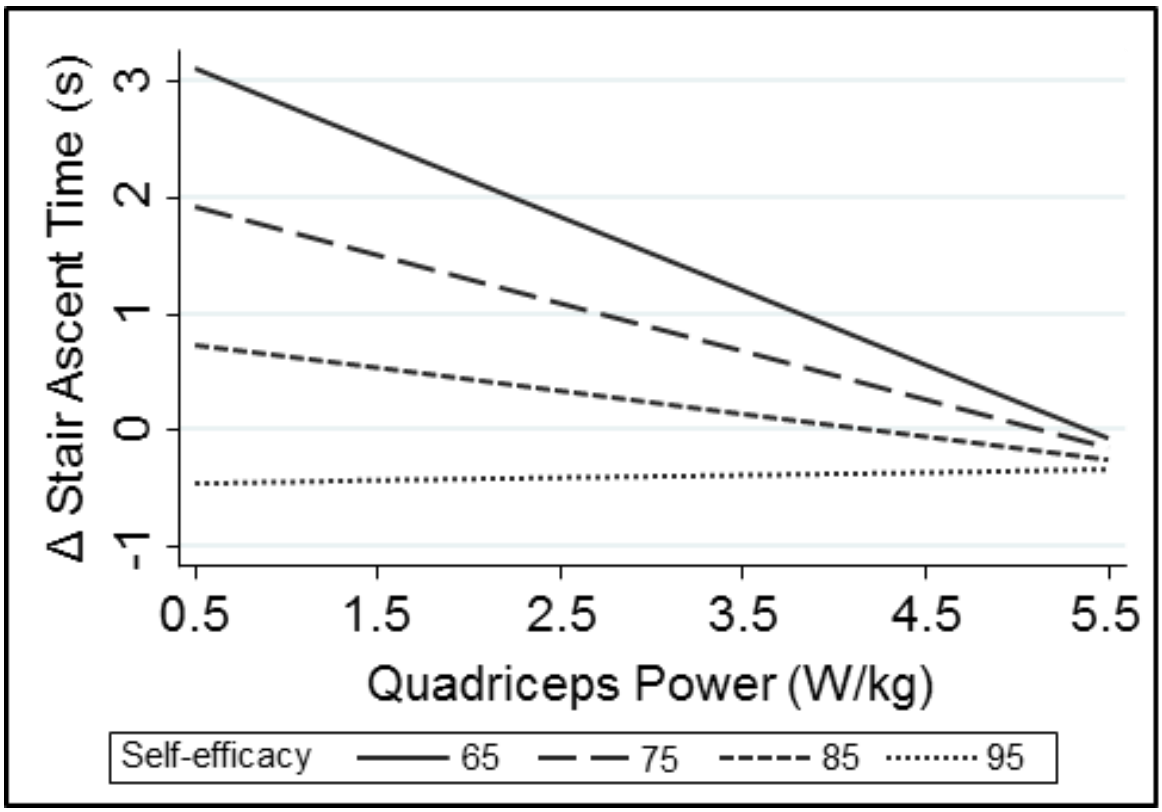

Figure 3-2. Interaction between baseline quadriceps power and self-efficacy for functional tasks, after adjusting for baseline covariates (age, body mass index, mobility score), in predicting change in stair ascent time over 2 years in women (n=37) with knee osteoarthritis. Lower scores indicate lower self-efficacy. The impact of power on change in stair ascent time is greater in those with lower self-efficacy.

CHAPTER 4

KNEE ADDUCTION MOMENT, BODY MASS INDEX & QUADRICEPS STRENGTH ARE IMPORTANT CLINICAL TARGETS IN KNEE OSTEOARTHRITIS

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RELATIVE AND ABSOLUTE TEST-RETEST RELIABILITIES OF BIOMECHANICAL RISK FACTORS FOR KNEE OSTEOARTHRITIS PROGRESSION: BENCHMARKS FOR MEANINGFUL CHANGE

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Abstract

Objective: Biomechanical factors are important treatment targets in knee osteoarthritis (OA). The knee adduction (KAM) and flexion (KFM) moments, quadriceps strength and power, physical activity, and body mass index (BMI) all have the potential to affect knee articular cartilage integrity by modulating forces across the joint. To identify clinically meaningful change, however, these measurements must be reliable and sensitive to change. This study estimated relative and absolute test-retest reliabilities over long periods of biomechanical risk factors for knee OA progression. *Design*: Data from a longitudinal, observational study were analyzed for knee OA patients with data at baseline, 6-month and 24-month follow-ups. Gait kinematics and kinetics, quadriceps strength and power, physical activity level and BMI were collected. Relative and absolute test-retest reliabilities of these measures were estimated using the intraclass correlation coefficient (ICC) and standard error of measurement (SEM), respectively. Minimal detectable change at the 95% confidence level (MDC95) was also calculated. *Results*: Data from 46 participants [36 women; mean age 61.0 (6.6) years] were included. Good-to-excellent relative reliabilities (ICC≥0.80) indicated that KAM peak and impulse, quadriceps strength and power, and BMI had a strong ability to discriminate amongst participants. Absolute reliabilities were high for quadriceps strength and BMI, which demonstrated reasonable within-participant variability (SEMs ≤11% of the mean). The MDC95 values supported the use of clinical interventions effective in reducing BMI and KAM, and increasing quadriceps strength. *Conclusions*: These data are useful to

researchers and clinicians in interpreting changes observed in biomechanical measurements during interventional or longitudinal investigations of knee OA.

Keywords: Arthritis; Biomechanical Phenomena; Muscle Strength; Muscle, Skeletal; Physical Fitness; Obesity

Running Headline: Reliability of biomechanical factors in knee OA

Introduction

Knee osteoarthritis (OA) progression can be characterized by joint tissue degradation, leading to worsening of symptoms (e.g., pain, swelling, stiffness) and ultimately functional disability. Biomechanical risk factors for the progression of structural knee OA include the knee adduction moment (KAM)[1–3], knee flexion moment (KFM)[1,4], muscle strength and power[5], physical activity[6,7], and body mass index (BMI)[3,8]. These factors are important modifiable treatment targets in knee OA, as each has the potential to affect joint tissue integrity by modulating compressive forces across the knee[9,10].

The external KAM is an indicator of the mechanical load distribution in the frontal plane, that is, between the medial and lateral compartments of the knee[10]. The KAM peak reflects a single maximum at one instance, whereas the KAM impulse incorporates both the magnitude and duration of load during stance. Larger magnitudes of KAM peak and impulse during gait predicted structural progression in knee OA[1–3]. The external KFM represents mechanical loading in the sagittal plane. A higher KFM peak during gait is speculated to be involved in knee OA structural progression; however, evidence supporting this claim remains conflicting[1–4]. The KFM is thought to work collaboratively with the KAM to modulate contact forces and the overall loading environment at the knee[1].

Strength and power are indicators of muscle capacity. Muscle strength is the ability to produce force; whereas muscle power represents the ability to generate as much force as possible, as quickly as possible. Individuals with knee OA often exhibit reduced quadriceps muscle capacity (i.e., weakness) compared to healthy knees, possibly caused

by disuse atrophy arising from load-bearing avoidance due to pain or arthrogenic inhibition[11]. Lower quadriceps capacity was associated with a higher risk for joint space narrowing and cartilage loss in knee OA[5].

Physical activity levels, or joint loading frequency, can also impact knee OA status. Disuse or overuse can result in irreversible cartilage degradation, while moderate levels of joint loading are paramount in maintaining knee joint tissue health[9]. Body mass index is commonly used to characterize body size and/or obesity. Higher BMIs are associated with joint tissue breakdown in knee OA[8], attributable to greater total accumulation of load and altered joint loading, as well as reduced tissue tolerance due to inflammation[12].

Since these biomechanical factors are modifiable, they represent potential targets for clinical intervention. Estimates of relative and absolute test-retest reliabilities must be established to ascertain whether the biomechanical risk factors are stable over time and can appropriately be used to characterize disease progression in knee OA. The reliability of these biomechanical measurements has been established previously, either in healthy populations[13–18], or in knee OA over a short period (i.e., within session or over several days)[19–24]. Mobility and patient-reported outcome (e.g., pain, physical function) measures are fairly stable over long periods (~3–5 years) in knee OA[25,26]. Therefore, it is fair to assume that test-retest reliabilities of biomechanical variables are also stable over time, though no study has confirmed this speculation. It is important to determine the reliability of these measurements over time, specific to knee OA, to identify their utility

in characterizing disease progression and to evaluate the outcome of therapeutic interventions.

The purpose of this study was to estimate both the relative and absolute test-retest reliabilities of biomechanical risk factors for progression of knee OA. The biomechanical risk factors of interest included the KAM peak and impulse, KFM peak, quadriceps muscle strength and power, physical activity level, and BMI. Because the goal of this analysis was parameter estimation, no hypotheses were formulated. The results will inform readers whether an observed change within a patient over time falls within the limits of measurement error or if it can be interpreted as true change.

Methods

This analysis was performed on a subset of data from a longitudinal, observational study, which was approved by the Hamilton Integrated Research Ethics Board at McMaster University, Canada. Data were analyzed for adults with clinical knee OA who had data at baseline, 6-month and 24-month follow-ups for at least one measurement of interest.

Participants

The larger cohort was comprised of a convenience sample of individuals (n=64) 40–70 years old with clinical knee OA. This sample was recruited from local rheumatology and orthopaedic surgery offices. Clinical knee OA was characterized according to the American College of Rheumatology specifications[27]. These criteria include having knee pain on most days of the month and at least three of the following: 50 years of age or

older, morning knee stiffness lasting less than 30 minutes, crepitus on active motion, bony tenderness, bony enlargement, and no palpable warmth of synovium[27]. Potential participants were excluded if they had other types of arthritis; past lower-limb joint injury and/or surgery; ipsilateral hip or ankle conditions; regular need for an adaptive walking aid; lower-limb trauma or used intra-articular therapies within the past 3 months. If participants had bilateral OA, the knee reported as having more severe symptoms was designated as the study knee. Participants provided written, informed consent.

Descriptive statistics were recorded at baseline, including age, sex and knee axis angle. Patient-reported outcomes were recorded using the Knee Injury and Osteoarthritis Outcome Score (KOOS)[28]. The radiographic disease severity was characterized by Kellgren-Lawrence (K-L) scores from anterior-posterior weight-bearing knee radiographs acquired in a standardized fixed-flexion position[29]. An experienced radiologist assessed all digital radiographs to yield anatomical knee axis angles and K-L scores.

Gait Analysis

Motion analyses were performed to calculate lower-limb kinematics and kinetics during barefoot gait at a self-selected speed. Participants wore a short-sleeved shirt and shorts. Infrared emitting diodes, arranged in triads on rigid bodies, were affixed to the sacrum, and lateral aspects of the mid-thigh, mid-shank and foot of the study limb. Three-dimensional kinematics were recorded at 100 Hz with a 9-camera high-speed motion capture system (Optotrak Certus, Northern Digital Inc., Waterloo, ON, Canada). Kinetics were collected synchronously at 1000 Hz with a floor-embedded force plate (OR6-7-1000, Advanced Mechanical Technology, Inc., Watertown, MA, USA). To create a

lower-limb model, the pelvis was digitized using bilateral anterior and posterior superior iliac spines, and greater trochanters. The leg was digitized at the greater trochanter; medial and lateral femoral and tibial condyles; tibial tuberosity; fibular head; medial and lateral malleoli; calcaneus; and first, second and fifth metatarsal heads to create rigid link-segment models of each participant. A static reference trial, with the participant standing in the anatomical position, defined neutral lower-limb joint angles. After practice, participants performed walking trials at a self-selected pace. To eliminate the effects of different shoes on dynamic knee loads, walking trials were performed barefoot. Five successful trials, where the foot of the study leg landed fully on the force platform, were analyzed.

Gait data were processed using commercial software (Visual 3D, C-Motion, Inc., Germantown, MD, USA). A second-order low-pass Butterworth bidirectional filter with 6 Hz cut-off was applied to marker and force plate data. External knee moments were calculated in a three-dimensional floating axis coordinate system[30]. The KAM peak and impulse, and KFM peak were determined for stance of five gait cycles, then averaged. Gait speed was computed. The KAM and KFM peaks were computed according to two common conventions: normalized to body mass (Nm/kg), and to percent bodyweight times height (%BW×HT). The KAM impulse was calculated using trapezoidal integration of only positive values (i.e., adduction) (Version 7.0.1, Matlab, MathWorks Inc., Natick, MA, USA) and expressed in non-normalized units (Nm×s) to reflect the absolute loading experienced by the medial knee, and normalized to percent bodyweight times height times second (%BW×HT×s).

Quadriceps Strength and Power

Quadriceps strength and power were measured with a dynamometer (System 3 Pro, Biodex Medical Systems, Inc., Shirley, NY, USA). Participants wore shorts and were positioned on the dynamometer according to manufacturer specifications. The knee joint center of rotation was aligned with the axis of rotation of the dynamometer, and straps were used to stabilize the chest, waist, mid-thigh and lower-leg. The weight of the lower-limb and dynamometer attachment was recorded while the knee was in slight flexion and muscles were relaxed, to correct torque data for gravity. Then, participants familiarized themselves with the protocol by flexing and extending their knee through full range of motion several times under minimal resistance.

Quadriceps strength was measured as participants executed five repetitions of a 5-second maximum voluntary isometric contraction of knee extensor muscles, with the knee in 60° of flexion. Full knee extension was defined as 0° flexion. A 5-second rest was given between each contraction. For strength tests, participants were instructed to "kick as hard as possible". Quadriceps power was measured during 10 consecutive knee extension-flexion cycles between 0° and 90° of flexion, with an arc of motion of at least 70°. For power tests, participants were instructed to "kick and bend their knee as fast and as hard as possible". Resistance during these isotonic contractions was set to 25% of the peak torque from maximum voluntary isometric contractions. For both the strength and power tests, participants were allowed to brace themselves using the handles or chest straps. Verbal encouragement and visual feedback were also provided to maximize volitional efforts.

The raw time, torque, and velocity data were extracted for each strength and power trial. Quadriceps strength was the mean of the three highest knee extensor peak torque values achieved during the isometric contractions. To generate measurements of power, velocities were transformed to radians/second and multiplied by torques. Quadriceps power was the mean of the three highest knee extensor peak power values achieved during the isotonic contractions. Quadriceps strength and power were computed according to two common conventions: normalized to body mass [strength (Nm/kg); power (W/kg)], and non-normalized [strength (Nm); power (W)].

Physical Activity

Physical activity was measured by a triaxial accelerometer (GT3X+, ActiGraph Corp., Pensacola, FL, USA). Participants were instructed to wear the accelerometer for seven consecutive days during waking hours, except for water activities. The accelerometer was attached to an adjustable belt around the waist, aligned with the anterolateral aspect of the study leg. Wear time and number of steps per day were computed (ActiLife 6, ActiGraph Corp., FL, USA) and verified subjectively using participant-reported physical activity logs. Only days during which the accelerometer was worn for at least 10 hours were retained[31]. Physical activity was characterized as the average number of steps per day (taken by both legs) over five days (selected chronologically).

Body Mass Index

Body mass and height were measured using a physician-quality scale and stadiometer. Body mass index was calculated as body mass divided by height squared (kg/m^2).

Statistical Analysis

Descriptive statistics including means, standard deviations, minimums and maximums for continuous variables, and counts for categorical data, were computed. Requisite assumptions for the various statistical tests were performed prior to proceeding with the analyses. Each measure was compared across the three assessment times with two-tailed paired *t*-tests. The relative test-retest reliability was estimated using Shrout and Fleiss type 2,1 intraclass correlation coefficients (ICCs), with 95% confidence intervals. The ICC represents the ratio of between-patient variability to total variability in a measure, where total variability captures both between- and within-patient variability. The ICC provides information about the ability of a measure to discriminate amongst participants, but it does not express measurement error in clinically meaningful terms, nor does it reveal the retest variability in its units of measurement[32]. We considered an ICC≥0.90 as high, 0.80–0.89 as moderate, and <0.80 as questionable[33]. The absolute test-retest reliability of the measures was estimated using the standard error of measurement (SEM), with 95% confidence intervals. The SEM captures the precision of a measure, or within-participant variability for a single test (i.e., 1 standard deviation of the distribution of error associated with a single test score), and quantifies the amount of measurement error in the same units as the original measurement[32]. A smaller SEM indicates that a measure

is more precise and potentially more sensitive to change. The minimal detectable change at the 95% confidence level (MDC95) was calculated by multiplying the SEM by the z-value associated with the corresponding confidence interval and the square root of two to account for measurement error on two test sessions (i.e., $MDC95=SEM\times1.96\times\sqrt{2}$). The MDC95 can be interpreted as 95% of truly stable patients will exhibit random variation less than this magnitude when assessed on repeated occasions; a change larger than MDC95 is often interpreted as a true change[32]. All tests were two-tailed with statistical significance set at $p<0.05$, and performed using Stata software (Version 13.1, StataCorp LP, College Station, TX, USA).

Results

Data for at least one measurement at all three time points (i.e., baseline, 6-month follow-up, 24-month follow-up) were available from 46 participants (36 women). These participants had the following baseline K-L scores: grade 1=2, grade 2=16; grade 3=15; grade 4=13. Additional descriptive statistics are presented in Table 4-1.

The mean (standard deviation) time between baseline and 6-month measurements is as follows: 6.2 (0.3) months for KAM peak, KAM impulse, KFM peak; 6.3 (0.5) months for quadriceps strength and power; 6.2 (0.4) months for physical activity; and 6.2 (0.4) months for BMI. The mean time between baseline and 24-month measurements is as follows: 24.4 (0.6) months for KAM peak, KAM impulse, KFM peak; 24.1 (0.7) months for quadriceps strength and power; 24.2 (0.6) months for physical activity; and 24.2 (0.5) months for BMI.

The biomechanical measurements at each time of assessment are displayed in Table 4-2. The mean KFM peak was different between baseline and 6-month follow-up (Nm/kg, p=0.055; %BW×HT, p=0.037), and between baseline and 24-month follow-up (Nm/kg, p=0.002; %BW×HT, p=0.001). No other systematic differences were observed across the three assessment times (p>0.05).

The relative and absolute reliability estimates, as well as MDC95 values for each biomechanical measurement are summarized in Table 4-3. Relative reliabilities were excellent for KAM impulse, quadriceps strength and BMI (ICC>0.90); good for KAM peak and quadriceps power (ICC=0.80–0.90); and questionable for KFM peak and physical activity (ICC<0.80). Absolute reliabilities were high for quadriceps strength and BMI, which demonstrated reasonable within-participant variability with SEMs ≤11% of the mean. To facilitate clinical interpretation, MDC95 values presented as percent error of the baseline mean (%MDC95), from smallest to largest were as follows: BMI (9%); quadriceps strength (30–31%), KAM impulse (45–50%); KAM peak (50–51%); quadriceps power (51–53%); KFM peak (56–57%); and physical activity level (57%).

Discussion

The current investigation expanded on previous work by reporting reliability estimates over longer intervals of biomechanical risk factors for the progression of knee OA. Relative reliability estimates were good-to-excellent (i.e., ICC>0.80) for KAM peak and impulse, quadriceps strength and power, and BMI, suggesting that these measurements are stable over time and can discriminate between individuals with knee OA. Absolute

reliability estimates were high for quadriceps strength and BMI, which demonstrated reasonable within-participant variability with SEMs ≤11% of the mean. The %MDC95 values suggested that BMI and quadriceps strength (and potentially KAM) represent appropriate targets of intervention, as true changes in these measurements are likely achievable. These data will aid clinicians and researchers establish cut-off values for patients at risk of disease progression, and interpret findings from interventional or longitudinal research by ascertaining whether observed changes over time in knee OA patients fall within the limits of measurement error or whether they can be interpreted as true change.

Biomechanical measurements have numerous sources of variability that can affect reliability estimates. Gait mechanics and muscle capacity are influenced by multiple factors. Knee moments are subject to sources of measurement error inherent to inverse dynamics (e.g., marker placement, skin motion artefact, error propagation by differentiating)[34], and also influenced by footwear, gait speed and joint pain[35–37]. Strength and power may be affected by verbal and visual encouragement and motivation, joint pain, and apprehension[38,39]. Physical activity levels can vary based on the day of the week, season, and other intrinsic and extrinsic factors[40]. Moreover, there are different disease trajectories in knee OA: patients may experience worsening, no change, or improvements over time[41–43]. These various trajectories in joint degradation, symptoms and physical function likely contribute to higher between-patient variability (and thus higher ICCs) but also higher within-patient variability over time, which may inflate SEMs and MDC95.

Relative reliabilities were good for KAM peak (ICC=0.84–0.85) and excellent for KAM impulse (ICC=0.92–0.93). The KAM peak exhibited SEMs of 0.07 Nm/kg (or 0.46 %BW×HT), and MDC95 of 0.20 Nm/kg (or 1.28 %BW×HT). Previous work has reported good-to-excellent repeatability of the KAM in healthy populations over separate days and weeks[13,14]. Reliability estimates from the current study are comparable to those noted in knee OA over shorter intervals. For example, when patients with medial knee OA (n=31) were tested twice within one week, KAM peak displayed an ICC=0.86, SEM=0.36 %BW×HT, and MDC95=1.00 %BW×HT[22]. In 20 patients with moderate knee OA assessed 2–11 weeks apart, KAM peak at early and late stance displayed ICCs=0.91–0.92 and SEMs=0.06 Nm/kg[23]. To our knowledge, this is the first study to report reliability estimates for the KAM impulse in knee OA. The SEMs for the KAM impulse was 1.77 Nm×s, slightly higher than that of 1.45 Nm×s reported for healthy individuals (n=30)[13].

On the other hand, the KFM peak displayed questionable ICCs (0.48–0.52), considerably lower than in healthy populations (i.e., ICC=0.88)[14]. Similarly, SEMs (0.13 Nm/kg) and MDC95 (0.36 Nm/kg) for KFM peak were higher than that reported for young healthy adults (i.e., SEM=0.04 Nm/kg; MDC95=0.10 Nm/kg)[14]. These poorer reliability estimates confirm previously reported data on knee OA, where KFM peak exhibited an ICC=0.57 and SEM=0.14 Nm/kg in knee OA patients (n=20) for measurements acquired twice over 2–11 weeks[23]. It is noteworthy that in the current sample, there was a systematic increase over time in mean KFM peak and mean gait speed [baseline: 1.24 (0.18) m/s; 6 months: 1.26 (0.17) m/s; 24 months: 1.35 (0.17) m/s].

These increases in KFM peak are likely due, at least in part, to increases in gait speed. Instability in KFM peak measurements over time may help explain why evidence linking the KFM with knee OA progression is inconsistent[1–4].

Biomechanical interventions with potential in altering the KAM include gait modifications, orthoses, modified shoes, and surgery. Contralateral cane use[44], increased step width[44], increased lateral trunk lean[44,45], lateral wedge insoles[46], modified shoes (e.g., stability, variable stiffness)[46], and valgus knee braces[47] showed mean reductions in KAM peak and impulse of less than 30%. These values are below the MDC95 thresholds, suggesting the interventions have questionable efficacy. More effective strategies include medial knee thrust gait[44] and medial opening wedge high tibial osteotomy[48], which can reduce the KAM peak and impulse by magnitudes nearing or exceeding the MDC95 thresholds. Achieving significant reductions in knee loads may require modifications to gait that are not feasible. Importantly, however, researchers must note that implementation of KAM-targeting interventions in knee OA may also indirectly modulate other joint mechanics, such as the KFM[44,47].

Quadriceps strength and quadriceps power exhibited excellent (ICC=0.91–0.93) and good (ICC=0.84–0.88) relative reliabilities, respectively. In healthy samples, quadriceps strength demonstrated good-to-excellent within and between-session reliabilities[15,16]. Short-term reliabilities of isometric quadriceps strength measured using a dynamometer have been examined in knee OA[19–21]. Within-session test-retest reliabilities ranged from good to excellent (ICC=0.83–0.94) for women (n=17)[19]. When assessed twice over 1 week, ICCs ranged from 0.82–0.96 depending on knee angle in 18

adults with mild symptomatic OA[20]. Further, isometric strength displayed an ICC=0.98, SEM=10.7 Nm, and a MDC90 of 25.0 Nm in 20 individuals with radiographic knee OA[21]. Overall, the short-term reliability estimates for quadriceps strength from the aforementioned studies of knee OA are comparable to those obtained in the current study.

Test-retest reliabilities of quadriceps power have been scarcely investigated. In young healthy individuals assessed over several days, average quadriceps power measured with a dynamometer displayed good-to-excellent between-session ICCs[15,16]. When tested on separate occasions one week apart, average quadriceps power displayed ICCs=0.92–0.94 in 18 adults with mild symptomatic knee OA[20], and peak power exhibited an ICC=0.82, SEM=9.9 W and MDC90=23 W in 20 patients with advanced hip or knee OA[24]. The ICCs for quadriceps power obtained in the current study are similar to previously reported values for knee OA. It should be noted that of the previous studies in knee OA samples, one measured average power using a dynamometer with velocity constant at 60 degrees/second[20], while the other measured peak power with a conventional knee extension machine where force remained constant[24]. In the latter work, four different unstandardized external resistances, estimated by the assessors, were tested. Values obtained from these tests were used to curve-fit force-velocity relationships, from which peak power was estimated. Comparisons of SEM and MDC values are not possible because external resistances were not reported[24] and likely very dissimilar as power magnitudes were 4–5 times greater in the present study.

Various knee muscle training programs are effective in increasing quadriceps strength in knee OA, well beyond the %MDC95 thresholds (30–31%)[49], suggesting that

quadriceps strengthening represents an important clinical target through which true changes in muscle capacity are possible. Muscle power training programs, on the other hand, are scarce. Limited evidence suggests that quadriceps power training has the potential to yield favorable (and real) improvements in quadriceps power in knee OA[50].

Of all biomechanical measurements examined in this study, BMI displayed the highest relative reliability estimate (i.e., ICC=0.96), and lowest within-participant variability, with an SEM=0.9 kg/m^2, and %MDC95=9%. In prior work, BMI measured twice in the same session or one week apart (by trained specialists and self-reported) demonstrated excellent test-retest relative reliability (i.e., ICC≥0.95) for healthy populations[17,18]. To our knowledge, no study has examined the test-retest reliability of BMI measurements in knee OA patients over short and/or longer follow-up periods. Nonetheless, it is important to characterize the magnitude of change in BMI that represents real change in individuals with knee OA to ascertain whether weight management strategies and/or interventions are truly effective. Weight loss can be achieved with exercise and dietary modifications, pharmacotherapy and bariatric surgery. The MDC95 values suggest that BMI is the biomechanical risk factor with the highest potential for clinical intervention to create meaningful change.

Physical activity level displayed a questionable ICC (0.64) and large within-participant variability with an SEM=1546 steps/day and %MDC95=57%. Physical activity frequency measured by accelerometry displayed an ICC=0.85 and SEM=1043 steps/day for healthy young adults (n=30) tested 2–4 weeks apart[13]. To our knowledge, the current study is the first to report reliability estimates for physical activity levels

measured objectively (as steps per day) in knee OA. For the current sample, ICCs were weaker and SEMs were larger than that reported for healthy adults[13]. Large within-participant variability is likely due to data being collected over different seasons and/or days of the week. Moreover, long-term physical activity habits are highly variable in a large number of adults, possibly due to differences in demographic, lifestyle, and health characteristics.

Study limitations should be acknowledged. Reliability estimates are only generalizable to older adults with clinical knee OA whose characteristics are comparable to those from the current sample. Data from the current study are also only applicable to knee OA patients whose measurements were acquired using equivalent experimental techniques and instrumentation.

In conclusion, good-to-excellent test-retest relative reliability estimates indicate that the KAM peak and impulse, quadriceps strength and power, as well as BMI have a strong ability to discriminate amongst individuals with knee OA. The absolute reliability estimates were high for quadriceps strength and BMI, indicating that these measures exhibit reasonable within-patient variability. The MDC95 values support the use of clinical interventions effective in reducing BMI and the KAM, and increasing quadriceps strength. These data are useful to researchers and clinicians in interpreting changes observed in these biomechanical measures in knee OA patients during interventional or longitudinal investigations.

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Author Contributions

Each author made substantial contributions to the study conception and design (PWS, MRM), and/or acquisition (NMB, MRM), analysis and interpretation of data (NMB, PWS, MRM). Each author was involved in drafting the manuscript or revising it critically for important intellectual content (NMB, PWS, MRM). All authors have read and approved the final submitted manuscript.

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The study sponsors were not involved in the study design, collection, analysis and interpretation of data, writing of the manuscript or decision to submit the manuscript for publication.

Competing Interest Statement

No financial support or other benefits from commercial sources have been received for the work reported on in the manuscript.

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Table 4-1. Descriptive statistics of participants at baseline (n=46).

Variable	Mean (SD)	Minimum–Maximum
Age (years)	61.0 (6.6)	41–70
Body mass (kg)	75.1 (16.3)	51.0–117.0
Height (m)	1.64 (0.09)	1.45–1.94
Knee axis angle (º) ϕ	182.0 (3.8)	174.1–191.3
Pain (0-100) †	77.6 (15.9)	44.0–100
Other symptoms (0-100) †	76.5 (14.7)	39.0–100
Function in daily living (0-100) †	84.1 (15.5)	35.3–100
Function in sports and recreation (0-100) †	68.8 (22.9)	25.0–100
Knee related quality of life (0-100) †	65.0 (18.7)	13.0–100

ϕ Value above 180º indicates valgus knee alignment.

† Pain, other symptoms, function in daily living, function in sports and recreation, and knee related quality of life were measured with the Knee Injury and Osteoarthritis Outcome Score. Scores range between 0 and 100, where lower scores reflect worse symptoms and function [28]

Table 4-2. Biomechanical measurements of participants at the three times of assessment.

			Baseline		**6 Months**		**24 Months**	
	Unit	*N*	*Mean (SD)*	*Min.–Max.*	*Mean (SD)*	*Min.–Max.*	*Mean (SD)*	*Min.–Max.*
KAM peak	Nm/kg	32	0.40 (0.17)	0.11–0.80	0.41 (0.19)	0.10–0.84	0.43 (0.20)	0.04–0.85
	%BW×HT	32	2.50 (1.11)	0.66–4.96	2.60 (1.22)	0.62–5.21	2.70 (1.26)	0.22–5.35
KAM impulse	Nm×s	32	9.73 (6.43)	0.84–24.91	9.85 (6.33)	1.36–25.63	9.62 (6.22)	0.17–24.27
	%BW×HT×s	32	0.84 (0.52)	0.07–2.16	0.86 (0.51)	0.11–1.96	0.83 (0.50)	0.01–2.08
KFM peak	Nm/kg	32	0.64 (0.20)	0.30–1.10	0.73 (0.19)	0.41–1.10	0.82 (0.24) ‡	0.30–1.43
	%BW×HT	32	3.94 (1.13)	1.91–6.41	4.55 (1.13) †	2.66–6.67	5.04 (1.41) ‡	1.90–8.87
Strength	Nm/kg	37	1.66 (0.58)	0.38–3.43	1.75 (0.62)	0.22–3.32	1.77 (0.68)	0.54–3.48
	Nm	37	120.7 (48.4)	41.0–322.4	126.7 (50.4)	25.4–313.3	126.4 (52.9)	40.5–325.5
Power	W/kg	37	4.08 (1.90)	0.67–9.75	4.23 (2.01)	0.35–9.50	4.20 (1.91)	0.68–8.38
	W	37	296.5 (154.3)	72.8–917.0	310.3 (168.1)	40.6–897.3	303.2 (149.5)	49.6–783.6
Physical activity	steps/day	41	7491 (2972)	2374–14064	6454 (2414)	2394–11887	6713 (2579)	2142–13059
BMI	kg/m^2	44	27.5 (4.9)	19.9–41.5	27.6 (4.8)	20.4–42.6	27.3 (4.8)	20.3–39.1

Note: Min.–Max. = Minimum–Maximum; KAM = knee adduction moment; KFM = knee flexion moment; BMI = body mass index.

† The mean at 6-month follow-up is statistically significantly different from the mean at baseline ($p<0.05$).

‡ The mean at 24-month follow-up is statistically significantly different from the mean at baseline ($p<0.05$).

Table 4-3. Summary of the relative (ICCs) and absolute (SEMs) test-retest reliabilities, as well as the minimum detectable change at the 95% confidence interval for biomechanical risk factors for knee osteoarthritis progression. Reliability estimates are based on data obtained at baseline, 6-month and 24-month follow-ups.

	Unit	**ICC (95% CI)**	**SEM (95% CI)**	**MDC95**
KAM peak	Nm/kg	0.84 (0.74, 0.91)	0.07 (0.06, 0.09)	0.20
	%BW×HT	0.85 (0.75, 0.92)	0.46 (0.39, 0.56)	1.28
KAM impulse	Nm×s	0.92 (0.87, 0.96)	1.77 (1.50, 2.14)	4.90
	%BW×HT×s	0.93 (0.88, 0.96)	0.14 (0.12, 0.17)	0.38
KFM peak	Nm/kg	0.52 (0.26, 0.72)	0.13 (0.11, 0.16)	0.36
	%BW×HT	0.48 (0.22, 0.69)	0.81 (0.69, 0.99)	2.25
Strength	Nm/kg	0.91 (0.85, 0.95)	0.18 (0.16, 0.22)	0.50
	Nm	0.93 (0.88, 0.96)	13.4 (11.6, 16.1)	37.2
Power	W/kg	0.84 (0.75, 0.91)	0.78 (0.67, 0.93)	2.15
	W	0.88 (0.81, 0.93)	54.8 (47.1, 65.4)	151.8
Physical activity	steps/day	0.64 (0.48, 0.78)	1546 (1339, 1829)	4284
BMI	kg/m^2	0.96 (0.94, 0.98)	0.9 (0.8, 1.1)	2.6

Note: ICC = intraclass correlation; SEM = standard error of measurement; CI = confidence interval; MDC95 = minimum detectable change at the 95% confidence interval; KAM = knee adduction moment; KFM = knee flexion moment; BMI = body mass index.

CHAPTER 5

DISCUSSION

Thesis Summary

The overarching objective of this thesis was to investigate the role of various factors involved in the progression of knee OA, including biomechanical, PRO and mobility measures. Knee OA is a multifactorial disease whose progression involves worsening joint structure, symptoms, and mobility (Lane et al., 2011). Thus, to acquire a comprehensive understanding of how knee OA evolves over time, it was important to consider the multiple factors involved in disease progression. Results from this thesis advance the present body of knowledge, specific to knee OA, concerning the association between mechanical joint loading exposure and in vivo longitudinal changes in cartilage morphology; the relationship of muscle capacity and PROs with longitudinal changes in mobility performance; and the reliability of biomechanical measurements over long time intervals.

In the first study, we demonstrated that large magnitude KAM peak and impulse at baseline each interacted with BMI to predict loss of medial tibial cartilage volume over 2.5 years among individuals with knee OA. These interactions suggested that larger joint loads in those with higher BMIs were associated with greater loss of medial tibial cartilage volume. Findings from the second study showed that, in women with clinical knee OA, lower baseline self-efficacy for functional tasks predicted decreased walking and stair ascent performances over 2 years. Higher baseline pain intensity/frequency also

predicted decreased walking performance. Furthermore, quadriceps strength and power each interacted with lesser self-efficacy to predict worsening stair ascent times over 2 years. These interactions suggested that among women with lower self-efficacy, the impact of lesser quadriceps strength and power on worsening stair ascent performance was more important. Results from the third study demonstrated that the KAM peak and impulse, quadriceps strength and power, and BMI had good-to-excellent relative reliabilities (ICC>0.80), suggesting that these measurements are stable over prolonged periods and appropriate to differentiate between knee OA patients. Absolute reliability estimates were high for quadriceps strength and BMI, which showed reasonable within participant variability with SEMs lower than 15% of the mean. The MDC95 values supported the use of clinical interventions effective in reducing BMI and the KAM (peak, impulse), and increasing quadriceps strength, as these variables are modifiable.

Examining Different Elements of Osteoarthritis

This thesis examined various elements involved in OA, a multifactorial disease, including worsening joint structure, symptoms and/or mobility. Of prime importance is the fact that there exist various disease trajectories in knee OA, where patients may experience worsening, no change, or improvements over time in diverse aspects of the disease (Bartlett et al., 2011; Bastick et al., 2016; Collins et al., 2014; Oiestad et al., 2016; White et al., 2016). While the interrelationships between changes in joint structure, symptoms and mobility remain unclear, data from various longitudinal studies demonstrate that the vast majority of individuals with knee OA experience relatively stable disease. Little

work has explored the trajectory of biomechanical factors involved in OA over time; this thesis contributes important data toward that goal.

Concerning structural disease progression, seven trajectories of joint space narrowing over two years were identified amongst 622 adults with symptomatic medial knee OA (Bartlett et al., 2011). Specifically, four groups (71% of individuals) exhibited joint space width stability (no change), which was unrelated to joint space width at baseline. Three atypical trajectories were identified: slow (20%), moderate (7%) and rapid progressors (2%). Slow and moderate progressors were older and heavier, while rapid progressors tended to be men. The three progressor groups had amongst the least joint space width at baseline (Bartlett et al., 2011).

With respect to the progression of symptoms, six distinct pain trajectories (assessed with a numerical rating scale) were identified in 705 individuals with early symptomatic knee OA (K-L≤1): constant mild pain (26%), constant severe pain (10%), moderate progression (27%), severe progression (5%), moderate regression (29%), and major regression (3%) (Bastick et al., 2016). Higher BMI, lower education, greater comorbidity, greater activity limitations, and joint space tenderness were more often associated with trajectories characterized by more pain at baseline and pain progression compared with the reference group with a constant mild pain trajectory. No association was observed between pain trajectories and baseline radiographic features (Bastick et al., 2016). Moreover, in 1,753 symptomatic knees with mild-to-severe radiographic OA (K-L≥2), five distinct pain trajectories (characterized by WOMAC pain scores) over 6 years were identified: severe pain (6%), high moderate pain (17%), low moderate pain (32%),

mild pain (35%), and no pain (11%) (Collins et al., 2014). None of the trajectories exhibited substantial worsening or improvement over time: individuals with moderate pain tended to remain in moderate pain, while those with more severe pain tended to stay in severe pain. In multivariate models, a higher K-L grade, obesity, depression, greater comorbidities, female sex, non-white race, lower education, and younger age were associated with trajectories characterized by worse pain (Collins et al., 2014).

Regarding changes in physical function and mobility, 802 individuals with incident symptomatic knee OA (i.e., had no symptomatic knee OA at baseline but had developed new disease at 30-to-36-month follow-up) were assessed over 54–72 months (Oiestad et al., 2016). Self-reported physical function (determined by the WOMAC physical function subscale) remained stable or slightly declined over time, while mobility performance during the 20-meter walk test (and in some cases, for the 5-time sit-to-stand test) worsened (Oiestad et al., 2016). Furthermore, trajectories of functional decline over 84 months, along with associated risk factors, were examined for 1055 older adults (2110 knees) without limitations at baseline and who had or were at risk of knee OA (White et al., 2016). Five trajectories of physical function (as determined by the WOMAC physical function subscale) were identified: high functioning (remained free of limitation, 54%), minimal limitation (slowly declined, 26%), late worsening (free of limitation for first 36 months and then declined, 9%), remitting (rapidly declined over first 12 months then gradually recovered, 6%), and progressive worsening (steadily declined, 5%). Worse radiographic disease, worse knee pain, obesity and depressive symptoms at baseline were associated with trajectories of worse functional decline (White et al., 2016).

In considering these previous findings, it is clear that each of the disease features – structure, symptoms and physical function – remains relatively stable over time for the majority of knee OA patients. Importantly though, in those who worsen over time, other factors (e.g., age, sex, obesity, and other comorbidities) seem to play a crucial role. This is an important consideration for knee OA clinical interventions as the patients who worsen over time represent the subgroup in need of most help. Interestingly, while worse symptomatic and structural disease at baseline each seem to be involved in worsening physical function (White et al., 2016), the link between symptoms and worsening structure (and vice versa) remains unclear (Bartlett et al., 2011; Bastick et al., 2016; Collins et al., 2014). Findings from these studies stress the importance of work – such as this thesis – that investigates the distinct, yet somewhat interrelated, disease attributes to gain a better understanding of knee OA evolution over time. Accordingly, this thesis found associations between mechanical joint loading and structural disease progression; and between each of pain and self-efficacy (and muscle capacity) with worsening mobility in knee OA.

Knee Adduction Moment & Obesity Interact in Predicting Cartilage Loss

This thesis observed interactions between each of the KAM peak and impulse with BMI. In the regression models, BMI was included as a covariate but its interaction terms with the biomechanical gait variables were also examined as they could bear clinical importance since BMI is modifiable. Consistent evidence has demonstrated the detrimental influence of obesity on cartilage defects (Mezhov et al., 2014). However, the

association between obesity and changes in knee cartilage morphology is less clear (Mezhov et al., 2014). The association between higher BMI and tissue breakdown can be attributed to a greater total accumulation of load as well as other factors including altered loading patterns, increased contact forces (compressive and shear) and increased dynamic loads at the knee (Browning & Kram, 2007; Griffin & Guilak, 2005; Harding et al., 2016; Messier et al., 2014; Segal et al., 2009). The greater loads imparted by adipose tissue appear to be directly associated with, or responsible for, altered knee dynamics implicated in cartilage breakdown, as suggested by the interaction between the KAM and obesity on cartilage volume reductions. Obesity is linked with joint degradation in the presence of loading likely due to the combination of: (i) altered spatiotemporal parameters such as prolonged stance duration (and thus duration of cartilage compression); and (ii) imbalanced loads across the knee joint surface with cartilage unable to adequately accommodate such load alterations, especially in the presence of reduced tissue tolerance due to inflammation. Shifting BMI from obesity to normal/overweight categories may represent a crucial strategy to curb structural disease progression associated with mechanical abnormal and over-loading in knee OA.

Knee Flexion Moment & Cartilage Loss

Medial knee contact forces can be better predicted using a combination of the KAM and KFM than just the KAM alone (Manal et al., 2015; Walter et al., 2010). The KFM is thought to act collaboratively with the KAM in modulating the loading environment at the knee (Chehab et al., 2014; Manal et al., 2015; Walter et al., 2010). While recent

research supports the role of the KFM in OA progression, evidence is conflicting (Chang et al., 2015; Chehab et al., 2014; Erhart-Hledik et al., 2015). Findings from the first thesis study – no association between the KFM peak (alone or in combination with the KAM peak) with longitudinal changes in cartilage morphology – corroborated those from a study with similar follow-up time and large sample (n=385 knees) that controlled for seven relevant covariates collectively (Chang et al., 2015). In contrast, one longitudinal study observed a relationship between greater baseline KFM peak and reduced medial tibial cartilage thickness over 5 years in 16 individuals with knee OA (Chehab et al., 2014). It is difficult to be confident in findings based on such a small sample size, especially when the inclusion of covariates in the statistical models was restricted (Chehab et al., 2014). Specifically, for each dependent variable of cartilage change, regression models were ran six times and included two predictor variables (i.e., KAM and KFM peaks) and one covariate at a time (i.e., age, gender, BMI, K-L grade, pain score, walking speed). The authors argued that this method (of adding one covariate at a time) was preferred in order to avoid an over-fitted model with all eight independent variables (Chehab et al., 2014). However, this approach is limited because these aforementioned covariates can have mediating effects on one another and on the dependent variable when included in one same regression model, which could drastically change the beta coefficients (or effect sizes). Furthermore, the multiple comparisons (i.e., multiplicity) tested with this approach and the lack of statistical correction for these comparisons (e.g., Bonferroni, Sidak) inflated the risk for type I errors, that is, detecting a significant effect when in fact there is not one.

Of interest, the interplay between the KAM and KFM on the loading environment may depend on OA severity (Erhart-Hledik et al., 2015). The impact of the KFM on degenerative cartilage changes may be more important in early stages of OA when symptoms are less severe (Erhart-Hledik et al., 2015). This supposition may explain why this thesis work found no association between the KFM and subsequent cartilage loss. The majority (61.5%) of the sample investigated in this thesis work had advanced disease (K-L≥3), while over half (56.3%) the sample in the work by Chehab et al. (Chehab et al., 2014) had early disease (K-L≤2). Conversely, the work by Chang et al. (Chang et al., 2015), which also found no association, examined a sample more comparable to that from Chehab et al. (Chehab et al., 2014) than ours, with 70.3% of participants having early structural disease (K-L≤2). Importantly, that work was adequately statistically powered to detect the observed effects (Chang et al., 2015). Moreover, findings from the third thesis study indicated through questionable relative and absolute test-retest reliabilities that the KFM peak is unstable over time in knee OA, which may also explain why evidence linking the KFM with disease progression is inconsistent. Future studies that are adequately powered statistically and control simultaneously for relevant covariates may shed light on the role of the KFM in knee OA progression.

Loading Frequency & Cartilage Loss

The response of cartilage to mechanical loading depends on the magnitude, duration, frequency and rate of loading (Chen et al., 1999; Jones et al., 2003; Lu & Mow, 2008; Qi & Changlin, 2006). The KAM and KFM peaks are features of the distribution of loading

magnitude; KAM impulse incorporates both the magnitude and duration of loading. Nonetheless, neither the peak nor impulse measures capture information about loading frequency, a crucial theoretical component that affects the way cartilage responds to mechanical stimuli. Only one known study has investigated the effect of in vivo loading frequency, measured objectively, on cartilage breakdown in knee OA (Oiestad et al., 2015b). Accelerometer-derived data on knee loading frequency are required to obtain an accurate measurement of knee loading frequency; self-report measures typically tend to overestimate physical activity levels (Dyrstad et al., 2014).

The first thesis study was amongst the first investigations to report in vivo loading frequency in individuals with knee OA. Results from this study found no association between baseline loading frequency and subsequent changes in medial tibial cartilage thickness or volume. This finding is in agreement with those observed over 2 years in 779 knees with early structural OA (i.e., K-L≤2) (Oiestad et al., 2015b). While these studies suggest no link between baseline loading frequency and further cartilage loss in knee OA, caution should be taken when interpreting these findings. The abovementioned studies used measurements of loading frequency at baseline but did not investigate whether changes in loading frequency over time related to cartilage changes. It may be that drastic changes in loading frequency are associated with concurrent changes in knee cartilage morphology. Interestingly, results from the third thesis study indicated that loading frequency (i.e., physical activity level) was relatively unstable over time in older adults with knee OA, with high within-participant variability (SEM=1546 steps/day) over longer periods. This finding may help explain why evidence linking loading frequency

with disease progression remains unclear. Examining longitudinal changes in loading frequency with concurrent changes in knee cartilage morphology in knee OA may yield stronger relationships between variables. Moreover, Oiestad and colleagues (Oiestad et al., 2015b) examined a sample with K-L grades 0–2. The sample investigated in this thesis was more heterogeneous as it comprised participants ranging from K-L grades 1–4. It is possible that loading frequency is more important to cartilage breakdown during later stages of the disease. The heterogeneity of our sample may have hindered our ability to detect such an effect. Finally, both studies included participants with relatively low physical activity levels [i.e., 7786 (3876) (Brisson et al., 2017) and 7185 (2565) (Oiestad et al., 2015b) total steps/day]. It may be that participants in these studies were not active enough to induce further cartilage loss. For instance, amongst 405 older community-dwelling adults, higher loading frequency (>10,000 steps/day) was associated with reductions in cartilage volume in those with lower baseline cartilage volume (Doré et al., 2013). The relatively small variability in the mean loading frequency data may have also masked the detection of effects of too little or too much loading frequency on cartilage changes. Future studies should evaluate the effect of in vivo loading frequency (and change in loading frequency) on cartilage changes in knee OA, while adjusting for the abovementioned shortcomings from previous studies.

Cumulative Knee Adductor Load & Cartilage Loss

Examining the individual effects of the KAM impulse and knee loading frequency may not provide a comprehensive understanding of the mechanical elements implicated in

cartilage loss longitudinally in knee OA. This thesis was the first to evaluate whether "cumulative knee adductor load" was valuable in understanding cartilage loss over time in knee OA. Cumulative knee adductor load incorporates the magnitude and duration of load (i.e., KAM impulse) as well as load frequency (i.e., steps/day). This concept was believed to more accurately reflect a mechanism of joint tissue degradation from overall accumulated exposure to medial knee loads (Robbins et al., 2009). Result from this thesis work demonstrated that the combination of KAM impulse and loading frequency into one regression model, representing cumulative load, was not associated with cartilage morphological changes over 2.5 years in knee OA. This conceptual measure may not have been useful in predicting cartilage changes in this study due to the previously discussed shortcomings of the loading frequency component (i.e., low mean and variability of the sample). It is interesting to note that cumulative load distinguished between healthy and osteoarthritic knees, results that were driven by the KAM impulse and not the loading frequency component (Maly et al., 2013). It may be that loading frequency is simply not a primary driver of further cartilage degeneration in established knee OA.

Pain & Mobility

While it seems intuitive that pain severity is inversely associated with mobility performance in knee OA, there is in fact limited evidence supporting this notion. An abundance of literature supports a negative relationship between pain and self-reported physical function (Davison et al., 2016; Riddle & Stratford, 2013; Sharma et al., 2003;

White et al., 2016) but data linking worse pain with worse performance-based mobility are inconsistent (Davison et al., 2016; Rejeski et al., 2001; Riddle & Stratford, 2013; Sharma et al., 2003; White et al., 2016). While self-reported measures of physical function are important in capturing patients' perceived performance, these measures do not necessarily reflect actual physical capabilities. Self-reported and performance-based physical function are only moderately correlated (Maly et al., 2006; Stratford et al., 2006).

Results from this thesis work supported a modest, negative association between knee pain and longitudinal change in walking (but not stair-climbing) performance in women with knee OA. Existing longitudinal evidence reporting on the association between pain and performance-based physical function may be confounded by various factors. Some investigations evaluated pain with instruments that were not specific to OA, and analyzed women and men conjointly (Rejeski et al., 2001; Sharma et al., 2003) though each sex typically tends to experience and report pain differently (Fillingim et al., 2009). It may also be that different pain types are more strongly related to mobility performance than others. For instance, increased constant (but not intermittent) pain predicted decreased chair-stands performance over 2 years in women (n=133), but not men (n=189), with knee OA (Davison et al., 2016). Future studies examining the link between pain and mobility performance in knee OA should use disease-specific PROs that are able to characterize the unique pain experienced by OA patients, and control for participant sex either statistically or by performing subgroup analyses.

Muscle Capacity & Patient-Reported Outcomes Interact on Mobility Changes

The second thesis study demonstrated that lower self-efficacy at baseline independently predicted decreased walking and stair ascent performances over 2 years, results that are in agreement with those from previous investigations (Rejeski et al., 2001; Sharma et al., 2003). Conversely, no independent association was found between each of baseline quadriceps strength or power with changes in mobility performance over 2 years in women with knee OA. This work was the first to investigate the idea that quadriceps power maybe a more critical determinant of mobility than strength in knee OA, though results did not confirm this speculation. Interestingly, however, interactions were observed between each of quadriceps strength and power with self-efficacy in predicting change in stair ascent performance over 2 years in women with knee OA, where the impact of lower quadriceps strength or power on change in stair ascent performance was more important in women with lower self-efficacy (compared to those with higher self-efficacy). In a similar manner, results from this thesis work noted a trend toward a statistically significant interaction between quadriceps strength and pain in predicting change in stair ascent time over 2 years in women with knee OA. The observed interactions between physical capacity and PROs suggest that these elements likely act together (rather than alone) in worsening mobility over time in women with knee OA, a notion scarcely reported on in previous literature (Miller et al., 2001; Rejeski et al., 2001).

Role of Biomechanics in the Progression of Knee Osteoarthritis

A common thread through this thesis was the evaluation of biomechanical factors in the progression of knee OA. While previous work has established that biomechanics are indeed implicated in OA progression, the strengths of the relationships between biomechanical factors and worsening disease were not particularly strong (Bennell et al., 2011b; Brisson et al., 2017; Chang et al., 2015; Chehab et al., 2014; Miller et al., 2001; Rejeski et al., 2001; Sharma et al., 2003). For instance, a KAM impulse larger by 1.0 %BW×HT×s was associated with a reduction of only 3.38% in medial tibial cartilage thickness over 2 years in knee OA, after adjusting for various covariates (Chang et al., 2015). Given the mean (SD) of the KAM impulse for the sample [0.60 (0.44) %BW×HT×s], a 1-unit difference in the KAM impulse is very large. In addition, evidence supporting a discrete link between each of the KFM and loading frequency with structural disease worsening is sparse and conflicting (Brisson et al., 2017; Chang et al., 2015; Chehab et al., 2014; Erhart-Hledik et al., 2015). Regarding reduced muscle strength, some work has shown it to be directly implicated in worsening mobility in knee OA (Davison et al., 2016; Sharma et al., 2003); whereas other research demonstrated that its effect on mobility was mediated by other factors (e.g., pain, self-efficacy) (Brisson et al., 2017; Miller et al., 2001; Rejeski et al., 2001). As a whole, findings from this thesis support (through relatively small effects) the notion that biomechanical factors play a modest independent role in OA progression. Alternatively, results support the fact that knee OA is not purely a wear-and-tear disease due to mechanical overuse. Rather, data

seem to indicate that biomechanical factors do not work in isolation, reflecting the multifactorial nature of OA.

On their own, biomechanical factors (i.e., mechanical loads, muscle capacity) seem relatively stable and modestly implicated in OA progression. However, in the presence of other circumstances – obesity, low self-efficacy, high pain intensity/frequency – biomechanical factors grab a hold and vastly worsen OA. This idea is supported by the observed interactions between the KAM and obesity on structural disease progression, and between quadriceps capacity and self-efficacy and pain on worsening mobility. Importantly, these data point to the idea that when knee OA patients present with clinical problems (e.g., obesity, pain, poor self-efficacy), there are probably biomechanical factors that are concurrently implicated in exacerbating the disease.

Developing Effective Treatment Strategies in Knee Osteoarthritis

Many conservative and surgical strategies aim to correct biomechanical abnormalities in knee OA. Such strategies typically include altering specific joint loading parameters such as the KAM (through gait modifications, orthoses/modified shoes or medial opening wedge high tibial osteotomy) or muscle capacity and obesity (through strengthening, exercise and/or weight loss) (Erhart-Hledik et al., 2017; Gerbrands et al., 2017; Lange et al., 2008; Moyer et al., 2015; Radzimski et al., 2012; Simic et al., 2012, 2011; Sischek et al., 2014; Whelton et al., 2017; Zacharias et al., 2014). Interestingly, it is not until fairly recently that evidence has been established supporting or opposing the effectiveness of these biomechanics-targeted interventions in altering the course of the disease (structural,

clinical outcomes) (Birmingham et al., 2009; McAlindon et al., 2014; Sischek et al., 2014). While some of these strategies have demonstrated potential in altering knee biomechanics, the stability of these measurements over time as well as the magnitude of change required to be interpreted as true change (beyond measurement error) in knee OA patients remained mostly unknown (Birmingham et al., 2007; Carpenter et al., 2006; Kean et al., 2010; Robbins et al., 2013; Villadsen et al., 2012; Wessel, 1996). Some work elucidated the MDC (at the 90% and 95% confidence levels) for the KAM peak, and quadriceps strength and power in knee OA, but these estimates were based over short periods (Birmingham et al., 2007; Kean et al., 2010; Villadsen et al., 2012). It was important to determine such estimates over longer intervals to match similar work conducted in patient-reported outcomes and mobility performance; to capture variability in these measures over time due to the natural course of disease progression; and to reflect the realistic nature of time needed to implement long-term treatment strategies. Work from this thesis underscores the fact that while there exist multiple strategies to alter biomechanical factors, only a few have the ability to create true change (beyond the MDC95 threshold). These include medial knee thrust gait and medial opening wedge high tibial osteotomy (Simic et al., 2011; Sischek et al., 2014) for reducing the KAM; muscle training programs for increasing quadriceps strength (Zacharias et al., 2014); as well as exercise and dietary modifications, pharmacotherapy and bariatric surgery for weight loss (i.e., reducing BMI) (Teichtahl et al., 2014).

Findings from this thesis also suggest that modifying or "fixing" the biomechanics in isolation is likely not enough when it comes to strategies aiming to curb structural

progression and improve clinical outcomes in knee OA. Instead of developing and implementing interventions that combine different biomechanics-altering strategies – for instance combining knee bracing with insoles or toe-out gait with high tibial osteotomy to reduce the KAM (Moyer et al., 2013; Whelton et al., 2017) – focus should be shifted to interventions that target biomechanical and clinical outcomes (i.e., weight loss, self-efficacy, pain) simultaneously. This approach would offer a greater ability to address the multifaceted nature of the disease, and likely enhance biomechanical, and more importantly, clinical outcomes. Accordingly, expert reviews of the management of OA supports a combination of intervention strategies, including weight loss, exercise and other measures to unload the damaged joint in addition to pharmacology and patient education (which can address pain and self-efficacy) to improve patient outcomes such as symptoms, physical function and quality of life (Hawkeswood & Reebye, 2010; McAlindon et al., 2014). Aligned with this notion is the recent development of randomized control trials and interventions targeting the combination of physical and psychosocial components in managing and treating knee OA (Button et al., 2015; Helminen et al., 2013; Skou et al., 2015).

Limitations

This thesis work was not without limitations. Measuring medial knee contact force is currently only possible using instrumented knee implants. The first study used external knee loads calculated from inverse dynamics, resulting in KAM and KFM variables, to predict changes in cartilage morphology in knee OA. While these external measurements

have demonstrated potential in inferring knee loads during gait, they are limited in their ability to predict actual knee contact forces (Kutzner et al., 2013; Meyer et al., 2013; Trepczynski et al., 2014; Walter et al., 2010; Zhao et al., 2007). Ultimately, the KAM represents the medial-to-lateral distribution of ambulatory loads across the knee, not the actual force on the medial compartment (Meyer et al., 2013). Accordingly, the KAM is also indicative of the medial-to-total force ratio, and is thus only a good indication of medial knee contact force when the total force remains constant (Moyer et al., 2014).

Also in the first study, cartilage volume and mean thickness for the medial knee compartment were analyzed. These reflect broader (less focal) measures of cartilage morphology. Cartilage volume provides only limited information, as it is a function of cartilage surface area and cartilage thickness. Therefore, changes in cartilage volume can result from a change in the surface area of cartilage and/or cartilage thickness (Eckstein et al., 2006). Further, cartilage mean thickness did not change over 2.5 years. The mean thickness for a whole cartilage plate may have washed out regional variations in cartilage thickness, as this measure is relatively insensitive to regional/focal changes affecting small parts of the surface (Eckstein & Glaser, 2004). Regional cartilage thickness analyses may have allowed detection of site-specific cartilage thickness changes, particularly in biomechanical analyses of knee OA where regional variations in thickness may be related to joint loading patterns (Koo & Andriacchi, 2007). While quantitative measures of in vivo knee cartilage morphology (i.e., "quantity") were acquired, we did not examine cartilage molecular composition (i.e., cartilage "quality"). Physiological imaging techniques can provide quantitative information about the content (i.e.,

molecular composition) of articular cartilage (Braun & Gold, 2012). Such techniques include transverse relaxation time (T2) mapping, delayed gadolinium enhanced MRI of cartilage (dGEMRIC), T1rho mapping, sodium MRI, and diffusion-weighted imaging (Braun & Gold, 2012). Furthermore, this thesis did not collect semi-quantitative MRI measurements (e.g., WORMS). Thus, our findings based on quantitative cartilage measurements cannot be directly compared to those from studies that exclusively used semi-quantitative cartilage measurements.

Pain in this thesis was evaluated with the pain subscale of the KOOS. This instrument is a common and recommended instrument for the evaluation of pain in knee OA (Juhl et al., 2012; Wang et al., 2010). Nonetheless, the KOOS pain subscale does not discriminate between types of pain (i.e., constant, intermittent) and only comprises one item about pain frequency. The KOOS pain subscale has also been criticized for being highly correlated with the KOOS physical function subscale and overlapping on the same factors (Faucher et al., 2002; Stratford & Kennedy, 2004). Consequently, the pain and physical function subscales might be capturing the same construct. To overcome these shortcomings, future work should use other pain measures (e.g., ICOAP) together with the KOOS to capture appropriately various pain constructs. The ICOAP assesses constant and intermittent pain separately, and has been shown to measure constructs of pain that are conceptually different from those measured by the KOOS (Davis et al., 2010).

Concerning statistical analyses, in general, a larger sample size could have been beneficial. A larger sample would have allowed adjustment for additional pertinent

covariates such as baseline K-L score, static knee alignment, knee pain severity, and other comorbidities. The sample of participants observed in this thesis was heterogeneous in terms of disease severity at baseline, as assessed by K-L score. This may have confounded the associations between loading parameters and cartilage morphology change as knee moments change with disease severity (Mundermann et al., 2004). Although we collected measurements of knee static alignment for this thesis work, we did not control for this variable in statistical models to avoid overfitting the data. Knee malalignment is an independent risk factor for the progression of structural knee OA. Varus malalignment can result in medial knee cartilage loss and changes in subchondral bone surface geometry, which in turn can lead to further malalignment (Tanamas et al., 2009). Walking mechanics are sensitive to pain, though the relationship between these variables is not straightforward. For instance, evidence is conflicted as both a positive and negative association between pain and the KAM have been demonstrated (Henriksen et al., 2010; Hurwitz et al., 2000; Thorp et al., 2007). Pain is thought to be a protective mechanism which can help reduce loading (Henriksen et al., 2010; Hurwitz et al., 2000). However, the relationship between these variables may be mediated by disease severity and dependent on whether patients exhibit a maladaptive response to pain (Maly et al., 2008; Thorp et al., 2007). Other comorbidities, such as depressive symptoms, were neither examined nor controlled for in our analyses. Depression is often noted in persons with knee OA, and associated with worse pain and functional status (Han et al., 2016; Lin et al., 2003).

Future Directions

This work has demonstrated that BMI interacts with the KAM to predict cartilage volume loss in the medial tibia over time in individuals with clinical knee OA. Among obese participants, large magnitude KAM peak and KAM impulse at baseline predicted cartilage volume loss over 2.5 years; whereas KAM was of little importance in predicting cartilage volume loss in individuals with a healthy/overweight BMI. Future research should aim to evaluate whether treatment strategies aimed at reducing BMI can effectively curb the progression of structural knee OA associated with mechanical loading. Furthermore, the current thesis showed that baseline self-efficacy interacted with each of knee extensor strength and power in predicting 2-year change in stair ascent performance in older women with clinical knee OA. Future work could explore the impact of developing knee muscle capacity in women with lower self-efficacy, and possibly greater pain, on mobility performance during tasks with different biomechanical demands. Finally, this thesis highlighted that, of various biomechanical risk factors for structural knee OA progression, BMI, KAM and quadriceps strength are truly amenable. Future research should target the development and evaluation of new interventions, and refinement of current techniques, that aim to reduce BMI and KAM, and increase quadriceps strength in patients with knee OA.

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