EFFECT OF COMMON GAIT MODIFICATIONS ON KNEE JOINT LOADING AND LOADING ENVIRONMENT IN PERSONS WITH KNEE OSTEOARTHRITIS

by

Christopher Henderson

A dissertation submitted to the Faculty of the University of Delaware in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Biomechanics and Movement Science

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LIST OF ABBREVIATIONS

ACCA	articular cartilage contact area
ACLR	anterior cruciate ligament reconstruction
ADL	activity of daily living
AP	anterior-posterior
BMI	body mass index
CI	confidence interval
JCF	joint contact force
KOOS	Knee Injury and Osteoarthritis Outcome Score
ML	medial-lateral
M/L	medial to lateral
MR	magnetic resonance
OA	osteoarthritis
x BW	times body weight (normalized unit of force)

ABSTRACT

Knee osteoarthritis (OA) is a leading cause of disability in older Americans affecting 12 percent of people greater than 60 years of age with these persons primarily complaining of knee pain and instability. Eighty percent of persons with painful OA report a limitation in functional mobility including 25 percent reporting they cannot perform a major activity of daily living (ADL). Walking is an important ADL frequently limited in this population and as such is frequently investigated with changes in preferred walking speed and knee kinematics being identified. The effectiveness, or lack thereof, of these gait modifications on joint loading is not currently well understood and was investigated in this dissertation. In Aim 1, we examined the effect of walking speed on cumulative joint loading after accounting for the distance traveled within the gait cycle and found that the reduced walking speed frequently exhibited by persons with knee OA is likely not an effective strategy to reduce cumulative joint loading. Furthermore, if these subjects were to increase their self-selected walking speeds to match that of their healthy older adult counterparts, a 2.7-10.4% reduction in cumulative joint loading would be possible. In Aim 2, we investigated the effect of the altered sagittal knee kinematics on the peak joint contact force (JCF) and identified that the reduced late stance knee extension exhibited by persons with knee OA was associated with a decrease in 2nd peak JCF; however the increased early stance knee flexion exhibited by these subjects was associated with an increase in the 1st peak JCF. The 2nd peak JCF was found to be of significantly greater

magnitude than the 1st peak, suggesting the altered sagittal knee kinematics observed by the population may be an effective strategy to reduce the magnitude of joint loading during gait. In addition to the duration and magnitude of joint loading, the area of loading distribution significantly influences the contact stresses experienced within the joint. The articular cartilage contact area has previously been found to be a valid surrogate for the area of loading distribution and we identified that accounting for the anthropometric variation in this measure before evaluating changes with the development of OA is an important consideration (Aim 3). Kinematic (Aim 4a) and kinetic changes (Aims 4b,c) that resulted in an increase in joint loading were associated with a corresponding increase in the area of loading distribution in healthy older adults, but not in subjects with knee OA suggesting that in addition to the elevated joint loading frequently observed in this population, the joint loading environment may also be altered. The results of these studies should be used as the basis for longitudinal studies to identify those at risk of developing knee OA and those with established OA with the long term goal of developing rehabilitation strategies to minimize the effect of the disease on ADLs.

Chapter 1

INTRODUCTION

Knee OA is a leading cause of disability in elderly Americans[1] affecting 12 percent of people greater than 60 years of age[2] with these persons primarily complaining of knee pain and instability[3]. Eighty percent of persons with painful OA report a limitation in functional mobility including 25 percent reporting they cannot perform a major ADL[4]. Walking is an important ADL frequently limited in this population and as such is frequently investigated with changes in preferred walking speed[5] and knee kinematics[6–8] being identified.

Reduced walking speed is hypothesized to be a compensatory strategy reflecting the impairments of pain and instability seen in this population[3]. Although a direct causal link has not been established[9], mechanical loading of the joint is frequently implicated in OA[10]. The peak knee adduction moment during gait has been found to strongly correlate with medial compartment loading[11] and predict radiographic progression of the disease[12]. A previous investigation found that subjects with knee OA were able to reduce their peak knee adduction moment, and possibly joint loading, through a reduction in walking speed[5]. The severity of knee OA symptoms during walking has also been correlated with the peak knee adduction moment[13], which may also help explain why persons with knee OA tend to choose a slower preferred walking speed[8,14]. The effectiveness, or lack thereof, of this gait modification on joint loading is not currently well understood.

Although the peak knee adduction moment is reduced with decreased walking speed, the knee adduction impulse, which may be more indicative of cumulative knee joint loading and more sensitive to identifying radiographic severities of OA[15], is increased[16]. Findings from a recent animal study suggest cumulative knee joint loading alone may be able to initiate OA[17] and the cumulative knee joint load has been found to be increased in a cohort of persons with OA when measured as a product of the knee adduction impulse and steps/day[18]. The authors of this study acknowledge the decreased walking speed of the OA group likely increased their knee adduction impulse; but fail to recognize it also likely increases the number of strides and therefore episodes of knee loading required to ambulate a fixed distance, such as is required to complete ADLs. A recent study of young healthy adults utilized a within subjects design to investigate the effect of speed on cumulative knee joint load[19]. The joint loading cost of locomotion, or joint loading indicator divided by stride length (Equation 1.1), was determined in self-selected walking and running with results of the study suggesting although peak JCF was three times greater in running, after normalizing to stride length there was no difference in the joint loading cost of locomotion.

$$\textbf{Equation 1.1}: \textit{Joint loading cost of locomotion} = \frac{\textit{Indicator of knee loading}}{\textit{Stride length}}$$

In effect, these results suggest the cumulative knee joint load experienced traveling a given distance may be similar regardless of whether the distance is walked or ran. As running is a relatively extreme deviation from the self-selected walking speeds of persons with OA, it is pertinent to understand whether the reduced walking speed actually decreases the joint loading cost of locomotion and will be explored in Aim 1.

Altered sagittal knee kinematics during gait have also frequently been seen in the OA population. OA subjects have been found to demonstrate increased knee flexion at initial contact[5,6,20,21], reduced early stance knee flexion[14,22], reduced late stance knee extension[21,22], reduced peak swing knee flexion[14,22], and reduced knee flexion excursion during loading response[6,21] when walking at self-selected speeds and compared with healthy subjects. The altered sagittal knee kinematics seen may also contribute to the reduced stride length seen in the gait of persons with OA[8,14]; however these studies frequently report reduced walking speeds in the OA subjects [8,14,21,22] which is likely to influence both the knee kinematics and stride lengths observed[23]. Little is currently known regarding the effect altered sagittal knee kinematics have on joint loading in OA.

A recent study of persons with medial knee OA found positive relationships between peak knee flexion moment and knee flexion at initial contact, peak knee flexion and knee flexion excursion during loading response, with peak knee flexion being the primary predictor of peak knee flexion moment[7]. Although peak knee flexion moment only serves as a proxy for knee joint loading, an external knee flexion moment must be opposed by an internal knee extension moment generated by the quadriceps, which are the primary contributors to the 1st peak JCF[24,25]. During normal gait, the 2nd peak JCF has been found to be of similar[11] or greater[26] magnitude to the 1st peak and is primarily generated by the gastrocnemius[24,25]. Given the gastrocnemius spans the knee joint, sagittal knee kinematics likely influence the 2nd peak JCF; however the relationship between sagittal knee kinematics and 2nd peak JCF is currently unknown. Musculoskeletal simulations offer the ability to non-invasively estimate *in vivo* tibiofemoral JCF and have previously been used in the OA population[27] with peak JCF estimates found to agree within 5% of those from an instrumented knee prosthesis when incorporating subject specific knee strength into the model[28]. Aim 2 will utilize these musculoskeletal models to identify whether a relationship exists between sagittal knee kinematics and 2nd peak JCF in persons with knee OA and healthy older adults.

Forces and moments alone likely do not characterize the joint loading environment. Articular cartilage morphology such as volume[29–31], thickness[32–34], and contact area[35–37] have been investigated in the tibiofemoral joint. Cartilage volume and thickness are intimately associated and a previous study has found thickness may be a more meaningful measure in OA[29]. Healthy articular cartilage has been found to be thickest in areas of loadbearing[33,34] and thinner following traumatic spinal cord injury[38]. As gait represents cyclic loading of the articular cartilage and is frequently involved in ADLs, relationships between gait characteristics and cartilage thickness have been investigated[32,39–41]. The sagittal plane location of thickest femoral articular cartilage has been found to correlate with knee flexion angle at initial contact in healthy young adults[32] and persons following ACLR[41], possibly supporting the hypothesis of increased cartilage thickness in the presence of increased joint loading. In these types of studies, it is important to appropriately account for anthropometric differences in subjects prior to analysis. The aforementioned studies normalized their cartilage data to the sagittal femoral length; however other studies have adjusted their data to height, weight, gender, bone cross sectional area, or some combination of these[36,39,42–44] which likely influences results[43].

Another potential technique to account for anthropometric differences is utilization of a medial to lateral compartment ratio[10,40]. An increase in medial relative to lateral femoral cartilage thickness was found to correlate with an increased 1st peak knee adduction moment in young healthy adults[40], while a negative correlation was identified in a small sample of persons with OA[10]. Hypothetically, the relative increase in medial femoral cartilage thickness indicates increased medial compartment loading, which matches well with the interpretation of the knee adduction moment and the notion that an altered loading environment is present in OA. Unfortunately, the same group of investigators recently reported the positive relationship between the medial to lateral cartilage thickness ratio and 1st peak knee adduction moment was unable to be reproduced in young and obese, old, or old and obese subjects, of which most of the OA population is comprised[39]. It is possible the altered self-selected walking speed seen in the OA population confounded the results as the peak knee adduction moment varies with walking speed[5].

Although results suggest cartilage thickness is associated with loading, ACCA also likely plays a significant role in transmission of loads across the joint. A novel study utilizing dual fluoroscopy and MR images has identified that tibiofemoral articular cartilage in contact is significantly thicker than the surrounding articular cartilage[34]. Tibiofemoral contact area has been frequently investigated in healthy adults and non-OA populations[35–37,45], while only limited studies have investigated the OA population[46,47] with results suggesting ACCA may increase in the early stages of OA[47] before decreasing with further disease progression[46]. Previous studies have looked at the movement of the cartilage contact centroid in non-OA populations during various types of knee flexion[37,48,49]; however the relationship between contact area and gait is currently unknown. In order to investigate this relationship, we will first identify the anthropometric or combination of anthropometric variables most associated with cartilage contact area in a cohort of healthy older adults (Aim 3) before using the normalized data to investigate relationships with gait kinematics (Aim 4a) and kinetics (Aim 4b).

The mechanical properties of the joint surface as well as the area over which the load is distributed likely contribute to the effect of the mechanical load on the tissue[44,50,51]. The ratio of load to area of load distribution, or contact stress, has frequently been investigated in cadaveric studies[52,53], and musculoskeletal simulations[54–56], which may not be indicative of the *in vivo* loading environment and are generally limited by small sample sizes. Instrumented total knee arthroplasties have also reported *in vivo* stresses[57]; however, the implants do not reproduce the joint loading environment and results are limited to only a few subjects. Although both the articular cartilage and menisci play an important role in load distribution across the knee[53], an elevated ratio of knee joint loading to ACCA alone has been shown to predict incidence of knee OA in older adults[58] and development of bone marrow lesions in subjects with knee OA[59]. Both studies investigating contact stress determined ACCA and joint loading by assuming a uniformly thick articular cartilage surface on bony geometry obtained from a static, non-weight bearing MR images leading to several limitations. First, a uniformly thick cartilage layer is likely inappropriate for persons with knee OA as imaging for patients with more advanced knee OA demonstrate intermittent bone on bone contact (Figure 1.1). Secondly, acquisition of data in weight bearing has been found to increase the ACCA in both healthy older adults and subjects with knee OA[46]. Finally, forces generated from mechanical strain in static images likely underestimate the experienced load during functional activities, such as gait, as peak forces several times body weight have been identified[11,27,60]. Therefore further investigation into contact stress during ADLs such as walking is warranted (Aim 4c).

Figure 1.1: Sagittal MR image of advance knee OA

1.1 Significance of Proposed Work

Aim 1

Walking is frequently performed as a part of ADLs and irrespective of walking speed, a fixed distance must be ambulated to perform necessary activities such as walking from the couch to the bathroom, from the house to the car, or from the produce section to the checkout in the grocery store. Cumulative knee loading has been found to be increased in persons with OA[18] and a recent study of the peak JCF in the walking and running of young healthy adults found no difference in joint loading cost of locomotion[19]. Although running is generally not recommended for the OA population[61], the effect of smaller changes in walking speed on the joint loading cost of locomotion is likely to provide insights into the efficacy of this compensation strategy.

Aim 2

Identifying the relationships between sagittal knee kinematics during gait and joint loading is important to interpret the effect of the altered knee kinematics in knee OA on joint loading. This work is an important first step in ultimately enabling clinicians to make more informed decisions regarding gait modifications as a compensatory strategy.

Although an increased peak knee flexion moment, and therefore likely increased 1st peak JCF[24,25], has been seen with increasing peak knee flexion during loading response in the OA population[7], the relationship between sagittal knee kinematics and the 2nd peak JCF is unknown. Furthermore, the effect of altered early stance knee kinematics on the 2nd peak JCF is unknown and a more thorough understanding is necessary before recommendations regarding gait modifications can be appropriately prescribed.

Aim 3

Appropriately accounting for anthropometric variations in ACCA data is essential in order to identify meaningful changes in OA. Previous *in vivo* studies of knee cartilage have scaled data based on varied anthropometric values[36,39,42–44]; however the rationale for selection of the specific anthropometric parameter, or parameters, is limited. Identification of the best anthropometric measures for scaling ACCA will enable investigators to identify meaningful changes in ACCA in the OA population.

Aim 4

An improved understanding of the relationship between ACCA and gait kinematics and kinetics is likely to yield additional insights on OA pathoetiology. Previous studies have identified relationships between cartilage thickness and gait kinematics[32,39,41] or kinetics[10,40]; however relationships between ACCA, which may serve as a proxy for the area of load distribution[58,59], are currently unknown. Contact stress in a static posture has previously been investigated in subjects with knee OA[58]; however as loading during gait is several times body weight[11,27,60], additional knowledge regarding the joint environment in OA is likely to be gleaned from contact stress investigations using these loads.

1.2 Innovation

This study is innovative in several aspects:

1. Accounting for the distance traveled within a gait cycle in the assessment of cumulative knee joint loading in subjects with knee OA has not previously been explored.

Cumulative joint load has been found increased in the OA population[18] and the results of a recent study in young healthy adults suggest there is no difference in the cumulative joint load between walking and running[19]. This study will be the first to investigate what effect the reduced self-selected walking speed demonstrated by OA subjects[8,14,21,22] has on cumulative knee joint loading.

2. The relationship between the magnitude of the 2nd peak JCF, which is generally greater than the 1st peak JCF, and sagittal knee kinematics is not well understood.

Altered sagittal knee kinematics have been seen in the gait of persons with knee OA[5,6,20]. Early stance knee flexion angle has been found to be most predictive of the external knee flexor moment[7], which has implications for the 1st peak JCF[24,25]. The gastrocnemius is the primary contributor to the 2nd peak JCF[24,25] and as it spans the knee joint, its contribution to JCF is likely influenced by sagittal knee kinematics. This study will be the first to identify the primary predictor of 2nd peak JCF as well as investigate the interplay between early stance kinematics shown to affect the 1st peak JCF on the 2nd peak JCF.

3. Although anthropometric measures have previously been implicated in ACCA, systematic evaluation of their relationships have not been previously investigated..

Although changes in ACCA have been identified with knee OA[46,47], a meaningful understanding of these changes is not possible without recognizing baseline differences in ACCA secondary to anthropometry. Research investigations of *in vivo* cartilage morphology have attempted to account for anthropometric variations through a number of methods[36,39,42–44]; however there is little consensus and limited rationale presented. This will be the first study to systematically investigate the relationships between anthropometric measures and ACCA.

4. Although changes in tibiofemoral ACCA with the progression of OA have been observed, the relationship between ACCA and gait kinematics and kinetics in knee OA is currently unknown.

Cartilage thickness has been found to exhibit a relationship with gait kinematics[32,41] and kinetics[10,40]. As ACCA has been found to serve as a proxy for area of load transmission across the knee joint[58,59], it would be of significant value to understand relationships between ACCA and gait kinematics and kinetics. This will be the first study to investigate these relationships in healthy older adults or persons with knee OA.

1.3 Specific Aims

Tibiofemoral or knee OA is a leading cause of physical disability in elderly Americans. Increased loading across the knee joint has been found to significantly correlate with increased pain complaints as well as incidence and progression of the pathology. Although gait modifications such as decreased walking speed and decreased early stance knee flexion have been seen in this population, the effect of these modifications on knee joint loading is not well understood and will be explored in this study.

Aim 1: Evaluate the joint loading cost of locomotion as a function of walking speed

We will collect kinematic and kinetic data on subjects with knee OA and healthy older adults at a controlled, self-selected, and fastest tolerable walking speed. Given that completion of activities of daily living requires ambulating a fixed distance irrespective of walking speed, the knee adduction impulse and 1st and 2nd peak knee adduction moments will be normalized to stride length to determine the joint loading cost of locomotion.

H 1.1: The joint loading cost of locomotion will: (a) decrease with increasing walking speed for the knee adduction impulse and (b) demonstrate no relationship for the peak knee adduction moments in subjects with knee OA and healthy older adults.

H 1.2: The joint loading cost of locomotion in subjects with knee OA will (a) decrease at a faster rate for the knee adduction impulse and (b) demonstrate no difference in the relationship for the peak knee adduction moments when compared to healthy older adults.

Aim 2: Evaluate the relationship between knee flexion kinematics during gait and peak knee joint contact force

We will build musculoskeletal simulations from the data collected at the controlled walking speed in Aim 1 to generate estimates of peak knee JCF. Relationships between knee kinematics and peak JCF will be studied.

H 2.1: Early stance knee flexion will be the sagittal knee kinematic parameter most associated with 1st peak JCF.

H 2.2: Late stance knee extension will be the sagittal knee kinematic parameter most associated with 2nd peak JCF.

Aim 3: Evaluate the relationship between articular cartilage contact area and anthropometric measures

We will determine medial and lateral tibiofemoral ACCA from MR images for 20 healthy older adults. Relationships between ACCA and anthropometrics will be investigated to determine if anthropometric scaling of articular cartilage contact area is indicated.

H 3.1: Total ACCA in healthy older adults will be most correlated with cross-sectional area of proximal tibia as determined by MR images.

H 3.2: When considering only anthropometric measures available during gait analysis, greater than 80% of variance in total ACCA will be predicted.

Aim 4: Evaluate the relationship between ACCA and gait kinematics and kinetics

We will determine ACCA for subjects with knee OA and healthy older adults using methods in Aim 3. Musculoskeletal simulations will be utilized to investigate relationships between ACCA and gait kinematics and kinetics.

H 4.1: Normalized total ACCA will exhibit a positive relationship with knee flexion at initial contact in both subjects with knee OA and healthy older adults.

H 4.2: Healthy older adults will demonstrate a positive relationship between medial to lateral ACCA ratio and indicators of medial compartment joint loading while OA subjects will demonstrate an inverse relationship.

H 4.3: Healthy older adults will demonstrate a significant relationship between peak JCF and total ACCA while knee OA subjects will not.

Chapter 2

AIM 1: EVALUATE THE JOINT LOADING COST OF LOCOMOTION AS A FUNCTION OF WALKING SPEED

2.1 Introduction

Arthritis is a leading cause of disability in older Americans with OA being the most common form[62]. Osteoarthritis of all joints is estimated to result in medical expenses and lost wages totaling nearly $60 billion per year in the United States alone[63]. The knee is one of the most affected joints and it is estimated that approximately 9 million Americans suffer from symptomatic knee OA[64].

Although a direct causal link between joint loading and progression of knee OA has not yet been demonstrated[9], mechanical loading of the joint[10], and in particular the medial compartment[12,65], is frequently implicated in the disease. As walking is an activity that is frequently limited in subjects with knee OA[63], joint loading assessed via the peak knee adduction moment has found positive correlations with symptom severity[12,13] and incidence of disease progression[12]. Recent results suggest persons with knee OA are able to reduce their peak knee adduction moment, and therefore possibly joint loading, by a reduction in walking speed[5], which may explain why this population frequently adopts a reduced self-selected walking speed[8,14].

Although a reduction in walking speed may reduce the peak knee adduction moment, stride length is also likely decreased[66]. If it is assumed that a fixed distance will be need to be ambulated in order to complete all activities of daily living, a reduction in stride length increases the number of gait cycles, and therefore episodes of joint loading. A recent animal model has demonstrated that cumulative loading alone is able to initiate OA[17] and subjects with knee OA have demonstrated increased cumulative loading compared with healthy older adults when calculated from the knee adduction impulse and a pedometer[18]. The knee OA subjects in the previous study exhibited a reduced walking speed, which has been shown to increase the knee adduction impulse[16] and potentially influenced the findings. The effect of walking speed on cumulative joint loading has also been investigated by dividing the indicator of joint loading by stride length to account for the distance traveled in the gait cycle[19]. Although the peak joint loading was three times greater in running, there was no difference between walking and running after accounting for the distance traveled. In effect, these results suggest the cumulative knee joint load experienced traveling a given distance may be similar regardless of whether the distance is walked or ran. As running is a relatively extreme deviation from the self-selected walking speeds of persons with OA, it is pertinent to understand whether reducing walking speed actually decreases the cumulative knee joint loading.

The aim of this study was to investigate the effect walking speed has on the joint loading cost of locomotion, or joint loading after accounting for the distance traveled in the gait cycle. The 1st and 2nd peak knee adduction moments and knee adduction impulse were divided by stride length and utilized as indicators of medial compartment joint loading. As the knee adduction impulse is reduced with increasing walking speed[16] and stride length is also likely increased, it was hypothesized that the joint loading cost of locomotion decreases with increasing walking speed for this indicator in both healthy older adults and subjects with knee OA. In contrast, the peak knee adduction moment increases with increasing walking speed[5], therefore it was hypothesized this increase would offset the increase in stride length and no relationship would exist between walking speed and the joint loading cost of locomotion for the peak knee adduction moments for either group. As OA subjects consistently demonstrate an elevated knee adduction impulse and peak knee adduction moment[13,18] when compared to healthy older adults, it was also hypothesized that changes in walking speed would have a greater influence on the joint loading cost of locomotion in the OA subjects when compared to the healthy older adults.

2.2 Methods

Persons with knee OA and healthy older adults were recruited from the local community. Subjects were included if they were aged 40-80 years and able to walk at their self-selected speed for five minutes. Primary exclusion criteria included BMI > 40 kg/m^2, diagnosed arthritis of other lower extremity joint, walking pattern affected by some condition other than knee OA, any medical condition that prevented moderate physical activity, lateral compartment dominant knee OA, or subjective report of symptomatic knee not corresponding with the radiographically more severe knee. Subjects with bilateral tibiofemoral OA were not excluded and the effect of patellofemoral OA was not considered in this investigation. Healthy older adults were additionally required to exhibit < 10% difference in maximal volitional isometric quadriceps strength and mean KOOS[67] ADL and Pain subscales > 90 indicating less that 10% impairment in these areas. The protocol for this study was approved by the Institutional Review Board and all subjects provided written informed consent prior to participation.

2.2.1 Radiographic Assessment

All subjects completed bilateral posterior-anterior radiographs with knees flexed to 30 degrees. Radiographs were read by an experienced radiologist for determination of KL grade[68] in both the medial and lateral compartments. Healthy older adults exhibited KL grades of 0-1 in the medial compartment, while OA subjects were ≥ 2.

2.2.2 Gait Analysis

Kinematic and kinetic data were collected at 60 and 1080 Hz, respectively, while subjects walked on an instrumented split-belt treadmill (Bertec Corp., Columbus, OH, USA) wearing 23 retro-reflective markers placed in a modified Helen-Hayes arrangement and tracked by six cameras. Subjects walked at a controlled speed of 1.0 m/s, their self-selected speed, and a fastest tolerable walking speed. Self-selected speed was determined via a 10 m over ground walking assessment and fastest tolerable walking speed was identified as the maximum speed at which the subject was able to safely walk on the treadmill without running or holding onto the handrails. Subjects were given sufficient time to acclimate to the treadmill environment prior to data collection[69] and 30 second trials were collected for each condition.

2.2.3 Data Processing

Data were processed in Cortex (Motion Analysis, Santa Rosa, CA, USA) prior to export to Visual 3D (C-Motion, Bethesda MD, USA) following application of a 6 Hz low pass filter to analog and marker data. Inverse dynamics and Euler angles (X-Y-Z) were used to calculate the knee adduction moment, which was normalized to body weight, but not time. A custom MATLAB (MathWorks, Natick, MA, USA) script was utilized to split the stance phase into 1st and 2nd epochs via the transition of anterior-posterior ground reaction force from negative to positive[70] before identifying the maximum value of the knee adduction moment during each half of stance. The knee adduction impulse was determined over the entire stance phase from the body mass normalized, non-time normalized knee adduction moment using a Riemann sum technique with a time step of 1/60 sec. Stride length was calculated using gait events calculated in Visual 3D, the known treadmill belt speed, and the change in position of the lateral ankle marker of the analyzed lower extremity from beginning to end of the gait cycle.

The joint loading cost of locomotion (Equation 2.1) was then calculated separately for the 1st peak, 2nd peak, and impulse of the knee adduction moment. Gait data were inspected for adverse events (e.g. stance phase crossover onto contralateral forceplate, loss of balance, utilizing handrails) and four gait cycles were included in the analysis.

$$\textbf{Equation 2.1}: \textit{Joint loading cost of locomotion} = \frac{\textit{Indicator of knee loading}}{\textit{Stride length}}$$

The more symptomatic knee was analyzed for the OA group while a randomly selected limb of the healthy older adult group was analyzed. Relationships between joint loading cost of locomotion and walking speed were determined for each subject via a best fit linear regression with the slope of the regression line describing the relationship between the two variables[5]. Individual subject slopes were averaged across each group and the mean with 95% confidence interval utilized to assess the relationship with walking speed. If the mean with 95% confidence interval does not cross zero, it follows that a statistically significant relationship exists between the variables. Additionally, t-tests were utilized to evaluate group differences in the relationship between walking speed and joint loading cost of locomotion with alpha set to 0.05.

2.3 Results

Data for 20 subjects with OA and 24 healthy older adults were analyzed. Subject characteristics are seen in Table 2.1. OA subjects were heavier and had an increased body mass index when compared to the healthy older adults ($p < 0.01$). They also demonstrated a reduction in both self-selected and fastest tolerable walking speeds ($p < 0.001$). OA subjects rated themselves significantly lower than the healthy older adults on all KOOS subscales ($p < 0.001$).

	OA	Healthy
Sample Size	20	24
Age (years)	65.4 ± 8.1	60.2 ± 10.8
Height (cm)	171.7 ± 10.1	167.8 ± 8.5
Mass (kg)	**88.2 ± 15.0**	**72.3 ± 14.7**
BMI (kg/m^2)	**30.0 ± 4.7**	**25.5 ± 4.1**
KL Grade	**2.5 ± 0.5**	**1.0 ± 0.0**
Gender (M/F)	8/12	10/14
Side Analyzed (L/R)	10/10	12/12
Bilateral OA (Yes/No)	13/7	NA
Self-Selected Speed (m/s)	**1.17 ± 0.09**	**1.31 ± 0.12**
Fastest Tolerable Speed (m/s)	**1.53 ± 0.15**	**1.84 ± 0.22**
KOOS Symptoms Subscale	**74.3 ± 18.4**	**96.0 ± 4.6**
KOOS Pain Subscale	**72.8 ± 17.0**	**97.8 ± 4.2**
KOOS ADL Subscale	**79.1 ± 16.0**	**99.3 ± 1.9**
KOOS Sport/Recreation Subscale	**63.6 ± 22.5**	**97.5 ± 5.9**
KOOS Quality of Life Subscale	**60.6 ± 14.4**	**95.8 ± 6.8**

Table 2.1: Subject characteristics in form of mean ± standard deviation. Bolded values indicate $p < 0.05$ between groups.

The results for a representative OA subject can be seen in Figure 2.1 confirming the presence of a linear relationship between the joint loading cost of locomotion and walking speed. Additionally, Figure 2.2 displays the mean R2 values for each relationship between the joint loading cost of locomotion and walking speed. No group differences in R^2 were observed and across all three indicators, the healthy older adults and subjects with knee OA averaged R^2 values of 0.83 and 0.79, respectively.

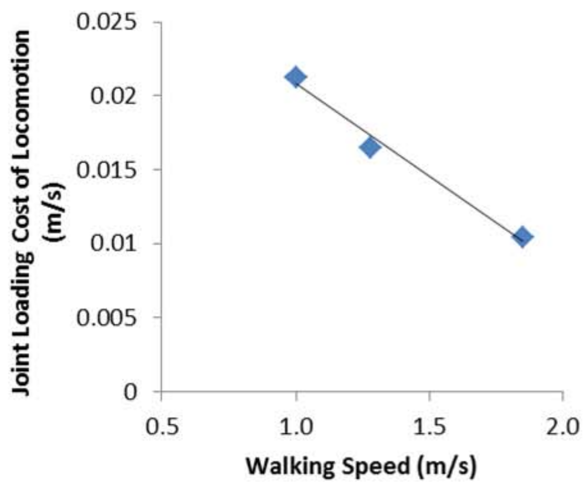

Figure 2.1: Joint loading cost of locomotion for representative OA subject utilizing knee adduction impulse. The slope of the regression line is used to characterize the relationship between the joint loading cost of locomotion and walking speed.

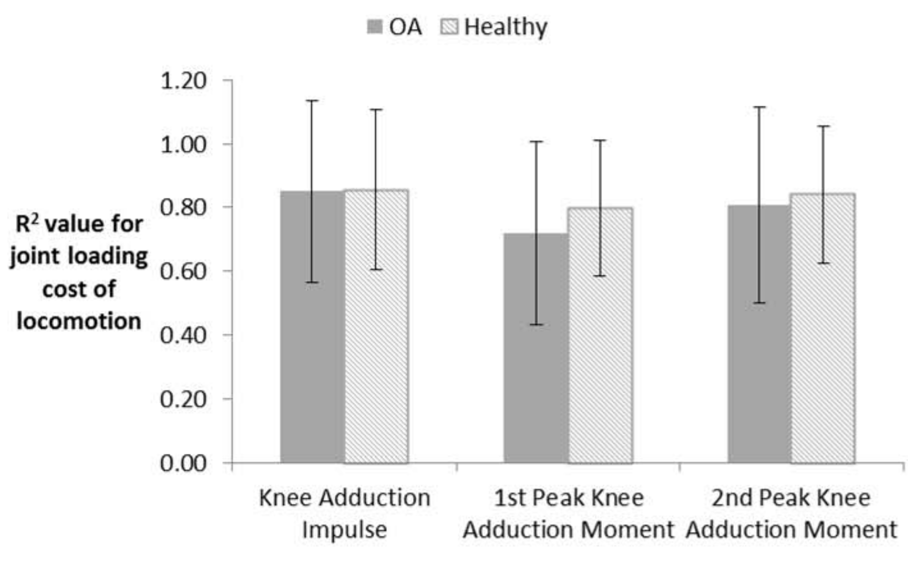

Figure 2.2: R^2 values for the strength of the linear relationship between the joint loading cost of locomotion and walking speed.

OA subjects reduced their joint loading cost of locomotion with increasing walking speed when considering the adduction impulse (-0.09, 95% CI [-0.05, -0.13]) and 2nd peak knee adduction moment (-0.13, 95% CI [-0.03, -0.24] s^{-1}), but demonstrated no relationship when considering the 1st peak knee adduction moment (-0.07, 95% CI [0.02, -0.15] s^{-1}). The healthy older adults reduced their joint loading cost of locomotion with increasing walking speed for the knee adduction impulse (-0.07, 95% CI [-0.05,-0.09]), 1st peak (-0.08, 95% CI [-0.03,-0.14] s-1) and 2nd peak knee adduction moments (-0.13, 95% CI [-0.09,-0.16] s^{-1}). The relationship between joint loading cost of locomotion and walking speed did not differ between the groups for any of the three joint loading indicators (Figure 2.3).

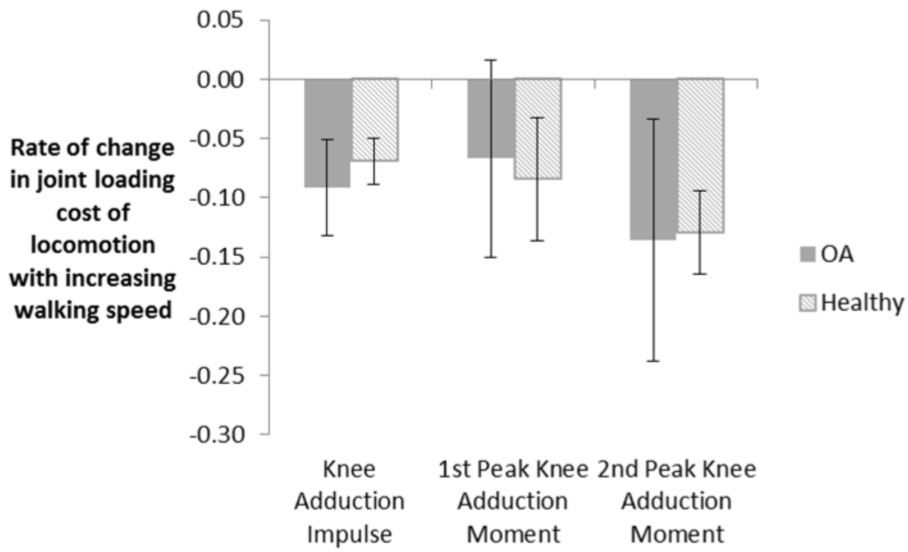

Figure 2.3: Mean linear regression slope describing the effect of increased walking speed on joint loading cost of locomotion for the knee adduction impulse and 1st and 2nd peak knee adduction moments (s^{-1}). Error bars represent 95% confidence intervals and are significant relationships if 95% confidence intervals do not cross zero. A negative mean value indicates joint loading cost of locomotion decreases with increasing walking speed.

2.4 Discussion

This is the first study to report that increasing walking speed is likely to reduce or at most have no effect on the cumulative joint loading of older adults or individuals with knee OA. It is important to account for distance traveled because persons with knee must ambulate a fixed distance to complete their ADLs. Although the groups did not significantly differ in their respective relationships between joint loading cost of locomotion and walking speed, they were functionally different as evidenced by the reduced self-reported knee function on all subsections of the KOOS in the knee OA group. Thus, reduced cumulative joint loading with increased walking speed may be possible in additional subject populations not considered within this investigation. Rather than looking across a cohort of subjects walking at their self-selected speed for relationships with walking speed[7], a strength of this study is our analysis of individual subject relationships with walking speed which provides insight to the effect of walking speed on joint loading for that individual[5]. Although joint loading is frequently implicated in OA progression, there currently does not exist a consensus regarding whether the magnitude of peak loading[12], cumulative loading[15,18], or even rate of loading[71] is the aspect of loading most associated with disease pathogenesis. As a recent animal model has demonstrated physiologic loading of increased frequency is able to initiate the disease process[17], it is likely that cumulative loading is an important factor in OA. It also follows that the reduced walking speed exhibited by persons with symptomatic OA is likely not an effective gait modification.

As walking speed increases, stride length also likely increases[66]. In order to elucidate the effect of stride length on the observed results, we compared the magnitude of change in the knee adduction impulse, peak knee adduction moments and stride length with walking speed using a similar linear regression analysis (Figure

2.4). As stride length has an inverse relationship with the joint loading cost of locomotion, the observed positive relationship between stride length and walking speed in both groups likely significantly contributes to the overall reduction in joint loading cost of locomotion exhibited with increasing walking speed. In a similar sense, the positive relationship between the 1st peak knee adduction moment and walking speed in the OA group has a direct relationship with the joint loading cost of locomotion. Therefore, when the 1st peak knee adduction moment and stride length are combined in calculating the joint loading cost of locomotion, it is not surprising that no relationship existed with walking speed for this indicator.

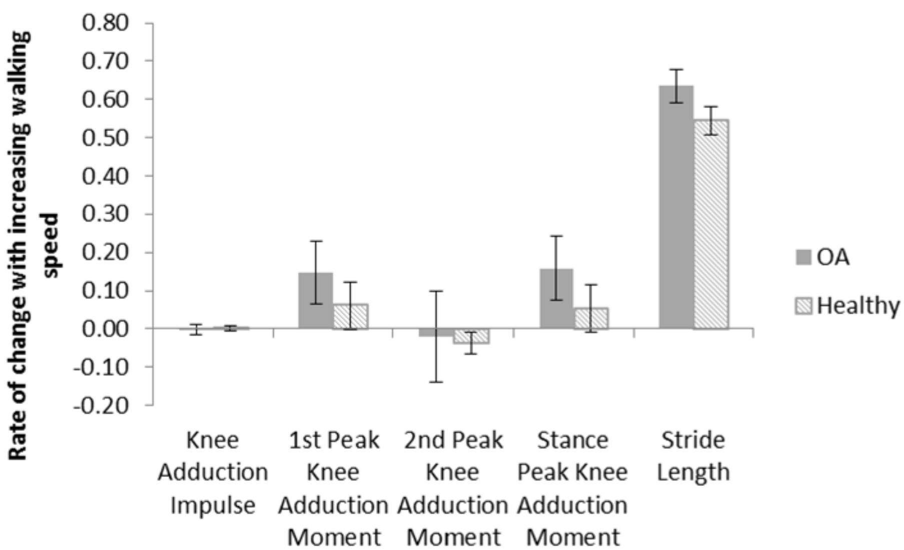

Figure 2.4: Mean linear regression slopes describing relationships between knee adduction impulse (m), peak knee adduction moments (m/s), and stride length (s) with walking speed. Error bars represent 95% confidence intervals and are significant relationships if 95% confidence intervals do not cross zero. A positive mean value indicates the variable increases with increasing walking speed.

We utilized the mean linear regression equation to determine the joint loading cost of locomotion for each indicator of joint loading in the OA group as a function of walking speed with Equation 2.2 displaying the result for the knee adduction impulse as an example.

$$\textbf{Equation 2.2}: OA\ joint\ loading\ cost\ of\ locomotion = -0.092 * walking\ speed\ (m/s) + 0.232$$

By determining the joint loading cost of locomotion for the self-selected walking speed of each group with this equation, if the OA subjects were to match their walking speeds to the healthy older adults, they would potentially reduce their cumulative joint loading by 2.7-10.4%, with the greatest benefit exhibited for the knee adduction impulse. Although cumulative joint loading may be reduced with increasing walking speed, the peak knee adduction moment was found to be elevated in the OA subjects with increasing walking speed and it has been previously seen that an elevated peak knee adduction moment is associated with increased severity of symptoms[12,13], therefore it may be difficult to persuade OA subjects that increasing their walking speed is beneficial and conclusions regarding clinical recommendations cannot be made given the cross-sectional design of this study.

Previous investigations of the knee adduction moment in OA gait have generally focused on the overall peak[5,18,72]; however, other studies have investigated only the 1st peak[73], or both peaks[13,70,74] which makes direct comparisons with our data challenging. As a result, the overall peak knee adduction moment during stance and its joint loading cost of locomotion were calculated to facilitate comparisons with previous literature. Previous studies have found positive relationships between walking speed and peak knee adduction moment in OA subjects[5,74] which matches with our findings. A positive relationship between the peak knee adduction moment and walking speed has also been seen in young healthy adults[16], but we did not see this in our cohort of older adults and may be explained by differences in populations studied. The knee adduction impulse has previously been found to have a negative relationship with walking speed in young healthy adults[16]; however, our results did not demonstrate this relationship in either group. The methods employed in our study included the negative, or external knee abduction moment, portions of the knee adduction moment curves, which differs from the aforementioned study. We believe that inclusion of this data is appropriate as gait data from subjects with instrumented knee prostheses suggest medial compartment loading is still present during periods of an external abduction moment[75]. A previous investigation of the joint loading cost of locomotion in young healthy adults found a reduction with increasing walking speed when considering the peak knee adduction impulse[19] which matches our findings for the healthy older adults. Daily cumulative loading utilizing a pedometer and the knee adduction impulse was found elevated in a cohort of OA subjects when compared to healthy older adults despite the OA subjects taking significantly less steps per day[18]. Interestingly, the OA subjects walked at a significantly slower speed which likely increases both their knee adduction impulse and number of steps required to complete their activities of daily living and negatively contributes to their cumulative knee joint loading.

There are several limitations to consider when interpreting the results of our study. First, there are known to be slight variations in how subjects modulate their walking speed on a treadmill when compared to overground[76]; however, these small differences are not anticipated to have significantly influenced our results. Additionally, it is also possible that OA subjects adopted an offloading strategy on their more painful side with increased walking speed. In order to address the potential of an offloading strategy to artificially reduce a measure such as the knee adduction impulse, where magnitude is dependent on the duration of stance, a bilateral joint loading cost of locomotion was calculated for all conditions and both groups. These data demonstrate identical relationships with walking speed as seen with our current unilateral analysis; therefore we do not believe this to have influenced our data. Finally, although a very strong linear relationship was consistently demonstrated between the selected indicators of joint loading and walking speed, it is not likely this relationship persists for all walking speeds outside the range of speeds considered. If so, this would imply that at some maximal speed, there is no joint loading, which is not plausible.

2.5 Conclusions

The relationship between joint loading cost of locomotion, or joint loading indicator divided by stride length, and walking speed was investigated in a cohort of healthy older adults and knee OA subjects. Similar to the healthy older adults, the OA subjects reduced their joint loading cost of locomotion with increased walking speed for the knee adduction impulse and 2nd peak knee adduction moment without an increase in the 1st peak knee adduction moment, suggesting that increased walking speed may reduce cumulative knee joint loading. If the OA subjects were to increase their walking speed to match that of the healthy older adults, they could potentially reduce their cumulative joint loading by 2.7-10.4%.

Chapter 3

AIM 2: EVALUATE THE RELATIONSHIP BETWEEN KNEE FLEXION KINEMATICS DURING GAIT AND PEAK JOINT CONTACT FORCE

3.1 Introduction

Among the 12% of older Americans with symptomatic knee OA, functional limitations with the sit to stand transition, stair climbing, and walking are frequently reported[77] and 25% report an inability to perform an essential activity of daily living[4]. Elevated mechanical loading of the joint has been implicated in the development[58], progression[12], and severity of symptoms[13] of the disease. Daily walking not only results in thousands of episodes of mechanical loading[18], but is also frequently limited in this population[77]. Persons with knee OA have been found to exhibit altered sagittal knee kinematics during gait when compared to healthy counterparts[5,6]. Recent studies have identified altered knee kinematics at initial contact[5,6,20], early stance knee flexion[14,22], and other phases of the gait cycle[6,21,22]. Sagittal knee kinematics are known to significantly influence muscle forces[24] which are the primary contributors to joint loading[27]. However, it is currently not well understood how the altered kinematics in the gait of persons with knee OA influence joint loading. Furthermore, subjects with knee OA frequently adopt a reduced self-selected walking speed[14,22], which is known to influence kinematics[23], limiting implications from previous studies.

A recent investigation looked at the relationship between peak knee flexor moment and early stance kinematic measures and found that early stance knee flexion was the primary predictor[7]. An external knee flexor moment would need to be resisted by the knee extensors, which are primarily responsible for the 1st peak JCF[24,25]; however moments only indirectly describe the JCF and have been shown to be weak indicators of this measure[26]. Furthermore when compared to the 1st peak JCF, the 2nd peak JCF is frequently of similar[11] or greater magnitude[26]. The gastrocnemius has been found to be the primary contributor to 2nd peak JCF[24,25] and as it spans the knee, is likely influenced by sagittal knee kinematics. Late stance knee extension is significantly associated with the 2nd peak JCF in the cerebral palsy population[24]; however, it is not known how sagittal knee kinematics influence the 2nd peak JCF in the OA population.

The purpose of this study was to investigate the relationship between sagittal knee kinematics and peak JCF in healthy older adults and persons with knee OA to better understand the association between these gait modifications in persons with knee OA and joint loading. Sagittal knee kinematics were specifically chosen over other kinematic or kinetic measures because they are able to be quantified during clinical gait assessment[78]. Based on the previously identified relationship between early stance knee flexion and peak knee flexor moment[7], it was hypothesized that early stance knee flexion would best predict 1st peak JCF. Previous work in the cerebral palsy population has found a strong relationship between late stance knee extension and the 2nd peak JCF[24], therefore it was hypothesized that this would best predict the 2nd peak JCF in both the healthy older adults and persons with knee OA.

3.2 Methods

Older adults with and without previous diagnosis of knee OA were recruited from the local community and were included if they were aged 40-80 years and able to walk at their self-selected speed for five minutes. Subjects were excluded if their BMI exceeded 40 kg/m^2, previously had been diagnosed with arthritis of any other lower extremity joint, walking pattern was affected by some condition other than knee OA, any medical condition that prevented moderate physical activity, lateral compartment dominant knee OA, or subjective report of symptomatic knee not corresponding with the radiographically more severe knee. The presence of bilateral tibiofemoral OA did not exclude subjects from participation in the study and the effect of patellofemoral OA was not considered in this investigation. The participants in the healthy older adult cohort were additionally required to demonstrate side to side differences in volitional isometric knee extension strength of no greater than 10% and average scores of > 90 on the KOOS[67] on the ADL and Pain subscales, indicating minimal functional limitation. The protocol for this study was approved by the Institutional Review Board and all subjects completed a written informed consent form prior to participation.

3.2.1 Radiographic Assessment

Bilateral semi-flexed posterior-anterior radiographs were acquired on each subject and each tibiofemoral compartment was graded by a radiologist according to the KL criteria[68]. OA subjects exhibited medial compartment KL grades ≥ 2, while the healthy older adults were 0-1.

3.2.2 Gait Analysis

Kinematic and kinetic data were collected as subjects walked on an instrumented treadmill (Bertec Corp., Columbus, OH, USA) at a controlled speed of 1.0 m/s and data were collected at 60 and 1080 Hz, respectively. A controlled speed was chosen rather than the subject’s self-selected speed as both sagittal knee kinematics[23] and JCF[79] have been shown to vary with walking speed. Subjects wore

23 retro-reflective markers in a modified Helen Hayes arrangement while being tracked by six cameras. Thirty seconds of data were collected after subjects acclimated to the treadmill environment according to previously identified criteria[69].

3.2.3 Data Processing

Data were processed in Cortex 1.3.0.675 (Motion Analysis, Santa Rosa, CA, USA) prior to export to OpenSim 3.2[80] using custom MATLAB (MathWorks, Natick, MA, USA) scripts. Musculoskeletal simulations were then constructed using a model that consisted of 19 degrees of freedom. Specifically, six degrees of freedom were allowed at the pelvis, a ball and socket joint existed at each hip and between the pelvis and torso, planar joints with coupled translation and rotation at each knee, and a revolute joint at each ankle. Patellas were added to more accurately represent the line of action of the knee extensors[81] and the motion of the model was actuated by 92 muscles. The generic model was first anthropometrically scaled, then strength scaled by the maximum isometric forces of the knee extensors and flexors according to a previously established method[82]. Inverse kinematics was utilized to apply the model constraints and the Residual Reduction Algorithm was applied to ensure dynamic consistency of the motion according to best practice guidelines[83]. Static optimization was performed with the goal of minimizing the sum of the muscle activations squared. The tibiofemoral JCF was determined along the long axis of the tibia using the Joint Reaction Analysis tool and normalized to body weight. Following separation of the stance phase into 1st and 2nd epochs via the transition of the anterior-posterior ground reaction force from negative to positive[70], a 10 Hz low pass filter was applied to the JCF data[82] and the 1st and 2nd peak JCFs were identified. Individual muscle contributions to the JCF were determined by manually zeroing the activation of a muscle following static optimization and subtracting the corresponding JCF result from the original calculation. Key kinematic measures were calculated in MATLAB using the definitions reported in Table 3.1.

Measure	Definition
Knee flexion at initial contact	Knee flexion when ipsilateral vertical ground reaction force > 20 N
Early stance knee flexion	Maximum knee flexion achieved during first epoch of stance
Late stance knee extension	Minimum knee flexion angle between early stance knee flexion and ipsilateral toe-off
Toe-off knee flexion	Knee flexion when ipsilateral vertical ground reaction force < 20 N
Peak swing knee flexion	Maximum knee flexion angle following ipsilateral toe-off prior to ipsilateral initial contact
Loading response knee excursion	Early stance knee flexion - knee flexion at initial contact
Midstance knee excursion	Early stance knee flexion - late stance knee extension
Terminal stance knee excursion	Knee flexion at ipsilateral toe-off - late stance knee extension

Table 3.1: Definitions for sagittal knee kinematics considered.

3.2.4 Statistical Analysis

The more symptomatic limb was utilized for the OA subjects while a randomly selected limb was selected for the healthy older adults. Data were time normalized and the kinematic measures of interested were determined for each of four gait cycles and then averaged. Linear regression was utilized to investigate the relationships between peak JCFs and sagittal knee kinematic measures in each group. SPSS v22 (IBM Corp., Armonk, NY, USA) was utilized for all statistical analyses and alpha was set at 0.05.

3.3 Results

Subject characteristics are seen in Table 3.2. OA subjects were heavier, with greater BMI, preferred significantly slower walking speeds, and subjectively rated themselves lower on all subscales of the KOOS.

	OA	Healthy
Sample Size	20	23
Age (years)	65.8 ± 7.9	60.7 ± 10.9
Height (cm)	170.3 ± 9.7	167.8 ± 8.7
Mass (kg)	**85.0 ± 14.0**	**72.1 ± 15.0**
BMI (kg/m^2)	**29.3 ± 4.4**	**25.5 ± 4.2**
KL Grade	**2.5 ± 0.5**	**1.0 ± 0.0**
Gender (Male/Female)	8/12	9/14
Side Analyzed (Left/Right)	8/12	12/11
Self-Selected Speed (m/s)	**1.15 ± 0.10**	**1.31 ± 0.12**
KOOS Pain Subscale	**73.1 ± 17.2**	**97.7 ± 4.2**
KOOS Symptoms Subscale	**73.1 ± 17.8**	**95.8 ± 4.7**
KOOS Activities of Daily Living Subscale	**76.8 ± 17.4**	**99.2 ± 1.9**
KOOS Sport/Recreation Subscale	**58.6 ± 23.9**	**97.4 ± 6.0**
KOOS Quality of Life Subscale	**57.8 ± 16.5**	**95.7 ± 6.9**

Table 3.2: Subject characteristics (mean ± standard deviation). Bolded values indicate $p < 0.05$ between groups.

The OA subjects also demonstrated significantly greater knee flexion at initial contact, greater early stance knee flexion, less late stance knee extension, and less 2nd peak JCF when compared with the healthy older adults (Table 3.3). Both groups also demonstrated significantly greater 2nd peak JCF when compared with their respective 1st peak JCF.

	Healthy	OA
Knee flexion at initial contact (deg)	**8.9 ± 6.7**	**13.2 ± 5.3**
Early stance knee flexion (deg)	**22.0 ± 6.2**	**25.6 ± 5.2**
Late stance knee extension (deg)	**8.8 ± 5.3**	**13.7 ± 5.2**
Toe-off knee flexion (deg)	48.4 ± 4.7	51.6 ± 6.0
Peak swing knee flexion (deg)	68.6 ± 4.3	69.6 ± 3.9
Loading response knee excursion (deg)	13.1 ± 4.0	12.4 ± 3.7
Midstance knee excursion (deg)	13.2 ± 4.5	11.8 ± 4.7
Terminal stance knee excursion (deg)	39.5 ± 4.2	37.9 ± 5.7
1^{st} peak JCF (x BW)	1.83 ± 0.42	1.87 ± 0.40
2^{nd} peak JCF(x BW)	**3.06 ± 0.55**	**2.67 ± 0.45**

Table 3.3: Group means ± standard deviations for kinematic measures and peak JCFs. Values in bold indicate $p < 0.05$ between groups.

Linear regression identified significant relationships between the 1^{st} peak JCF and knee flexion at initial contact ($r = 0.72$, $p < 0.01$), early stance knee flexion ($r = 0.88$, $p < 0.01$), late stance knee extension ($r = -0.67$, $p < 0.01$), and midstance knee excursion ($r = -0.44$, $p = 0.04$) in healthy older adults (Figure 3.1). Subjects with knee OA demonstrated significant relationships between the 1^{st} peak JCF and knee flexion at initial contact ($r = 0.45$, $p = 0.05$), early stance knee flexion ($r = 0.57$, $p < 0.01$), and midstance knee excursion ($r = 0.59$, $p < 0.01$). In regards to the 2^{nd} peak JCF, healthy older adults exhibited significant relationships with terminal stance knee excursion ($r = 0.64$, $p < 0.01$) and late stance knee extension ($r = 0.69$, $p < 0.01$) while OA subjects demonstrated a significant relationship with terminal stance knee excursion ($r = 0.45$, $p = 0.05$) and a trend towards a relationship with late stance knee extension ($r = 0.40$, $p = 0.08$). Greater quadriceps contribution to 1^{st} peak JCF was associated with greater early stance knee flexion in both the healthy older adults ($r = 0.79$, $p < 0.001$) and subjects with knee OA ($r = 0.80$, $p < 0.001$). Similarly, greater late stance knee extension was associated with greater gastrocnemius contribution to the 2nd peak JCF in both the healthy older adults ($r = 0.69$, $p < 0.001$) and persons with knee OA ($r = 0.71$, $p < 0.001$).

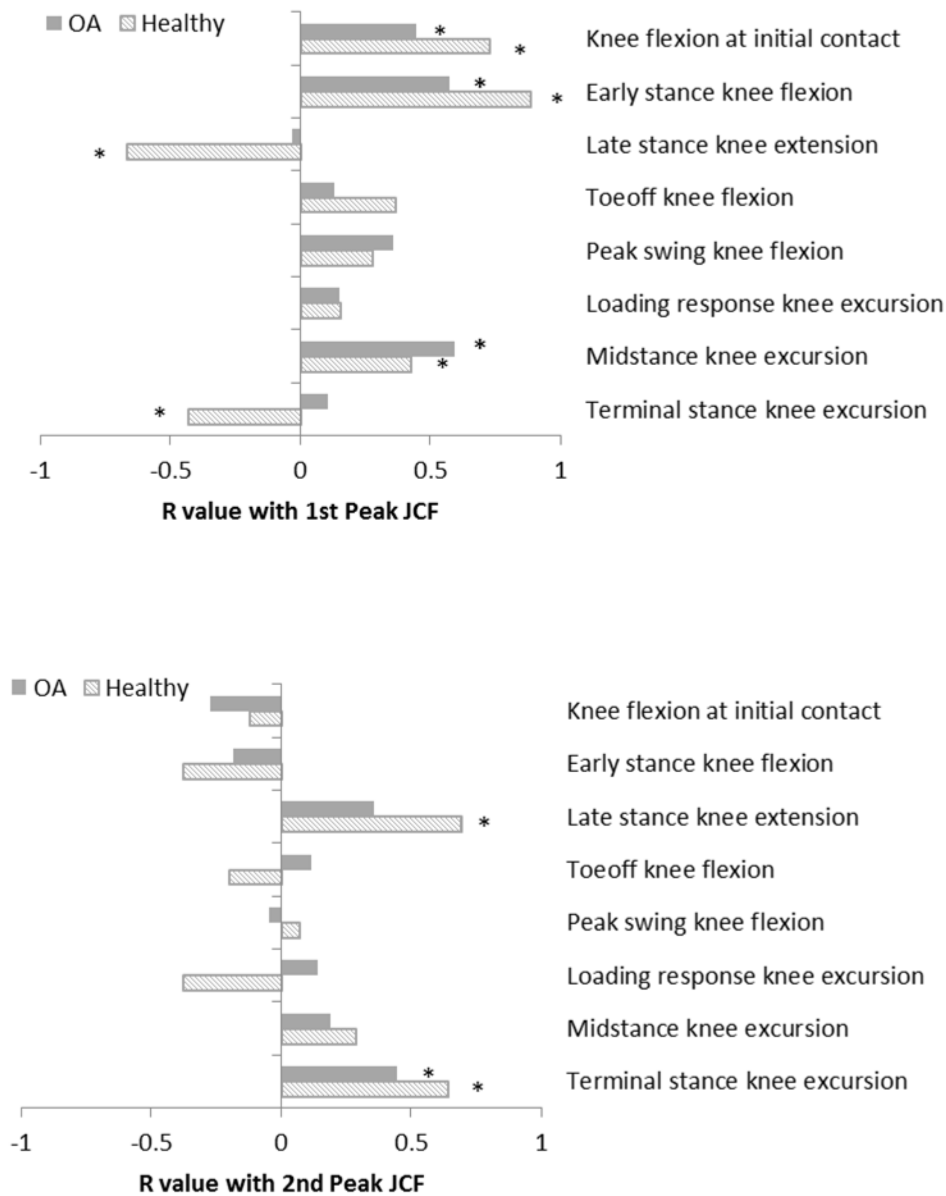

Figure 3.1: Correlations between sagittal knee kinematics and peak JCF in healthy older adults and persons with knee OA. * $p < 0.05$

3.4 Discussion

The purpose of this study was to investigate the relationship between sagittal knee kinematics and peak joint loading in healthy older adults and persons with knee OA, and it was found that several key sagittal knee kinematics were significantly associated with each peak JCF. Across both groups, greater knee flexion at initial contact and greater early stance knee flexion were positively associated with the 1st peak JCF. The subjects with knee OA exhibited significantly elevated mean values of both knee flexion at initial contact and early stance knee flexion suggesting that the gait modifications in persons with knee OA are associated with a greater 1st peak JCF. When evaluating the relationship between the 2nd peak JCF and sagittal knee kinematics, it was observed that the healthy older adults demonstrated a positive relationship between the 2nd peak JCF and late stance knee extension, while the OA subjects exhibited a trend towards a similar relationship. As a group, subjects with knee OA exhibited a significant reduction in late stance knee extension suggesting this gait modification may be an effective strategy to reduce the 2nd peak JCF. The 2nd peak JCF was significantly greater than the 1st peak in both groups, suggesting the gait modifications observed in persons with knee OA may be an effective strategy to reduce the overall magnitude of JCF during gait.

The 1st peak JCF was highly associated with early stance knee flexion in both groups, which agrees with previous work investigating the relationship between early stance knee flexion and the peak external knee flexor moment[7]. The external knee flexor moment is resisted by the quadriceps and we identified a significant relationship between the quadriceps contribution to 1st peak JCF and peak stance knee flexion in both groups. Late stance knee extension was positively associated with the 2nd peak JCF in our cohort of healthy adults and exhibited a trend towards a similar relationship in our subjects with knee OA which agrees with previous work in the cerebral palsy population[24]. It was observed that a more extended knee was associated with greater gastrocnemius contribution to the 2nd peak JCF. As the gastrocnemius is known to be the most significant contributor to the 2nd peak JCF[24], changes in its function are most likely to drive a corresponding change in overall JCF magnitude. During late stance, the gastrocnemius is known to provide vertical support for the center of mass[84]. Vertical displacement of the center of mass is required to achieve late stance knee extension; therefore an increase in gastrocnemius force would likely be required.

When comparing the results of this study to previous investigations, our findings of greater knee flexion at initial contact[6,21] and decreased late stance knee extension[21] within the OA subjects are in agreement with previous work. We also identified that the OA subjects exhibited significantly more early stance knee flexion which conflicts with previous studies that have identified a decrease in this measure[14,22] and is likely a result of walking speed being uncontrolled in those studies as walking speed has been shown to influence sagittal knee kinematics[23]. The results of this study suggest midstance knee excursion is most associated with the 1st peak JCF in subjects with knee OA which differs from a previous investigation that found early stance knee flexion was most associated with early stance joint loading[7]. Midstance knee excursion was not considered in the aforementioned study and our results suggest that early stance knee flexion is also significantly associated with the 1st peak JCF. It has previously been observed that a positive quadratic relationship exists between average stance phase knee flexion and average stance phase JCF[24]; however, our results suggest that although greater knee flexion in the 1st epoch of stance was associated with greater JCF; it was negatively associated with JCF in the

2^{nd} epoch. This suggests that the previously observed relationship between average stance phase knee flexion and JCF may only generally capture the relationship between sagittal knee kinematics and JCF. Our estimates of peak JCF are similar to the 2.1-2.8 x BW reported during self-selected walking in persons with instrumented knee prostheses[75,85,86]. Although early stance loading is generally the focus of research investigations, we identified that the 2^{nd} peak JCF was greater than the 1^{st} peak in both groups. This finding agrees with recent work involving instrumented knee prostheses investigating both total[26,75,87] and medial compartment[88] loading.

An interesting finding of this study was that peak knee flexion angles were most associated with peak JCF in our cohort of healthy older adults while knee excursions were most associated in our OA subjects. In order to understand this difference, we investigated the timing of the 1^{st} peak JCF relative to early stance knee flexion and the timing of the 2^{nd} peak JCF relative to late stance knee extension using time normalized data. The 1^{st} and 2^{nd} peak JCFs were found to occur at early stance knee flexion and late stance knee extension, respectively, while the peak JCFs occurred slightly later in the subjects with knee OA (Figure 3.2). The slight delay in the timing of the peak JCF results in their occurrence during the knee flexion excursion that was most significantly associated with the respective peak JCF and likely contributes to our findings.

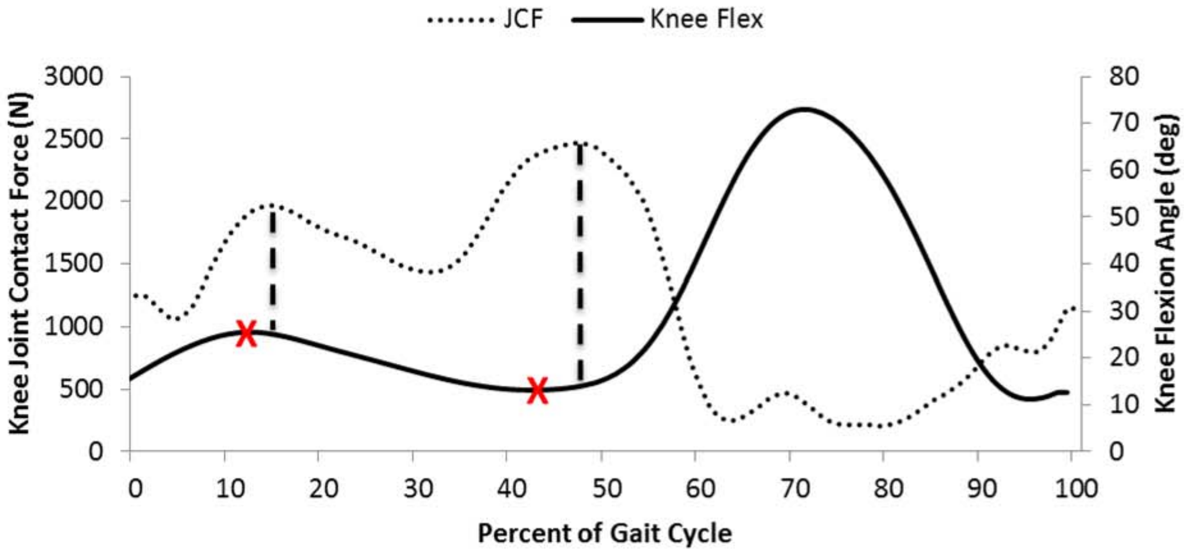

Figure 3.2: The knee flexion angle and JCF trajectories throughout the gait cycle for a typical OA subject. From left to right, the X's identify early stance knee flexion and late stance knee extension, while the dashed lines match the timing of the 1st and 2nd peak JCF with the knee flexion.

When evaluating the results of this study, there are limitations that must be considered. Data for this study were collected at a controlled walking condition as walking speed has previously been shown to influence sagittal knee kinematics in this population[23]; however this may mean that the results are not directly transferrable to the self-selected walking speeds ambulated by persons with knee OA. Additionally, although joint loading is known to be associated with development and progression of the disease as well as pain severity, we cannot confirm that the intent of the gait modification is to reduce joint loading. The gait modifications observed in persons with knee OA may be associated with knee flexion contractures[6,89,90], instability[3], maximizing articular cartilage contact or general pain management; all of which were not considered in this study.

In conclusion, the relationship between sagittal knee kinematics and peak JCF was investigated in a cohort of healthy older adults and persons with knee OA and it was found that the gait modifications observed in persons with knee OA were associated with an increase in the 1^{st} peak JCF, but a reduction in the 2^{nd} peak JCF. As the 2^{nd} peak JCF was found to be of greater magnitude, these gait modifications may be an effective strategy to reduce the overall magnitude of joint loading during ambulation.

Chapter 4

AIM 3: EVALUATE THE RELATIONSHIP BETWEEN ARTICULAR CARTILAGE CONTACT AREA AND ANTHROPOMETRIC MEASURES

4.1 Introduction

Knee OA is a leading cause of disability in older adults with 80% of those with symptomatic knee OA reporting a limitation in functional mobility and 25% reporting an inability to perform a major activity of daily living[4]. As articular cartilage is central to the disease, changes in cartilage morphology, such as thickness[33,43], volume[91,92], and contact area[36,46], with disease progression have been investigated.

Although previous investigations have identified that cartilage morphology varies with subject characteristics such as age, gender, height, weight, and bone size[43,91,92], recent studies either do not account for this baseline variation[33,46,93], or do not agree on which subject characteristics to account for in their data[32,36,91]. Accounting for such baseline differences in cartilage morphology is likely to be vital to identify variations from normative measures, such as those related to the development and progression of knee OA.

The purpose of this study was to investigate the relationship between tibiofemoral ACCA and anthropometric measures in order to determine whether anthropometric variation should be accounted for in cross-sectional analyses of ACCA. We hypothesized that total tibiofemoral ACCA would be most associated with the medial-lateral width of the proximal tibia, as the proximal tibia is smaller than the distal femur and it therefore likely limits the area of articular cartilage available for contact. Additionally, ACCA has been found to be a valid surrogate for the area of loading distribution in the tibiofemoral joint[58,59] which significantly influences local contact stresses[94]. However, the acquisition of MR images and resultant processing to determine ACCA is financially expensive and computationally intensive, therefore we were interested in assessing whether total tibiofemoral ACCA in healthy older adults could be predicted from subject characteristics acquired during gait analysis. We hypothesized that a regression equation utilizing only the subject characteristics acquired during gait analysis could predict greater than 80% of the variance in total ACCA.

4.2 Materials and Methods

Following Institutional Review Board approval, older adults were recruited from the local community for participation in this study, and all subjects completed a written informed consent form after the nature of the study was fully explained. Subjects were included if they were aged 40-80 years and able to walk at their self-selected speed for five minutes. Exclusion criteria included: BMI > 40 kg/m^2, previous diagnosis of arthritis of any lower extremity joint, medical condition that prevented moderate physical activity, extreme claustrophobia, implanted pacemaker, or implanted metal with magnetic qualities. Subjects that met these criteria underwent radiographic assessment of their tibiofemoral joints using posterior-anterior semi-flexed radiographs which were read by a radiologist to confirm the absence of osteoarthritis in either tibiofemoral joint compartment. Additionally, all subjects completed the KOOS[67] and were required to have average Pain and Activity of Daily Living subscales > 90, indicating minimal functional limitation from their knees. Based on previous studies, global subject characteristics such as gender, height, mass, BMI, age were included in analyses[43,91] in addition to scalar lengths and approximations to axial plane cross-sectional areas of the distal femur and proximal tibia[32,91,92]. A list of all anthropometric measures evaluated in this study and their definitions can be seen in Table 4.1.

Measure	Acquired from MR Images?	Definition
Gender	No	Self-reported
Height	No	Self-reported (m)
Mass	No	Calculated during static standing trial on forceplate (kg)
Age	No	Date of data collection - date of birth (years)
BMI	No	Mass (kg) / (height (m))^2
Ankle Width	No	Distance between medial and lateral malleoli (cm)
Knee Width	No	Distance between femoral epicondyles (cm)
Shank Length	No	Distance between midpoint of femoral epicondyles and medial/lateral malleoli (cm)
Thigh Length	No	Distance between hip joint center (determined in Visual 3D) and midpoint of femoral epicondyles (cm)
Leg Length	No	Sum of thigh and shank lengths (cm)
Femur AP Length	Yes	Distal femur AP dimension in femoral coordinate system (cm)
Femur ML Width	Yes	Distal femur ML dimension in femoral coordinate system (cm)
Femur Cross-section	Yes	Product of distal femur AP length and ML width (cm^2)
Tibia AP Length	Yes	Proximal tibia AP dimension in tibial coordinate system (cm)
Tibia ML Width	Yes	Proximal tibia ML dimension in tibial coordinate system (cm)
Tibia Cross-section	Yes	Product of proximal tibia AP length and ML width (cm^2)
ACCA	Yes	Nearest femoral cartilage < 0.5 mm from tibial cartilage (mm^2)

Table 4.1: Operating definitions for anthropometric measures considered for relationships with ACCA

MR images of both knees were acquired in a 0.6 T open MR scanner (Upright Multi-position MRI, Fonar Corporation, Melville, NY) with the table five degrees posterior from vertical resulting in near full bilateral weight bearing. A T1 fast spin echo sequence consisting of 30 sagittal slices, each 3 mm thick, spaced 3.3 mm apart, with a field of view of 25 cm, echo time of 20 ms, repetition time of 355 ms, and a display matrix of 512 X 512 was utilized. The subject was positioned in zero degrees knee extension and the scans were oriented along the long axis of the femur with the 15th slice aligned with the femoral notch. Distal femur, proximal tibia, and tibiofemoral articular cartilage surfaces were manually traced on a digitizing tablet (Wacom Technology Corp., Vancouver, WA) using IMOD software[95] before input into an existing three-dimensional modeling method that has previously been found reliable[96] for calculating medial and lateral compartment tibiofemoral ACCA. Points on the tibial cartilage surface were considered to be in contact with the femoral cartilage if the minimum distance was less than 0.5 mm. Total ACCA was measured by taking the sum of the medial and lateral ACCA. An existing knee joint coordinate system was applied[97]. In order to determine the length and width of the distal femur and proximal tibia, the three dimensional models of the bones were reduced to a two dimensional projection along the coordinate axes describing the AP length and ML width. The extents of the each coordinate axes was identified as the corresponding AP length and ML width of each bone and used in the formulation of the axial plane bone cross-sectional area measures (Table 4.1).

As part of a larger study, gait analysis was conducted for all subjects on an instrumented treadmill (Bertec Corp., Columbus, OH, USA). From this gait analysis, data from a static standing trial consisting of 27 retro-reflective markers placed in a modified Helen Hayes arrangement was exported to Visual 3D (C-Motion, Bethesda, MA, USA) where the location of the hip joint center was estimated from the locations of the bilateral anterior superior iliac spine and the sacrum[98].

A randomly selected limb was chosen for analysis. Linear regression, with alpha set at 0.05, was utilized to determine relationships between subject characteristics and total tibiofemoral ACCA. Additionally, a backwards elimination automated regression procedure, with the criteria of minimizing the adjusted R^2, was used to determine the simplest predictive model of which total ACCA could be estimated from data only available during gait analysis. The variables that were included in the procedure included: gender, height, mass, age, BMI, ankle width, knee width, shank length, thigh length, and leg length.

4.3 Results

Twenty subjects participated in this study (Table 4.2) and Pearson correlation coefficients are seen in Figure 4.1. A statistically significant positive relationship was observed between total tibiofemoral ACCA and each of the MR image-based subject characteristics with the cross-section of the femur being the largest ($r = 0.73$, $p < 0.001$). Additionally, height ($r = 0.71$, $p < 0.01$), being male ($r = 0.51$, $p = 0.02$) and mass ($r = 0.44$, $p = 0.05$) were significantly associated with total ACCA.

Sample size	20
Analyzed Limb (L/R)	10/10
Gender (M/F)	**9/11**
Height (m)	**1.69 ± 0.09**
Mass (kg)	**75.5 ± 14.8**
Age (years)	58.0 ± 9.6
BMI (kg/m^2)	26.4 ± 4.3
Ankle Width (cm)	7.54 ± 0.55
Knee Width (cm)	**13.0 ± 1.5**
Shank Length (cm)	39.2 ± 1.9
Thigh Length (cm)	38.1 ± 3.6
Leg Length (cm)	77.3 ± 4.6
Femur AP Length (cm)	**4.3 ± 0.4**
Femur ML Length (cm)	**7.4 ± 0.7**
Femur Cross-section (cm^2)	**31.8 ± 5.4**
Tibia AP Length (cm)	**5.8 ± 0.5**
Tibia ML Length (cm)	**7.4 ± 0.6**
Tibia Cross-section (cm^2)	**32.3 ± 5.7**
Medial tibiofemoral ACCA (mm^2)	**196.7 ± 82.8**
Lateral tibiofemoral ACCA (mm^2)	**158.6 ± 53.6**
Total tibiofemoral ACCA (mm^2)	355.4 ± 114.6

Table 4.2: Subject characteristics. Data are presented as mean ± standard deviation. Values in bold indicate $p < 0.05$ with total ACCA.

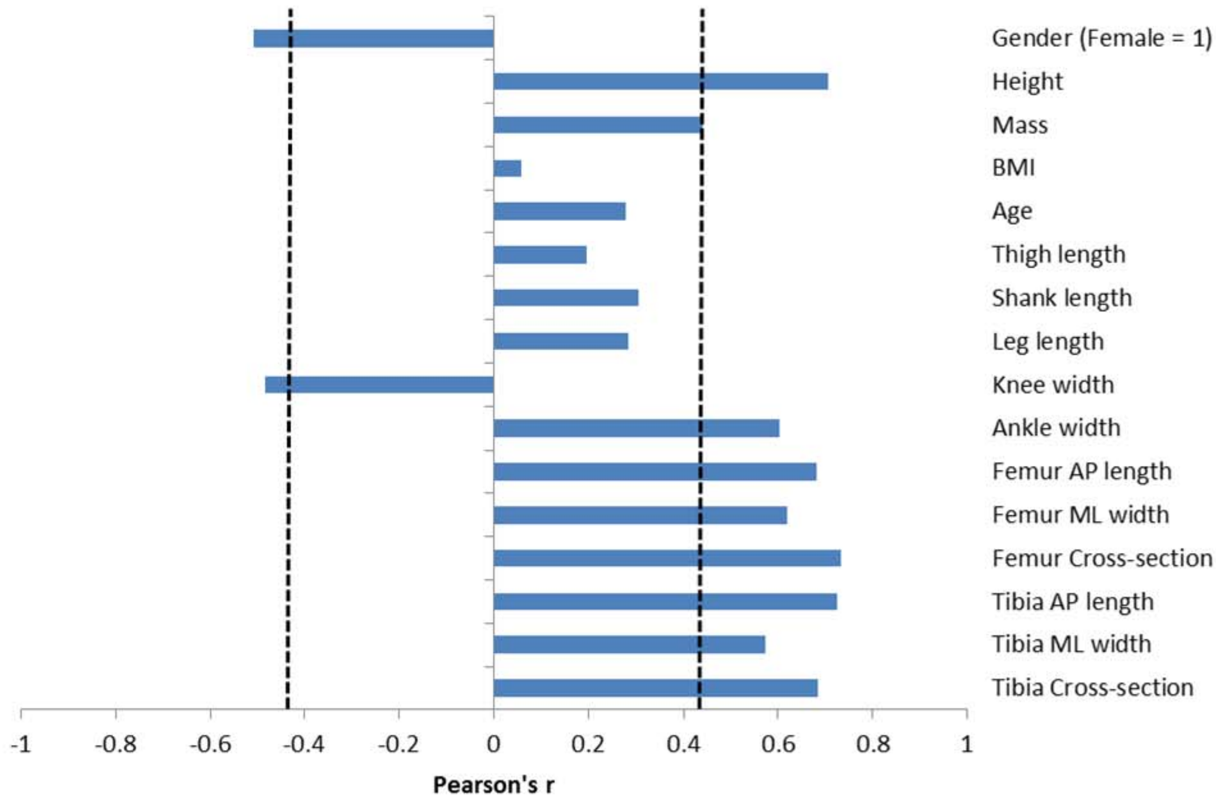

Figure 4.1: Results of linear regression analysis between subject characteristics acquired from MR images and gait analysis with total ACCA.

The results from the backward elimination regression procedure (Table 4.3) found that 83% of the variance in total ACCA can be accounted for by height, age, knee width, and thigh length (Table 4.4).

Model	R^2	ΔR^2	Adjusted R^2
(Constant), Ankle width, BMI, Age, Thigh length, Shank length, Knee width, Gender, Height, Mass	.85	.85	.71
(Constant), Ankle width, Age, Thigh length, Shank length, Knee width, Gender, Height, Mass	.85	.00	.73
(Constant), Age, Thigh length, Shank length, Knee width, Gender, Height, Mass	.85	.00	.76
(Constant), Age, Thigh length, Shank length, Knee width, Height, Mass	.85	.00	.77
(Constant), Age, Thigh length, Shank length, Knee width, Height	.84	-.01	.78
(Constant), Age, Thigh length, Knee width, Height	.83	-.01	.78

Table 4.3: Results of backwards regression analysis. The bottom model was selected based on its adjusted R^2

Variables Included	***b***	95% Confidence Interval	***t***	***p***
(Constant)	-360.2	-358.2 to -362.2	-0.984	0.341
Height (m)	1153.1	808.3 to 1497.9	6.555	0
Age (years)	2.9	0.9 to 4.9	2.26	0.039
Thigh length (cm)	-21.9	-11.8 to -32.0	-4.251	0.001
Knee width (cm)	-43.3	-22.4 to -64.2	-4.069	0.001

Table 4.4: Regression equation coefficients for predicting total ACCA in healthy older adults. Gender, mass, BMI, shank length, leg length, and ankle width were removed by the backward elimination regression procedure.

4.4 Discussion

The relationship between anthropometric measures and total ACCA was investigated in this study, and it was found that total ACCA varies with a number of these measures. Accounting for this baseline variation therefore would appear to be an important consideration when attempting to discern pathological changes by comparison with normative values. The measure that approximated distal femur axial cross-sectional area was most associated with total tibiofemoral ACCA, which differs from our initial hypothesis of ML tibial width, although this measure was also significantly associated with total tibiofemoral ACCA. Based on these results, we therefore suggest that parameters that approximate the axial cross-sectional area of the distal femur may be good candidates for the normalization of tibiofemoral ACCA.

We were not surprised to find that the MR image-based subject characteristics were all highly associated with total tibiofemoral ACCA, as we had expected them to correlate with the overall variability in anatomical size. However, we were surprised that the MR image calculated ML width of the femur and the knee width determined during gait analysis, which should capture very similar data, demonstrated a weak and non-significant relationship with each other ($r = -0.34$, $p = 0.14$), and also demonstrated opposing relationships with total ACCA. The width of the knee, as determined during gait analysis, includes not only the width of the femur, but also any adipose tissue that may be present. Knee width determined during gait analysis may be a stronger indicator of obesity than of the width of the femur, as supported by the significant association between knee width and BMI ($r = 0.57$, $p = 0.001$). The significant positive relationship between total ACCA and the gait analysis measured width of the ankle, where there is generally less adipose tissue, is also of note. It is also interesting to note that height was strongly correlated with total ACCA, whereas other longitudinal axis measures of thigh, shank, or leg length were not. This may indicate that a person's height captures some aspect of anthropometric data not transferred to individual segment lengths, or the sensitivity of these measures to retro-reflective marker placement.

The secondary purpose of this study was to develop a linear regression equation to predict total tibiofemoral ACCA in the tibiofemoral joint of healthy older adults, exclusively from anthropometric measures that can be identified from gait analysis. Although joint loading has been implicated in OA[12], the area over which this load is distributed also significantly contributes to the local stresses experienced[94] and although the meniscus is known to play a significant role in transmission of loads across the knee[53], ACCA alone has previously been shown to sufficiently approximate the area of loading distribution[58]. While the regression equation does not exactly predict total ACCA, when combined with an indicator of joint loading, its utilization to estimate the area of loading distribution may provide insights to identify older adults at risk for developing OA. Interestingly, application of a similar methodology utilizing only the MR image-based measures generated a regression equation capable of explaining only 63% of the variance. This suggested that anthropometric measures acquired during gait analysis may be more useful in estimating total ACCA.

Limited data are available investigating the relationships between cartilage morphology and subject characteristics. A previous study identified positive relationships between cartilage volume and height, mass, and the male gender[43] which agrees with our findings for ACCA. In a separate study that investigated tibiofemoral ACCA, data were normalized by the ratio of the individual subject's femoral epicondylar width to the group mean epicondylar width[36]. As the findings of our study suggest that the epicondylar width, or femoral ML width, is highly associated with total ACCA, this may be an appropriate technique; however, also scaling the data by the group mean epicondylar width limits the external validity of these results. A previous study of patellofemoral ACCA[44] found no gender differences after accounting for the cross-sectional area of the patella. We also identified significantly elevated ACCA in our male subjects ($p < 0.01$); however, after normalizing the data to the cross-sectional area of the distal femur, the difference was no longer significant ($p = 0.14$).

This study has several important strengths to consider. MR images were acquired in near full weight bearing, which is important since the addition of weight bearing has been shown to affect contact area[44,46]. We also utilized radiographs to confirm that all subjects were free of even early OA and excluded subjects with subjective report of functional limitations related to their knee in addition to those that have previously been diagnosed. As knee OA is most frequently observed in older adults[4], our sample of healthy older adults is an appropriate comparison group to determine baseline anthropometric variations in tibiofemoral ACCA. Although we did not identify a statistically significant relationship between age and total ACCA, age has been previously shown to influence cartilage morphology such as volume[91,92].

The primary limitation to our study is our sample size. With a larger sample, we would likely be able to improve the accuracy of our regression equation and more clearly identify the subject characteristic most associated with total tibiofemoral ACCA as several were highly associated. The frontal plane knee alignment likely influences the distribution of ACCA between the medial and lateral compartments and as we did not have this data we elected to use total tibiofemoral ACCA; however it is currently unknown whether the frontal plane alignment simply redistributes the tibiofemoral ACCA or also influences its magnitude[99].

In conclusion, total tibiofemoral ACCA was found to vary in healthy older adults as a function of anthropometric measures acquired from MR images and gait analysis. Future studies that have the goal of discerning pathological variations in cartilage contact conditions from those in normative groups should account for these baseline differences. The findings of the study suggest further exploration of normalization to an area parameter which scales anatomically with the joint but is independent of pathological variations.

Chapter 5

AIM 4A: EVALUATE THE RELATIONSHIP BETWEEN THE KNEE FLEXION ANGLE AT INITIAL CONTACT DURING GAIT AND ARTICULAR CARTILAGE CONTACT AREA

5.1 Introduction

OA of the knee is one of the most common forms of the disease[63] with patients frequently reporting limitations in functional mobility, especially walking[4]. Progression of the disease is characterized by wearing away of the articular cartilage[65,100] and hypothesized to result from mechanical loading of the joint[10]. Static and dynamic loading of cartilage have been found to alter its cellular organization[101–103] and likely contributes to the altered material properties in areas of loadbearing[104,105]. At the tissue level, it has previously been observed that healthy articular cartilage thickens with increased physical activity[106,107] and thins following traumatic spinal cord injury[108] suggesting cartilage morphology is also influenced by mechanical loading. It is currently unknown whether morphological changes in the articular cartilage in response to loading continue to be observed with the development of osteoarthritis.

Walking is the most common knee joint loading activity performed and results in thousands of loading cycles daily[18]. As a consequence, healthy cartilage morphology is likely influenced by the magnitude and frequency of knee joint loading experienced during gait. Although several studies have investigated the relationship between articular cartilage morphology, such as contact centroid[49,109] or volume[34,110] during various movements, little is known regarding whether the high loads experienced during gait[111] are associated with the morphology of tibiofemoral articular cartilage. A previous study combined dual-fluoroscopy and MR imaging to investigate cartilage contact area, thickness, and deformation throughout the stance phase of gait[112]; however relationships between specific gait characteristics and cartilage morphology were not assessed. The relationship between the ratio of medial to lateral compartment articular cartilage thickness and the peak knee adduction moment has been positively correlated in young adults[40], but demonstrated no association with older adults[39] and mixed observations in older adults with knee OA[33,39]. More recently, it has been observed that the anterior-posterior location of thickest articular cartilage on the medial femur is correlated with the knee flexion angle at initial contact[32] in young healthy adults. The knee flexion angle at initial contact is significantly associated with the magnitude of the 1st peak joint contact force (Aim 2) and likely plays a significant role in determining the average knee flexion angle across the stance phase which is quadratically associated with mean joint contact force[24]. It is possible that the increased medial femoral cartilage thickness in contact at this phase of the gait cycle indicates a morphological change associated with the mechanical loading experienced by the joint.

When compared to healthy older adults, the knee flexion angle at initial contact is altered in persons with OA (Aim 2). Although previous work has identified a significant relationship between the knee flexion angle at initial contact and 1st peak JCF (Aim 2), the relationship between knee flexion angle at initial contact and articular cartilage contact area (ACCA) is unknown. Articular cartilage in areas of contact area is thickest[34] which may serve to reduce local stresses[113]. Furthermore, it has been suggested that articular cartilage contact area is a viable surrogate for the area of loading distribution[58,59] making changes in ACCA an important consideration in the disease process. Therefore, the purpose of this study was to investigate the relationship between the knee flexion angle at initial contact and tibiofemoral ACCA. It was hypothesized that healthy older adults would demonstrate a relationship between the knee flexion angle at initial contact and ACCA and therefore possibly indicating morphological changes to increased mechanical loading while persons with knee OA would not demonstrate a similar relationship.

5.2 Methods

Older adults were recruited from the local community and included in this study if they were able to walk for five minutes at a self-selected speed and aged 40-80 years. Exclusion criteria included: BMI > 40 kg/m^2, diagnosed arthritis of other lower extremity joints, walking pattern affected by some condition other than knee OA, any medical condition that prevented moderate physical activity, lateral compartment dominant knee OA, or subjective report of symptomatic knee not corresponding with radiographically more severe knee. Subjects with bilateral tibiofemoral OA were not excluded and the effect of patellofemoral OA was not considered in this study. Subjects in the healthy older adult group were additionally required to demonstrate < 10% side to side difference in maximal volitional isometric knee extensor strength and an average disability < 10% on the ADL and Pain subscales of the KOOS[67]. The protocol for this study was approved by the Institutional Review Board and all subjects completed a written consent form prior to participation in the study.

5.2.1 Radiograph

All subjects completed bilateral semi-flexed posterior-anterior tibiofemoral radiographs which were scored in the medial and lateral compartments according to the KL grading criteria[68]. Healthy older adults exhibited medial compartment KL grades < 2 while OA subjects were ≥ 2.

5.2.2 Gait Analysis

All subjects walked on an instrumented split belt treadmill (Bertec Corp., Columbus, OH, USA) while a modified Helen Hayes marker set consisting of 23 retro-reflective markers tracked the position of their body segments. Kinematic data were collected at 60 Hz while kinetic data were collected at 1080 Hz. The self-selected speed of each subject was determined during a 10 m over ground walking assessment prior to treadmill ambulation. Subjects were given sufficient time to acclimate to the treadmill environment[69] prior to data acquisition. Data were processed in Cortex (Motion Analysis, Santa Rosa, CA, USA) before export to OpenSim v3.2[80] using custom written MATLAB (MathWorks, Natick, MA, USA) scripts where the knee flexion angle at initial contact was identified.

5.2.3 MR Images

Images were acquired in a 0.6 T open MR scanner (Upright Multi-position MRI, Fonar Corp., Melville, NY) with the table oriented five degrees posterior from vertical resulting in near full bilateral weight bearing. A T1 fast spin echo sequence consisting of 30 sagittal slices, each 3 mm thick, spaced 3.3 mm apart, with a field of view of 25 cm, echo time of 20 ms, repetition time of 355 ms, and a display matrix of 512 X 512 was utilized. Data were acquired for each knee separately with each subject's knee in zero degrees extension. Scans were oriented along the long axis of the femur and the 15th slice aligned with the femoral notch. A digitizing tablet (Wacom Technology Corp., Vancouver, WA, USA) and IMOD software[95] was utilized to manually identify the surface features of the distal femur, proximal tibia, and medial and lateral compartment articular cartilage of each bone. Tracings were input into a reliable[96] modeling method to determine medial and lateral compartment ACCA. An established joint coordinate system[97] was applied to the model to determine the knee flexion angle during the MR image acquisition and the anthropometric qualities of the distal femur. ACCA was normalized by the axial cross-sectional area of the distal femur prior to analysis (Aim 3).

5.2.4 Statistical Analysis

A single limb was used from each subject for analysis with the more symptomatic limb utilized in the OA group and a randomly selected limb in the cohort of healthy older adults. Statistical analyses were performed in SPSS v22 (IBM Corp., Armonk, NY, USA). The relationship between knee flexion angle at initial contact and total ACCA was investigated utilizing linear regression. Alpha was set at 0.05.

5.3 Results

Data were collected on 15 healthy older adults and 13 subjects with knee OA. Subjects with knee OA were older, had increased knee flexion at initial contact, walked at a reduced self-selected speed and scored themselves lower on all aspects of the KOOS ($p = 0.001 - 0.03$) (Table 5.1).

	OA	Healthy
Sample Size	13	15
Age (years)	**64.1 ± 7.6**	**56.8 ± 9.2**
Height (cm)	169.8 ± 9.6	169.3 ± 9.3
Mass (kg)	85.0 ± 15.2	74.9 ± 16.5
BMI (kg/m^2)	29.6 ± 5.3	26.0 ± 4.7
KL Grade	**2.4 ± 0.5**	**1.0 ± 0.0**
Gender (M/F)	5/8	7/8
Side Analyzed (L/R)	4/9	7/8
Self-Selected Speed (m/s)	**1.15 ± 0.11**	**1.36 ± 0.11**
KOOS Pain Subscale	**76.3 ± 14.1**	**97.4 ± 4.7**
KOOS Symptoms Subscale	**75.0 ± 11.8**	**96.2 ± 4.6**
KOOS ADL Subscale	**78.4 ± 16.0**	**99.5 ± 0.9**
KOOS Sport/Rec Subscale	**60.0 ± 23.5**	**98.7 ± 3.0**
KOOS QOL Subscale	**60.1 ± 16.6**	**97.1 ± 6.2**
Total Tibiofemoral ACCA (mm^2)	363.2 ± 172.6	358.1 ± 117.4
Normalized Total Tibiofemoral ACCA	0.11 ± 0.05	0.11 ± 0.03
Knee Flexion at Initial Contact (deg)	**13.7 ± 4.4**	**7.5 ± 3.1**
Knee Flexion angle during MR Imaging (deg)	**6.3 ± 5.8**	**-4.5 ± 5.5**

Table 5.1: Subject characteristics. Values in bold indicate $p < 0.05$

OA subjects also exhibited increased knee flexion during MR image acquisition ($p < 0.001$). No differences were observed in ACCA ($p = 0.93$) or normalized ACCA ($p = 0.89$). The knee flexion angle at initial contact was significantly associated with the mean stance phase knee flexion angle in both groups ($p < 0.01$). Linear regression analysis found a trend towards a relationship between the tibiofemoral ACCA and knee flexion angle in the healthy older adults ($r = 0.49$, $p = 0.07$) while no relationship was observed for the OA subjects ($r = -0.24$, $p = 0.42$) (Figure 5.1). A post-hoc power analysis for the healthy older adults indicates a statistical power of 0.66 was achieved.

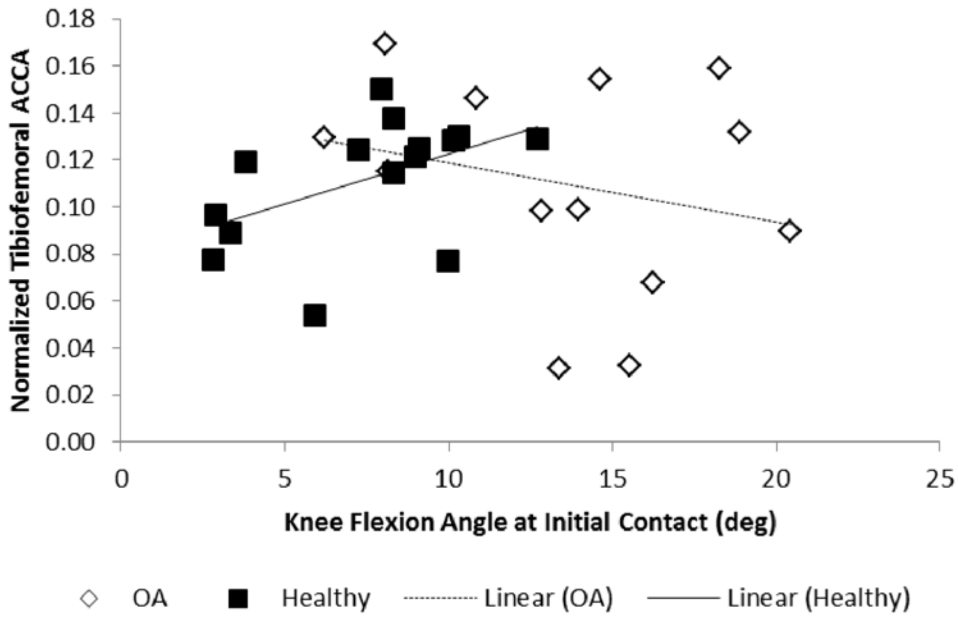

Figure 5.1: Relationship between normalized tibiofemoral ACCA and knee flexion angle at initial contact for both groups.

5.4 Discussion

The relationship between knee flexion angle at initial contact and total articular cartilage contact area was investigated. It was found that the healthy older adults exhibited a trend towards a positive relationship and the OA subjects demonstrated no relationship between the knee flexion angle at initial contact and ACCA despite similar ACCA, which supports our initial hypothesis that a morphological response to loading may not be present in OA. The knee flexion angle at initial contact is an important kinematic indicator for joint loading during gait as it is significantly associated with the 1st peak JCF (Aim 2) and the mean stance knee flexion angle, which is quadratically associated with the mean JCF across stance phase[24]. As both magnitude[12,114] and duration of loading[17,18,115] have been implicated in the disease process, the association of knee flexion angle at initial contact with each aspect is an important consideration when evaluating the implications from this study.

We know that healthy articular cartilage can alter its morphology in response to the loading environment[106–108]. Therefore, although self-selected speed is known to be decreased in persons with knee OA[8,14], it was the most appropriate walking condition to consider in this investigation because it best represents the normal joint loading environment. Interestingly, when we applied the methodology from Aim 1 to investigate the relationship between knee flexion angle at initial contact and walking speed [slope ± 95% confidence interval], the healthy older adults demonstrated a reduction in the knee flexion angle with decreasing walking speed (0.0019 ± 0.0017 deg*s/m), while the OA subjects demonstrated no relationship (0.0007 ± 0.0022 deg*s/m). An increase in knee extension at initial contact would correspond to an increase in ACCA[36,116] as well as a possible reduction in 1st peak JCF (Aim 2), and may be associated with the reduction in preferred walking speed in this population. However, the persons with knee OA may not be able to increase their knee extension at initial contact due to the knee flexion contractures frequently observed in this population[6,89,90]. Alternatively, the altered knee flexion angle at initial contact may be a gait modification aimed at minimizing pain with ambulation.

In this study, the healthy older adults group average ACCA of 358 mm^2 is lower than previously reported in young healthy adults (394-707 mm^2)[36,116,117] and slightly above what has previously been reported for older adults (255-340 mm^2)[46] and likely results from the acquisition of MR images in weight bearing, which has been shown to increase the ACCA[46]. Gait is a weight bearing activity; therefore acquisition of our MR images in weight bearing was an important consideration. MR sequence attributes have also been shown to influence the magnitude of ACCA[46], which limits the external validity of ACCA studies, but was uniform in our study. Others have identified similar positive relationships between magnitude of load and area of loading distribution during gait in healthy adults[32,40,41] and absent[39] or negative[33] relationships in OA. The ACCA obtained from the MR images was normalized to the cross-sectional area of the distal femur to account for anthropometric differences in ACCA. Accounting for anthropometric variation in cartilage morphology is an important consideration in cross-sectional studies; however, it is inconsistently performed[46,116,117] or performed without specific rationale[36] in previous investigations of cartilage morphology.

Caution should be utilized when interpreting the results of our study given our small sample size. With a larger cohort, it is anticipated than we would be able to detect a significant relationship between the knee flexion angle at initial contact and ACCA; however our sample size was limited by our selective inclusion criteria in terms of pain, function, strength, and co-morbidities. Subjects were instructed to evenly distribute their weight during acquisition of the MR image; therefore it is anticipated that approximately 50% of their body weight was transferred through each limb; however we do not have data to confirm this. The knee flexion angle during MR image acquisition significantly differed between the groups. Individual MR sequences lasted approximately six minutes and the entire data collection lasted approximately two hours. Due to the extended duration of standing, and therefore muscle activation required, it is possible the subjects slightly adjusted their posture to a more comfortable position. It is not uncommon for healthy older adults to have slight knee hyper-extension[6,118] while persons with knee OA are frequently found to have deficits in knee extension range of motion[6,89,90].

In conclusion, the relationship between knee flexion angle at initial contact and ACCA was investigated and it was found that healthy older adults demonstrate a strong trend towards a positive relationship which may indicate an increase in ACCA in response to the increased magnitude and duration of loading experienced during ambulation. Despite similar ACCA, subjects with knee OA demonstrated no such relationship indicating that although the joint loading environment is important in OA, cartilage morphology may not be associated with joint loading during gait. Additional research is required to understand whether the altered loading environment precedes the development of OA.

Chapter 6

AIM 4B: EVALUATE THE RELATIONSHIP BETWEEN THE KNEE ADDUCTION MOMENT DURING GAIT AND THE MEDIAL TO LATERAL DISTRIBUTION OF ARTICULAR CARTILAGE CONTACT AREA

6.1 Introduction

Among the 12% of American adults with symptomatic knee OA, functional limitations with the sit to stand transition, stair ascent, and walking are frequently reported[77]. Additionally, 25% of persons with symptomatic knee OA report an inability to perform a major activity of daily living[4] making an improved understanding of the pathophysiology of the disease a research priority.

Joint loading is frequently implicated in the disease process[12,17] and the knee is exposed to thousands of loading cycles during ambulation daily[18]. Although joint loading may be elevated in the OA population[12,18], cartilage contact geometry also plays a significant role in determining load distribution[94]. Cartilage contact stresses have been investigated in cadaveric studies[52,53] and musculoskeletal simulations[55,56,119], which may not be indicative of the *in vivo* loading environment and are generally limited by small sample sizes. Instrumented total knee arthroplasties have also reported *in vivo* contact stresses[57]; however, the implants do not reproduce the joint loading environment and results are limited to only a few subjects. Although both the articular cartilage and menisci play an important role in load distribution across the knee[53], elevated contact stresses using only the ACCA have been seen to predict incidence of OA[58] and development of bone marrow lesions in persons with

OA[59]. The loads experienced during dynamic gait are several times what is experienced in static standing[11] and to date, no study has investigated the relationship between the dynamic loads associated with gait and the area over which these loads are transmitted across the knee joint in the knee OA population.

The knee adduction moment has been seen to strongly correlate with the M/L distribution of joint loading[11] and is commonly used as a surrogate[12,16,18]. The purpose of this study was to investigate the relationship between M/L loading ratio, as indicated by the knee adduction moment, with the corresponding area of load distribution, as indicated by the M/L ratio of ACCA. A positive relationship between these variables would indicate preservation of the local contact stresses even in the presence of increased loading and it was hypothesized this would be exhibited by a cohort of healthy older adults, while persons with knee OA would not demonstrate this relationship.

6.2 Methods

Older adults with and without knee OA were recruited from the local community and included in the study if they were able to walk for five minutes at self-selected speed and aged 40-80 years. Primary exclusion criteria included BMI > 40 kg/m^2, diagnosed arthritis of other lower extremity joint, walking pattern affected by some condition other than knee OA, any medical condition that prevented moderate physical activity, lateral compartment dominant knee OA, or subjective report of symptomatic knee not corresponding with the radiographically more severe knee. Subjects with bilateral tibiofemoral OA were not excluded and the effect of patellofemoral OA was not considered in this investigation. Subjects in the cohort of healthy older adults were additionally required to demonstrate < 10% side to side difference in isometric volitional knee extensor strength and an average disability of < 10% on the ADL and Pain subscales of the KOOS[67]. The protocol for this study was approved by the Institutional Review Board and all subjects completed a written consent form prior to participation.

6.2.1 Radiographic Assessment

All subjects completed bilateral semi-flexed posterior-anterior radiographs which were read by a radiologist and scored according to the Kellgren-Lawrence (KL) grading criteria for each tibiofemoral joint compartment[68]. KL grades in the medial compartment were 0-1 in the healthy older adults and ≥ 2 in the OA subjects.

6.2.2 Gait Analysis

Subjects walked on a split-belt instrumented treadmill (Bertec Corp., Columbus, OH, USA) while marker and analog data were collected at 60 Hz and 1080 Hz, respectively. Twenty-three retro-reflective markers were placed on each subject in a modified Helen Hayes arrangement and tracked by six cameras. OA subjects are frequently reported to self-select a reduced walking speed when compared to healthy older adults[18,120]. Since walking speed has been found to influence relevant kinematic and kinetic measures[23], gait data were collected both at self-selected speed and a controlled condition of 1.0 m/s. Self-selected walking speed was determined during an over ground walking assessment prior to gait analysis. Subjects were given sufficient time to acclimate to the treadmill environment prior to data collection[69] and 30 second trials were collected for each condition. Data were processed in Cortex (Motion Analysis, Santa Rosa, CA, USA) before export to Visual 3D (C-Motion, Bethesda, MA, USA) for determination of the knee adduction moment following application of a

6 Hz low pass filter to both the marker and analog data. The knee adduction moment was normalized to the subject's mass and the 1st and 2nd peaks were calculated using a custom MATLAB (MathWorks, Natick, MA, USA) script which separated the stance phase of the gait cycle into 1st and 2nd epochs using the transition of anterior-posterior ground reaction force from negative to positive[70] before identifying the maximum adduction moment in each epoch of the stance phase. The non-time normalized knee adduction impulse was calculated over the entire stance phase using a Riemann sum technique with a time step of 1/60 sec.

6.2.3 MR Imaging

Imaging data were acquiring in a 0.6 T open MR image scanner (Upright Multi-position MRI, Fonar Corporation, Melville, NY) with the subject in near full bilateral weight bearing as the imaging table was oriented five degrees posterior from vertical at the request of the imaging clinic for patient safety. A T1 fast spin echo sequence consisting of 30 sagittal slices, each 3 mm thick, spaced 3.3 mm apart, with a field of view of 25 cm, echo time of 20 ms, repetition time of 355 ms, and a display matrix of 512 X 512 was utilized. Data were acquired on each knee separately with the subject's knee in zero degrees extension and scans were oriented along the long axis of the femur with the 15th slice aligned with the femoral notch. The surfaces of the femur, tibia, and respective medial and lateral articular cartilage surfaces were manually traced using a digitizing tablet (Wacom Technology Corp., Vancouver, WA) and IMOD software[95] and input into an existing three-dimensional modelling method[121,122] that has been previously been shown reliable[96] to determine medial and lateral compartment ACCA and resultant M/L ACCA ratio.

6.2.4 Statistical Analysis

Data from the more symptomatic knee of the OA subjects and a randomly selected limb in the healthy older adults were utilized in analysis. Data for the 1st and 2nd peak knee adduction moments and knee adduction impulse were averaged across four representative gait cycles to more accurately represent their values. Group relationships between each of the three knee adduction terms and the M/L ACCA ratio were individually studied using linear regression analysis. Alpha was set at 0.05.

6.3 Results

Subjects in the OA group were older, walked at a reduced self-selected speed, and functionally score themselves lower on all aspects of the KOOS when compared with the healthy group (Table 6.1). No statistically significant differences were observed in group mean ACCA or any of the knee adduction terms at either walking speed.

		OA	Healthy
Sample Size		13	15
Age (years)		**64.1 ± 7.6**	**56.8 ± 9.2**
Height (cm)		169.8 ± 9.6	169.3 ± 9.3
Mass (kg)		85.0 ± 15.2	74.9 ± 16.5
BMI (kg/m^2)		29.6 ± 5.3	26.0 ± 4.7
KL Grade		**2.4 ± 0.5**	**1.0 ± 0.0**
Gender (M/F)		5/8	7/8
Side Analyzed (L/R)		4/9	7/8
Self-Selected Speed (m/s)		**1.15 ± 0.11**	**1.36 ± 0.11**
KOOS Pain Subscale		**76.3 ± 14.1**	**97.4 ± 4.7**
KOOS Symptoms Subscale		**75.0 ± 11.8**	**96.2 ± 4.6**
KOOS ADL Subscale		**78.4 ± 16.0**	**99.5 ± 0.9**
KOOS Sport/Rec Subscale		**60.0 ± 23.5**	**98.7 ± 3.0**
KOOS QOL Subscale		**60.1 ± 16.6**	**97.1 ± 6.2**
Medial Tibiofemoral ACCA (mm^2)		220.5 ± 145.9	204.0 ± 83.7
Lateral Tibiofemoral ACCA (mm^2)		142.6 ± 37.4	154.1 ± 52.6
Controlled Speed	1st Peak Adduction Moment (Nm/kg)	0.43 ± 0.19	0.37 ± 0.15
	2nd Peak Adduction Moment (Nm/kg)	0.30 ± 0.18	0.28 ± 0.13
	Adduction Impulse (Nms/kg)	0.16 ± 0.10	0.13 ± 0.08
Self-Selected Speed	1st Peak Adduction Moment (Nm/kg)	0.44 ± 0.18	0.39 ± 0.15
	2nd Peak Adduction Moment (Nm/kg)	0.27 ± 0.16	0.29 ± 0.13
	Adduction Impulse (Nms/kg)	0.15 ± 0.08	0.11 ± 0.06

Table 6.1: Subject characteristics in form of mean ± standard deviation. Values in bold indicate $p < 0.05$ between groups.

In the self-selected walking condition, healthy older adults demonstrated significant relationships between the M/L ACCA ratio and 1st ($r = 0.57$, $p = 0.03$) and 2nd ($r = 0.59$, $p = 0.02$) peak knee adduction moments as well as knee adduction impulse ($r = 0.55$, $p = 0.04$). The OA subjects demonstrated no relationships between the M/L ACCA ratio and 1st ($r = -0.25$, $p = 0.41$) or 2nd ($r = 0.00$, $p = 1.00$) peak knee adduction moment or knee adduction impulse ($r = -0.12$, $p = 0.69$) (Figure 6.1).

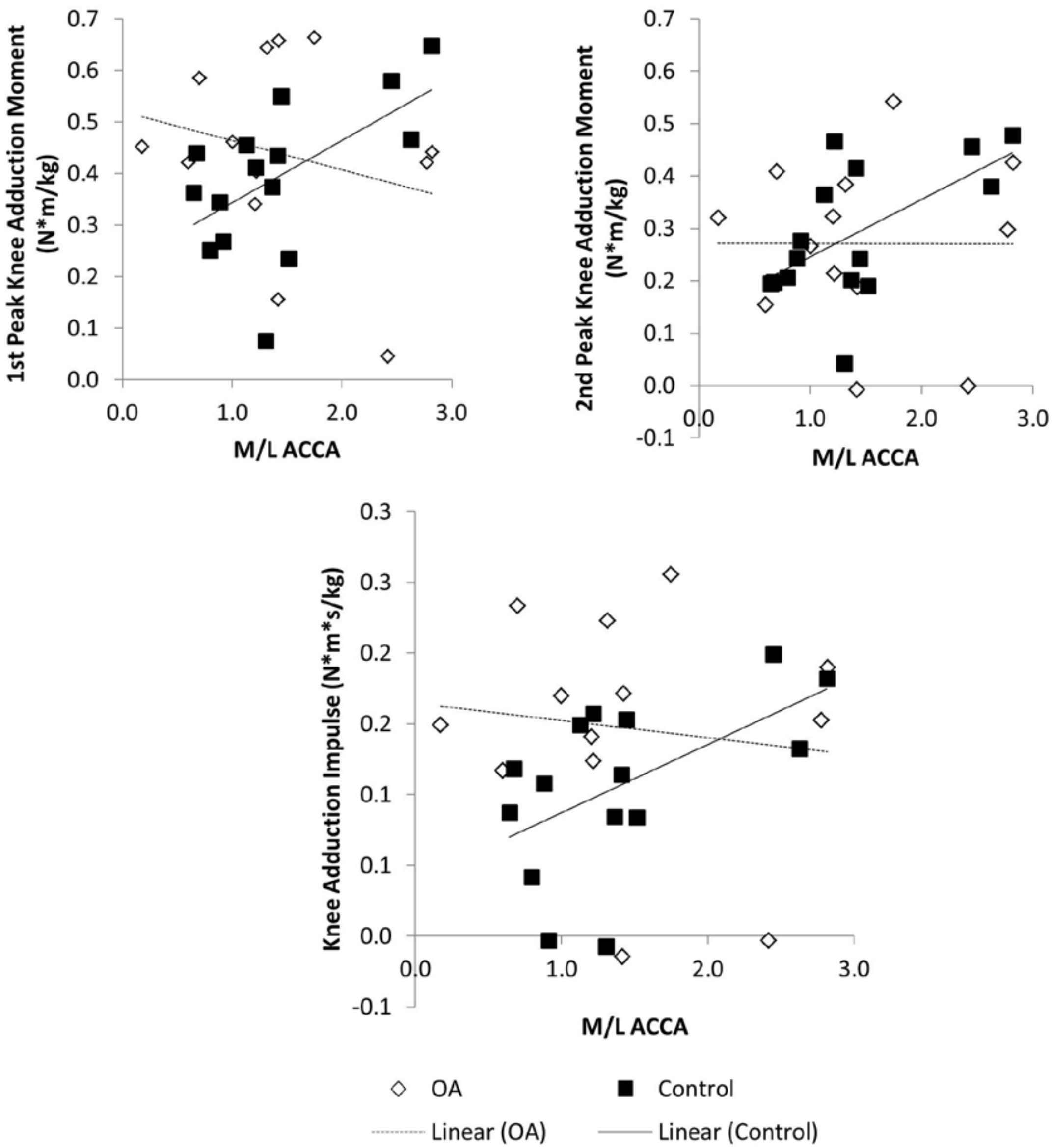

Figure 6.1: The relationship between indicators of M/L compartment loading in OA subjects and healthy older adults. Linear regression lines are displayed.

During the controlled speed, the healthy older adults demonstrated positive relationships between the 2^{nd} peak knee adduction moment ($r = 0.54$, $p = 0.04$) and knee adduction impulse (r = 0.57, p = 0.03) with M/L ACCA ratio. The 1st peak knee adduction moment showed evidence of a trend (r = 0.42, p = 0.12) towards a similarly positive relationship with M/L ACCA ratio. As at the self-selected speed, OA subjects demonstrated no relationship between the 1st (r = -0.25, p = 0.41) or 2nd (r = -0.02, p = 0.95) peak knee adduction moments or knee adduction impulse (r = -0.07, p = 0.83) with M/L ACCA ratio.

6.4 Discussion

This is the first study to suggest that in subjects with knee OA, the medial to lateral ratio of dynamic knee loading during gait may not reflect the medial to lateral ratio of area of loading. Although the knee adduction moment is strongly correlated with the medial to lateral loading ratio in the tibiofemoral joint[11], it is unclear as to whether the peak knee adduction moment[12] or knee adduction impulse[15] is a more relevant measure for the OA population. In order to circumvent this issue, we studied both indicators. Our results suggest that within our healthy older adults, the cartilage loading environment may be relatively similar in the medial and lateral compartments despite differences in load within each compartment. This significantly differed from our OA subjects where no relationships were observed between any of the M/L loading indicators and the M/L area of loading distribution. This suggests that a maladaptive loading environment may be present in addition to the elevated medial compartment loads frequently observed in this population[14,18].

Previous *in vivo* studies have identified a M/L ACCA ratio of 1.36-2.70[36,46,116,117] when subjects were placed in a similar test position which compares well with our healthy older adults who average 1.41. It is likely that a number of factors influence both the ACCA and M/L ACCA ratio. There is a high prevalence of asymptomatic meniscal tears in both individuals with OA and healthy older adults[123] which will likely increase the ACCA because contact between the cartilage and meniscus would transition into cartilage on cartilage contact and contact between the meniscus and articular cartilage was not considered in this investigation. It is known that the frontal plane knee alignment influences the knee adduction moment during gait[124,125]; however, it also likely influences the distribution of ACCA between the medial and lateral tibiofemoral compartments. For example, an increase in varus alignment would likely result in a relative increase in medial compartment and reduction in lateral compartment ACCA. In our healthy older adults, there was a trend towards a relationship ($p = 0.06$) between frontal plane knee alignment in static standing and M/L ACCA, therefore frontal plane knee alignment likely significantly contributes to our study findings within this group. A similar relationship was not observed in the OA subjects ($p = 0.96$).

Although no other studies have investigated the ratio of M/L ACCA to dynamic loading during gait, articular cartilage thickness, which has been found elevated in regions of articular cartilage contact[34], has been previously studied[33,38,40]. A positive relationship between the M/L articular cartilage thickness ratio and the peak knee adduction moment during gait was found in young healthy adults[40], but not in older adults[39]. Mixed results have been exhibited in the OA population with results identifying no relationship[38] or a negative relationship[33]. Taken together, the results of these studies suggest older adults may not demonstrate a relationship between M/L compartment loading and M/L cartilage thickness regardless of whether they have knee OA and suggests the relationship between M/L compartment loading and M/L area of loading distribution may be able to better characterize the loading environment.

In our study, the observed relationships between the knee adduction moment and M/L ACCA were similar in both the self-selected and controlled walking conditions. Persons with knee OA are known to prefer a reduced self-selected walking speed[18,120], which influences the knee adduction moment[5] and is unable to be appropriately accounted for in statistical analyses[126]. In order to address this limitation, previous studies have collected walking data at a pre-determined speed for both groups[12,72]; however this likely does not reflect the loading environment during activities of daily living. By demonstrating similar relationships in both walking conditions, we have increased confidence in the relevance of findings. To capture the effect of weight bearing which is known to alter ACCA[46], we acquired our MR images in weight bearing. Previous studies have attempted to account for individual variations in cartilage measures based solely on anthropometric differences in a variety of ways including accounting for gender[42], height and weight[42,43], age[39], femoral epicondylar width[36] and sagittal width of the femur[32,41]. As there currently exists no best practice regarding this topic, by evaluating a within subject ratio we are able to account for any anthropometric variation in the observed data.

Our study also has limitations that must be considered when interpreting the results. Our sample size was relatively small and it is possible that observed relationships, or absence of relationships, could change with an increased sample size. The acquired MR images were static in nature and it has been shown that contact area varies through the gait cycle[112] and is affected by the duration of loading[127]. We also cannot confirm that the frontal plane knee angle during the static MR image is similar to the angle at the instants of the 1st and 2nd peak knee adduction moments. We compared the frontal plane knee angle during a static standing trial to the angle at the instant of each of the peak knee adduction moments during gait and found no differences in the healthy older adults ($p > 0.05$), but did find that the OA subjects were significantly more varus at the instant of both peak knee adduction moments when compared to static standing in both walking conditions ($p < 0.01$). These results conflict with a previous study that found increased dynamic varus in healthy young adults and no change in varus in the OA subjects[128]. The observed differences may be a result of their OA cohort including both medially and laterally dominant OA rather than exclusively medially dominant as medial OA is associated with increased dynamic varus[70]. There was no relationship between dynamic varus and the M/L ACCA ratio in either group ($p > 0.05$), therefore it is unlikely that the dynamic varus observed in the OA subjects influenced the findings of this study.

The relationship between medial to lateral loading distribution during gait and the medial to lateral area of loading distribution was investigated in a cohort of healthy older adults and persons with medial knee OA. The healthy older adults demonstrated a positive relationship indicating that even in the presence of increased joint loading, preservation of the loading environment is possible given a corresponding increase in ACCA. A similar relationship was not observed in the OA subjects, suggesting that in addition to the elevated joint loads frequently observed in this population, a maladaptive loading environment is likely present.

Chapter 7

AIM 4C: EVALUATE THE RELATIONSHIP BETWEEN PEAK JOINT LOADING DURING GAIT AND THE AREA OF LOADING DISTRIBUTION

7.1 Introduction

An estimated 9.3 million Americans have symptomatic knee OA[64] which frequently results in pain and instability[3] as well as a reduced ability to perform necessary activities of daily living, especially walking[4]. Mechanical loading of the knee joint has been implicated in the disease pathogenesis[10,12] and as walking results in thousands of loading cycles each day[18], it is the subject of frequent investigation in this population[13,16,23].

Although the magnitude of joint loading seems to play a role in the disease[12,65], the area over which this load is distributed contributes to the local contact stresses[94,129]. Contact stress, or magnitude of loading per unit area, has been previously investigated in the tibiofemoral joint of cadaveric specimens[51,53,130], musculoskeletal simulations[54–56], and instrumented total knee prostheses[57,85,131]; however, implications from these studies are limited as the experimental conditions may not necessarily recreate the *in vivo* loading environment and/or are limited by exceedingly small sample sizes. Although the meniscus has been shown to play a significant role in the distribution of loading across the knee joint[53], the ratio of joint loading to ACCA alone has shown ability to predict the incidence of OA[58], and development of bone marrow lesions in persons with established OA[59].

The purpose of this study was to investigate the knee joint loading environment, as indicated by the relationship of peak knee joint loading during gait to the ACCA, in healthy older adults and persons with established knee OA. It was hypothesized that healthy older adults would demonstrate a positive relationship between peak joint loading and ACCA indicating preservation of the loading environment, even in the presence of increased joint loading, while persons with OA would not. Additionally, as previous studies have suggested that ACCA increases in early knee OA[47] and decreases in advanced OA[46] we investigated whether changes in ACCA and contact stress were present with radiographic progression of the disease.

7.2 Methods

Older adults were recruited from the local community for participation in a research study and included if they were able to walk for five minutes at a self-selected speed and aged 40-80 years. Subjects were excluded from participation if BMI exceeded 40 kg/m^2, previous diagnosis of arthritis of other lower extremity joints, walking patterns affected by some condition other than knee OA, any medical condition that prevented moderate physical activity, lateral compartment dominant knee OA, or subjective report of symptomatic knee not corresponding with the radiographically more severe knee. Subjects with bilateral tibiofemoral OA were not excluded and the effect of patellofemoral OA was not considered in this study. Healthy older adults were additionally required to demonstrate side to side differences in maximal isometric volitional knee extensor strength not greater than 10% and self-report minimal functional knee disability as indicated by KOOS[67] Pain and ADL subscales averaging > 90%. The protocol for this study was approved by the

Institutional Review Board and all subjects completed a written consent form prior to participation in any aspect of the study.

7.2.1 Radiograph

All subjects completed bilateral semi-flexed posterior-anterior radiographs for assessment of severity of their osteoarthritis using the KL grading criteria[68]. Subjects with medial compartment KL grades ≥ 2 were considered osteoarthritic, while subjects < 2 were considered healthy.

7.2.2 Gait Analysis

All subjects completed an instrumented gait analysis (Bertec Corp., Columbus, OH, USA) while kinematic and kinetic data were collected at 60 and 1080 Hz, respectively. A modified Helen Hayes marker set was utilized to track their body segments. All subjects walked at a controlled walking speed of 1.0 m/s, as walking speed has been shown to influence JCF[79], and were given sufficient time to acclimate to the treadmill environment prior to data acquisition[69]. Data were processed in Cortex (Motion Analysis, Santa Rosa, CA, USA) prior to export to OpenSim v 3.2[80] using custom MATLAB (Mathworks, Natick, MA, USA) scripts.

7.2.3 Musculoskeletal Model and Determination of Peak Joint Contact Force

The musculoskeletal model utilized in OpenSim consisted of 19 degrees of freedom including six at the pelvis, a ball and socket joint at each hip and between the interface of the pelvis and torso, planar joints with coupled translation and rotation at each knee, and a revolute joint at each ankle. Motion of the model was controlled by 92 muscle actuators and included patellas to more realistically model the line of action of the quadriceps[81]. The generic model was first anthropometrically scaled, then the knee flexors and extensors were volitionally strength scaled using a previously established methodology shown to improve calculation of peak JCF[82]. Following this step, inverse kinematics was utilized to apply the degree of freedom limitations to the kinematic data. Dynamic consistency was achieved through application of the Residual Reduction Algorithm according to best practice guidelines[83]. Following this step, static optimization was performed by minimizing the sum of the muscle activations squared. The knee JCF along the long axis of the tibia was then determined via the Joint Reaction Analysis tool. The transition of the anterior-posterior ground reaction force from negative to positive was utilized to separate the stance phase into two epochs[70] and after application of a 10 Hz low pass filter[82], the 1st and 2nd peak JCFs and corresponding knee flexion angles at that instant in time were identified.

7.2.4 Articular Cartilage Contact Area

MR images were acquired using a 0.6 T open MR scanner (Upright Multi-position MRI, Fonar Corp., Melville, NY). MR scans consisted of a T1 fast spin echo sequence with 30 sagittal slices, each 3 mm thick, spaced 3.3 mm apart, with a field of view of 25 cm, echo time of 20 ms, repetition time of 355 ms, and a display matrix of 512 X 512. Scans were oriented along the long axis of the femur and the 15th slice aligned with the femoral notch. A total of 4 MR scans were acquired for each knee. First, a near full bilateral weight bearing image was acquired with the imaging table oriented five degrees posterior to vertical and the knee in full extension. Following this scan, the table was moved to 45 degrees posterior from vertical, resulting in partial bilateral weight bearing, and MR images were acquired of each knee at three different knee flexion angles of approximately 0, 15, and 30 degrees. The full bilateral weight bearing image was always acquired first, followed by the partial weight bearing images in a random order. The order of limbs was also randomized. The distal femur, proximal tibia and articular cartilage surfaces were manually digitized on a tracing tablet (Wacom Technology Corp., Vancouver, WA, USA) using IMOD software[95]. An existing three dimensional modeling technique that has previous demonstrated reliability[96] was used to generate subject specific tibiofemoral joints. Locations on the surface of the tibial cartilage were considered to be in contact with the femoral cartilage if the distance between the surfaces was ≤ 0.5 mm. Total ACCA was determined by taking the sum of the medial and lateral tibiofemoral compartments. An established coordinate system[97] was applied to determine the knee flexion angle during MR image acquisition and ACCA from MR scan that best matched the knee flexion angle at peak JCF was utilized in analyses.

7.2.5 Statistical Analysis

The more symptomatic knee was selected for analysis in the OA group while a randomly selected limb was chosen in the cohort of healthy older adults. The peak JCFs and corresponding knee flexion angles at that instant in time were extracted from 4 gait cycles and averaged for each subject. For each peak JCF, the corresponding MR scan that best matched the knee flexion angle at the instant of the peak JCF was utilized to approximate the ACCA at that instant. Statistical analyses were performed in SPSS v22 (IBM Corp., Armonk, NY, USA). The relationship between each of the peak JCFs and total ACCA was investigated separately for both groups using linear regression with alpha set at 0.05. Group differences were additionally evaluated using t-tests. In order to assess whether normalized ACCA (Aim 3) or contact stress at either peak JCF varied based on KL grade, one-way ANOVAs with Tukey-Kramer post-hoc tests were utilized.

7.3 Results

Subject characteristics for each group can be seen in Table 7.1. OA subjects were significantly older, walked at a slower self-selected speed, and subjectively rated themselves lower on all subscales of the KOOS.

	OA	Healthy
Sample Size	13	14
Age (years)	**64.1 ± 7.6**	**57.3 ± 9.3**
Height (cm)	169.8 ± 9.6	169.5 ± 9.7
Mass (kg)	85.0 ± 15.2	74.9 ± 17.1
BMI (kg/m^2)	29.6 ± 5.3	26.0 ± 4.8
KL Grade	**2.4 ± 0.5**	**1.0 ± 0.0**
Gender (Male/Female)	5/8	6/8
Side Analyzed (Left/Right)	4/9	7/7
Self-Selected Speed (m/s)	**1.15 ± 0.11**	**1.36 ± 0.11**
KOOS Pain Subscale	**76.3 ± 14.1**	**97.2 ± 4.9**
KOOS Symptoms Subscale	**75.0 ± 11.8**	**95.9 ± 4.6**
KOOS Activities of Daily Living Subscale	**78.4 ± 16.0**	**99.5 ± 0.9**
KOOS Sport/Recreation Subscale	**60.0 ± 23.5**	**98.6 ± 3.1**
KOOS Quality of Life Subscale	**60.1 ± 16.6**	**96.9 ± 6.4**

Table 7.1: Subject characteristics (mean ± standard deviation). Values in bold indicate $p < 0.05$ between groups.

No group differences were observed in peak JCF, normalized ACCA, knee flexion angle at instant of peak JCF, or contact stress (Figure 7.1), although the OA subjects exhibited a trend towards an increased knee flexion angle at both JCF peaks ($p = 0.06$-0.08) and a trend ($p = 0.09$) of an increase in the contact stress ratio at the 1st peak JCF when compared to the healthy older adults.

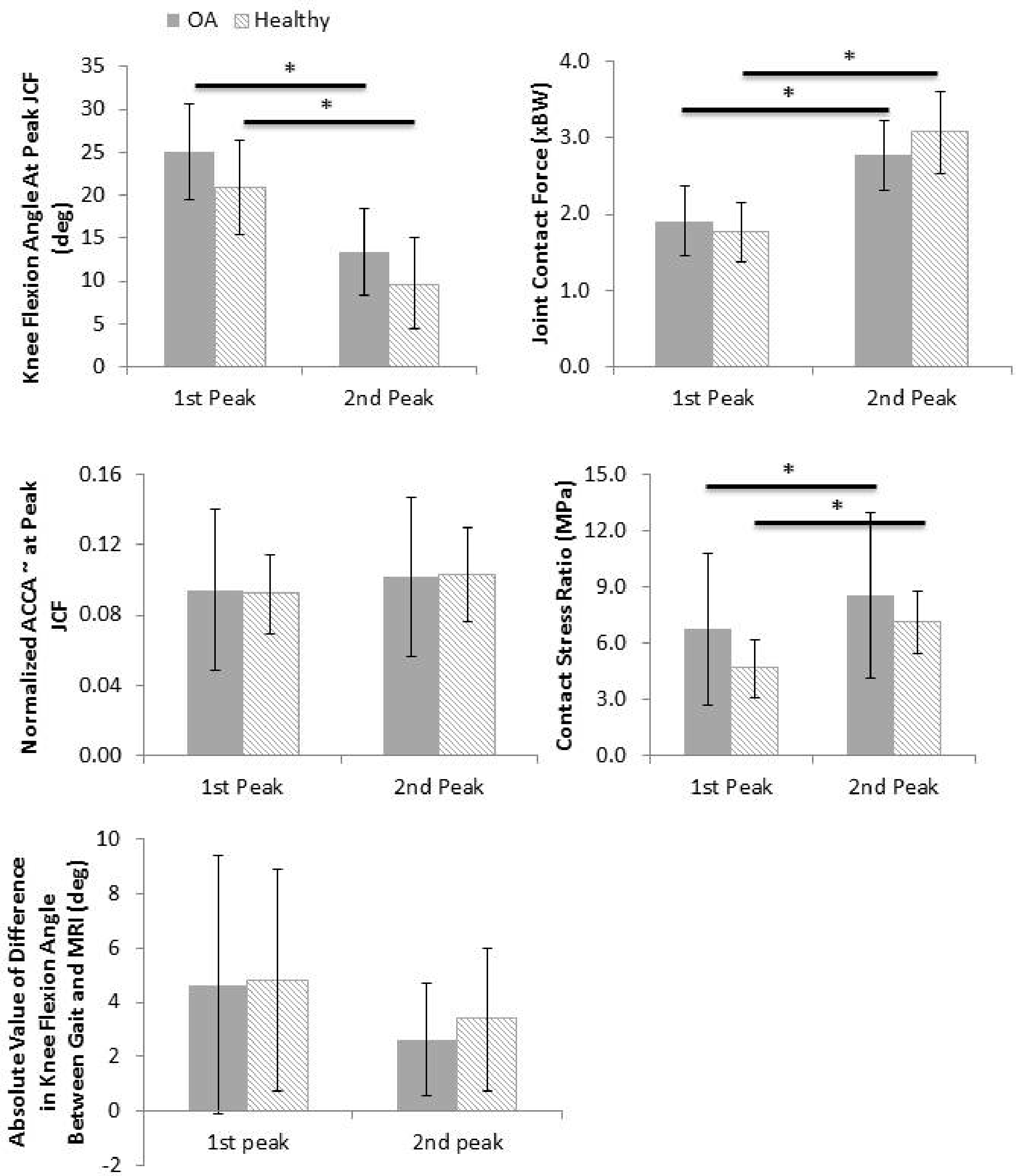

Figure 7.1: Group differences at instants of peak JCF. No significant between group differences were observed although trends towards significant relationships were seen with several variables. * $p < 0.05$

The difference between the knee flexion angle during MR image acquisition and peak JCF averaged 3.9 ± 3.6 degrees across both groups and peaks with the maximum deviation occurring at the 1st peak JCF in the healthy older adults and averaged 4.8 ± 3.7 degrees. The healthy older adults demonstrated a significant relationship between total ACCA and the 1st peak JCF ($r = 0.54$, $p = 0.05$) and a trend towards a similar relationship with the 2nd peak JCF ($r = 0.42$, $p = 0.13$). The OA subjects demonstrated no relationship between total ACCA and the 1st peak JCF ($r = 0.32$, $p = 0.29$) and a trend towards a relationship with the 2nd peak JCF ($r = 0.42$, $p = 0.13$) (Figure 7.2).

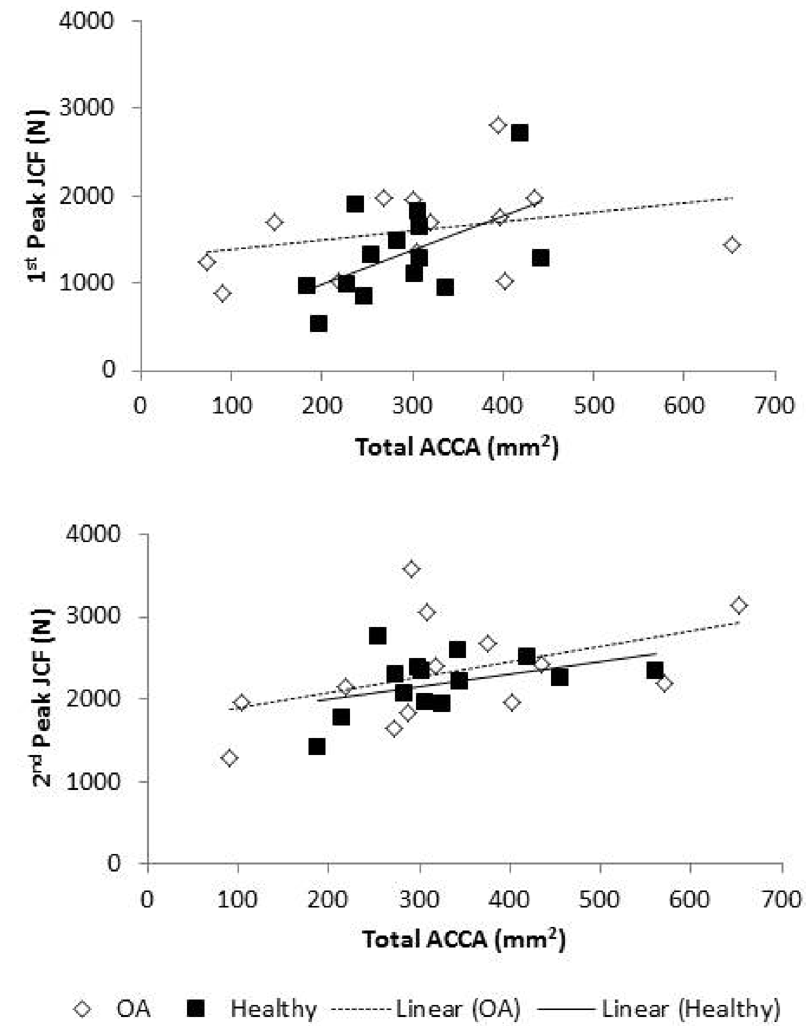

Figure 7.2: Contact stress ratio for the groups. The only significant relationship observed was between the healthy older adults and the 1st peak JCF.

When evaluating the KL grades separately, no significant differences were observed in normalized total ACCA or the contact stress at the 2nd peak JCF (Figure 7.3). Significant differences were observed between KL grades in the contact stress at the 1st peak JCF ($p = 0.05$) with the Tukey-Kramer post-hoc test identifying significant differences between KL 1 and 3 ($p < 0.05$).

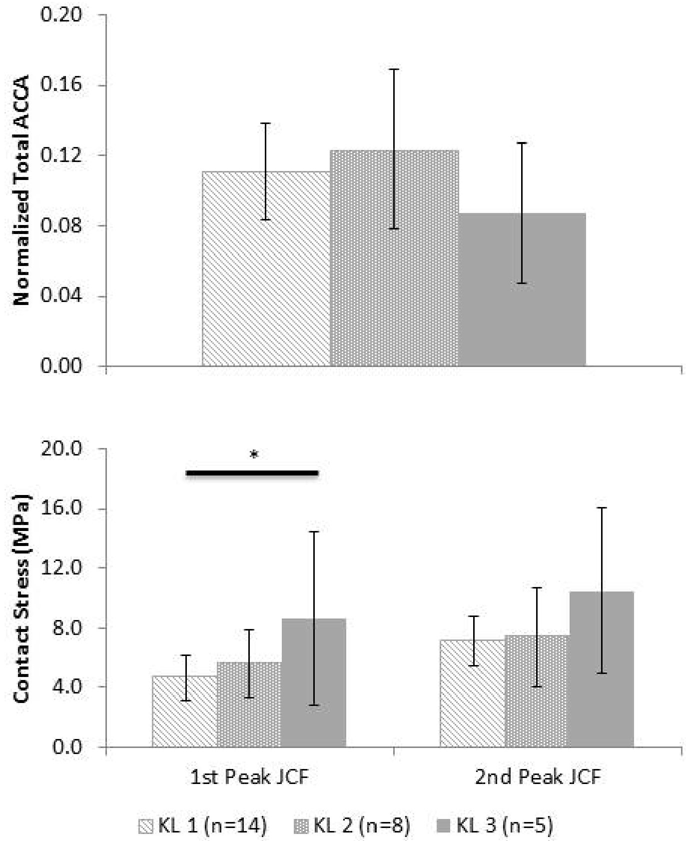

Figure 7.3: Comparisons of normalized ACCA at full knee extension and near full bilateral weight bearing and stress ratios during gait grouped by KL grade (1 = possible OA, 2 = definite OA, 3 = advanced OA, 4 = severe OA). * $p < 0.05$

7.4 Discussion

The purpose of this study was to investigate the relationship between peak loading during gait and the area of loading distribution and it was found that the healthy older adults demonstrated a significant positive relationship between 1st peak JCF and total ACCA which indicates that even in the presence of additional joint loading, the loading environment may be preserved. These subjects also demonstrated a trend towards a similar relationship with the 2nd peak JCF, which given our limited sample size suggests that our initial hypothesis regarding healthy older adults would be supported with additional data. The OA subjects demonstrated a trend towards a relationship with the 2nd peak JCF, but no relationship with the first which partially supports our preliminary hypotheses that these subjects would not exhibit a relationship between the variables. It is interesting that although both the body weight normalized 1st peak JCF and normalized ACCA at 1st peak were similar between groups, the group relationships were not which supports the premise of an altered loading environment present in OA.

When we separated our subjects by KL grade, we observed that ACCA seems to increase early in the disease before decreasing with further progression. Although this difference was not significant in our study, it agrees with previous results[46,47] and our non-significant findings are likely a result of our small sample size.

The first loading peak is frequently the focus of research investigations[7,73] with the second peak infrequently considered although it has previously been shown to be of similar[11] or greater magnitude[26]. We observed that the 2nd peak JCF was significantly greater in magnitude than the first in both groups. The knee was significantly more extended at the 2nd peak in both groups, and although ACCA is known to increase with knee extension[116,132], we found that the contact stress ratio at the 2nd peak JCF was significantly greater than the 1st in both groups, suggesting that the loading environment at the 2nd peak JCF is likely to play a significant role in the disease.

There are limited previous studies investigating knee contact stress. Cadaver studies have identified mean contact stresses between 0.5-1.8 MPa during static loading conditions[51,53,130] and up to 1.75 MPa during simulated gait cycles[133]. Our group average values were higher likely due to both the increased loads present during gait resulting from muscle forces[27] and our exclusion of the menisco-cartilage contact, which would increase the contact area and reduce the contact stress ratio. *In vivo* static loading using dual radiographs and MR images[58,59], while considering only cartilage on cartilage contact, identified maximum contact stresses of 3.92 MPa[58] and mean contact stresses of 2.47 MPa[59] during 0.3 x BW of loading supporting the hypotheses that not including menisco-cartilage contact would increase the contact stress observed. Several studies investigated contact stresses using musculoskeletal models of gait combined with finite element analysis; however these studies only reported peak values, which ranged from 7.4 - 17.0 MPa[56,134] and possibly in agreement with our mean values of 7.1 MPa for the healthy older adults and 8.6 MPa for the subjects with knee OA. Data from the instrumented knee prosthesis identified maximum contact stresses of 30 MPa[57]; however this likely reflects the altered loading environment as a result of the prosthesis geometry rather than the typical *in vivo* environment.

Our study utilized peak joint loads during gait, which is an important functional activity that is frequently limited in the OA population[4]. ACCA was determined during weight bearing MR imaging, which is a key consideration when evaluating a weight bearing activity[46]. We collected MR images in partial weight bearing due to concern that pain with prolonged weight bearing would limit the ability of the OA subjects to complete the data collection. No differences were observed in ACCA between the partial and full weight bearing conditions in similar knee postures; however, our limited sample size precludes us from confidently reporting data was acquired in sufficient weight bearing to accurately capture the loading environment.

Caution should be applied when interpreting the results of this study given our limited sample size. Additionally as MR images at only three knee flexion angles were acquired, we were not able to exactly match the position of the MR image to the knee flexion angle of interest. Additionally, the magnitude of ACCA has been shown to be influenced by both the magnitude[46] and duration of loading[127]. The bilateral weight bearing during MR acquisition indicates that approximately 0.5 x BW was transmitted through each limb, which is less that the approximately 3.0 x BW experienced during normal gait[111]. Each MR scan took approximately six minutes to acquire, which also differs from what is experienced during gait. A previous study using dual fluoroscopy to investigate ACCA during gait found very similar ACCA measures at both the 1st and 2nd peak vertical ground reaction forces[112], which strongly correlate with the peak JCFs[24]. This suggests that the forces experienced by the knee at a given instant may play a more significant role than the angle of knee flexion in determining the ACCA during gait. As all of the subjects walked at a controlled walking speed rather than their self-selected speed, these results may not directly translate to the gait of persons with OA during their activities of daily living; however as JCF is known to be affected by walking speed[79], we felt controlling this variable was important in order to meaningfully evaluate differences between the groups.

In conclusion, healthy older adults demonstrate preservation of the knee joint loading environment even in the presence of increased loads, as indicated by the corresponding increase in ACCA, while an altered loading environment may be present in persons with knee OA. An important finding from this study was that the contact stress ratio at the 2nd peak JCF was significantly greater than the 1st peak in both groups and future studies should investigate the loading environment at the 2nd peak JCF.

Chapter 8

CONCLUSIONS

Although joint loading has not conclusively been demonstrated to cause OA[9], it is very likely involved[12,17,65]. While previous studies investigating knee OA have identified differences in walking speed[14,18] and knee kinematics during gait[5,6,20], the effect of these gait modifications on joint loading was not well understood. In Aims 1 and 2 we sought to understand the relationships between these gait modifications and joint loading. Additionally, the area of loading distribution likely plays a significant role in determining whether the experienced loads are detrimental to the structures of the knee[94]. The latter half of the dissertation investigated the relationship between a surrogate for the area of loading distribution and kinematic and kinetic measures associated with joint loading. The conclusions for each of the studies are presented below.

8.1 Aim 1: Evaluate the Joint Loading Cost of Locomotion as a Function of Walking Speed

The joint loading cost of locomotion decreased with increasing walking speed for the knee adduction impulse and 2nd peak moment in both groups and the 1st peak moment in the healthy older adults. The OA subjects demonstrated no relationship with the 1st peak knee adduction moment suggesting that at worst, no increase in cumulative joint loading would be experienced by increasing their self-selected walking speed to match that of the healthy older adults; however a 2.7-10.4% reduction in cumulative joint loading is likely.

When evaluating the results of this study, it is possible that the observed changes during treadmill ambulation may not transfer to over ground gait[76]. Additionally, although a linear relationship between the joint loading cost of locomotion and walking speed was observed in the range of speeds considered, it is unlikely that this holds true for all walking speeds as it would suggest that at some maximal speed, there is no joint loading, which is not plausible.

Future studies should address these limitations by verifying the results with an over ground assessment and collecting data at additional walking speeds both within and outside the range of those considered to better understand the joint loading cost of locomotion. As symptoms associated with knee OA are associated with increased magnitude of joint loading[13], future work should also aim to understand whether there is an optimal walking speed that balances the increase in magnitude of joint loading with the corresponding reduction in joint loading cost of locomotion.

8.2 Aim 2: Evaluate the Relationship between Knee Flexion Kinematics during Gait and Peak Joint Contact Force

Several sagittal knee kinematics were found to be significantly associated with peak joint loading in both groups. Greater early stance knee flexion was associated with a greater 1st peak JCF in both groups. Greater knee flexion in early stance was associated with an increase in the quadriceps contribution to the JCF, which is known to be the primary source of joint loading[24,25]. Late stance knee extension was positively associated with the 2nd peak JCF and the contribution of the gastrocnemius to the 2nd peak JCF. During late stance, the gastrocnemius primarily functions to provide vertical support to the center of mass[84] and greater late stance knee extension likely requires greater vertical displacement of the center of mass from its position during early stance knee flexion.

The subjects with knee OA exhibited greater knee flexion at initial contact and early stance knee flexion when compared with the healthy older adults suggesting that these gait modifications are associated with an increase in the 1st peak JCF. Conversely, the decreased late stance knee extension demonstrated by the subjects with knee OA was associated with a reduction in the 2nd peak JCF. Since the 2nd peak JCF was found to be of greater magnitude than the 1st peak in both groups, the gait modifications exhibited by persons with knee OA may be an effective strategy to reduce the overall magnitude of joint loading during walking.

Although the peak JCF estimates generated from the musculoskeletal model utilized in this study correlate well with an instrumented knee prosthesis[82], it is unknown whether the altered muscle activation patterns frequently exhibited by this population[135,136] are appropriately captured in this model. Additionally, as tibiofemoral OA predominates in the medial compartment[3], the ability to separate the JCF into medial and lateral compartments would be of great utility and should be utilized in future studies.

8.3 Aim 3: Evaluate the Relationship between Articular Cartilage Contact Area and Anthropometric Measures

Tibiofemoral ACCA was found to significantly vary with a number of anthropometric measures sourced both from MR images and gait analyses. The cross-sectional area of the distal femur was most associated with total tibiofemoral ACCA ($r = 0.73$) and was utilized to normalize data to account for baseline differences in ACCA prior to evaluating for group differences in both healthy older adults and persons with knee OA. Additionally, a regression equation utilizing only anthropometric data determined from gait analysis accounted for 83% of the variance in total tibiofemoral ACCA. This is likely to be of great utility to future studies that wish to estimate ACCA without collecting MR data.

The primary limitation to this study was the limited sample size. Several anthropometric measures were highly associated with total ACCA and it is likely that a different measure might be more significantly associated with total ACCA. We were also limited to investigating relationships between anthropometrics and total ACCA, rather than the medial and lateral compartments as the frontal knee alignment was unknown and is likely to influence our results. Future studies should include acquisition of long limb radiographs for determination of the frontal plane knee alignment and investigation of its relationship to ACCA.

8.4 Aim 4a: Evaluate the Relationship between the Knee Flexion Angle at Initial Contact during Gait and Articular Cartilage Contact Area

Subjects with knee OA had significantly greater knee flexion at initial contact and no differences in ACCA were observed between groups. Healthy older adults exhibited a trend ($r = 0.49$, $p = 0.07$) towards a relationship between the knee flexion angle at initial contact and ACCA while the OA subjects did not ($r = -0.24$, $p = 0.42$). The trend towards a relationship between knee flexion angle at initial contact and ACCA in the healthy older adults may indicate a change in the cartilage morphology in response to the experienced joint loading. Despite similar ACCA, subjects with knee OA demonstrated no such relationship which likely indicates the presence of an altered response to joint loading.

A post-hoc power analysis indicates a statistical power of 0.66 was achieved suggesting that additional subjects are required to appropriately investigate this relationship. In order to address the differing knee flexion angles at MR acquisition, future studies should aim to refine the MR sequencing to reduce the data acquisition time and assess passive range of motion to exclude those with a knee flexion contracture[90].

8.5 Aim 4b: Evaluate the Relationship between the Knee Adduction Moment during Gait and the Medial to Lateral Distribution of Articular Cartilage Contact Area

The results of this study support our hypotheses that positive relationships between the knee adduction moment and medial to lateral distribution of ACCA would be present in the healthy older adults and not in those with knee OA. Similar findings at both the self-selected and controlled walking speeds add additional evidence to these findings. These results suggest that even in the presence of increased joint loads, preservation of the joint loading environment may occur in healthy older adults given the corresponding increase in cartilage contact area. A similar relationship was not observed in the osteoarthritic subjects suggesting that in addition to the increased joint loads frequently observed in this population, a maladaptive loading environment is likely present.

The primary limitation to this study is the small sample size. With additional subjects, it is possible the observed relationships might change. Additionally, menisco-cartilage contact was not considered and as the meniscus plays a significant role in load transmission through the knee[53], future studies should incorporate the meniscus into the area of loading distribution.

8.6 Aim 4c: Evaluate the Relationship between Peak Joint Loading during Gait and the Area of Loading Distribution

Both groups were found to demonstrate a trend towards a positive relationship with the 2nd peak JCF while the healthy older adults demonstrated a positive relationship with the 1st peak JCF and the OA subjects did not. Although this only partially supports our initial hypotheses, our findings were limited by our small sample size. An interesting finding of this study was that although the knee is more extended at the 2nd peak JCF, and therefore likely has increased ACCA when compared to the 1st peak JCF, the contact stress was greater at the 2nd peak indicating that the increase in ACCA did not offset the increase in JCF.

As the knee flexion angles at MR acquisition only approximated the knee flexion angle at the instant of peak JCF, future studies should collect the gait data prior to MR acquisition to exactly match the knee flexion angle. Additionally, as the duration of loading has been shown to influence the magnitude of ACCA[127], future studies should aim to develop MR sequences that are shorter in duration.

8.7 Overall Conclusions

Gait modifications frequently observed by persons with knee OA were found to influence joint loading. We observed that the reduced walking speed frequently preferred by persons with knee OA is likely not an effective strategy to reduce cumulative joint loading; however, the altered sagittal knee kinematics may reduce the peak magnitude of joint loading. Furthermore, when considering the area over which these loads are distributed, it was observed via kinematic and kinetic indicators of joint loading that healthy older adults exhibited a positive association between joint loading and the area of loading distribution, whereas persons with OA do not. It is currently unknown whether these changes in cartilage morphology precede disease initiation. This work should serve as a basis for future studies aimed at developing clinical interventions to mitigate the effect of OA on ADLs.

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Appendix A

INFORMED CONSENT FORM

Risk factors for progression of osteoarthritis of the knee

Summary

You are invited to participate in a research study conducted by Dr. Jill Higginson to investigate the progression of knee osteoarthritis (OA). This is a two-part longitudinal study involving (1) strength and walking trials and (2) MRI scans. You will be asked to repeat both parts in approximately 18 months. In this study, we will compare muscle and joint forces with cartilage properties in 30 adults with diagnosed knee OA and 30 healthy adults.

Study Description

Participants: Healthy adults with no history of orthopedic injury and adults with diagnosed osteoarthritis of the knee will be eligible for this study. You must be between 30 and 85 years of age to participate. If you decide to participate, Dr. Higginson or her research associates will ask you to complete two questionnaires. One will assess your overall health status and your ability to safely complete the experiment. The second questionnaire will assess your knee pain, symptoms and physical function. You will be also be asked about conditions for which MRI poses risks, such as implanted metal or electronic devices.

Part 1

This part of the study will occur in the biomechanics lab in Spencer Laboratory and you will be asked to wear shorts, t-shirt and comfortable walking shoes. We will measure your weight and height and ask about your current level of knee pain, if any. For the strength test, we will ask you to sit on the strength testing chair and push/pull as hard as you can against a non-movable arm three times on each leg. Each push will last about 3 seconds. We will assess your comfortable walking speed in the hallway. We will place surface electrodes on your legs with tape in order to measure the electrical output of your muscles. The attachment sites will be cleaned and shaved if necessary. While you are seated, we will attach reflective markers to your legs and upper body with tape. You may be asked to walk on a treadmill in five conditions (slow, comfortable speed, as fast as you can, slow speed with moderate load equal to 1/6 body weight, and comfortable speed with load) for less than two minutes at each speed. You may be asked to complete three additional walking trials at the follow-up visit. The movement of your legs and upper body will be recorded using special cameras which detect reflective objects attached to your body segments. The electrical activity of your leg muscles will be recorded during the walking trials using surface electrodes applied previously. We may also collect video for comparison with the motion data. You will have at least two minutes to rest between trials.

Total time: Setup will take approximately 1 hour, strength testing will take approximately 15 minutes, and the walking trials should take less than 30 minutes. The total time for your participation in this session will be no longer than 3 hours per visit.

Part 2

This test session will occur at Diagnostic Imaging Associates of Wilmington (Brandywine Office). We will contact you to schedule the appointment. You will be responsible for transportation to the Imaging center. You will be asked to wear shoes, t-shirt and comfortable walking shoes. We will use a magnetic resonance imaging (MRI) scanner to acquire images of both knees. Unlike most MRI scanners in which the patient lies down, the open MRI scanner we will use has a bed that can be inclined to any angle between vertical and horizontal positions. We will image your knees while you are standing in a near uptight position (5° from vertical). We will also image your knees with the table tilted at a position of 45° from the horizontal (head up) which puts less load on your legs. In the reclined position, three scans will be performed with the knees flexed to 0, 15 and 30°, respectively. You will be required to maintain this position during scanning. A total of 8 scans of varying durations will be acquired, which should each last up to seven minutes.

Total time: A total of 8 scans of varying durations will be acquired and the total duration of the testing session will not exceed two hours.

Conditions for Participation

You may have been referred to us by your physician or physical therapist as having some degree of OA of the knee, or you may have responded to advertisements posted in the University community or by word-of-mouth. You will be asked several questions by phone to assess your ability to perform physical activities and will be excluded if your answers suggest you should not physically exert yourself.

You should not participate in this project if you are currently pregnant or have a muscle, bone or nervous system disorder (other than osteoarthritis). In addition, we will calculate your body mass index which is a measure of body fat and must be less than 40 for you to participate. Your personal information will remain confidential and will not be released (including any publication) without your written consent. Data obtained from this study will be recorded on a computer and archived indefinitely. If you agree, video acquired during this study may be used as part of educational presentations and we will block out your face so that your identity will not be revealed. We will contact you for the second evaluation approximately 18 months following your first visit.

Financial Considerations

You will receive $40 each for completing parts (1) and (2) of this study at the initial visit and follow-up visit 18 months later (total of $160). You will not be compensated additionally for any travel expenses you incur.

Risks and Benefits

The type of MRI imaging procedure being used in the study is performed routinely. MRI does not involve exposure to radiation. Claustrophobia, experienced by some during MRI, is not a factor for this study since the scanner being used has an open design. There is a possibility of a small amount of discomfort due to fatigue from maintaining a stationary position during scanning and there is a risk of fainting or nausea.

Strength testing may result in mild soreness that is associated with exertion of muscles during strengthening exercises. Recording the electrical activity of your muscles using surface electrodes poses very little risk. There may be some minor irritation of the skin around the site of the electrode following the experiment. As with any physical activity, risks during walking include dizziness, discomfort in breathing and heart problems. While walking on the treadmill, you will wear a protective harness and a handrail will be within reach.

You will receive first aid in the event of injury during this project. If you require additional medical treatment, you will be responsible for the cost. Although there may be no direct benefit to you, it is hoped that your participation in this project will improve our understanding of the progression of knee OA.

Contacts

Further information regarding this study may be obtained from the project director, Dr. Jill Higginson, at telephone number (302) 831-6622. Other questions about your rights as a research subject can be directed to the Chair of the University of Delaware Human Subjects Review Board at (302) 831-2136.

Subject Consent

I agree to participate in the research study described above. I understand that I may withdraw from this study or the principal investigator may terminate the study at any time without penalty.

Name:____ (please print)

Signature:_____________________________________Date:__________________

Video Consent

I will allow video to be taken during data collection. YES/NO Initial:______

I will allow vide to be used as part of educational presentations, provided that my identity is not revealed. YES/NO Initial:______

Appendix B

APPROVAL LETTER FROM UNIVERSITY OF DELAWARE INSTITUTIONAL REVIEW BOARD FOR WORK WITH HUMAN SUBJECTS

RESEARCH OFFICE

210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE:	October 28, 2009
TO:	Jill Higginson, PhD
FROM:	University of Delaware IRB
STUDY TITLE:	[138671-1] Risk factors for progression of osteoarthritis of the knee
IRB REFERENCE #:	
SUBMISSION TYPE:	Revision
ACTION:	APPROVED
APPROVAL DATE:	October 21, 2009
EXPIRATION DATE:	October 20, 2009
REVIEW TYPE:	Full Committee Review

Thank you for your submission of Revision materials for this research study. The University of Delaware IRB has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

This submission has received Full Committee Review based on the applicable federal regulation.

Please remember that informed consent is a process beginning with a description of the study and insurance of participant understanding followed by a signed consent form. Informed consent must continue throughout the study via a dialogue between the researcher and research participant. Federal regulations require each participant receive a copy of the signed consent document.

Please note that any revision to previously approved materials must be approved by this office prior to initiation. Please use the appropriate revision forms for this procedure.

All SERIOUS and UNEXPECTED adverse events must be reported to this office. Please use the appropriate adverse event forms for this procedure. All sponsor reporting requirements should also be followed.

Please report all NON-COMPLIANCE issues or COMPLAINTS regarding this study to this office.

Please note that all research records must be retained for a minimum of three years.

Based on the risks, this project requires Continuing Review by this office on an annual basis. Please use the appropriate renewal forms for this procedure.

If you have any questions, please contact Elizabeth Peloso at 302-831-8619 or epeloso@udel.edu. Please include your study title and reference number in all correspondence with this office.

Appendix C

PROGRESS REPORT FROM UNIVERSITY OF DELAWARE INSTITUTIONAL REVIEW BOARD FOR CONTINUED WORK WITH HUMAN SUBJECTS

RESEARCH OFFICE

210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE:	February 12, 2014
TO:	Jill Higginson, PhD
FROM:	University of Delaware IRB
STUDY TITLE:	[138671-7] Risk factors for progression of osteoarthritis of the knee
SUBMISSION TYPE:	Continuing Review/Progress Report
ACTION:	APPROVED for Data Analysis Only
APPROVAL DATE:	February 10, 2014
EXPIRATION DATE:	October 19, 2014
REVIEW TYPE:	Expedited Review
REVIEW CATEGORY:	Expedited Category # 9

Thank you for your submission of Continuing Review/Progress Report materials for this research study. The University of Delaware IRB has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

This submission has received Expedited Review based on the applicable federal regulation.

Please remember that informed consent is a process beginning with a description of the study and insurance of participant understanding followed by a signed consent form. Informed consent must continue throughout the study via a dialogue between the researcher and research participant. Federal regulations require each participant receive a copy of the signed consent document.

Please note that any revision to previously approved materials must be approved by this office prior to initiation. Please use the appropriate revision forms for this procedure.

All SERIOUS and UNEXPECTED adverse events must be reported to this office. Please use the appropriate adverse event forms for this procedure. All sponsor reporting requirements should also be followed.

Please report all NON-COMPLIANCE issues or COMPLAINTS regarding this study to this office.

Please note that all research records must be retained for a minimum of three years.

Based on the risks, this project requires Continuing Review by this office on an annual basis. Please use the appropriate renewal forms for this procedure.

If you have any questions, please contact Nicole Farnese-McFarlane at (302) 831-1119 or nicolefm@udel.edu. Please include your study title and reference number in all correspondence with this office.