CONTRA-LATERAL KNEE JOINT FUNCTION IN MODERATE KNEE OSTEOARTHRITIS: AN ELECTROMYOGRAPHIC INVESTIGATION OF KNEE MUSCLE CO-CONTRACTION

by

Michelle L. Jones

Submitted in partial fulfilment of the requirements
for the degree of Master of Science

at

Dalhousie University
Halifax, Nova Scotia
July 2017

Table of Contents

List of Tables

List of Figures

Abstract

Unilateral knee osteoarthritis (OA) often progresses to bilateral disease, yet studies focused on joint function during walking often test the symptomatic knee only. The thesis objectives were: i) identify whether co-contraction between the contra-lateral limb of an OA group (CONTRA) and asymptomatic controls (ASYMP) are different, ii) identify whether knee joint biomechanics were different between groups, and iii) quantify inter-limb co-contraction differences in a healthy control group.

Muscle activation was recorded in 20 individuals with moderate OA and 20 asymptomatic individuals for the gastrocnemii, hamstrings and quadriceps after 6 minutes of walking. Co-contraction indices were calculated for loading response, mid-stance and terminal stance, as well as gait biomechanical variables in the sagittal and frontal planes. Co-contraction was not different in between groups, however gait biomechanics were. Results suggest from a co-contraction perspective, the contra-lateral knee in individuals with unilateral symptomatic moderate knee OA is behaving similar to a healthy limb.

List of Abbreviations Used

ANOVA – Analysis of Variance

ASIS – Anterior Superior Iliac Spine

ASYMP – Random limb of an asymptomatic control group

CCI – Co-Contraction Index

CONTRA – Contra-lateral limb of the MOA group

EMG – Electromyography

GRF – Ground Reaction Force

IC – Initial contact

ICF – International Classification of Functioning, Disability and Health

KAM – Knee Adduction Moment

KFM – Knee Flexion Moment

KOOS – Knee Osteoarthritis Outcome Score

MG – Medial Gastrocnemius

MH – Medial Hamstring

LG – Lateral Gastrocnemius

LH – Lateral Hamstring

MOA – Moderate Symptomatic Medial Compartment Osteoarthritis

NPRS – Numerical Pain Rating Scale

NSHA – Nova Scotia Health Authority

NSHRF – Nova Scotia Health Research Foundation

OA – Osteoarthritis

OARSI – Osteoarthritis Research Society International

REB – Research Ethics Board

RF – Rectus Femoris

RMS – Root Mean Square

ROM – Range of Motion

TKA – Total Knee Arthroplasty

VL – Vastus Lateralis

VM – Vastus Medialis

WOMAC – The Western Ontario and McMaster Universities Arthritis Index

Acknowledgements

There are a number of people I would like to thank for my experience throughout the Rehabilitation Research Master's program in the School of Physiotherapy at Dalhousie University. I would first like to thank my supervisor, Dr. Derek Rutherford for his guidance throughout the last two years. His patience, enthusiasm and encouragement motivated me to further appreciate the research process, and it is my hope that the quality of the work presented in this thesis reflects his exceptional mentorship.

I would also like to thank Dr. Cheryl Kozey, Dr. Janie Wilson and Dr. Rebecca Moyer for their guidance as committee members, and for providing their time and effort to provide further advice on this project.

A special thank you to the members of the Dynamics of Human Motion (DOHM) and Joint Action Research (JAR) labs for their assistance over the last two years, whether it was in data collection and processing, or offering their various perspectives throughout the development this project.

Finally, I would like to thank my family for providing me with encouragement through this experience. Their pride and enthusiasm motivated me to work hard through the especially busy final months and their continued support inspires me to always continue learning.

Chapter One – Introduction

Osteoarthritis (OA) is a joint disease caused by cell stress and degradation. It progresses to show anatomic and physiological changes in the joint, including articular cartilage breakdown, osteophyte formation, bone remodeling and loss of joint function[1]. OA is also defined by the symptomatic response to these changes, including stiffness, aching/pain, and disability[1]. It is expected that within the next thirty years, one in four (25%) Canadians will be living with OA, and almost one third of the labour force will experience difficulties working due to the disease. This creates a significant concern as OA has significant direct and indirect cost, through treatment and loss of work production from the affected individuals[2].

Lower extremity OA has significant implications for mobility and creates an environment of functional limitation[3]. Unfortunately, Canadians are experiencing the signs and symptoms of this disease earlier in their lives than previous. Between 1994 and 2005, the number of Total Knee Arthroplasties (TKA) performed as a result of advanced knee OA more than doubled for males (125% increase) and nearly tripled for females (175% increase) between the ages of 45 and 54[4]. When combined with increasing life expectancy, a higher percentage of revisions will be required when these younger patients outlive their replacements, increasing the already existing economic burden.

Many individuals initially present with unilateral symptoms of knee OA that affect function and mobility[5]. Over time, knee OA may progress bilaterally and both joints become symptomatic[6]. Contra-lateral knee OA progression rates of up to 80% have been reported within 12 years of baseline unilateral OA[7]. Contra-lateral TKA risk after initial TKA have been reported as high as 37% within 10 years[8]. The contra-lateral knee

is the most common second joint to be replaced[6], suggesting bilateral disease is significant, impacts patient function and needs to be considered when understanding disease pathomechanics of aetiology and OA progression.

Given the reciprocal impact of knee OA on mobility and joint mechanics, gait analyses are frequently performed to understand the implications of OA on knee joint function. Panjabi (1999)[9] provides a framework to understand the factors implicated in maintaining joint function and stability in the spine, however it has been more recently discussed in the context of the OA knee[10]. Panjabi introduces three systems, including the passive osteoligamentous, active muscular and neurological control systems[9]. Given OA is primarily thought of as a disease of the passive system (cartilage, bone, synovium etc.)[1], alterations to the neuromuscular system are needed to ensure the knee joint remains functional, maintains its ability to bear weight, and moves and protects the internal structures that provide lubrication, stability, and longevity.

Understanding the impact of OA on the muscular system during walking has been achieved through the use of surface electromyography. Many studies support that knee muscle activation amplitudes and patterns are altered in those with knee OA[11–16] and recently these activations have been suggested to play a role in disease progression[17,18]. To date, the focus of knee OA gait study in electromyography has been on the symptomatic leg. Given the importance of muscle control for joint function[19] and the role that co-contraction may have in disease progression[18], our paucity of information on contra-lateral knee joint function (particularly the potential for altered muscle activation) is concerning given the increasing burden of bilateral OA for disease management.

Focusing on the symptomatic knee using cross-sectional designs, many studies have investigated muscle activation in combination with gait biomechanics in individuals with medial compartment knee OA. Through these studies, common gait characteristics associated with OA compared to asymptomatic controls have been identified. Increased[11,14,15,20] and prolonged[12,14,20,21] activation have been found in the quadriceps and lateral hamstring during stance in moderate OA (MOA) groups, while increased activation in early stance[11,12] has been associated with OA in the medial gastrocnemius using Principal Component Analysis (PCA) and discrete measures. While these activation patterns and discrete variables have been investigated in individual muscles or groups, the role of agonist-antagonist co-contraction to stabilize the knee has also been a focus of knee OA muscle activation studies.

The most common method of understanding co-contraction is through the use of a co-contraction index (CCI), which quantifies agonist-antagonistic muscle activity between paired muscles in both medial and lateral orientations about the knee joint[19,22]. Increased quadriceps/hamstrings CCIs have frequently been identified during weight acceptance in the symptomatic limb of OA groups compared to controls[13,16,23], as well as increased lateral-medial quadriceps/hamstrings co-contraction ratios[13,24]. These alterations observed in muscle activation may be in response to symptoms associated with OA, such as pain[25] and instability[26]. Increased medial quadriceps-gastrocnemii CCIs have also been identified in an OA symptomatic knee, and have been associated with increased medial joint laxity associated with cartilage deterioration[19]. However, contraction of major muscle groups surrounding a weight bearing joint increases

compressive forces within the joint and can contribute to a negative loading environment[27].

Longitudinal studies have been developed recently to understand the implications of altered muscle function on joint health over time. A shift in lateral gastrocnemius activity[18], as well as increased medial co-contraction duration[17] have been associated with structural progression of OA over time, while increased lateral co-contraction duration was found to be protective of cartilage health[17]. This suggests that specific muscle activation characteristics may protect the joint while others may create an unfavourable environment for OA progression.

In addition to muscle activation changes, biomechanical alterations have been found in an OA knee compared to healthy individuals, supporting an interrelationship to exist between how the joint moves, the moments that are created and muscle activation. Commonly, less dynamic flexion-extension range of motion (RoM)[28–30], less dynamic flexion-extension moment range[31] and decreased flexion excursion[19] have been identified in an OA knee compared to controls. Greater peak external knee adduction moments (KAM) and KAM impulse[11,29,32,33] have also been found, where the KAM has been associated with medial compartment knee forces[34] and femoral cartilage deterioration[35]. Sagittal and frontal plane changes are suggested as a strategy to stabilize the knee joint during stance, and are often accompanied by altered muscle activation in those studies to describe symptomatic joint function during walking.

Where altered muscle activation features have been associated with the presence of OA and longitudinal progression, a lack of evidence exists to support natural inter-limb differences in healthy groups. A common assumption exists that similar between-

limb gait is observed in healthy groups and a random limb can be used for statistical comparisons to OA groups in cross-sectional studies. To the author's knowledge, no studies currently investigate between-limb muscle activation or co-contraction differences in a healthy group. This leaves a significant gap as we move forward to understand altered knee function in individuals with medial compartment OA.

Though previous findings highlight the importance of understanding gait biomechanics and muscle activation to further investigate joint function, these studies have limited their assessment to the symptomatic knee and fail to determine if any of these findings are present in the contra-lateral knee; the knee that may silently progress over time to ultimate failure and require a total joint replacement. So far, studies that investigate contra-lateral muscle activation characteristics have focused on severe OA groups only. It has been known for more than a decade[30] that contra-lateral disease is significant and can effect gait mechanics, and perhaps these gait mechanics can foster contra-lateral disease progression.

Two studies currently exist to investigate muscle activation of the contra-lateral knee in groups with severe OA (defined as awaiting surgical intervention), with comparisons made to a control group. Metcalfe et al. (2013)[36] found that the medial and lateral quadriceps-hamstrings CCIs were elevated in the contra-lateral limb of the OA group compared to a significantly younger control group (~38 years) over the entire stance phase. Muscle activation amplitude differences similar to the ones seen in this study have previously been associated with age[37,38]. Lewek et al. (2006)[30] reported lower medial quadriceps-gastrocnemius CCIs in a control group compared to the contra-lateral limb of an age-matched OA group, but did not identify any differences in quadriceps-

hamstrings CCIs. Increased KAM impulse has been found in the contra-lateral knee of a severe OA group compared to age-matched controls[36].

Alterations in gait biomechanics and muscle activation regarding co-contraction have been identified in the symptomatic knee of MOA groups compared to asymptomatic groups[13,16,23], and differences have previously been identified in both the contra- and ipsilateral limbs in those with severe knee OA[30,36], however a lack of knowledge exists regarding contra-lateral joint function in a moderate symptomatic medial compartment OA group. A concern that many people report being worried about their contra-lateral knee exists, as symptoms continue to worsen ipsilaterally and compensations favouring the contra-lateral limb are felt. Thus it is important to gain an understanding of the mechanical environment that exists in the contra-lateral limb compared to a control group early in the disease process, when such a high rate of progression to bilateral disease currently exists.

1.1 – Objectives

The overall study purpose is to determine whether contra-lateral knee muscle co-contraction is increased in individuals with moderate medial compartment knee OA (MOA), as an indication of altered joint function and a potential mechanism for contra-lateral disease progression. Muscle activation levels and gait biomechanics have been suggested to influence joint compartment loading and cartilage deterioration, and frequently reported differences have been established between the symptomatic leg of OA groups and control groups. Unfortunately in clinical work and research, this focus of attention leaves a dearth of information to understand contra-lateral knee function. In addition, co-contraction differences have been found between knee OA and

asymptomatic groups, however magnitudes are difficult to interpret as currently a lack of knowledge exists on how levels of co-contraction vary in healthy individuals between limbs during walking. This thesis sought to test hypotheses relating to these current deficiencies in understanding knee muscle co-contraction during gait.

1.2 – Specific Objectives

Three main objectives exist for this study. The specific objectives are:

1. To determine whether differences exist between the contra-lateral limb of a MOA group (CONTRA) and a randomly chosen limb from a control group (ASYMP) in medial and lateral quadriceps-hamstring and quadriceps-gastrocnemius CCI pairs during loading response (1-20% gait cycle), mid-stance (21-40%), and terminal stance (41-60%).

2. To determine whether group differences exist between CONTRA and ASYMP in the following biomechanics features:
    - Peak net external KAM
    - Net external KAM impulse
    - Knee flexion excursion (KFA at initial contact to peak KFA during stance)
    - Sagittal RoM during stance (peak KFA to minimum flexion during terminal stance)
    - Sagittal net external moment range (peak KFM to peak extension moment)

3. To quantify absolute inter-limb root mean squared differences in medial and lateral quadriceps-hamstring and quadriceps-gastrocnemius CCI pairs during

loading response (1-20% gait cycle), mid-stance (21-40%), and terminal stance (41-60%) for an asymptomatic control group.

1.3 – Hypotheses

The specific hypotheses for the first two objectives of this study are:

1. A phase effect will be observed ($p<0.05$) for all four CCI muscle pairings, where loading response > mid-stance > terminal stance.
2. Group effects or interactions will be significant ($p>0.05$) in any of the four CCI pairings between the contra-lateral limb of the MOA group and the asymptomatic control limb.
3. Gait biomechanics will be significantly different ($p>0.05$) between the contra-lateral knee of the MOA group and the asymptomatic control group.

Chapter Two – Review of Literature

2.1 – What is Osteoarthritis?

Normal joint function is dependent on a number of factors including stability through RoM, proper load distribution, and fluid movement between the articulating surfaces[39] where articular cartilage absorbs load and provides a smooth surface for facilitating movement[40]. OA is defined as disease of moveable joints most commonly occurring in weight bearing joints. It is characterized by cell stress and degradation as a result of micro and macro injury, initiating maladaptive repair responses[1,3]. Initially, OA is shown as abnormal tissue metabolism at the molecular level, progressing to anatomic and physiologic abnormalities including cartilage degradation, bone remodeling, osteophyte formation, joint inflammation and loss of joint function[1,3,39]. The Osteoarthritis Research Society International (OARSI) has recently included symptomatic response to the definition of OA including pain, crepitus, stiffness, instability and loss of function[41].

2.2 – The Burden of Osteoarthritis

Osteoarthritis creates both a national economic burden and economic, physical and emotional stress to the affected individual. Common symptoms of OA can negatively impact an individual's quality of life. Joint pain can lead to disability and workplace limitation, significantly affecting the lives of the affected individuals and their families[3].

One in eight (13%) Canadians are currently affected by OA, and it is expected to increase to one in four (25%) within the next thirty years[2]. Using the International Classification of Functioning, Disability and Health (ICF), impairment due to OA has

shown a direct relationship with activity limitations and participation restrictions, resulting in economic and emotional burdens[42]. With the projected increased incidence of OA, 30% of the labour force is expected to experience limitations working[2], closely followed by an indirect national economic burden through decreased work production.

The most effective way to reduce pain and restore joint function of knees affected by end stage OA is a total joint replacement[3,43,44] or total knee arthroplasty (TKA). It is worrying that in North America, there is a disproportionately high number of younger individuals undergoing TKA[44]. From 1994-2005 in Canada, the incidence of knee replacement surgery more than doubled for males (125%) and nearly tripled for females (175%) between the ages of 45 and 54[4], and a rise in the number of individuals outliving their knee replacement and requiring a revision is expected[44]. Recommendations have been established for the management of OA in populations that are classified as mild to moderate, as an attempt to prevent or delay end-stage OA. Non-pharmacological interventions that have been recommended by OARSI include canes, exercise, strength training, weight management, education on self-management, and biomechanical interventions (knee braces, sleeves and foot orthoses)[45]. At this point however, it is not clear if these interventions in fact alter disease progression.

Much of the previous literature on knee OA focuses on only the primary symptomatic joint, though studies have shown that bilateral pain is a frequent issue. Knee OA tends to affect one joint initially and non-randomly progresses to a bilateral disease with time[6,7]. Metcalfe et al. (2012)[7] reported that 80% of individuals presenting with unilateral knee OA at baseline progressed to bilateral radiographic changes within 12 years, and it has also been reported that 34% of women with unilateral knee OA

progressed to bilateral OA within only two years[46]. After TKA is performed on the primary joint in individuals with end-stage knee OA, a risk of requiring contra-lateral TKA also exists. Shakoor et al. (2002)[6] reported in 414 OA patients that had an initial TKA and went on to have a second joint replacement, 92% required contra-lateral TKA (as opposed to a contra- or ipsilateral total hip replacement). A second total replacement of the cognate joint on the contra-lateral side is required more frequently than either of the non-cognate joints[6], and a 37.2% risk of requiring contra-lateral TKA has been reported within 10 years after TKA on the primarily affected joint[8].

The current problem exists that much of the research on intervention focuses on symptom management rather than maintaining or improving physical health of both joints. While these strategies may prolong the need for TKA and improve the quality of life for the affected individuals, it does not stop the increasing demand for TKA in the aging population. Additionally, with evidence that the contra-lateral joint is experiencing structural changes prior to symptom onset it is narrow sighted to focus on only the symptomatic joint in individuals with OA. Increasing focus on the contra-lateral knee, that may have structural changes but does not yet present with the symptomatic disease of OA, could allow us to identify mechanical changes that might be occurring at the earliest stages of the disease.

2.3 – Classifying Osteoarthritis

Past literature has defined OA as having both a disease and an illness component[41]. The "disease" component refers to abnormalities of joint structure and function, and the "illness" component refers to the human response to the disease. It is common in OA for the disease and illness components to not coincide, where an

individual may have definite structural features of OA but these findings do not match the reported symptoms or functional limitations[47,48]. At some point after the onset and progression of the disease component of OA, a clinical threshold is reached where OA becomes symptomatic and the patient feels like they should go to the doctor. At this point the illness component is introduced, as shown in Figure 2.1[1].

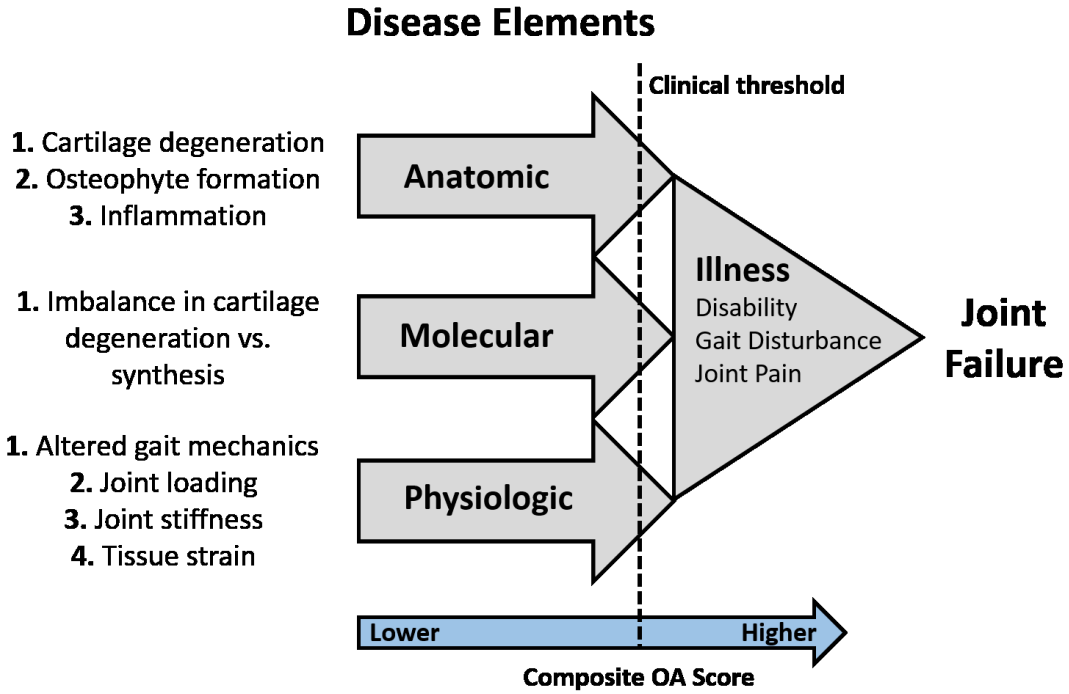


Figure 2.1. Disease and Illness elements of OA. Modified from Kraus et al (2015).

Diagnosis of OA often comes when symptoms manifest and it becomes a clinical problem, though it is most frequently graded based on the structural appearance of the targeted joint. A widely used criteria for grading OA severity is through radiographs using the Kellgren and Lawrence (KL) scale[11,29,35,49], established in 1957[50] and accepted by the World Health Organization in 1961[51,52]. The KL scale ranges from 0 (no evidence) to 4 (severe). Four main features are used when grading OA using the KL scale, including (i) the formation of osteophytes on the tibial spine, (ii) periarticular ossicles

(used mainly when assessing interphalangeal joints), (iii) narrowing of joint cartilage, and (iv) pseudocystic areas in the subchondral bone[50]. Radiographs of knees with OA severities ranging I-IV are shown in Figure 2.2. While the KL scale has been criticized in the past for its emphasis on osteophytes, it is still widely used in clinical settings for making decisions on treatment[8,53].

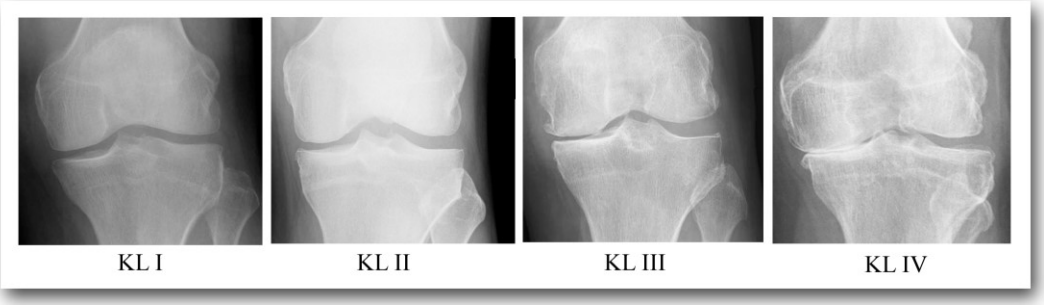


Figure 2.2. Randomly selected knees with OA radiograph scores from 1-4 on the Kellgren and Lawrence scale[54].

The use of radiographic imaging to grade structural OA severity has limitations. The changes that are measured with this technique, including osteophyte formation and joint space narrowing, only occur in later stages of the disease. Degradation of the articular cartilage or menisci cannot be evaluated using radiographs, and magnetic resonance imaging (MRI) is considered to be a more accurate imaging technique to assess knee OA at an early stage[55]. Using MRI, structural abnormalities such as cartilage loss, synovitis, subchondral bone marrow lesions and effusion can be identified[56].

Unfortunately, there is no way to determine with confidence whether some of these early changes are merely associated with aging[57] or whether they are significant for our understanding of the disease. With such a high rate of progression to bilateral OA, the assumption can be made that these early structural changes may be occurring in the contra-lateral joint before any symptoms become present. It is plausible that the contra-

lateral knee in those with OA could be used as a model for investigating gait-related changes at an early stage of the disease process.

2.4 – Mechanics and OA

While the exact pathology of OA is not yet fully understood, it is often described as a mechanically driven disease and is frequently associated with changes in the mechanical environment of the affected joint[58]. In Panjabi's framework to understand joint stability[9], three components are addressed (Figure 2.3): 1) the passive subsystem made up of ligamentous tissue, which primarily provides stability at the end ranges of motion; 2) the active subsystem consisting of muscle and tendons surrounding the joint, which provides the required stability to the joint through all ranges of motion; and 3) the neural control subsystem, which determines the needs for stability and modulates the active subsystem to provide what is needed[9]. Joint impairment can occur due to injury or dysfunction in any of the three subsystems. If injury occurs to the passive subsystem, the neural subsystem will attempt to compensate for the deficiencies that are created through the active subsystem to regain stability of the joint. These adaptations, which may include abnormal joint kinematics, loading, and muscle activation, could regain overall stability but lead to negative consequences on the structures within the joint[9].

One of the most frequently mentioned risk factors that may alter gait mechanics and contribute to OA onset and progression is obesity, which may affect the knee joint through excessive compressive joint loading. Increased joint moments[59] and differences in muscle activation[60] have been observed in individuals with a higher BMI, and associations have been made between BMI and TKA risk[61], where 40% and 2.7-fold increased risks of requiring TKA were found in overweight (BMI 25-30) and obese III

(BMI>40) OA groups compared to those classified as healthy (BMI<25), independent of age, sex, lifestyle, and socioeconomic status. Weight reduction has also been shown to improve the lives of those living with OA and to prevent OA development[3]. In individuals with unilateral symptomatic OA, obesity has an effect on loading in both knees yet only one knee has progressed as symptomatic, suggesting something else must be contributing to the deterioration of joint health.

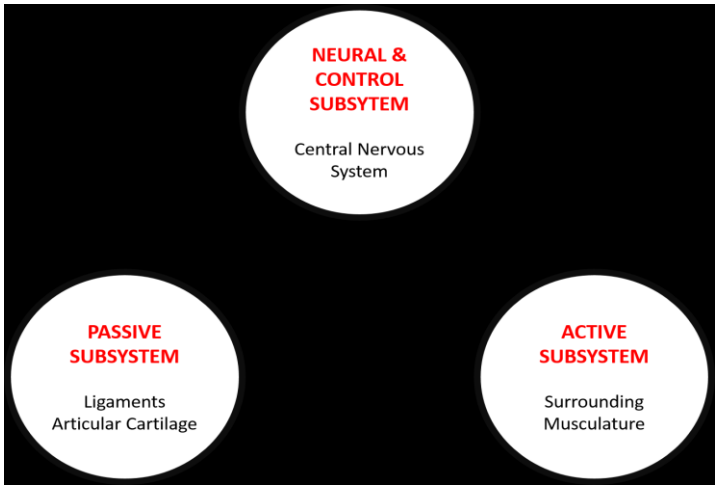


Figure 2.3. Panjabi's framework to understand joint stability. Modified from Panjabi et al. (1992)

OA has previously been thought to be associated with overloading, and bilateral progression could be a result of overloading the asymptomatic joint. Information on potential bilateral changes occurring when one knee becomes symptomatic could contribute to the possibility of strategies preventing bilateral progression in individuals with unilateral symptomatic OA.

Based on past evidence regarding OA and knee joint loading, both the absence of[40] and overloading the knee[60,62] can contribute to a negative mechanical environment, and there likely exists a window of optimal joint loading. Walking is an activity performed every day essential to independence, and it is important to understand the

effect human gait has on the mechanical environment of the knee. Both obesity and sedentary behaviour would not only affect the symptomatic knee joint, which is the only one investigated in these studies. Both the symptomatic and contralateral joints would experience human gait alterations, furthering the need for research on bilateral progression and whether lifestyle changes such as increased activity and weight loss may prevent OA progression in a knee that may be considered to be experiencing early structural changes of the disease process.

2.5 – Knee Joint Biomechanics during Gait

Modern gait analyses have been utilized for over two decades and provide valuable information on how the body responds during an activity like walking, where an individual's ability to walk has a direct impact on their ability to perform daily activities[63]. Knee OA can be understood from a mechanical standpoint using three-dimensional motion capture to investigate joint movement (kinematics) and when combined with ground reaction forces/moments and subject specific anthropometrics, joint moments can be calculated (kinetics). Kinematics are primarily used to describe movement of a limb segment during the gait cycle, as well as to derive joint moments, which describe the direction and magnitude of loading that occurs at the joint. These are typically investigated in the frontal[28,29,31,35] and sagittal[28,35] planes of the knee.

In a symptomatic OA knee compared to asymptomatic controls, less dynamic flexion-extension angle ranges during the loading phase of gait have frequently been observed[28–30] and thought to represent a general "stiffening" of the knee to maintain stability and joint function[26]. Decreased peak flexion angles during early stance were found to be associated with OA severity[28], and decreased flexion excursion (flexion at

initial contact to peak flexion during stance) in a symptomatic OA group was found compared to asymptomatic controls[19]. Baliunas et al. (2002)[29] found no difference in flexion angles between groups at mid-stance or terminal extension, however they did report a decrease in RoM over the full gait cycle in their OA group. Together these studies highlight that sagittal plane changes are occurring when OA becomes present.

In the frontal plane, symptomatic OA knees also showed greater peak external knee adduction moments and greater KAM impulse[11,29,32,33] compared to asymptomatic control groups. It has been implicated that increased loads on the medial compartment of the knee contribute to the development and progression of knee OA, which more commonly affects the medial compartment of the knee[29,33], and the KAM has been associated with medial compartment knee forces[34] and femoral cartilage deterioration[35]. KAM magnitudes have also been linked to radiographic OA severity[28] and progression[32,64].

Evidence has recently been observed that the external knee flexion moment can also have an influence on the medial contact force that occurs at the knee[34,35,65]. Both the external KAM and KFM has accounted for uncorrelated amounts of the variability on peak medial compartment loading[65], and Chehab et al. (2014)[35] found baseline KFM to be the driving influence on changes in tibial medial cartilage thickness. Landry et al. (2007)[31] found a reduced dynamic range in MOA participants compared to controls in external KFM throughout stance, and a smaller amplitude in the peak flexion moment that occurs during early stance. Astephen et al. (2008)[28] showed a progressive change with OA severity in the minimum KFM during early stance.

It is clear from the literature that differences exist in the sagittal and frontal planes of the knee joints between OA and asymptomatic groups. Increased KAM, as well as less dynamic flexion/extension motion and moments are reported in the literature in an OA group compared to controls. Sagittal and frontal plane changes are suggested as a 'knee stiffening strategy' as an attempt to stabilize the joint during the stance phase of the gait cycle, and often accompanied by altered muscle activation in those studies providing a comprehensive assessment of symptomatic joint function during walking. While these biomechanical variables provide a good measure of the external forces acting on the knee joint, they do not provide any information on the internal muscular forces created to maintain dynamic joint function through the gait cycle, hence the importance of including measures of muscle function together with biomechanical assessments. It is important to look at this information in combination with activation of the musculature surrounding the knee joint to gain a more complete picture of what mechanical stresses are placed on both knees (both symptomatic and contra-lateral) in individuals with OA.

2.6 – Surface Electromyography during Gait

As previously described, OA is associated with changes in the mechanical environment of the affected joint. The primary role of skeletal muscle is to move and provide active stability to joints and in doing so, they produce compressive loading on those joints[66]. In Panjabi's framework of achieving joint stability, the neural control subsystem determines the needs for stability and modulates the active subsystem to provide what is needed[9]. The neural subsystem acts to regain stability of the joint if injury occurs to the active or the passive subsystems. Adaptations to the neuromuscular

component of stability could change the balance of loading acting on the joint and lead to negative consequences on the structures within[9].

Surface electromyography (EMG) is a tool that is used often in biomechanical research to determine muscle function or to try to relate EMG output to tension produced by the muscle. Difficulties have arisen trying to describe the EMG-force relationship, including changes in muscle length and contraction type and velocity[67], but EMG still provides easy access to the electrical processes that are needed in order to make a given muscle contract[68]. Past literature investigating activation of muscle groups surrounding the knee joint through surface EMG suggests individuals living with knee OA walk with altered knee joint muscle activation amplitudes and patterns when compared to a healthy population[14,21,69]. Common findings of the symptomatic knee of an OA group between studies include increased and prolonged quadriceps (primarily rectus femoris (RF) and vastus lateralis (VL)) activation[11,12,14,21,70], increased lateral hamstring (LH) activation[11,14,15,20], and prolonged medial gastrocnemius (MG) activation (becoming more active earlier during stance)[11,12,20]. The following subsections will describe common findings among the primary force producing muscles of the knee joint including, quadriceps, hamstrings and gastrocnemius individually and as understood using the co-contraction index (CCI).

2.6.1 – Quadriceps

As the primary extensor muscles of the knee, the quadriceps muscle group is understood as an important stabilizer of the joint, and it has been suggested that weakness in the quadriceps would reduce their ability to distribute loads and protect the knee joint[71,72]. Increased tension provided by the quadriceps muscles would increase stability

of the knee, however it would also increase compressive forces on the joint and therefore accelerate degeneration of articular cartilage within the joint[17,66]. Recent literature on muscle activation and knee OA gait has focused on, quadriceps activation levels and patterns, trying to define altered amplitude and temporal characteristics associated with the presence and progression of knee OA.

Less dynamic sagittal plane motion and moments have been identified in individuals with knee OA, a characteristic in the past been described as a 'quadriceps avoidance' gait pattern[73]. However, increased overall mean RF amplitudes have been identified in individuals with OA compared to asymptomatic controls[11,14], as well as VL activity[14,70] (Figure 2.4). In a 2013 review by Mills et al. (2013)[72], nine of the ten studies investigating quadriceps activation amplitudes using surface EMG during gait showed increases in RF and VL activation, thought to be a compensation strategy for potential lack of joint stability associated with OA. Medial-lateral muscle activation imbalances have also been reported in OA study groups, though not consistently.

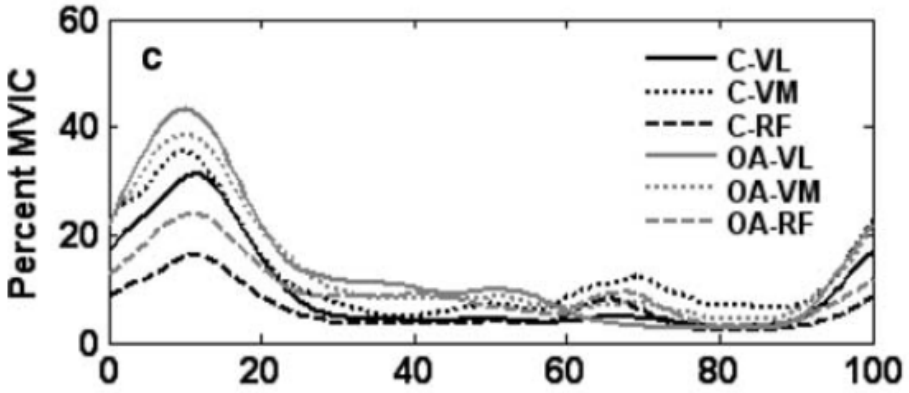


Figure 2.4. Waveforms of VL, VM, and RF activation for asymptomatic control (C) and OA groups during the gait cycle. Taken from Hubley-Kozey et al. (2006).

Prolonged RF and VL activity have also been identified in a number of studies through both temporal and discrete analyses[12,14,21]. In three studies reporting prolonged

VL and RF activation, the OA group had a greater average BMI than the asymptomatic group, where similar neuromuscular differences have been identified in high BMI groups, regardless of OA[60]. Obesity affects the loading on both the symptomatic and contra-lateral joints, however these individuals are more symptomatic in one limb and these studies are only investigating the symptomatic limb. The quadriceps muscles are thought to provide primary dynamic control of knee stability and function during gait, and it is important to investigate activation in the symptomatic and contra-lateral knees to make implications on compressive loading through muscle contraction, compared to asymptomatic groups.

2.6.2 – Hamstrings

The hamstring muscles are the primary flexors of the knee joint, extensors of the hip and contribute to active knee joint stability with the quadriceps. They have been suggested with the quadriceps to have a direct impact on medial/lateral compartment loading distributions by differentially activating the medial and lateral muscles crossing the knee[74,75]. Hubley-Kozey et al. (2006)[14], and Rutherford et al. (2010)[20] found similar medial hamstring (MH) amplitude and duration between a MOA group and asymptomatic controls, however Astephen et al., (2011)[25] reported increased MH amplitudes during early and late stance with higher pain severities in individuals with OA. Increased MH activation was suggested as an adaptation to increase joint stiffness to reduce pain, while the lack of differences were suggested as an attempt to prevent further increases in medial compartment loading[14,20].

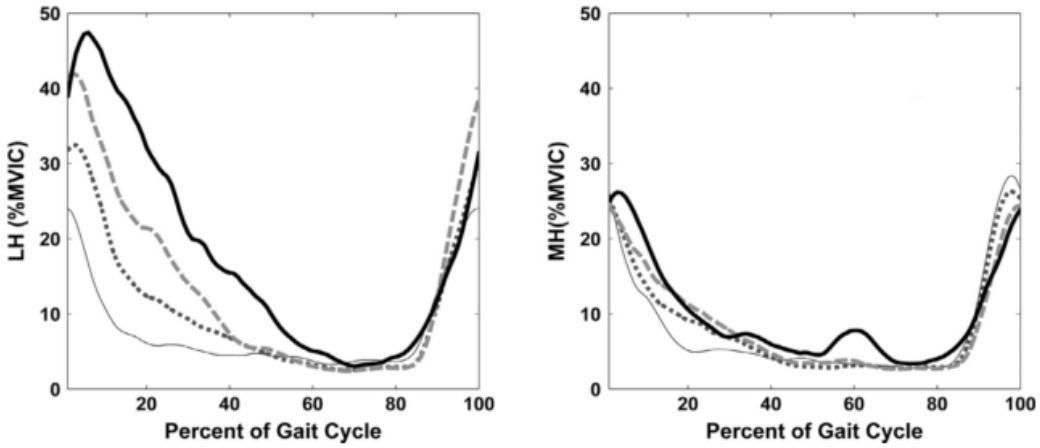


Figure 2.5. LH (left) and MH (right) waveforms for asymptomatic control (solid grey), KL-II (dotted black), KL-III (dashed grey) and KL-IV (solid black) groups. Taken from Rutherford et al. (2013).

In contrast, the LH has shown consistent increases in activation amplitudes and duration with the presence of knee OA[14,15,20,25]. Rutherford et al. (2013)[10] identified an association between increasing LH activation and structural severity, with no differences observed in the MH (Figure 2.5). Thus the suggestion is made that a medial-lateral muscle imbalance forms in the hamstrings with the progression of structural knee OA. These changes have been associated with the increased KAM, also present in individuals with knee OA[13]. A greater lateral-medial activation ratio may exist to create an internal valgus (abduction) moment and balance that increased overall KAM, a representation of loading on the medial compartment of the knee[13,15]. It is currently unknown whether these activation differences exist in the contra-lateral knee, which may affect the compressive loading on the joint compartment.

2.6.3 – Gastrocnemii

At this point in time, research investigating the gastrocnemii in OA populations is limited compared to the quadriceps and hamstrings, though some studies have tried to identify characteristics in gastrocnemii activation that may be associated with the

presence of knee OA. Hubley-Kozey et al. (2006)[14] reported reduced MG amplitudes in symptomatic knees compared to controls during the propulsion (late stance) phase of the gait cycle, later supported by Astephen et al. (2008)[11] and Rutherford et al. (2013)[10]. This reduction in MG activity in OA groups during late stance has been thought of as a protective strategy to reduce compressive loading on the medial compartment applied by major muscle groups during stance. Significant amplitude differences have not consistently been found in MOA groups compared to asymptomatic groups in the lateral gastrocnemius (LG)[14,21], however alterations have been identified in groups with higher structural severity[10], including higher activation amplitudes during early stance.

Childs et al. (2004)[12] found the gastrocnemii activated above baseline levels for 1.5x longer during the gait cycle in an OA group compared to a control group, while Astephen et al. (2008)[11] identified greater MG activation during early stance in a severe OA group compared to asymptomatic/MOA. Greater MG amplitudes in early stance compared to late stance have also been associated with increasing OA structural severity[10] and increased medial laxity[19]. Greater activation amplitudes of the MG during early stance may be an adaptive strategy to try to stiffen or stabilize the medial compartment of the knee early in the gait cycle[11].

Further investigation is needed to determine whether these alterations in the quadriceps, hamstrings and gastrocnemii contribute to a negative loading environment and accelerate the OA process. While information on individual muscle activation throughout the gait cycle is useful, it does not provide a picture of what is happening cumulatively on the medial and lateral sides of the knee at different phases of the gait cycle. This information may be provided by calculating CCIs between the primary

agonists and antagonists on both sides of the knee through specific phases of the gait cycle.

2.6.4 – Co-contraction

Co-contraction (also described as co-activation) offers quantified information on combined agonist-antagonist muscle activity throughout movement. It represents the relative activation between the agonist and antagonist muscles during a specific time phase of the gait cycle. Excessive antagonistic muscle activity can contribute to a negative mechanical environment through the potential to increase compressive forces on a joint as well as to increase metabolic cost[76]. Individuals with knee pathologies such as OA have reported changes in joint stability, a potential source of increased antagonistic activation[23].

Co-contraction is determined by different methodologies throughout the literature, with the most common being the calculation of a CCI, first reported by Rudolph et al. (2000)[22] and further modified by Lewek et al. (2004)[19] to describe a CCI over a specific period:

$$CCI = \frac{1}{n}\sum_{i=1}^{n}\left[\frac{lower\ EMG_i}{higher\ EMG_i}\ x\ (lower\ EMG_i + higher\ EMG_i)\right] \quad [1]$$

where n=the number of samples within the time frame being used for the calculation, lower EMG=the activation level of the lesser activated muscle, and higher EMG=the activation level of the more activated muscle[22]. CCIs are commonly used to describe activation during the weight acceptance phase of the gait cycle, beginning 100ms prior to IC and ending at the peak KAM[19,24,30,77,78], or peak knee flexion angle[16]. The first 20% of a time-normalized gait cycle has also been taken[23] to represent the initial loading phase

after IC, and Schmitt & Rudolph (2007;2008)[16,70] calculated CCIs for three separate phases: i) preparatory (100ms prior to IC through IC); ii) weight acceptance (IC through peak knee flexion angle); and iii) mid-stance (peak knee flexion angle through peak knee extension angle).

Increased co-contraction has been found between the knee flexors and extensors in individuals with OA compared to controls[13,16,23] and have been associated with decreased knee flexion during early-mid stance, described in the past as a joint stiffening strategy[16]. In medial and lateral sites individually, increased medial CCIs have been reported in OA groups compared to controls[19], which were associated with increased laxity on the medial side of the joint[19]. A larger CCI on the medial side has also been suggested to increase compression on the compartment and contribute to further cartilage degeneration. Increasing VL-LH CCIs have been associated with OA severity[24], a result of both VL and LH activation amplitudes increasing with severity from late-swing to peak KAM, while VL-LG, VM-MH, and VM-MG CCIs all had greater CCIs in a severe OA group only, compared to MOA and asymptomatic groups. Information on co-contraction can help us understand the effects that interventions such as knee braces or lateral heel wedges have on balancing medial-lateral joint loading and improving stability[24].

Frequently reported findings suggest that individuals with OA co-activate the muscles around the knee differently than healthy groups, and gives insight to the internal compressive loading that is occurring on the joint at a later stage of the disease process. Co-contraction still needs to be better understood at earlier stages of OA, and information is needed on whether differences in medial/lateral CCIs at an early stage attribute to

disease progression. It is also suggested that CCIs should be calculated during more than one interval of the gait cycle (as was done by Schmitt & Rudolph (2007;2008)[16,70]), as different functional demands are placed on the muscles through weight acceptance, mid-stance (single-limb), and terminal stance (propulsion).

In OA groups, the VL, RF, and LH consistently showed higher activation amplitudes during the loading phase of gait when compared to control groups. The MG has also shown reduced activation amplitudes during propulsion (late stance). No consistent differences were found in the MH or LG in the literature. Two longitudinal studies currently exist investigating muscle activation and OA progression. Hubley-Kozey et al., (2014)[18] found altered more active early stance LG activity to be associated with progression structurally in ~8 years compared to those who did not progress, who showed a trend toward prolonged MH activity. Hodges et al. (2016)[17] found increases in VM-MH CCI duration was correlated with loss of cartilage volume over time, while longer VL-LH CCIs showed an inverse correlation with volume loss, suggesting it may be more protective to cartilage health in the medial compartment.

While increased co-contraction of the quadriceps and hamstrings may be required to achieve joint stability due to increased medial laxity in knees affected by OA, and increased lateral activation may be needed to balance the larger KAM reported in individuals with knee OA, elevated activation of the major muscle groups surrounding the knee can increase compressive forces on the joint compartment and contribute to accelerated cartilage deterioration[76]. Previous findings in co-contraction are specific to the more symptomatic knee, and it is important to understand whether CCIs are elevated in the contra-lateral limb as well as the symptomatic limb in an OA group.

2.6.5 – Limitations of Surface Electromyography

Surface electromyography comes with limitations that must be considered when interpreting results, where methodological problems can present themselves in the design of an EMG-focused investigation. Across studies standardizing preparation, collection and processing protocols are necessary to allow for inter-study comparisons to be made. Care must be taken with electrode placements, and it is suggested studies use widely-cited electrode placement guidelines (such as the Surface EMG for the Non-Invasive Assessment of Muscles). Skin-artifact motion can also have an influence on electromyographs in subject pools with a higher BMI and more subcutaneous tissue. Tension provided over the skin to minimize motion may limit excessive skin motion during gait to address this issue.

Strength differences in the lower limb may exist between OA and control populations, which effects surface EMG waveforms when they are amplitude normalized. Normalizing waveforms to peak or mean waveform activation does not provide information on the activation of an individual's muscles relative to their maximum potential. Amplitude normalization to Maximum Voluntary Isometric Contractions (MVICs) allows inter-subject comparisons, though OA groups have shown muscle weakness and activation failure during maximum contractions[79]. Activation failure can be addressed by providing adequate instruction, warm up, feedback, rest, encouragement and multiple attempts of maximum contractions. With standardization, only a 2.7% difference existed between OA and control groups in average maximum volitional activation relative to a stimulated maximum[79]. Using a standardized approach, good day-to-day within-subject reliability has been shown in MVIC-normalized EMG signals[77].

The existing literature investigating muscle activation in OA groups can be difficult to interpret across studies due to the differences in collection and processing protocols, as well as statistical analysis methods. Studies looking at discrete measures such as peak activation, mean activation, or duration of activation do not fully capture the potential differences that can exist in muscle activation waveforms during gait. In the last decade, studies have begun to adopt PCA to try to capture patterns within the waveforms (PCs) that account for the most variability among subjects, and testing the PCs for group differences. This statistical method provides more information on a complex data set like a muscle activation waveform, however it is complex and focuses on individual muscle waveforms. The purpose of this dissertation is centred on co-contraction, which is quantified as a single discrete metric, and therefore PCA is not used for the current work.

A clear focus exists on mechanical loading in the symptomatic knee compared to a control group, and a number of biomechanical and neuromuscular variables are commonly different in groups of individuals diagnosed with MOA, including: i) less dynamic sagittal plane kinematics; ii) increased peak and overall KAM; iii) increased and prolonged quadriceps and LH activation; iv) prolonged MG activation; and v) increased VL-LH CCIs. These changes have implications on knee function, as increased muscle activation and reduced sagittal motion has been suggested to be necessary to provide and maintain dynamic joint stability while simultaneously increasing compressive forces on the joint compartment.

We need to determine what biomechanical changes are present in the contra-lateral knee before OA is fully established, where symptoms may not yet be present even though it can be assumed structural changes are occurring. Gaining an understanding on

the changes occurring in the other knee before it is symptomatic will create opportunities clinically for the development of early intervention strategies that treats both knees rather than just the knee that is painful.

2.7 – The Contra-lateral Knee

The influence of gait on the ipsilateral knee is well established. However it's been shown that the progression from unilateral to bilateral OA is non-random[6]. We also know that clinically, people will report that at some point both knees have bothered them but only one gives them continued trouble, and that they feel reliant on their contra-lateral knee. It has been hypothesized in the literature that altered load distribution in one lower extremity could have significant effects on the contra-lateral joint, resulting in an increased risk of multi-articular OA progression[80]. It is important, then, to understand the mechanical stresses that are occurring in the contra-lateral knee and whether asymmetries between the two knees exist.

Many studies use a random limb for statistical comparisons with a symptomatic OA group[21,30,58,78] because a common assumption exists that symmetrical gait is observed in healthy groups. It is not currently clear if differences that have been found in OA groups are different from inter-limb variability that would be associated with healthy gait. No studies have thus far investigated whether clinically relevant differences exist in healthy populations during gait in EMG. Lathrop-Lambach et al. (2013) investigated inter-limb symmetry of knee biomechanics in healthy groups, and reported inter-limb asymmetries (defined as >10% difference) in knee moments. Sadeghi (2003) investigated bilateral modeled muscle moments in a healthy group using an inverse-dynamics modeling approach, and reported local asymmetries at the knee through the weight

acceptance. The lack of information on inter-limb EMG in healthy populations leaves a significant knowledge gap as we work to understand knee function bilaterally in individuals with medial compartment OA.

2.7.1 – Joint Biomechanics

There are a few studies that try to understand contra-lateral limb biomechanics in individuals with OA. It has been suggested that sagittal plane knee angles and external moments are influenced by pain but not structural OA, where a painful limb experiences smaller peak values[58] compared to a non-painful or control limb[58]. Mills et al. (2013)[80] found inter-limb asymmetries in a mild/moderate bilateral OA group compared to those with unilateral OA, including decreased flexion angles at IC in the contra-lateral knee. These differences were suggested to be a result of individuals trying to unload the more painful limb[80]. In severe OA groups, Worsley et al. (2013)[83] found an increased external vertical knee reaction in the contra-lateral knee, as well as a reduced external KAM compared to the symptomatic knee, while Metcalfe et al., (2013)[84] reported increased KAM at mid-stance and KAM impulse in both the symptomatic and contra-lateral knees compared to an age matched control group.

The current research addressing the contra-lateral limb from a biomechanical perspective yields mixed results, where more consistent external loading alterations seem to be apparent in groups with severe-to-end-stage OA, as well as in limbs that have progressed to experience pain. As pain and stability in groups with OA has also been linked to muscle activation[26], surface electromyography should also be used to investigate muscle activation bilaterally in OA groups compared to controls.

2.7.2 – Surface Electromyography

It has been hypothesized that neuromuscular adaptations place greater loads on the contra-lateral knee and could play a role in the development of multi-articular OA in the lower limbs, and the internal loads being generated by the surrounding muscle groups should be understood bilaterally[6]. Altered loading in the contra-lateral limb from a neuromuscular perspective has been identified in an OA group in two studies, though they were completed by the same principal investigator and it is believed that the same study groups were used for both studies based on group demographics[36,84].

Metcalfe et al. (2013)[36] investigated medial and lateral co-contraction in a severe OA group bilaterally using peak-task amplitude normalized EMG to calculate CCIs over the entire stance phase of the gait cycle, and found elevated medial (VM-MH) and lateral (VL-LH) CCIs in contra-lateral limb compared to a control group. It is difficult to interpret CCIs – an amplitude based measure – on task normalized EMG data where each peak waveform peaks at 100%, however these results may suggest prolonged elevated co-contraction during stance in both knees of the OA group resulting in higher average CCIs. In a separate case-by-case analysis on TKA recovery in 14 participants, recovery of medial and lateral CCIs towards asymptomatic values was variable and inconsistent in the contra-lateral knee. This was suggested to be a 'learned chronic osteoarthritic gait' at a neuromuscular level in both knees, and that mechanical stresses remain elevated post operatively, even with symptom relief[84].

Using MVIC normalization and CCI calculations, Lewek et al. (2006)[30] did not identify any differences between the contra-lateral limb of an OA group and controls during weight acceptance for any CCIs except VM-MG, where controls had lower co-

contraction (Figure 2.6). The radiographic severity of this OA group was not specified and participants were scheduled for a high tibial osteotomy, a procedure contrary to a TKA is not specific for end stage OA. It is possible that the participants in this study could have KL grades ranging from I-IV with this criteria, as has been seen in previous work[85].

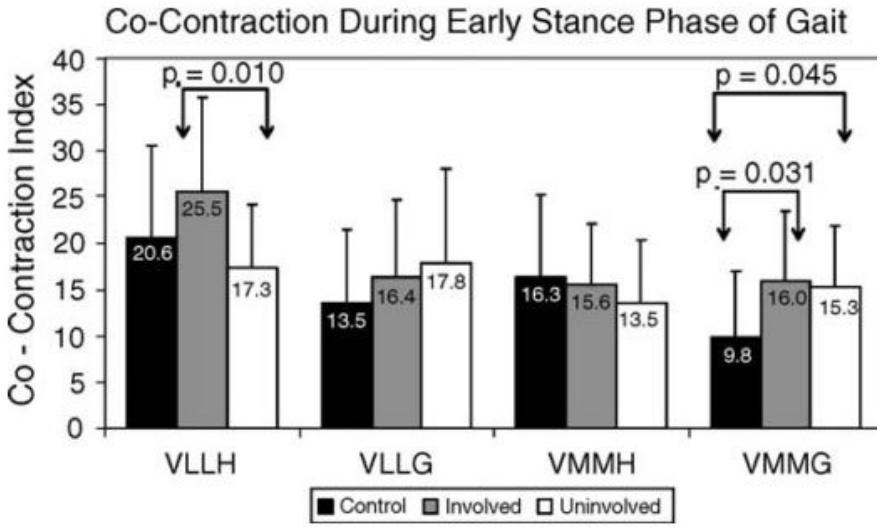


Figure 2.6. CCIs of affected and contra-lateral limbs compared to a control limb. Taken from Lewek et al., 2006.

A knowledge gap exists when looking at biomechanical and neuromuscular differences bilaterally in individuals with knee OA. The research is limited and the studies that have so far investigated contra-lateral loading show conflicting results that cannot be directly compared due to discrepancies in methodologies. A need exists for future research to focus on the contra-lateral limb in individuals with knee OA with the same level of depth as that which currently exists between knee OA and control groups, as an understanding is needed on inter-limb differences in gait mechanics with regards to knee OA to try to reduce the burden of bilateral progression.

Chapter Three – General Methodology

The primary objectives of this thesis focused on muscle activation during gait in both asymptomatic control and moderate symptomatic knee OA groups. Inter-group comparisons were made between a random control limb and the contra-lateral limb of a MOA group for medial and lateral CCI pairings (both quadriceps-hamstrings and quadriceps-gastrocnemius). For Objective two, sagittal plane motion, moments and frontal plane moments were investigated to assist in the understanding of the electromyograms. The subject recruitment, data collection, data processing and statistical analysis of this study were used to investigate the objectives described in Chapter one and were approved by the Nova Scotia Health Authority (NSHA) Research Ethics Board (REB). This study was partly funded from a Nova Scotia Health Research Foundation (NSHRF) Establishment Grant.

3.1 – Subject Recruitment

3.1.1 – Individuals with Moderate Symptomatic Knee OA

The author took on the role of research assistant for this study, aiding in participant recruitment, data collection including lab management, data processing, and statistical analysis. Individuals with knee OA were be recruited primarily from the clinics of Dr. Ivan Wong at the Queen Elizabeth II Health Sciences Centre and Dr. William Stanish at the Orthopaedic and Sports Medicine Clinic of Nova Scotia. All patients recruited have been diagnosed with knee OA in accordance with the American College of Rheumatology guidelines, had radiographic evidence of knee OA[51] that affected the medial compartment to a greater degree than the lateral compartment and self-reported

the following functional criteria previously used in the literature: Ability to walk a city block, run five metres, or climb stairs in a reciprocal fashion[14,86]. Individuals who met the inclusion criteria were given a letter outlining the study details and provided consent for further contact. Additional inclusion criteria for this study was as follows:

- Unilateral symptomatic knee pain
- Radiographic evidence of knee OA (KL scale; medial compartment > lateral compartment)
- Have not yet been identified as a candidate for a total knee replacement
- No cardiovascular disease (high blood pressure okay if controlled)
- No neurological disease
- No musculoskeletal disease or injury other than knee OA
- No lower limb surgery within the past year
- Ability to walk independently without the use of an ambulatory aid

3.1.2 – Asymptomatic Group

The group of asymptomatic participants were age and sex matched to the OA group. They were recruited from the local area using email, poster advertising, social media and word of mouth. Individuals interested in the study were sent a letter outlining the study details, and once individuals confirmed interest they were contacted via telephone to determine eligibility. The inclusion criteria for the asymptomatic group was the same as that for the OA group, excluding OA specific criteria. The asymptomatic group were not diagnosed with knee OA, did not have radiographs and had no evidence of knee pain. When eligibility was determined, details of the walking study were discussed, a date and time for collection was arranged, and directions to the Joint Action Research Laboratory in the School of Physiotherapy were given.

3.1.3 – Sample Size

The sample size chosen for this study is driven by already existing literature investigating CCIs between OA and control groups. Previous studies identified significant differences in medial and lateral co-contraction indices of 6.3 and 11.7, with standard deviations of 9.6 and 7.3, and group sample sizes of 12 and 18 participants[19,23]. The difference in CCIs were chosen because it is the primary objective of this study that will be tested for statistical significance. Beta (β) was set to 20% to determine the probability of detecting a false positive on the null hypotheses of Objective one. Power was set to 80% (1-β) to accurately calculate the sample size required to confidently reject the null hypotheses of Objective one. The power and sample size calculations were calculated using a series of 2-sample t-tests, as it will be used for Post-hoc testing.

Two-sample t-test (absolute difference and standard deviation from Zeni et al., 2010[23]:
Testing mean paired difference = 0 (versus not = 0)
Calculating power for mean paired difference = 0.8
$\alpha = 0.05$
Assumed standard deviation of paired difference = 9.6

Difference	Sample Size	Target Power	Actual Power
11.7	12	0.8	0.814

Two-sample t-test (absolute difference and standard deviation from Lewek et al., 2004[19]:
Testing mean paired difference = 0 (versus not = 0)
Calculating power for mean paired difference = 0.8
$\alpha = 0.05$
Assumed standard deviation of paired difference = 7.3

Difference	Sample Size	Target Power	Actual Power
6.3	23	0.8	0.816

CCI differences used from Zeni et al. (2010) recommended a sample size of 12 in order to identify statistically significant differences with a power of 80%. However, as a mean difference of 11.7 seems large compared to statistically significant differences in CCIs identified in other studies[19,24], identified differences from Lewek et al. (2004)[19] were also taken into consideration. The smaller group difference of 6.3 recommended a sample size of 23 to maintain 80% power. As a result, a sample size of 20 was chosen for each participant group.

3.2 – Procedures

3.2.1 – Participant Preparation

Upon arrival to the Joint Action Research Laboratory in the School of Physiotherapy at Dalhousie University, participants were introduced to the laboratory equipment given a brief overview of study objectives and collection procedures. Written informed consent was then obtained, and participants were asked to complete the Knee Osteoarthritis Outcome Survey (KOOS) questionnaires. From the KOOS questionnaire, the Western Ontario and McMaster Universities Index (WOMAC) scores were calculated. The KOOS has been shown as reliable and valid in past literature[87].

Participants were asked to change into tight fitting shorts provided by the Joint Action Research Laboratory and to remove their shoes. Anthropometric measurements were taken including height and weight, as well as hip, waist, thigh, and shank circumference using standardized procedures. Participants with OA were asked to rate the pain in their symptomatic knee on the numeric pain rating scale (NPRS), as well as whether they had pain in their contra-lateral knee at the time (NPRS) or if they have previously had trouble with that knee. These data were used for descriptive purposes. All

participants then walked barefoot along the GAITRite™ portable pressure sensitive walkway at their self-selected speed at least 15-20 times. Five trials were recorded randomly and used to determine the participant's individual self-selected walking speed for the treadmill walking. The GAITRITE^{TM} system has been shown as a valid[88] and repeatable[89] tool for calculating walking velocity (ICC>0.9) when compared to already established motion capture and video-based systems.

3.2.1.1 – Surface Electromyography

A standardized protocol was used for preparation and acquisition of surface electromyographic data. This protocol was in accordance with previously accepted guidelines by Surface EMG for the Non-Invasive Assessment of Muscles (SENIAM). Two AMT-8 (Bortec, Inc., Calgary, Alberta, Canada) eight channel EMG measurement systems (Input Impedance: ~10GΩ, CMRR: 115dB at 60Hz, Band-pass 10-1000Hz) were used to amplify collected EMG recordings and bipolar skin-surface electrodes (3M^{TM} Red Dot^{TM}, Repositionable Monitoring Electrodes, St. Paul, MN; Ag/AgCl, 10mm diameter, 0.72cm^2 surface area, 30mm inter-electrode distance) were affixed to the skin over the knee joint muscle of interest. Guidelines presented by SENIAM were followed to approximate each muscle belly location (Table 3.1, Figure 3.1).

Once muscle sites were determined and marked with non-permanent ink, electrode placement happened as follows:

- Skin was be shaved and cleaned with alcohol-water solution to reduce skin artifact interference. A series of isometric muscle contractions were used to verify muscle location with respect to guidelines. Electrodes were then placed in

parallel to the underlying muscle fibers, also in the direction of the electrical activity propagating along the corresponding muscle.

- Lead wires with 500x pre-amplification were connected to the electrode pairs on each muscle. A single ground was connected to the anterior shaft of the tibia.
- Electrode placements were verified for quality and crosstalk with manual muscle testing, and amplifier gains were set (500-5000x) for each individual muscle to maximize amplitude but avoid signal saturation. Manual muscle testing consisted of the following for each muscle group[90]
    - Quadriceps: Isometric knee extension, and mini-squat
    - Hamstrings: Isometric knee flexion at ~60°
    - Gastrocnemii: Unilateral heel raise

When EMG signal quality was verified and amplifier gains were set, three-dimensional motion capture set-up took place.

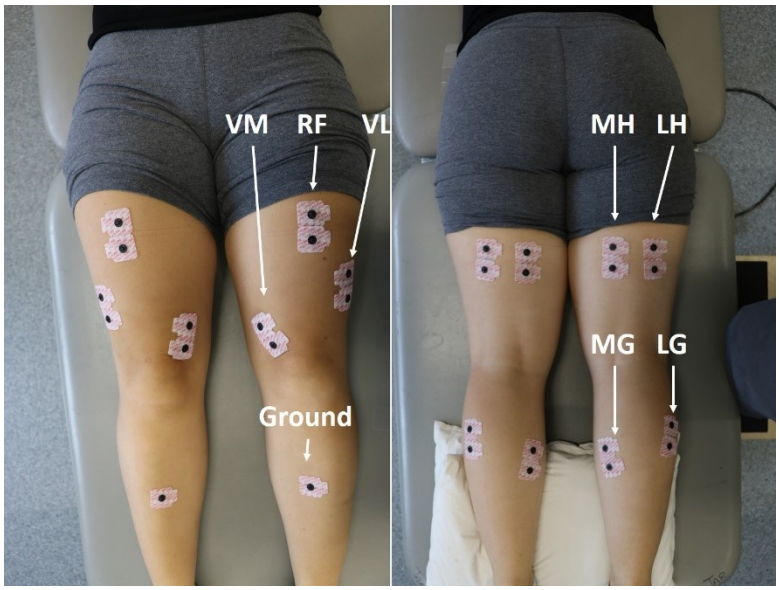


Figure 3.1. Anterior (left) and posterior (right) bipolar electrode placement, in accordance with SENIAM guidelines

Table 3.1. SENIAM guidelines of standardized electrode placement for the lower limb.

Muscle	Muscle Site
Vastus medialis (VM)	80% distance anterior superior iliac spine (ASIS) to medial joint line
Vastus lateralis (VL)	67% distance ASIS to lateral joint line
Medial hamstring (MH)	50% distance ischial tuberosity to medial joint line
Lateral hamstring (LH)	50% distance ischial tuberosity to lateral joint line
Medial gastrocnemius (MG)	35% distance medial joint line to calcaneus
Lateral gastrocnemius (LG)	30% distance lateral joint line to calcaneus

3.2.1.2 – Three-Dimensional Motion Capture

An eight-camera Qualisys® Oqus 500 (Qualisys®, Gothenburg, Sweden) motion analysis system and passive retro-reflective skin surface markers were used to collect three-dimensional movement data. Markers were affixed to pre-determined anatomic landmarks for each participant, and fixed clusters of four markers were placed on rigid body segments (thorax, pelvis, thighs, shanks, feet). Individual markers were placed on the following, bilaterally[38] (Figure 3.2):

- Lateral aspect of the shoulders, below the acromion
- Spinous process of the 7th cervical vertebra (C7)
- Greater trochanter
- Lateral and medial femoral epicondyles
- Lateral and medial tibial epicondyles
- Lateral and medial malleoli
- Head of the 1st, 2nd and 5th metatarsals
- Posterior heels

3.2.2 – Calibration

After marker placement and prior to walking, participants stood on the R-Mill (Motekforce Link, Culemborg, the Netherlands) dual-belt instrumented treadmill that was used for the walking protocol. They stood with their feet shoulder width apart and facing forward (Figure 3.2), and knees straight as a two-second standing trial was collected.

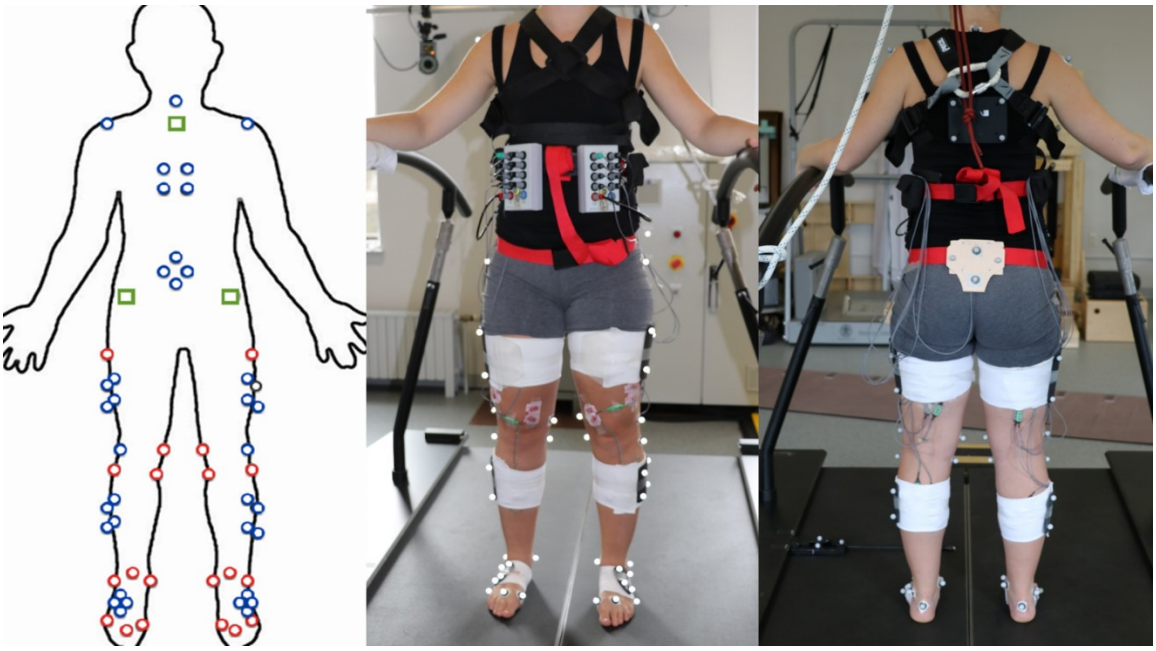


Figure 3.2. Digitized (green), virtual (red) and remaining (blue) markers collected throughout calibration and walking protocol (left), as well as anterior (centre) and posterior (right) retro-reflective full marker set-up.

The greater trochanter, medial and lateral tibial epicondyles, medial femoral epicondyle, medial malleolus, and 1st and 5th metatarsal markers were then removed to improve the subject's ability to walk naturally. Three two-second virtual point trials were collected using a pre-digitized calibration wand to determine the virtual position of the sternal notch and the right and left anterior superior iliac spine (ASIS). Virtual markers, individual markers, and clusters are shown in Figure 3.2.

3.2.3 – Walking Protocol

After the calibration trials, participants began walking on the R-Mill at the speed determined from the GAITRite™ instrumented walkway. Participants who did not have any prior experience on a treadmill or were not comfortable with their ability to walk on the treadmill were harnessed to the ceiling using an upper torso harness system attached to a rope, with enough slack to allow natural movement of the lower extremity. Participants were instructed to remain in the middle of the R-Mill with one foot on each belt, and walk barefoot for ~eight minutes. They refrained from using the railings on the treadmill from just prior to the end of the first minute for the remainder of the collection. The first five minutes were used as the treadmill acclimatization period, as previously recommended for asymptomatic young adults[91], asymptomatic older adults[92] and older adults with OA[92]. At minute six, three-dimensional motion at 100Hz, surface electromyography at 2000Hz, and ground reaction forces and moments at 2000Hz were simultaneously collected for 20 seconds through Qualisys Track Manager V2.10 (QTM). Electromyographic and ground reaction force data was analog to digital converted (16bit, +/-5V) and synchronized with motion capture data through QTM.

3.2.4 – Maximum Voluntary Isometric Contractions

Immediately following the walking protocol, all retro-reflective markers and clusters were removed from the participant, while the surface electromyography system remained. Participants were instructed to lie supine on a therapy bed and completely relax their lower extremities. A one-second subject bias trial was collected.

A HUMAC®/NORM™ (Computer Sports Medicine, Inc., Stoughton, MA) Testing and Rehabilitation System was used to complete the knee flexor and extensor

Maximum Voluntary Isometric Contraction exercises (MVIC). Isometric contractions minimize the potential for pain during repetitions and allow both torque and EMG normalization data to be collected within the same trial. Isometric exercises have been used frequently in past literature to amplitude normalize EMG waveforms[93–95]. Using the HUMAC2009 program, the participants were set up sitting, with the hip flexed 90°, the knee flexed ~45°, and restraints placed on the waist, thighs and shanks. A gravity correction value was recorded prior to maximum exercises, and was either subtracted (during flexion) or added (during extension) to account for the effect of gravity associated with limb segment mass on the final torque values. (Figure 3.3). For each lower extremity, at least one warm-up/practice contraction was used for familiarization to the testing (or until the participant feels comfortable with the task). This was followed by two, three-second maximum effort knee flexion and knee extension trials, and a standardized 40-second rest occurred between the two reps of each exercise.

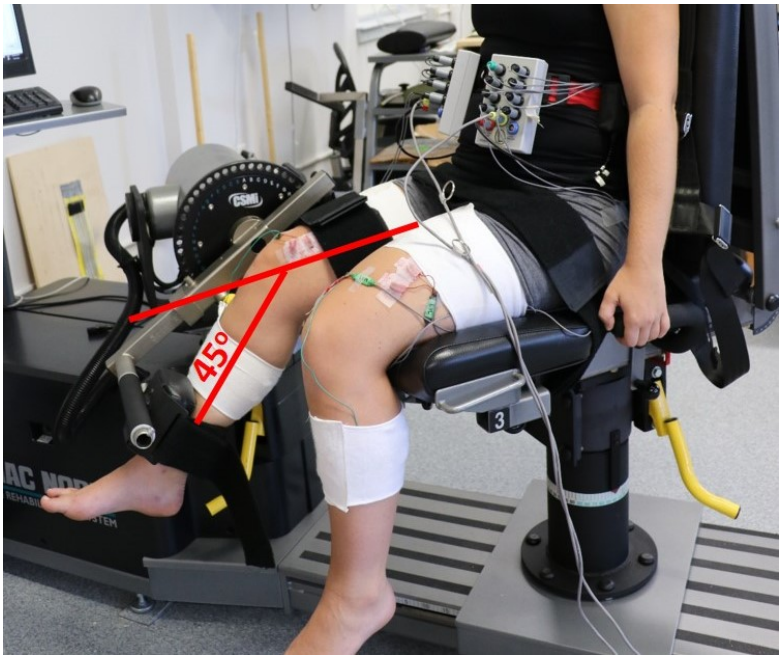


Figure 3.3. Rest position for knee extension and knee flexion maximum voluntary isometric contractions, with the knee at a 45 degree angle and restraints at the ankle, thigh and hips.

Surface electromyography was collected simultaneously with each repetition to collect the maximum voluntary activation in each muscle during the exercises. It was expected maximum quadriceps activation would occur during knee extension, and maximum hamstrings activation would occur during knee flexion. Additionally, two three-second single-leg standing calf raise trials were collected on each leg in order to obtain maximum voluntary activation of the gastrocnemii[95].

A 500-ms moving average algorithm was applied on gravity-corrected torque values produced during knee extension and knee flexion exercises. The maximum torque out of the two trials was gathered as the maximum torque produced by the participant for each exercise.

3.3 – Data Processing

3.3.1 – Surface Electromyography

Electromyographic data was processed in a custom program (JAR3) written in Matlab™ R2015a (The Mathworks Inc., Natick, Massachusetts, USA). All collected EMG signals were visually checked in real time for noise and range saturation, and fast Fourier transforms were performed on the signals of each amplifier in all participants to produce a discrete-frequency representation of the signal and verify the power density spectrum of the signal[96,97], and to ensure the majority of the signal is within the generally accepted frequency range of 10-500Hz[98] . All raw data was corrected for subject bias and gain to convert to microvolts (Figure 3.4).

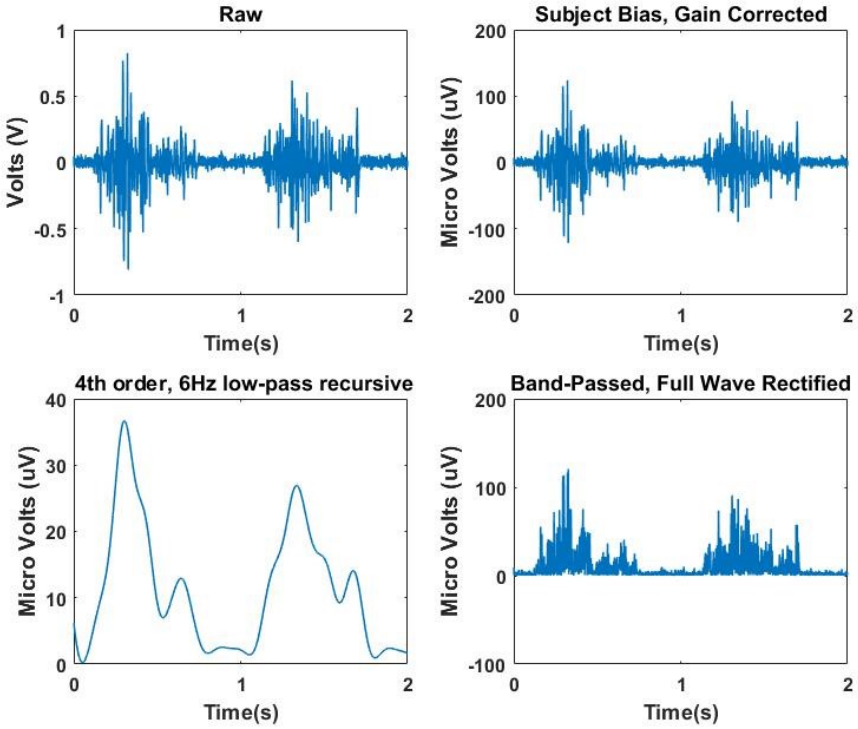


Figure 3.4. Raw (top left), subject bias corrected/gain corrected (top right), band-passed/full wave rectified (bottom right), and low-pass filtered (bottom left) electromyographs for the VM over two seconds

Following, all corrected signals (gait and MVIC) were full-wave rectified and low-pass filtered (Butterworth Fc=6Hz, 4th order low pass, recursive). The EMG signal collection and processing methods have been described in previous literature[21,77]. Surface EMG recordings have shown good day-to-day reliability using the same parameters (skin preparation, electrode location, collection frequency, input impedance, CMRR, band-pass) as those described previously[77], and have been used frequently for gait analyses of individuals with osteoarthritis[38,92,99]

On all twelve MVIC exercises, a 100-ms moving average window (99-ms overlap) was used to calculate the maximum amplitude for each muscle as described in Hubley-Kozey et al (2006)[14]. Muscle EMG waveforms from gait trials were amplitude normalized to the maximum amplitude value of that muscle (%MVIC)[93]. Occasionally,

maximal amplitudes for the quadriceps and hamstrings came from the standing plantarflexion trials (performed to target the gastrocnemii). When this happened, these values were excluded and the maximum was taken from the strength test designed to target the respective muscle group.

3.3.2 – Three-Dimensional Motion Capture Data

3.3.2.1 – Kinematic Data

Kinematic data was processed using pre-written software (JAR3) in Matlab ver R2015a (The Mathworks Inc., Massachusetts, USA). Motion data was first low-pass filtered (Butterworth 4th order, 6Hz – recursive), and from it local technical and anatomical coordinate systems for the pelvis, thigh, foot and shank were calculated from the skin markers, surface clusters and virtual points.

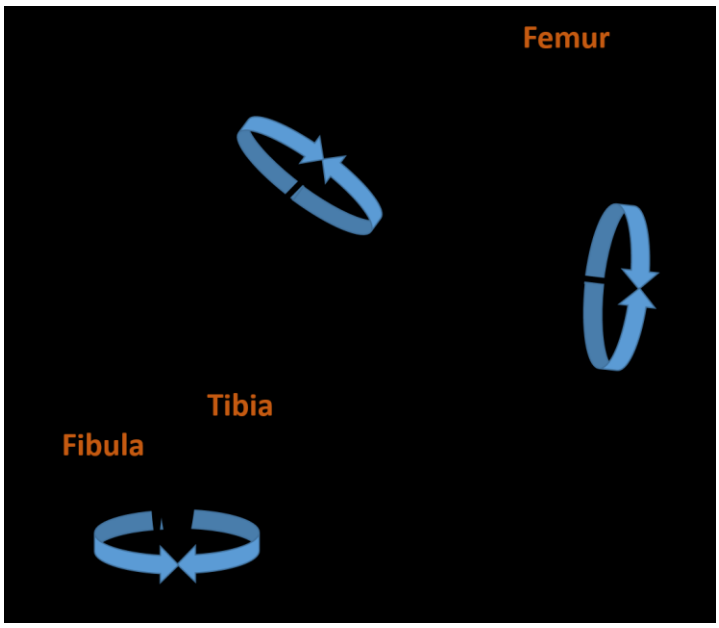


Figure 3.5. Axes of rotation for the shank segment moving about the fixed thigh segment. Modified from Grood & Suntay, 1983.

Joint angles were calculated from these Cartesian coordinate systems using Cardan/Euler rotations, in the order Flexion/Extension, Abduction/Adduction, Internal/External

Rotation. Flexion, abduction and internal rotation about the knee were described as positive motion as a result of these coordinate systems, and knee joint angles were described as the shank (distal segment) moving about a fixed thigh (proximal segment), shown in Figure 3.5[100].

3.3.2.2 – Kinetic Data

Within each force plate six sensors provided, using a calibration matrix (Motekforce Link, Culemborg, the Netherlands), three-dimensional ground reaction forces (GRF) and moments. Forces and moments from the force plates were processed on a pre-programmed software (JAR3) written in Matlab Ver R2015a (The Mathworks Inc, Massachusetts, USA). GRF data was low-pass filtered (Butterworth 4th order, 30Hz – recursive) and used in combination with kinematics, subject anthropometrics, and segment inertial properties to calculate external joint moments using an inverse dynamics algorithm[101]. Net external moments were projected using a floating axis into the joint coordinate system, low-pass filtered (Butterworth -10Hz 4th order – recursive) and amplitude normalized to body mass. Ampitude normalization to mass was completed reduce the variability due to a persons mass, so that differences due to gait can be investigated[102].

Given the primary thesis objective, a brief overview of the biomechanical processing methods have been provided. A more complete description can be found in previous literature[103].

3.4 – Data Analysis

All kinematic and electromyographic data was time normalized to 101 data points for each limb from initial contact (IC) to subsequent IC using a cubic spline, while

external moments were normalized to 101 data points from IC to toe off, representing stance only. Initial contact was determined when the magnitude of the vertical GRF surpassed 30N. Between 13 and 18 consecutive strides, taken from the 20 second recording were ensemble averaged for each leg (Right/Left in the asymptomatic group and symptomatic/contralateral in the knee OA group). For knee motion, the range from IC to peak knee flexion angle during stance and the range from peak knee flexion in stance to minimum flexion during terminal stance was calculated. For knee moments, the peak KAM, KAM impulse and the range between peak flexion and peak extension moment was extracted and used as a descriptive biomechanical variables. From the electromyographic waveforms, peak activation and mean activation during the stance phase of gait (defined as 0-60% of the gait cycle) was calculated to be used as supplementary information to the CCIs. CCIs were calculated for four pairings (VL-LH, VM-MH, VL-LG, VM-MG) using the equation previously described[19,24], modified to represent the average of each phase of loading:

$$CCI = \frac{1}{20}\sum_{i=1}^{20}\left[\frac{lower\ EMG_i}{higher\ EMG_i}\ x\ (lower\ EMG_i + higher\ EMG_i)\right]$$

The CCI time intervals included the loading response (1-20%), mid-stance (21-40%) and terminal stance (41-60%) of the gait cycle, in order to capture the primary quadriceps-hamstrings activation during early/mid-stance and quadriceps-gastrocnemius activation during late-stance.

For Objective three, CCIs were calculated for the right and left legs of the asymptomatic group using the same method described above. The absolute RootMeanSquared (RMS) between-limb difference was then calculated for each of the

CCIs representing LR, MID and TERM. The means and standard deviations of the RMS values were averaged across participants for each phase to represent the between-limb difference that is observed in an asymptomatic group.

Example (for loading response):

For left and right legs:

$$CCI\ (LR) = \frac{1}{20}\sum_{i=1}^{20}\left[\frac{lower\ EMG_i}{higher\ EMG_i}\ x\ (lower\ EMG_i + higher\ EMG_i)\right] \quad [1]$$

$$\text{RMS (LR)} = \text{rms}\ [\text{CCI(LR)}^{\text{Left}} - \text{CCI(LR)}^{\text{Right}}] \quad [2]$$

3.5 – Statistical Analysis

Unpaired t-tests (α=0.05) were completed between the MOA and control groups on participant demographics including age, height, weight, BMI, as well as walking velocity. For CCI pairings, normality and equal variance and was tested using a Kolomogrov-Smirnov and Levene's test (α=0.05) respectively. Assumptions for two-factor mixed-model ANOVA (analysis of variance) testing is as follows: (1) The within-subjects factor consists of at least two categorical related groups, where the same subjects are present in each group; (2) The between-subjects factor consists of at least two categorical independent groups; (3) No significant outliers exist in any group defined by the within-subjects factor or the between-subjects factor, and the dependent variable is normally distributed for each combination of groups; (4) Variances of the differences between the groups defined by the between-subjects and within-subjects factors must be equal.

A two-factor mixed model ANOVA (α=0.05) was used to detect phase (loading response, mid-stance, terminal stance) and group (CONTRA and ASYMP) main effects and interactions in all CCI pairings to complete objective one of this study. If an

interaction was identified ($p<0.05$), post-hoc testing took place using a series of paired and unpaired t-tests. Bonferroni adjustments were made to correct for all multiple comparisons ($\alpha=0.05$). For Objective two, unpaired t-tests ($\alpha=0.05$) were performed on all biomechanical measures, and unpaired t-tests ($\alpha=0.05$) were used to identify knee extension and flexion torque differences between the MOA contra-lateral and random control limbs. All statistical analyses were completed in Minitab™ v.17 (Minitab Inc., Pennsylvania, USA).

Chapter Four - Co-contraction is not altered in the contra-lateral limb of individuals with moderate knee osteoarthritis compared to healthy controls

4.1 – Introduction

It is expected that within 30 years, 25% of Canadians will be living with osteoarthritis (OA)[2]. This creates significant concern, as lower extremity OA has a substantial impact on mobility and joint function[3]. Of the three major joints in the lower extremity, the knees are the most commonly affected by OA[104]. Given the role of the knee in ambulation, and the impact this disease has on mobility, gait analyses are frequently performed to understand the implications of knee OA on joint function.

Traditionally, gait studies have focused on joint biomechanics[28,29,33] , where alterations have been found in an OA knee compared to healthy individuals. Less dynamic flexion-extension range of motion (RoM) during stance[28–30], less dynamic flexion-extension moment range[31], and decreased flexion excursion (flexion angle at initial contact to peak flexion during stance)[19] have been identified and suggests the OA knee may be stiffer during stance. Greater peak external knee adduction moments (KAM) and KAM impulse[11,29,32,33] have been found, where the KAM impulse has been associated with medial compartment knee forces[34] and peak KAM has shown a relationship with femoral cartilage loss[35].

Biomechanical changes are often accompanied by altered muscle activation to fully describe joint function during gait. Understanding mechanisms underlying altered biomechanics has led to an emphasis on the muscular system given the purported role of the neuromuscular system to support the OA knee[10,23]. Muscle activation amplitudes and patterns are altered in those with moderate stages of OA[13,15,16]. Muscle activation

strategies have been thought to represent altered neuromuscular control in the presence of altered knee OA joint structure to maintain function[10,23], and muscle activation characteristics have been associated with disease progression in recent studies[17,32].

Surface electromyography (EMG) gait analysis findings typically support increased and prolonged rectus femoris[11,12], vastus lateralis[12,14], and lateral hamstring[20,25] activation in an OA limb compared to controls, as well as prolonged medial gastrocnemius[12] activation, and reduced late stance[14] amplitudes. Using a co-contraction index, increased quadriceps-hamstrings co- contraction in MOA limbs compared to controls during weight acceptance has been found[13,16,23]. Increased lateral compared to medial co- contraction specifically has been identified in MOA limbs[13], and lateral quadriceps-hamstrings CCIs have been positively associated with radiographic OA severity[24]. Together, these findings highlight associations with gait alterations in MOA individuals, and altered activation of major muscle groups surrounding the knee can give us information on joint stability and loading that cannot be observed through joint biomechanics.

To date, the focus of gait studies has been on the symptomatic leg. It has been known for more than a decade that contra-lateral disease can have a significant impact on gait mechanics[30]. Given high rates of contra-lateral progression[6,7] and the mechanical aetiology of OA development and progression[106], contra-lateral joint mechanics have been a focus of recent attention to strengthen the link between altered mechanics and OA development and progression[30,36,80]. Two studies currently investigate gait in the contra-lateral limb of individuals with severe knee OA (defined as awaiting surgical intervention). Lewek et al. (2006)[30] found reduced lateral quadriceps-hamstrings CCIs

during weight acceptance compared to ipsilateral and the only difference between contra-lateral and control CCIs was found in medial quadriceps-gastrocnemius CCIs, where the control group had lower values. Metcalfe et al. (2013)[36] found that medial and lateral quadriceps-hamstrings CCIs were elevated in the contra-lateral knee of a severe OA group compared to younger controls, and identified an increase in KAM impulse in the contra-lateral knee compared to age-matched controls. Together, these results provide preliminary evidence of altered joint function, contra-lateral to the knee with severe OA, during walking.

To understand mechanical factors of altered joint function in OA progression, knowing whether findings of altered contra-lateral joint function in individuals with severe knee OA translate to earlier disease states is lacking. Where previously the focus has been on symptomatic knee function in early disease, to thwart the overall burden of disease and have a positive impact on mobility, contralateral knee function is important to understand.

Therefore, the objective of this study was to determine whether differences exist between the contra-lateral limb (CONTRA) of individuals diagnosed with medial compartment unilateral symptomatic knee MOA and randomly chosen limbs (ASYMP) from an asymptomatic group in medial and lateral quadriceps-hamstrings and quadriceps-gastrocnemius CCI pairs during loading response, mid-stance, and terminal stance. The second objective was to determine whether gait biomechanics (sagittal plane motion, moments and frontal plane moments) differ between ASYMP and CONTRA limbs. It was hypothesized that CCIs, frontal plane moments, and sagittal plane kinematics and moments would be different between groups given the suspected early radiographic

changes and previously identified differences in the contra-lateral knee of severe OA groups.

4.2 – Methods

4.2.1 – Participants

Twenty individuals diagnosed with unilateral symptomatic primarily medial compartment MOA and twenty age and gender matched asymptomatic controls were recruited for this study. The MOA group was recruited from orthopaedic and physiotherapy clinics and met the following inclusion criteria: (i) diagnosed with OA by a clinician according to the American College of Rheumatology guidelines; (ii) radiographic evidence of medial compartment OA > lateral compartment OA (iii) not a candidate for a total knee arthroplasty; (iv) no cardiovascular or neurological disease; (v) no musculoskeletal disease other than knee OA; (vi) no lower limb surgery within the last year; and (vii) ability to walk independently without assistance or aids. Additionally, the ability to confidently self-report standard functional criteria previously used to describe moderate symptomatic OA [14] was required, and included: (i) walk one city block; (ii) jog five metres; and (iii) climb stairs in a reciprocal fashion (one foot on each step). Asymptomatic controls were considered a sample of convenience and recruited from the local area, that was age and sex matched to MOA, and was given the same inclusion criteria excluding the knee OA requirements. Participants provided consent for study procedures, in accordance with the local institutional ethics review board (Romeo #1017467).

4.2.2 – Preparation

After informed consent was obtained, participants were asked to fill out the Knee Osteoarthritis Outcome Survey (KOOS). They were also asked to rate their symptomatic knee pain on a numerical pain rating scale (NPRS), and were asked about any history of CONTRA pain. After anthropometric measurements (height, weight, limb segment circumferences) were taken, participants walked barefoot along a GAITRite™ portable pressure sensitive walkway (CIR Systems, Inc., Franklin, NJ) at their self-selected speed at least 15-20 times. Five trials were randomly taken to determine each individual's self-selected walking speed.

A standardized protocol was followed for preparation and acquisition of surface EMG data, in accordance with previously accepted Surface EMG for the Non-Invasive Assessment of Muscles (SENIAM) guidelines. Two AMT-8 (Bortec, Inc., Calgary, Canada) eight channel EMG measurement systems (Input Impedance: ~10GΩ, CMRR: 115dB at 60Hz, Band-pass 10-1000Hz) were used to amplify EMG recordings and bipolar skin-surface electrodes (3M™ Red Dot™, Repositionable Monitoring Electrodes, St. Paul, USA; Ag/AgCl, 10mm diameter, 0.72cm^2 surface area, 30mm inter-electrode distance) were affixed to the skin over knee joint muscles of interest, including the vastus lateralis (VL) and medialis (VM), lateral (LH) and medial (MH) hamstrings, and lateral (LG) and medial (MG) gastrocnemii. Guidelines presented by SENIAM were followed to approximate each muscle belly location, and electrode placements were verified for quality and crosstalk with manual muscle testing[90].

An eight-camera Qualisys® Oqus 500 (Qualisys®, Gothenburg, Sweden) motion analysis system and passive retro-reflective skin surface markers were used to collect three-dimensional movement data. Markers were affixed to pre-determined anatomic

landmarks for each participant, and fixed clusters of four markers were placed on rigid body segments (thorax, pelvis, thighs, shanks, feet). Individual markers were placed on the following bilaterally: Lateral aspect of the shoulders below the acromion, spinous process of the 7th cervical vertebra (C7), greater trochanter, lateral and medial femoral and tibial epicondyles, lateral and medial malleoli, posterior heel, head of the 1st, 2nd, and 5th metatarsals. The anterior superior iliac spines (ASIS) and sternal notch were virtual points determined by a pre-digitized calibration wand. All individual markers but the lateral femoral epicondyles, lateral malleoli, heels and 2nd metatarsals were removed prior to walking[103].

4.2.3 – Protocol

Participants were asked to walk barefoot on a dual-belt R-mill instrumented treadmill (Motekforce Link, Culemborg, the Netherlands) at their self-selected speed (determined from the GAITRite™ instrumented walkway) for ~8 minutes. They were asked to walk with one foot on each plate and refrain from using hand-rails before the end of the first minute of walking. The first five minutes of walking were used for treadmill acclimatization, as previously recommended for asymptomatic young adults[92]. Three-dimensional motion at 100Hz, surface EMG at 2000Hz, and ground reaction forces and moments at 2000Hz were simultaneously collected for 20 seconds through Qualisys Track Manager V2.10 (QTM) at the end of the 6th minute of walking. Ground reaction force and EMG data were analog to digital converted (16bit, +/-4V) and synchronized through QTM.

All passive markers were removed following walking and a one-second subject bias trial was collected with the participant lying supine and relaxed on a therapy bed. A

HUMAC®/NORM™ (Computer Sports Medicine, Inc., Stoughton, USA) Testing and Rehabilitation System was used to complete knee flexor and extensor Maximum Voluntary Isometric Contraction exercises (MVICs). At least one warm-up/practice contraction was used for familiarization to the testing (or until the participant felt comfortable with the task). This was followed by two, three-second maximum effort knee flexion and knee extension trials, and a standardized 40-second rest occurred between the two reps of each exercise. Surface electromyography was collected simultaneously with each repetition to collect maximum voluntary activation in each muscle during the exercises. These were followed by two, three second repetitions of standing plantarflexion on each limb[95].

4.2.4 – Data Processing

Motion capture, EMG and strength data were processed using a custom program (JAR3) written in Matlab™ R2015a (The Mathworks Inc., Natick, USA). A 500-ms moving average algorithm was used on gravity-corrected torque values collected during knee extension and knee flexion MVICs. The maximum value out of the two trials was gathered as the maximum torque produced by the participant for each exercise.

All raw EMG data was corrected for subject bias and gains, converted to microvolts, full-wave rectified and low-pass filtered (Butterworth Fc=6Hz, 4^{th} order low pass, recursive) as described in previous literature[38]. A 100-ms moving average window (99-ms overlap) was used on corrected EMG signals from all MVIC trials to calculate maximum amplitudes for each muscle[14]. All EMG waveforms from gait trials were amplitude normalized to maximum amplitude values (%MVIC) for each muscle.

Motion data was low-pass filtered (Butterworth 4th order, 6Hz – recursive), and knee joint angles were calculated from Cartesian coordinate systems using Cardan/Euler rotations, with Flexion, adduction and internal rotation about the knee described as positive motion[100]. Ground reaction force data was low-pass filtered (Butterworth 4th order, 30Hz – recursive) and used in combination with kinematics, subject anthropometrics and segment inertial properties to calculate external joint moments with an inverse dynamics algorithm[101]. Net moments projected into the knee joint coordinate system were low-pass filtered (Butterworth -10Hz 4th order – recursive) and amplitude normalized to body mass. A more complete description of these methods can be found in previous literature[103].

All kinematic, kinetic and electromyography waveforms were time normalized to 101 data points, from IC (30N vertical GRF threshold) to subsequent IC to represent a full gait cycle. At least 13-18 consecutive strides, taken over the 20-second trial was ensemble averaged for each leg. The range from initial contact to peak knee flexion angle during stance and the range from peak knee flexion in stance to minimum flexion during terminal stance were calculated from sagittal motion data. For knee moments, peak KAM, KAM impulse and the range between peak flexion and peak extension moment was extracted[92].

CCIs were calculated for four pairings (VL-LH, VM-MH, VL-LG, VM-MG) using the equation previously described[19,24], modified to represent the average of each phase of loading:

$$CCI = \frac{1}{20}\sum_{i=1}^{20}\left[\frac{lower\ EMG_i}{higher\ EMG_i}\ x\ (lower\ EMG_i + higher\ EMG_i)\right]$$

The CCI time intervals included loading response (LR; 1-20%), mid-stance (MID; 21-40%) and terminal stance (TERM; 41-60%) in the gait cycle.

4.2.5 – Statistical Analysis

Knee Osteoarthritis Outcome Scores were tabulated and Western Ontario McMaster Osteoarthritis Index Scores (WOMAC) scores were calculated from the KOOS for the symptomatic leg. Normality and equal variance were tested on statistical pairings using Kolomogrov-Smirnov and Levene's tests (α=0.05), respectively. Two-sample unpaired t-tests (α=0.05) were completed between MOA and control groups on age, height, weight, BMI, walking velocity, and between ASYMP and CONTRA gait biomechanical outcomes and knee flexor and extensor strength. A two-factor mixed model ANOVA was used to detect phase (LR, MID, TERM) and group (CONTRA, ASYMP) main effects and interactions on CCI pairings. If an interaction was identified, post-hoc testing took place using a series of paired and unpaired t-tests (α=0.05). Bonferroni adjustments were made for multiple comparisons. All statistical analyses were completed in Minitab™ v.17 (Minitab Inc., Pennsylvania, USA).

4.3 – Results

Twenty individuals participated in each of the MOA and asymptomatic groups. Groups were matched for age, sex and walking velocity (Table 4.1). Additional group demographics are shown in Table 4.1. Higher WOMAC pain, stiffness and physical function scores, and lower KOOS scores for symptoms, pain, function in activity of daily living, function in sport and recreation, and quality of life ($p<0.001$) (Table 4.1) were reported in the MOA symptomatic knee compared to controls ($p<0.001$).

Table 4.1. Mean (SD) KOOS, WOMAC, and strength (torque) information for the symptomatic limb in the MOA group and the asymptomatic group, as well as CONTRA radiograph information. KOOS and WOMAC values in the MOA group are for the symptomatic knee, while strength values in the MOA group are reported for the contra-lateral knee

	MOA (n=20)	Asymptomatic (n=20)	p-value
Age	60 (7)	61 (7)	0.619
Male (Female)	9 (11)	9 (11)	
BMI (kg/m^2)	29.4 (4.3)	23.4 (3.1)	**<0.001**
Walking Velocity (m/s)	1.11 (0.10)	1.17 (0.12)	0.054
	WOMAC		
Pain	6.1 (3.5)	0.2 (0.7)	**<0.001**
Stiffness	3.1 (1.5)	0.1 (0.2)	**<0.001**
Physical Function	17.3 (14.1)	0.2 (0.7)	**<0.001**
	KOOS		
Symptoms	61.1 (17.5)	98.6 (3.7)	**<0.001**
Pain	66.3 (15.4)	98.9 (3.5)	**<0.001**
Activities of Daily Living	74.6 (20.7)	99.7 (0.9)	**<0.001**
Sport/Recreation	57.5 (23.6)	98.8 (4.6)	**<0.001**
Quality of Life	44.1 (19.0)	98.1 (6.1)	**<0.001**
	Knee Strength		
Knee Extension (Nm)	134.9 (58.4)	109.9 (30.0)	0.100
Knee Flexion (Nm)	79.7 (39.2)	69.7 (18.8)	0.310
	Radiograph Information (K-L Scale)		
Median KL grade (SYMP)	II		
Median KL grade (CONTRA)	I		
# Participants with same KL-grade bilaterally	10/20		

No KOOS information was provided for the contra-lateral limb of the OA group, however it was recorded that 4 MOA participants did self-report recent pain at the time of collection, and the median Kellgren-Lawrence grade of CONTRA was I.

Table 4.2. Mean (SD) CCI values during the three phases of stance.

	CONTRA	ASYMP
	CCI - Loading Response	
VL-LH	17.0 (13.5)	14.2 (6.3)
VM-MH	14.6 (10.2)	17.8 (16.3)
VL-LG	17.3 (9.9)	19.1 (9.9)
VM-MG	12.7 (9.1)	14.4 (7.8)
	CCI – Mid-stance	
VL-LH	6.9 (6.2)	3.9 (3.6)
VM-MH	6.1 (8.6)	4.4 (2.5)
VL-LG	10.0 (7.9)	11.5 (10.2)
VM-MG	8.0 (8.0)	6.8 (7.0)
	CCI - Terminal Stance	
VL-LH	3.9 (3.6)	4.1 (2.6)
VM-MH	3.6 (3.4)	2.5 (1.2)
VL-LG	5.7 (4.2)	4.9 (5.6)
VM-MG	4.2 (4.4)	3.2 (3.1)

Average CCIs for all four muscle pairings across the three phases of stance are shown between the two groups in Figure 4.1, and mean and SD CCI values are shown in Table 4.2. Ensemble average group waveforms for CONTRA and ASYMP are shown for the quadriceps, hamstrings, and gastrocnemii in Figure 4.2 (see Appendix A for individual subject waveforms).

A main phase effect ($p<0.001$) was identified for all CCI pairings, indicating greater co- contraction during LR compared to MID and TERM, and greater co-contraction during MID compared to TERM (LR>MID>TERM). No main group effects or interactions ($p>0.05$) were identified for any CCI pairings (Table 4.3). No significant differences were identified between CONTRA and ASYMP for both peak knee flexion and peak knee extension strength (torque). There was however an 18.5% difference

between groups in the knee extension strength, and a 12.5% difference in knee flexion strength where CONTRA>ASYMP.

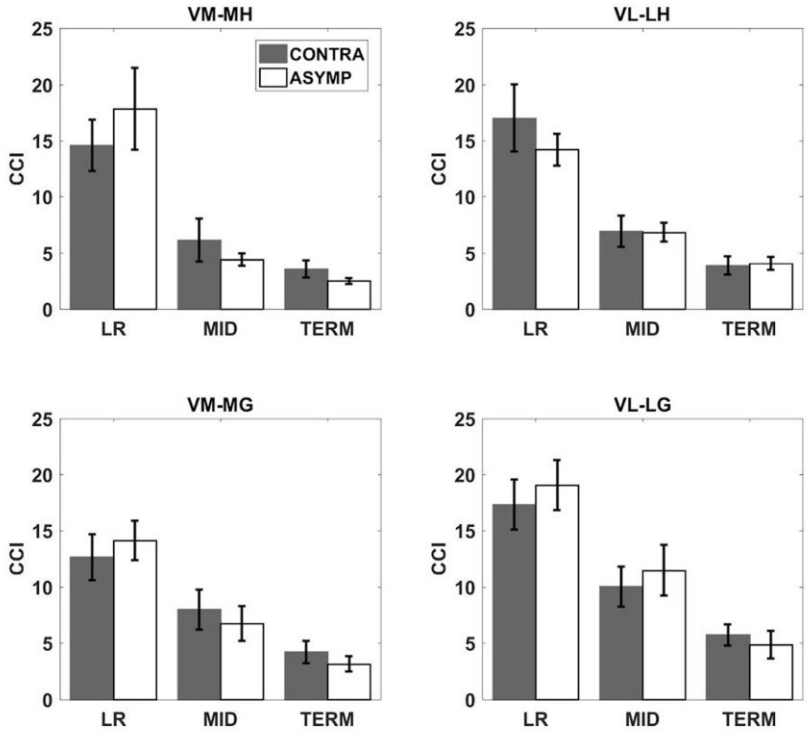


Figure 4.1. Co-contraction indices for VM-MH (top left), VL-LH (top right), VM-MG (bottom left), and VL-LG (bottom right) muscle pairings across loading response (LR), mid-stance (MID), and terminal stance (TERM) between CONTRA (grey) and ASYMP (white). Error bars represent standard error

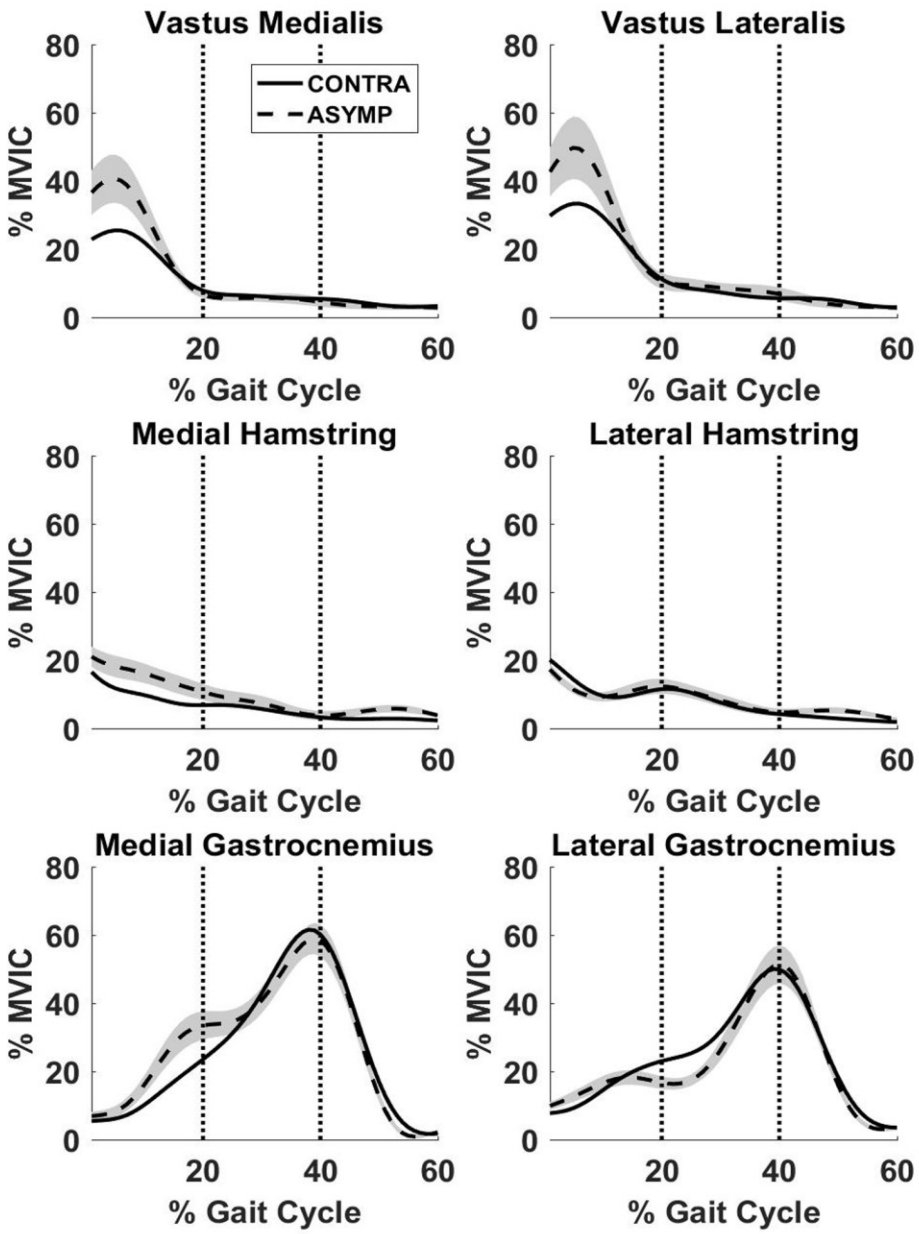


Figure 4.2. Ensemble averaged muscle activation waveforms of the quadriceps (top row), hamstrings (middle row) and gastrocnemii (bottom row) for CONTRA (solid) and ASYMP (dashed - with standard errors) legs, normalized to the gait cycle and amplitude normalized to %MVIC. Shaded area represents ASYMP standard error.

Table 4.3. Two-factor mixed model ANOVA results for CCI pairings, mean (SD) and unpaired t-test results for biomechanical variables

CCI Two-factor mixed model ANOVA (p-value)			
	Group Main Effect	**Phase Main Effect**	**Interaction**
VL-LH	0.683	**<0.001**	0.512
VM-MH	0.886	**<0.001**	0.314
VL-LG	0.985	**<0.001**	0.145
VM-MG	0.646	**<0.001**	0.351
Gait Biomechanics			
	CONTRA	**ASYMP**	**p-value**
Knee flexion excursion (deg)	13.9 (2.7)	15.6 (4.4)	0.135
KFA stance ROM (deg)	9.8 (3.0)	14.4 (1.4)	**0.002**
Peak KAM (Nm/kg)	0.41 (0.13)	0.32 (0.08)	**0.01**
KAM Impulse (Nm/kg*s)	0.14 (0.04)	0.10 (0.04)	**0.03**
KFM Range (Nm/kg)	0.66 (0.18)	0.86 (0.06)	**0.009**

The mean biomechanical variables calculated for ASYMP and CONTRA are shown in Table 4.3. RoM from peak stance flexion to minimum flexion during terminal stance (p=0.002) and range between peak flexion and peak extension moment (p=0.009) was reduced. Increased peak KAM (p=0.010) and KAM impulse (p=0.030) were observed in CONTRA compared to ASYMP. Differences in initial contact to peak stance flexion were not found between groups (p=0.135).

4.4 – Discussion

The findings of this study support that contra-lateral limb co-contraction during stance, as measured using the customary CCI, in individuals with moderate symptomatic knee OA was not significantly different from an asymptomatic knee during walking. Thus, the main study hypothesis was rejected. On the contrary, contra-lateral joint biomechanics were significantly different from the asymptomatic group suggesting

biomechanical changes are occurring without greater demand on the neuromuscular system to preserve contralateral joint function in moderate knee OA gait, supporting the secondary hypothesis of this study.

Individuals with MOA recorded WOMAC scores for their symptomatic limb, consistent with what is seen in previous MOA groups[10], and there were no differences between groups in age, sex balance or walking velocity. Median KL radiograph scores for CONTRA was I, which in combination with the group reporting that knee as asymptomatic, suggests there is no definite radiographic evidence of OA[107]. Additionally, CONTRA recorded peak knee extension strength and knee flexion strength 18.5% and 12.5% higher compared to ASYMP, respectively, where strength deficits are often seen in a MOA symptomatic knee[10,79]. Taken together, these data support the designation of a MOA group and factors that have been suggested to confound between group comparisons in other studies may have a minimal effect in the current work.

4.4.1 – Quadriceps-Hamstrings Co-Contraction

The hypothesis that the CONTRA would experience greater VL-LH or VM-MH CCIs compared to ASYMP is not supported by these data. Main group effects and interactions were not significant ($p>0.05$), indicating no differences occurred during any of the three phases investigated. CONTRA was generally self-reported as asymptomatic, despite half of the MOA group having the same KL grade between both knees. It was previously reported higher overall LH activation is associated with symptomatic OA[11], in comparison to asymptomatic individuals with the same KL grade, and greater and prolonged VL and LH activation are common findings in a MOA symptomatic knee[15,20,25] compared to controls. The CCI results in this study are consistent with

previous findings, where an asymptomatic knee with a KL grade of I or II would have reduced activation amplitudes in comparison to a symptomatic knee, and more comparable to an asymptomatic group.

The current study was consistent with Lewek et al. (2006)[30], who found no VL-LH or VM-MH differences between the contra-lateral limb of an OA group and controls during loading response. Metcalfe et al. (2013)[36] suggested severe OA groups experience abnormal contra-lateral joint loading through increased VL-LH and VM-MH co-contraction compared to healthy younger controls. Younger healthy adults exhibit reduced quadriceps-hamstrings co-contraction[37] and lower overall activation magnitudes in individual muscles[38] compared to older healthy adults during walking, and is likely responsible for these differences. The current investigation suggests VL-LH and VM-MH co-contraction is similar between CONTRA and ASYMP during three stance phases of the gait cycle. Given the role of the quadriceps and hamstrings to provide knee stability during walking[24], these findings suggest that these demands are not present in the contra-lateral knee.

4.4.2 – Quadriceps-Gastrocnemii Co-contraction

Main group effects and interactions were not significant ($p>0.05$) for VL-LG or VM-MG CCIs, findings which were in support of the hypothesis of this study. Previous literature has reported that no significant changes occur in LG activation between healthy asymptomatic limbs and a symptomatic MOA limb[21], and while increased VL activation may contribute to a greater VL-LG CCI in the symptomatic limb[24], this is not consistent for the contra-lateral limb in a severe OA group[30]. An interaction effect for VM-MG where CONTRA would show greater CCIs than ASYMP during LR would have

assimilated previous findings in a severe OA group[30]. Prolonged, elevated MG activation is observed in symptomatic MOA limbs during early and mid-stance compared to asymptomatic groups[10,12], which may contribute to a higher CCI during early stance in symptomatic knees. Lewek et al. (2006)[30] found these differences in the contra-lateral limb in severe OA groups. The current findings support that disease severity has implications for contra-lateral knee CCI outcomes, suggesting co-contraction alterations in CONTRA are not present in earlier stages of symptomatic OA however a transition to altered neuromuscular demands may occur as disease severity increases.

4.4.3 – Biomechanical variables

While there are no differences in muscle co-contraction between CONTRA and ASYMP, the knee is still showing altered joint function through frontal and sagittal motion and moments, suggesting these alterations may not require active compensation via the muscular to preserve knee function in MOA. KAM impulse is used in the literature as a measure of medial-to-lateral compartment loading ratios during gait[34], and has been associated with medial compartment cartilage loss longitudinally[108]. Increased peak KAM and KAM impulse were observed in CONTRA compared to ASYMP in this study, supporting previous research on the contra-lateral limb in severe OA groups[36]. These data suggest the medial compartment of CONTRA is experiencing abnormal external loading compared to a healthy knee during the stance phase of the gait cycle[36]. Figure 1 illustrates that the only CCI outcome during loading response, where the demands on the knee musculature are greatest, where CONTRA>ASYMP was for VL-LH. Altered lateral hamstring activity has been related to KAM features[13], and while VL-

LH was not significant, this trend may indicate a subtle alteration to compensate for greater KAM impulse and peak.

Less dynamic sagittal motion has previously been described as a "knee stiffening strategy" as an attempt to stabilize the joint during gait[26], and has been associated with increased co-contraction of muscles surrounding the knee joint[19]. While co-contraction differences were not identified in this study, sagittal RoM during stance was reduced in CONTRA compared to ASYMP, along with less dynamic sagittal moments. Alterations in external moments have been associated with MOA symptoms[99], while less dynamic sagittal motion during stance has been associated with clinical severity, encompassed by a combination of symptomatic and radiographic severity[28]. The findings support that biomechanical compensations are occurring in the contra-lateral knee of individuals that are in the direction of those previously found for the symptomatic knee, however may not be of sufficient magnitude to trigger a neuromuscular response to maintain joint function in this MOA group. Whether there is a transition point as symptomatic knee OA worsens, remains to be fully determined.

4.4.4 – Limitations

Some considerations had to be made when interpreting EMG results of this study. While there are no differences between CONTRA and ASYMP in any CCIs, it is important to note that using a CCI results in a significant loss of information. CCIs do not highlight individual muscle activity, and only one metric is used to describe simultaneous relative muscle activation over 20% of the gait cycle. It is possible that individual muscle waveforms are entirely different between groups, while CCIs are identical[24]. CCIs were however still used as the current existing previous literature looking at contra-lateral knee

in severe groups[30,36] also uses this metric and it allowed comparisons to be made. Individual muscle waveforms (Figure 4.2) highlight that CONTRA appears to have reduced activation amplitudes compared to ASYMP in the quadriceps and MH, though these are not highlighted in the CCI data. Extracting discrete variables from knee motion and moment waveforms also do not capture all alterations that may be occurring. Use of a pattern recognition technique such as Principal Component Analysis, as has been used previously for biomechanical and EMG analyses of treadmill walking[92] is suggested for future use, in order to fully capture amplitude, temporal, and pattern related differences that may be present in EMG and biomechanical waveforms.

During the MVICs, CONTRA was 18.5% and 12.5% stronger than ASYMP for knee extension and flexion, respectively, which may impact amplitude differences and make amplitude-dependent EMG results like a CCI difficult to interpret and explain, where on Figure 4.2, the CONTRA quadriceps and MH activations were lower than ASYMP. Limitations regarding EMG amplitudes can be addressed by matching groups for knee flexion and extension strength in future investigations or considering analysis techniques that do not rely on amplitude specific features.

4.5. Conclusion

The results of this study suggest that altered co-contraction is not present in CONTRA of individuals with MOA. In addition, increased frontal plane moments and less dynamic sagittal motion and moments observed in CONTRA. These findings suggest biomechanical changes are occurring, likely as a compensation for the symptomatic knee, however without greater demand on the neuromuscular system to preserve contralateral joint function in moderate knee OA gait.

Chapter Five – Inter-limb RMS differences for co-contraction in an asymptomatic healthy group

5.1 – Introduction

Pathological conditions such as knee osteoarthritis (OA) can have a significant impact on knee muscle co-contraction patterns during walking[13,16,24] given the altered joint structure and pain associated with this disease. To date, much of this understanding has been derived from comparisons between individuals with healthy asymptomatic joints and individuals with OA joints. The assumption is made in these studies that in an asymptomatic group, the two limbs are behaving similarly and any differences between a randomly chosen limb and that of a pathological limb are a result of disease or injury, and not random error due to inter-limb differences. Unfortunately, there has been little attention paid to understanding the differences in muscle activation that would be expected between limbs in a healthy asymptomatic group and whether between limb differences are in fact of a similar magnitude to between group differences previously shown.

Evidence quantifying the natural between-limb muscle activation variability in a healthy group is limited, and this leaves a significant gap in our knowledge as we try to identify significant changes between healthy and pathological gait. Using a biomechanical analysis, Lathrop-Lambach et al. (2013)[81] found significant asymmetries in peak net external knee moments (flexion and adduction), where more than half of their sample of healthy asymptomatic individuals exceeded a 10% asymmetry. To our knowledge, no previous studies have quantified absolute inter-limb differences in asymptomatic groups for knee muscle activation using the co-contraction index (CCI),

the most widely used index in knee OA gait literature pertaining to muscle co-contraction. These data will assist to provide a foundation to interpret the CCI, previously employed in knee OA gait investigations and for future work in this novel area of study.

The purpose of this brief report was to quantify the inter-limb differences of four main co-contraction indices (CCIs) in an asymptomatic group of individuals, who were age matched to MOA groups previously reported in the literature[10,17,69].

5.2 – Methods

5.2.1 – Participants

Twenty asymptomatic individuals were recruited from the local area using email, poster advertising, social media and word of mouth. Participants were not eligible if they reported any history of cardiovascular, neurological or musculoskeletal disease, or lower limb pain or injury within the past year. All participants provided written informed consent, approved by the local institutional ethics review board, for gait analysis procedures.

5.2.2 – Preparation

A standardized protocol was followed for preparation and acquisition of surface electromyography (EMG) data, in accordance with the previously accepted Surface EMG for the Non-Invasive Assessment of Muscles (SENIAM) guidelines. Surface EMG recordings were amplified and bipolar skin-surface electrodes (3M^{TM} Red Dot^{TM}, Repositionable Monitoring Electrodes, St. Paul, MN; Ag/AgCl, 10mm diameter, 0.72cm^2 surface area, 30mm inter-electrode distance) were affixed to the skin over the knee joint muscle of interest including vastus lateralis (VL), medialis (VM) as well as the medial

(MG) and lateral (LG) gastrocnemius and medial (MH) and lateral (LH) hamstrings. Guidelines presented by SENIAM were followed to approximate each muscle belly location, and electrode placements were verified for quality and crosstalk with manual muscle testing[90].

5.2.3 – Protocol

Participants walked barefoot along a GAITRite™ portable pressure sensitive walkway (CIR Systems, Inc., Franklin, NJ) at least 15-20 times to determine their self-selected speed. Participants were then asked to walk barefoot on a dual-belt R-Mill instrumented treadmill (Motekforce Link, Culemborg, the Netherlands) at their self-selected speed (determined from the GAITRite™ instrumented walkway) for ~8 minutes. The first five minutes of walking were used for treadmill acclimatization[92]. Surface EMG and ground reaction forces and moments at 2000Hz were simultaneously collected for 20 seconds through Qualisys Track Manager V2.10 (QTM) at the end of the 6th minute of walking.

A one-second subject bias trial was collected with the participant lying supine and relaxed on a therapy bed. A HUMAC®/NORM™ (Computer Sports Medicine, Inc., Stoughton, MA) Testing and Rehabilitation System was used to complete the knee flexor and extensor Maximum Voluntary Isometric Contraction exercises (MVICs). Two, three-second maximum effort knee flexion and knee extension trials were performed with a standardized 40-second rest occurred between the two reps of each exercise. Surface electromyography was collected simultaneously. Two, three second repetitions of standing plantarflexion were also performed on each limb[95].

5.2.4 – Data Processing

Electromyographic and strength data were processed in a custom program written in Matlab™ R2015a (The Mathworks Inc., Natick, Massachusetts, USA). A 500-ms moving average algorithm was used on the gravity-corrected torque values collected during knee extension and knee flexion MVICs. All raw EMG data was corrected for subject bias and gains and filtered as described in previous literature[38]. Maximum EMG amplitudes were calculated using methods previously described by Hubley-Kozey et al. (2006)[14]. All EMG waveforms from gait trials were amplitude normalized to the maximum amplitude values (%MVIC) for each muscle.

All electromyography waveforms were time normalized to a full gait cycle (initial contact to initial contact (IC) using a 30N vertical ground reaction force threshold. Between 13 and 18 consecutive strides taken over the 20-second trial were ensemble averaged for each leg. CCIs were calculated for four pairings (VL-LH, VM-MH, VL-LG, VM-MG) using the equation previously described[19,24] to represent loading response (LR; 1-20%), mid-stance (MID; 21-40%) and terminal stance (TERM; 41-60%) phases of the gait cycle of the left and right leg:

$$CCI = \frac{1}{20}\sum_{i=1}^{20}\left[\frac{lower\ EMG_i}{higher\ EMG_i}\ x\ (lower\ EMG_i + higher\ EMG_i)\right]$$

The absolute inter-limb RMS difference was calculated between the CCIs of both legs for each interval, representing the average between-limb difference during each phase of the gait cycle (see equation 2 in Chapter 3). The RMS difference was also calculated between the right and left limbs for maximum gravity corrected knee extension and flexion torque.

5.3 – Results

Demographics, walking velocity, and knee strength are shown on Table 5.1. The group was on average, 61 (±7) years old, with a BMI of 23.4 (±3.1). Knee extension and flexion peak torque values for the stronger and weaker limbs were consistent with what has previously been reported in an asymptomatic group [14].

Table 5.1 – Group demographics, WOMAC scores, and peak knee torque

	Asymptomatic group (n=20)	
Age	61 (7)	
Male (Female)	9 (11)	
BMI (kg/m^2)	23.4 (3.1)	
Walking Velocity (m/s)	1.17 (0.12)	
	Knee Strength (Nm)	
	Stronger limb	*Weaker Limb*
Knee Extension	116 (32)	105 (28)
Knee Flexion	72 (17)	69 (20)

The absolute inter-limb RMS differences of the CCIs during the loading response, mid-stance and terminal stance are shown in Table 5.2. During loading response, the VM-MH reported the highest inter-limb difference (9.3 ± 8.5), followed by the VL-LH (8.1 ± 7.9), VL-LG (6.4 ± 4.6) and VM-MG (5.5 ± 6.0). During mid-stance differences were 5.3 (± 5.5) for the VL-LG, 5.1 (± 7.0) for the VM-MG, 4.7 (±5.2) for the VL-LH, and 2.0 (±1.6) for the VM-MH. Knee extension torque had an inter-limb RMS difference of 12 (±12) and flexion torque differed by 7 (±4).

Table 5.2. Absolute inter-limb RMS differences during the three phases for the four CCI pairings, as well as maximum strength (torque) RMS differences in asymptomatic group.

	Inter-limb RMS Differences		
	Loading Response	*Mid-stance*	*Terminal Stance*
VL-LH	8.1 (7.9)	4.7 (5.2)	1.5 (1.4)
VM-MH	9.3 (8.5)	2.0 (1.6)	1.6 (2.1)
VL-LG	6.4 (4.6)	5.3 (5.5)	2.6 (2.5)
VM-MG	5.5 (6.0)	5.1 (7.0)	2.9 (3.8)
	Knee Strength (Torque)		
Knee Extension (Nm)	12 (12)		
Knee Flexion (Nm)	7 (4)		

5.4 – Discussion

The purpose of this brief report was to quantify the inter-limb differences of four main co-contraction indices in an asymptomatic group of individuals. These magnitudes of difference help us to determine clinically relevant differences in co-contraction between pathological and healthy knees. Some notable between-limb RMS differences were found. The average inter-limb RMS difference during loading response was 7.4 for the four CCI pairings. It was reduced to 4.3 during mid-stance and 2.2 during terminal stance. The VM-MH and VL-LH CCIs reported greater inter-limb RMS differences compared to the VM-MG and VL-LG CCIs during loading response, and the inverse occurred during mid-stance and terminal stance. These results were expected based on the equation above, as the activation amplitudes of the quadriceps and hamstrings are increased during loading response, and the gastrocnemius activation amplitudes are increased during mid- and terminal stance, which would allow for more between-limb variability in activation amplitudes.

Previous literature investigating co-contraction differences between typical and pathological gait as a result of a chronic condition (such as knee OA) uses a variety of EMG processing and CCI calculation methods. Differences in amplitude normalization techniques are apparent, ranging from peak task normalization[70] to MVIC normalization [19,24,91]. It has also been common to calculate CCIs from 100ms prior to IC to peak knee adduction moment[19,24] or knee flexion angle[16], though weight acceptance has also been previously defined as the first 20% of the gait cycle[23].

This paper provides a reference for past and future investigations trying to understand pathological gait through the use of CCI metrics on MVIC normalized EMG data. Hubley-Kozey et al. (2009)[24] found significant progressive increases in co-contraction from asymptomatic to MOA, and moderate to severe OA groups during weight acceptance (defined as 100ms before initial contact to peak KAM). The magnitudes of those group differences were not reported, and they may not be beyond the natural between-limb CCI differences quantified in this report. Zeni et al (2010)[23] reported an 11.7 CCI difference for loading response (1-20% gait cycle) between MOA and asymptomatic groups for a VL-MH pairing[23], which is greater than but comparable to the RMS seen for both VL-LH and VM-MH pairings in this study. In this report, loading response defined as 1-20% of the gait cycle, and some variability may occur when this phase varies as commonly used gait features such as peak KAM can occur at any point in the gait cycle. Caution should be taken when comparing CCI differences to those in this report, depending on how the phases of the gait cycle are defined and how CCIs are calculated. These values represent the absolute difference between two limbs during each phase of stance, and do not account for directional changes between the higher and lesser

activated limbs, which may occur when comparing between individuals or groups. Investigations may in the future, determine whether the significant differences they are finding are beyond those seen in an asymptomatic group here, and make implications on clinically significant findings.

Chapter Six – Discussion

6.1 – Summary

The purpose of this study was to understand muscle co-contraction of the contra-lateral knee in a MOA group compared to a healthy limb, and to quantify the inter-limb co-contraction differences that occur in a healthy control group. While gait is frequently investigated in the symptomatic limb of a knee OA group, the contra-lateral limb does not receive enough attention. Individuals with symptomatic OA often report they feel they are relying on or 'overloading' their contra-lateral knee due to impairments in the symptomatic knee. High progression rates exist[7] to bilateral symptomatic OA. Previous literature investigating contra-lateral knee co-contraction has focused on individuals awaiting total joint arthroplasty or high tibial osteotomy (i.e. more severe knee symptomatic OA). This thesis work targeted a moderate knee OA group given;

1) Knee OA gait literature studying the effect of disease severity uncovered biomechanical and muscle activation pattern differences between moderate and severe knee OA gait, supporting biomechanical heterogeneity of the symptomatic leg in this disease process. Thus, given the current work, the assumption that all people with knee OA walk in a similar manner is not true and by extension, it was expected that contra-lateral joint mechanics and muscle co-contraction would also show this disparity between severity groups.

2) There is growing concern that early disease management is failing to reduce the burden of end stage disease[41]. Too common is the focus of this intervention targeting the symptomatic knee both in early and late stages.

> As stated in this thesis, bilateral disease is prevalent and common among individuals first seeking care for one knee. Focusing on a MOA group will allow us to identify any alterations at an earlier stage of the disease, providing researchers and clinicians to information pertinent to managing knee OA bilaterally.

Furthermore, many of the investigations to date, regardless of knee OA disease severity, have utilized an age matched asymptomatic group to determine OA related gait alterations. Selecting which asymptomatic leg will be utilized in this comparison is often completed through a randomization process. Regarding the CCI, studies have looked at a random asymptomatic leg to compare against the knee OA related outcome. Understanding the natural variability in co-contraction that occurs around healthy joints is important to determine whether significant differences between OA and healthy knees are clinically significant. Addressing this limitation in the current literature made up the final objective of this thesis.

Panjabi's model of joint function and stability describes the three inter-related sub-systems contributing to joint stability[9]. OA primarily involves damage to the passive osteoligamentous subsystem, and compensations should be made in the active muscular and neural systems to preserve stability and overall joint function during walking. The neuromuscular system is examined in this study through the use of surface electromyography to determine co-contraction in the contra-lateral limb of an OA group and both limbs of a healthy group, while three-dimensional motion capture and ground reaction forces are used to describe joint motion and external moments. Three separate objectives in this study are used to determine inter-group (CONTRA vs ASYMP)

differences in CCIs and joint biomechanics, and quantify inter-limb (healthy group only) CCI differences. The objectives and key findings are described below:

6.1.1 – Objective one: Co-contraction in CONTRA and ASYMP

The first objective of this thesis (Chapter 4) was to determine whether differences exist between the contra-lateral limb of a MOA group (CONTRA) and a randomly chosen limb from a control group (ASYMP) in medial and lateral quadriceps-hamstring and quadriceps-gastrocnemius CCI pairs (Rudolph et al., 2000) during loading response (1-20% gait cycle), mid-stance (21-40%), and terminal stance (41-60%). The groups were matched for age, gender-balance, and walking velocity. Previous literature has identified gender[109] and walking velocity[31] differences in gait biomechanics, and studying a cohort that is matched for these variables allows for control of variables that may potential confound our assessment of knee OA gait. The alterations found in the biomechanical variables are consistent with those previously found between an OA symptomatic limb and controls. Key CCI findings are summarized below:

Primary Thesis Objective 1:

Co-contraction

- A phase effect occurred in all four CCI pairings, including VL-LH, VL-LG, VM-MH, VM-MG (Table 4.X). Loading response (1-20% of the Gait Cycle) consistently had the greatest CCIs, followed by mid-stance (21-40% of the Gait Cycle), and finally terminal stance (41-60% of the Gait Cycle).

- No group effects or interactions were found in any CCI pairings.

- Mean group differences for each CCI over each loading phase of the gait cycle (Table 4.2) are summarized below (positive=contra-lateral OA is higher):

VL-LH

- Loading Response: 2.8 (13.0)
- Mid-stance: 3.0 (4.7)
- Terminal Stance: -0.2 (4.1)

VM-MH

- Loading Response: -3.2 (18.7)
- Mid-stance: 1.7 (9.0)
- Terminal Stance: 1.1 (3.9)

VL-LG

- Loading Response: -1.8 (14.2)
- Mid-stance: -1.5 (13.7)
- Terminal Stance: 0.8 (7.8)

VM-MG

- Loading Response: -1.7 (11.2)
- Mid-stance: 1.2 (11.6)
- Terminal Stance: 1.0 (6.0)

The specific hypothesis regarding contra-lateral co-contraction for this objective was rejected, suggesting that the contra-lateral limb of a MOA group is experiencing similar levels of co-contraction as a healthy control limb during loading response, mid-stance and terminal stance. The lack of significant differences in CCIs might be explained by the relative asymptomatic nature of the contra-lateral knee, and any other mechanical alterations may not sufficient to trigger a neuromuscular response.

No statistically significant differences were reported in any CCIs between groups, however it is important to also understand the clinical significance of the differences observed in this thesis. Objective three provides a quantified reference to the CCI differences that might be expected to occur between limbs in a healthy group.

6.1.2 – Objective two: Gait biomechanics in CONTRA and ASYMP

The second objective of this thesis was developed to assist in the interpretation of the electromyograms. While co-contraction provides information on joint loading during gait, it does not on its own create a full picture of mechanical function, which is further provided through knee joint biomechanics. Objective two determined whether sagittal and frontal plane moments and sagittal plane joint angles were different between the contra-lateral OA limb and a random knee from an asymptomatic control group, and are summarized below:

Biomechanics

- A greater net external KAM impulse occurred in the contra-lateral limb of the MOA groups compared to the random limb of a control group.
    - Difference = 0.04 Nm/kg*s

- A greater peak net external KAM occurred in the contra-lateral limb of the MOA groups compared to the random limb of a control group.
    - Difference = 0.09 Nm/kg

- Less dynamic sagittal RoM (peak flexion mid-stance to peak extension terminal stance) was present in in the contra-lateral limb of the MOA groups compared to the random limb of a control group.
    - Difference = 4.6 deg

- Less dynamic sagittal net external moment range (peak flexion moment to peak extension moment) occurred in in the contra-lateral limb of the MOA groups compared to the random limb of a control group.
    - Difference = 0.20 Nm/kg

Despite the lack of group differences in CCI results through all three phases of gait, biomechanical differences identified from Objective two suggest that the contra-lateral OA knee does have altered dynamic function. The previously summarized biomechanical differences found in the contra-lateral OA knee are consistent to alterations that have been previously reported in an OA symptomatic knee compared to

controls[28,99] and have been associated with knee OA progression[32]. Increases in KAM impulse have been suggested to indicate greater medial compartment loading[34] which may be detrimental to cartilage health[108], and peak KAM has been associated with longitudinal progression[110]. Less dynamic sagittal motion and moments have been previously described as a "stiff knee" adaptation in response to knee instability[26].

6.1.3 – Objective three: Inter-limb root-mean-square CCI differences in a healthy asymptomatic group

The third objective (Chapter 5) of this thesis quantified the inter-limb RMS differences for CCI pairings during loading response, mid-stance, and terminal stance in a healthy asymptomatic group. No specific hypotheses were made as the purpose of this chapter was to provide a clinical reference of healthy gait variability, rather than to identify significant differences between two clinically healthy limbs. Absolute between-limb differences allow us to quantify how two limbs differ without the effect of the direction in which these differences occur. Subject variability exists in whether the right or left limb is co-contracting higher. Calculating a directional mean difference would result in a reduction of the magnitude of the absolute differences reported in Chapter 5[81].

Means and standard deviations of RMS differences for each CCI over each loading phase of the gait cycle (Table 5.2) are summarized below:

VL-LH

- Loading Response: 8.1 (7.9)
- Mid-stance: 4.7 (5.2)
- Terminal Stance: 1.5 (1.4)

VM-MH

- Loading Response: 9.4 (8.5)
- Mid-stance: 2.0 (1.6)
- Terminal Stance: 1.7 (2.2)

VL-LG

- Loading Response: 6.4 (4.6)
- Mid-stance: 5.3 (5.5)
- Terminal Stance: 2.7 (2.5)

VM-MG

- Loading Response: 5.5 (6.0)
- Mid-stance: 5.1 (7.0)
- Terminal Stance: 2.9 (3.9)

Collectively, the findings from Objectives one and three in this dissertation provide information on the co-contraction in the contra-lateral limb of a MOA group compared to healthy controls. These findings provide insight into contra-lateral knee joint function and extend the current understanding of knee OA gait mechanics in three ways.

First, it allows us to better understand mechanical function during gait in a group of individuals with moderate unilateral symptomatic OA. As it has been previously found muscle co-contraction is elevated or prolonged in more severe groups[36], this is not seen in a MOA group and therefore something else must occur between these two states to trigger that change. Increased KAM impulse has previously been found in an asymptomatic contra-lateral knee compared to controls[36] and may be either compensation for the symptomatic limb or due to early structural changes within the joint.

Secondly, it provides information on the role of pain in altered gait mechanics. The OA group in this study is not self-reporting pain in their contra-lateral knee, and altered gait mechanics, including changes in frontal and sagittal plane moments[111], have

found to be associated longitudinally with self-reported pain reduction. Astephen et al. (2016)[99] also identified significant differences in RMS muscle activation amplitudes for the VM, VL and LH between symptomatic and asymptomatic knees with a KL grade of II, which may be indicative of greater co-contraction in the symptomatic knee despite the similar structural severity. Instability may also contribute to altered joint mechanics. Increased co-activation around the symptomatic joint has primarily been suggested as a stiffening strategy associated with increased medial joint laxity[19], which may not be occurring at this stage. In Panjabi's model, alterations to the neural and muscular sub-systems are thought to result from damage to the passive sub-system associated with OA. The contra-lateral knee in this group was asymptomatic and therefore only the disease component of OA was present. It is suggested muscle co-contraction may be more directly tied to symptoms in the contra-lateral knee, and CCI alterations are in response to the manifestation of the illness component at a later stage of the disease.

Finally, it allows us to look at between-group CCI differences with respect to the natural inter-limb differences that are seen in healthy individuals, and to determine whether any between-group differences are greater than that which can be normally found between the two limbs of a healthy individual, which will be discussed further in the next section.

6.2 – Implications

Table 6.1 provides information on the magnitude of the CCI differences between CONTRA and ASYMP relative to the between-limb RMS differences quantified in Objective three. For a complete description of the magnitude of these differences, refer to Tables 4.2 and 5.2.

Table 6.1. CONTRA-ASYMP CCI magnitude differences compared to ASYMP inter-limb RMS CCI differences. ↓ = CONTRA-ASYMP CCI difference is smaller.

	Loading Response	Mid stance	Terminal Stance
VL-LH	↓	↓	↓
VM-MH	↓	↓	↓
VL-LG	↓	↓	↓
VM-MG	↓	↓	↓

The inter-group CCI differences from Objective one were smaller than the inter-limb RMS differences found in Objective three for all CCI pairings and during all loading phases of gait. These results suggest the co-contraction observed in the contra-lateral OA limb is neither statistically nor clinically significant compared to a healthy control limb, and that co-contraction does not play a significant role to contra-lateral OA development at this stage. It does however appear there is a response in the passive subsystem to the early structural changes that are occurring in the contra-lateral limb of a MOA group shown through joint biomechanics. 3D kinematic and kinetic differences were observed in the contra-lateral limb compared to healthy controls, suggesting that joint motion and external loading is altered at an early/pre-disease stage while CCIs are not. The increased frontal plane moment variables (Table 4.3) are consistent with those seen between symptomatic OA and asymptomatic knees[34,99], and have been associated with disease progression longitudinally[32,35]. Changes in frontal and sagittal moments occurred in opposite directions, which raises the question of whether the external load is actually altered. Increases in peak KAM has been associated with femoral cartilage loss longitudinally[35], while increases in peak KFM have been associated with tibial cartilage loss[35]. It can be suggested that each measure independently impacts the structural health of the joint surface, and altered KAM measures may still have a negative impact on longitudinal health despite the reduced KFM seen in Objective two.

The primary focus of this dissertation was to investigate co-contraction in the contra-lateral limb of a MOA group. This study provides information on knee muscle activation and joint biomechanics in contra-lateral joint function. While these data do not provide enough information to make implications on disease progression, it is observable that the contra-lateral knee is behaving differently than that of a healthy asymptomatic individual, even if not from an EMG co-contraction perspective.

6.3 – Limitations and Future Directions

In the last 10 years, there have been studies on contra-lateral joint function in regards to muscle activation on more severe OA groups[30,36,84]. This dissertation provides information on contra-lateral function in a MOA group, as well as a reference for what magnitudes of differences may or may not be clinically significant. There are however key limitations that stem from the use of surface EMG and the calculation of a CCI, which are listed below:

6.3.1 – Limitations

1. The use of a CCI over 20% phase of the gait cycle results in a significant loss of information on the individual muscle activity within that phase. CCIs provide information on simultaneous activation between two paired muscles surrounding a joint. A high CCI indicates high levels of activations between both muscles, while a low CCI indicates either low simultaneous activation or selective activation of one muscle over the other. CCIs were chosen despite these limitations as the previous works investigating the contra-lateral knee in severe OA groups[30,36] also focus on this metric, and the next step was to determine whether the group differences when using a MOA were different from those

observed in studies focusing on severe OA. As a result of the limitations of CCIs, individual muscle waveforms were provided in this dissertation (Figure 4.2) to allow implications to be made on individual muscle contributions.

2. When using a cross-sectional design, results do not allow us to determine cause and effect. Several confounding variables can affect gait biomechanics and muscle activation in addition to knee OA, including age[38], gender disparity[112], and walking velocity[31]. In this study however, the inclusion and exclusion criteria as well as matching for age, gender disparity and walking velocity allow us at the best of our ability to control for the effect these variables may have on results[31,109].

3. Knee radiographs were not completed on the asymptomatic control group, and as a result, any evidence of structural OA within the joints of this group is unknown. It has been reported that 3.9% of asymptomatic individuals have KL II level structural impairment at the age group used in this dissertation[113], although others have reported amounts as high as 88%[99]. There is therefore a chance some of the individuals in this group have definite structural changes, however no history of pain was reported in the contra-lateral limb, which therefore was not diagnosed with clinical OA according to ACR guidelines.

6.3.2 – Future Directions

From this study, future research questions were identified to be a logical way to move forward in this area of research. Chapter 4 was focused on identifying co-contraction differences between the contra-lateral OA limb and a control group, but

several other comparisons can be made to provide additional information on the dynamic function of the contra-lateral limb at this stage, and when in the disease process future alterations may occur. Questions that may help with this are outlined in the following sections:

Future Direction One

Chapter 4 provided information on muscular co-contraction surrounding the knee during gait in the contra-lateral limb. No significant differences were found between the contra-lateral OA limb and controls, but the waveforms shown in Figure 4.2 suggest some changes may be occurring. No statistical testing was performed on the individual muscle waveforms, and the next step would be to investigate the activation waveform features in the contra-lateral limb of a MOA group compared to healthy controls using a pattern recognition technique frequently used in the last 10 years[32,86,112] called Principal Component Analysis. Identifying and comparing specific waveform features for each individual muscle will allow us to expand our knowledge on whether neuromuscular changes may be occurring in the contra-lateral limb compared to a control group, beyond the scope of co-contraction.

Future Direction Two

The information provided by Chapter 4 was from a comparison between a group with moderate symptomatic unilateral knee osteoarthritis and asymptomatic controls, where the median KL score was II in the symptomatic limb and I in the contra-lateral limb of the OA group. While no differences in CCIs were found in this group, previous increased CCIs have been reported in more severe OA groups, who may be more

progressed in the contra-lateral knee. The question is formed "Is co-contraction in the contra-lateral limb specific to ipsilateral knee OA severity, and is there a threshold where CCIs become elevated in the contra-lateral limb?" Do individuals with a contra-lateral KL grade of II actually have higher CCIs than those with a 0 or I? A future step in this research would involve increasing the sample size of the OA group, classifying the OA group based on KL score in the contra-lateral limb, and performing a CCI comparison based on severity. This information can provide health care professionals with a threshold of whether co-contraction in the contra-lateral limb needs to be addressed based on radiographs, regardless of pain.

Future Direction Three

Objective two suggests that some biomechanical alterations are taking place in the contra-lateral limb, even though co-contraction is not yet significant. Longitudinal studies have recently been developed in the symptomatic limb to determine baseline characteristics associated with disease progression, and there is a need for the same to be done in the contra-lateral knee. Future work to determine whether any of these biomechanical alterations this early in the disease process are associated with longitudinal bilateral OA progression would be clinically beneficial. This information would provide direction for the implementation of strategies to prevent contra-lateral OA progression prior to symptom onset.

6.4 – Concluding Remarks

Osteoarthritis is a chronic, debilitating disease that affects an individual's ability to perform activities of daily living, and can affect quality of life[42]. There is currently a

high prevalence of total knee arthroplasties, the only treatment for end-stage OA[114], and a moderate risk for contra-lateral TKA within 10 years of the first replacement[8]. Through loss of work production and treatment, OA places a large economic burden nationally[3] and TKA incidence is expected to continue to increase. With such a high progression rate to contra-lateral symptomatic OA[7], it is important to understand mechanical function in the contra-lateral limb before symptom onset. Information on function in the contra-lateral limb can have clinical implications for individuals with unilateral symptomatic OA, and rehabilitation strategies can be implemented to target the contra-lateral as well as the symptomatic knee to delay or prevent bilateral disease progression.

In conclusion, this dissertation provides important information on contra-lateral knee joint function in individuals with moderate unilateral symptomatic OA, and whether CCI differences seen in past, future and the current study are beyond that which may be seen in a healthy asymptomatic group. The results of this study have the potential to contribute to rehabilitation strategies targeting unilateral symptomatic OA, to bring attention to the importance of maintaining function in the contra-lateral knee, and to augment the results of future works investigating co-contraction in OA populations.

References

1. Kraus VB, Blanco FJ, Englund M, Karsdal MA, Lohmander LS. Call for standardized definitions of osteoarthritis and risk stratification for clinical trials and clinical use. *Osteoarthr Cartil*. 2015;23(8):1233-1241. doi:10.1016/j.joca.2015.03.036.
2. O'Donnell S, Lagace C, McRae L, Bancej C. *Life with Arthritis in Canada: A Personal and Public Health Challenge*.; 2011.
3. Bombardier, C, Hawker, G, & Mosher D. the Impact of Arthritis in Canada : Today and Over the Next 30 Years. *Arthritis Alliance of Canada*. 2011.
4. Canadian Institute of Health Information. *Hip and Knee Replacements in Canada: Canadian Joint Replacement Registry 2006 Annual Report*.; 2006.
5. Messier SP, DeVita P, Cowan RE, Seay J, Young HC, Marsh AP. Do older adults with knee osteoarthritis place greater loads on the knee during gait? A preliminary study. *Arch Phys Med Rehabil*. 2005;86(4):703-709. doi:10.1016/j.apmr.2004.05.015.
6. Shakoor N, Block JA, Shott S, Case JP. Nonrandom evolution of end-stage osteoarthritis of the lower limbs. *Arthritis Rheum*. 2002;46(12):3185-3189. doi:10.1002/art.10649.
7. Metcalfe AJ, Andersson MLE, Goodfellow R, Thorstensson CA. Is knee osteoarthritis a symmetrical disease? Analysis of a 12 year prospective cohort study. *BMC Musculoskelet Disord*. 2012;13:153. doi:10.1186/1471-2474-13-153.
8. McMahon M, Block JA. The risk of contralateral total knee arthroplasty after knee replacement for osteoarthritis. *J Rheumatol*. 2003;30(8):1822-1824. doi:0315162X-30-1822 [pii].
9. Panjabi M. The stabilizing system of the spine. Part I. Function, dysfunction, adaptation, and enhancement. *J Spinal Disord*. 1992;5(4):383-389.
10. Rutherford DJ, Hubley-Kozey CL, Stanish WD. Changes in knee joint muscle activation patterns during walking associated with increased structural severity in knee osteoarthritis. *J Electromyogr Kinesiol*. 2013;23(3):704-711. doi:10.1016/j.jelekin.2013.01.003.
11. Astephen JL, Deluzio KJ, Caldwell GE, Dunbar MJ, Hubley-Kozey CL. Gait and neuromuscular pattern changes are associated with differences in knee osteoarthritis severity levels. *J Biomech*. 2008;41(4):868-876. doi:10.1016/j.jbiomech.2007.10.016.
12. Childs JD, Sparto PJ, Fitzgerald GK, Bizzini M, Irrgang JJ. Alterations in lower extremity movement and muscle activation patterns in individuals with knee osteoarthritis. *Clin Biomech*. 2004;19(1):44-49. doi:10.1016/j.clinbiomech.2003.08.007.
13. Heiden TL, Lloyd DG, Ackland TR. Knee joint kinematics, kinetics and muscle co-contraction in knee osteoarthritis patient gait. *Clin Biomech*. 2009;24(10):833-841. doi:10.1016/j.clinbiomech.2009.08.005.

14. Hubley-Kozey CL, Deluzio KJ, Landry SC, McNutt JS, Stanish WD. Neuromuscular alterations during walking in persons with moderate knee osteoarthritis. *J Electromyogr Kinesiol*. 2006;16(4):365-378. doi:10.1016/j.jelekin.2005.07.014.
15. Lynn SK, Costigan PA. Effect of foot rotation on knee kinetics and hamstring activation in older adults with and without signs of knee osteoarthritis. *Clin Biomech*. 2008;23(6):779-786. doi:10.1016/j.clinbiomech.2008.01.012.
16. Schmitt LC, Rudolph KS. Influences on knee movement strategies during walking in persons with medial knee osteoarthritis. *Arthritis Care Res*. 2007;57(6):1018-1026. doi:10.1002/art.22889.
17. Hodges PW, van den Hoorn W, Wrigley T V., et al. Increased duration of co-contraction of medial knee muscles is associated with greater progression of knee osteoarthritis. *Man Ther*. 2016;21:151-158. doi:10.1016/j.math.2015.07.004.
18. Hubley-Kozey CL, Costello KE, Hatfield GL, Astephen-Wilson J, Stanish WD. Baseline three-dimensional knee joint biomechanics and muscle activation patterns differ between those with moderate OA who have radiographic progression versus those who do not. *Osteoarthr Cartil*. 2014;22(2014):S83. doi:10.1016/j.joca.2014.02.165.
19. Lewek MD, Rudolph KS, Snyder-Mackler L. Control of frontal plane knee laxity during gait in patients with medial compartment knee osteoarthritis. *Osteoarthr Cartil*. 2004;12(9):745-751. doi:10.1016/j.joca.2004.05.005.
20. Rutherford DJ, Hubley-Kozey CL, Stanish WD. The neuromuscular demands of altering foot progression angle during gait in asymptomatic individuals and those with knee osteoarthritis. *Osteoarthr Cartil*. 2010;18(5):654-661. doi:10.1016/j.joca.2010.01.005.
21. Rutherford DJ, Hubley-Kozey CL, Stanish WD, Dunbar MJ. Neuromuscular alterations exist with knee osteoarthritis presence and severity despite walking velocity similarities. *Clin Biomech*. 2011;26(4):377-383. doi:10.1016/j.clinbiomech.2010.11.018.
22. Rudolph KS, Axe MJ, Snyder-Mackler L. Dynamic stability after ACL injury: who can hop? *Knee Surg Sports Traumatol Arthrosc*. 2000;8(5):262-269. doi:10.1007/s001670000130.
23. Zeni JA, Rudolph K, Higginson JS. Alterations in quadriceps and hamstrings coordination in persons with medial compartment knee osteoarthritis. *J Electromyogr Kinesiol*. 2010;20(1):148-154. doi:10.1016/j.jelekin.2008.12.003.
24. Hubley-Kozey CL, Hill NA, Rutherford DJ, Dunbar MJ, Stanish WD. Co-activation differences in lower limb muscles between asymptomatic controls and those with varying degrees of knee osteoarthritis during walking. *Clin Biomech*. 2009;24(5):407-414. doi:10.1016/j.clinbiomech.2009.02.005.
25. Astephen Wilson JL, Deluzio KJ, Dunbar MJ, Caldwell GE, Hubley-Kozey CL. The association between knee joint biomechanics and neuromuscular control and moderate knee osteoarthritis radiographic and pain severity. *Osteoarthr Cartil*. 2011;19(2):186-193. doi:10.1016/j.joca.2010.10.020.

26. Farrokhi S, O'Connell M, Gil AB, Sparto PJ, Fitzgerald GK. Altered Gait Characteristics in Individuals With Knee Osteoarthritis and Self-Reported Knee Instability. *J Orthop Sport Phys Ther*. 2015;45(5):351-359. doi:10.2519/jospt.2015.5540.
27. Hodge WA, Fijan RS, Carlson KL, Burgess RG, Harris WH, Mann RW. Contact pressures in the human hip joint measured in vivo. *Proc Natl Acad Sci U S A*. 1986;83(9):2879-2883. doi:10.1073/pnas.83.9.2879.
28. Astephen JL, Deluzio KJ, Caldwell GE, Dunbar MJ. Biomechanical changes at the hip, knee, and ankle joints during gait are associated with knee osteoarthritis severity. *J Orthop Res*. 2008;26(3):332-341. doi:10.1002/jor.20496.
29. Baliunas AJ, Hurwitz DE, Ryals AB, et al. Increased knee joint loads during walking are present in subjects with knee osteoarthritis. *Osteoarthr Cartil*. 2002;10(7):573-579. doi:10.1053/joca.2002.0797.
30. Lewek MD, Scholz J, Rudolph KS, Snyder-Mackler L. Stride-to-stride variability of knee motion in patients with knee osteoarthritis. *Gait Posture*. 2006;23(4):505-511. doi:10.1016/j.gaitpost.2005.06.003.
31. Landry SC, McKean KA, Hubley-Kozey CL, Stanish WD, Deluzio KJ. Knee biomechanics of moderate OA patients measured during gait at a self-selected and fast walking speed. *J Biomech*. 2007;40(8):1754-1761. doi:10.1016/j.jbiomech.2006.08.010.
32. Hatfield G, Stanish WD, Hubley-Kozey CL. Three-dimensional knee biomechanics during gait predict knee osteoarthritis progression. *Osteoarthr Cartil*. 2013;21(2013):S22-S23. doi:10.1016/j.joca.2013.02.069.
33. Hurwitz DE, Case JP, Block JA. The knee adduction moment during gait in subjects with knee osteoarthritis is more closely correlated with static alignment than radiographic disease severity , toe out angle and pain. *J Orthop Res*. 2002;20:101-107.
34. Creaby MW. It's not all about the knee adduction moment: The role of the knee flexion moment in medial knee joint loading. *Osteoarthr Cartil*. 2015;23:1038-1040. doi:10.1016/j.joca.2015.03.032.
35. Chehab EF, Favre J, Erhart-Hledik JC, Andriacchi TP. Baseline knee adduction and flexion moments during walking are both associated with 5year cartilage changes in patients with medial knee osteoarthritis. *Osteoarthr Cartil*. 2014;22(11):1833-1839. doi:10.1016/j.joca.2014.08.009.
36. Metcalfe A, Stewart C, Postans N, Dodds AL, Holt CA, Roberts AP. The effect of osteoarthritis of the knee on the biomechanics of other joints in the lower limbs. *Bone Joint J*. 2013;95-B(3):348-353. doi:10.1302/0301-620X.95B3.30850.
37. Mian OS, Thom JM, Ardigò LP, Narici M V., Minetti AE. Metabolic cost, mechanical work, and efficiency during walking in young and older men. *Acta Physiol*. 2006;186(2):127-139. doi:10.1111/j.1748-1716.2006.01522.x.
38. Rutherford D, Baker M, Wong I, Stanish W. The effect of age and knee osteoarthritis on muscle activation patterns and knee joint biomechanics during dual belt treadmill gait. *J Electromyogr Kinesiol*. 2017;34:58-64. doi:10.1016/j.jelekin.2017.04.001.

39. Bullough PG, Jagannath A. The morphology of the calcification front in articular cartilage. Its significance in joint function. *J Bone Jt Surg Br Vol*. 1983;65-B:72-78.
40. Vanwanseele B, Lucchinetti E, Stüssi E. The effects of immobilization on the characteristics of articular cartilage: Current concepts and future directions. *Osteoarthr Cartil*. 2002;10(5):408-419. doi:10.1053/joca.2002.0529.
41. Lane NE, Brandt K, Hawker G, et al. OARSI-FDA initiative: Defining the disease state of osteoarthritis. *Osteoarthr Cartil*. 2011;19(5):478-482. doi:10.1016/j.joca.2010.09.013.
42. Pollard B, Johnston M, Dieppe P. Exploring the relationships between International Classification of Functioning, Disability and Health (ICF) constructs of Impairment, Activity Limitation and Participation Restriction in people with osteoarthritis prior to joint replacement. *BMC Musculoskelet Disord*. 2011;12(I):97. doi:10.1186/1471-2474-12-97.
43. Chen S-R, Chen C-S, Lin P-C. The effect of educational intervention on the pain and rehabilitation performance of patients who undergo a total knee replacement. *J Clin Nurs*. 2014;23(1-2):279-287. doi:10.1111/jocn.12466.
44. Hamilton DF, Howie CR, Burnett R, Simpson AHRW, Patton JT. Dealing with the predicted increase in demand for revision total knee arthroplasty: Challenges, risks and opportunities. *Bone Jt J*. 2015;97-B(6):723-728. doi:10.1302/0301-620X.97B6.35185.
45. McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthr Cartil*. 2014;22(3):363-388. doi:10.1016/j.joca.2014.01.003.
46. Spector TD, Hart DJ, Doyle D V. Incidence and progression of osteoarthritis in women with unilateral knee disease in the general population: the effect of obesity. *Ann Rheum Dis*. 1994;53(9):565-568. doi:10.1136/ard.53.9.565.
47. Finan PH, Buenaver LF, Bounds SC, et al. Discordance between pain and radiographic severity in knee osteoarthritis: Findings from quantitative sensory testing of central sensitization. *Arthritis Rheum*. 2013;65(2):363-372. doi:10.1002/art.34646.
48. Bedson J, Croft PR. The discordance between clinical and radiographic knee osteoarthritis: a systematic search and summary of the literature. *BMC Musculoskelet Disord*. 2008;9:1-11. doi:10.1186/1471-2474-9-116.
49. Felson DT, Goggins J, Niu J, Zhang Y, Hunter DJ. The effect of body weight on progression of knee osteoarthritis is dependent on alignment. *Arthritis Rheum*. 2004;50(12):3904-3909. doi:10.1002/art.20726.
50. Kellgren JH, Lawrence JS. Radiological Assessment of Osteo-Arthrosis. *Ann Rheum Dis*. 1957;16(4):494-502. doi:10.1136/ard.16.4.494.
51. Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis Rheum*. 1986;29(8):1039-1049. doi:10.1002/art.1780290816.

52. Altman RD, Fries JF, Bloch D, et al. Radiographic assessment of progression in osteoarthritis. *Arthritis Rheum*. 1987;30(11):1214-1225.
53. Emrani PS, Katz J, Kessler C, et al. Joint space narrowing and Kellgren-Lawrence progression in knee osteoarthritis. *Osteoarthr Cartil*. 2009;16(8):873-882. doi:10.1016/j.joca.2007.12.004.Joint.
54. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthosis. *Ann Rheum Dis*. 1957;16:494-502.
55. Podlipská J, Guermazi A, Lehenkari P, et al. Comparison of Diagnostic Performance of Semi-Quantitative Knee Ultrasound and Knee Radiography with MRI: Oulu Knee Osteoarthritis Study. *Sci Rep*. 2016;6(February):22365. doi:10.1038/srep22365.
56. Alizai H, Roemer FW, Hayashi D, Crema MD, Felson DT, Guermazi A. An update on risk factors for cartilage loss in knee osteoarthritis assessed using MRI-based semiquantitative grading methods. *Eur Radiol*. 2014;25(3):883-893. doi:10.1007/s00330-014-3464-7.
57. Hudelmaier M, Glaser C, Hohe J, et al. Age-related changes in the morphology and deformational behavior of knee joint cartilage. *Arthritis Rheum*. 2001;44(11):2556-2561. doi:10.1002/1529-0131(200111)44:11<2556::AID-ART436>3.0.CO;2-U.
58. Creaby MW, Bennell KL, Hunt MA. Gait differs between unilateral and bilateral knee osteoarthritis. *Arch Phys Med Rehabil*. 2012;93(5):822-827. doi:10.1016/j.apmr.2011.11.029.
59. Browning RC, Kram R. Effects of obesity on the biomechanics of walking at different speeds. *Med Sci Sports Exerc*. 2007;39(9):1632-1641. doi:10.1249/mss.0b013e318076b54b.
60. Amiri P, Hubley-Kozey CL, Landry SC, Stanish WD, Astephen Wilson JL. Obesity is associated with prolonged activity of the quadriceps and gastrocnemii during gait. *J Electromyogr Kinesiol*. 2015;25(6):951-958. doi:10.1016/j.jelekin.2015.10.007.
61. Leyland KM, Judge A, Javaid MK, et al. Obesity and the Relative Risk of Knee Replacement Surgery in Patients With Knee Osteoarthritis: A Prospective Cohort Study. *Arthritis Rheumatol*. 2016;68(4):817-825. doi:10.1002/art.39486.
62. Messier SP, Pater M, Beavers DP, et al. Influences of alignment and obesity on knee joint loading in osteoarthritic gait. *Osteoarthr Cartil*. 2014;22(7):912-917. doi:10.1016/j.joca.2014.05.013.
63. Deluzio KJ, Astephen JL. Biomechanical features of gait waveform data associated with knee osteoarthritis An application of principal component analysis. *Gait Posture*. 2007;25:86-93. doi:10.1016/j.gaitpost.2006.01.007.
64. Erhart-Hledik JC, Favre J, Andriacchi TP. New insight in the relationship between regional patterns of knee cartilage thickness, osteoarthritis disease severity, and gait mechanics. *J Biomech*. 2015;48(14):3868-3875. doi:10.1016/j.jbiomech.2015.09.033.
65. Manal K, Gardinier E, Buchanan TS, Snyder-Mackler L. A more informed evaluation of medial compartment loading: The combined use of the knee adduction and flexor moments. *Osteoarthr Cartil*. 2014;23(7):1107-1111. doi:10.1016/j.joca.2015.02.779.

66. Herzog W, Longino D, Clark A. The role of muscles in joint adaptation and degeneration. *Langenbeck's Arch Surg*. 2003;388(5):305-315. doi:10.1007/s00423-003-0402-6.
67. Soderberg GL, Cook TM. Electromyography in biomechanics. *Phys Ther*. 1984;64(12):1813-1820. http://www.ncbi.nlm.nih.gov/pubmed/6505026.
68. De Luca C. The use of surface electromyography in biomechanics. *J Appl Biomech*. 1997;13(2):135-163. doi:10.1016/j.explore.2013.08.001.
69. Liikavainio T, Bragge T, Hakkarainen M, Karjalainen PA, Arokoski JP. Gait and muscle activation changes in men with knee osteoarthritis. *Knee*. 2010;17(1):69-76. doi:10.1016/j.knee.2009.05.003.
70. Schmitt LC, Rudolph KS. Muscle stabilization strategies in people with medial knee osteoarthritis: The effect of instability. *J Orthop Res*. 2008;26(9):1180-1185. doi:10.1002/jor.20619.
71. Fitzgerald GK, Piva SR, Irrgang JJ, Bouzubar F, Starz TW. Quadriceps activation failure as a moderator of the relationship between quadriceps strength and physical function in individuals with knee osteoarthritis. *Arthritis Rheum*. 2004;51(1):40-48. doi:10.1002/art.20084.
72. Mills K, Hunt MA, Leigh R, Ferber R. A systematic review and meta-analysis of lower limb neuromuscular alterations associated with knee osteoarthritis during level walking. *Clin Biomech*. 2013;28(7):713-724. doi:10.1016/j.clinbiomech.2013.07.008.
73. Fisher NM, White SC, Yack HJ, Smolinski RJ, Pendergast DR. Muscle function and gait in patients with knee osteoarthritis before and after muscle rehabilitation. *Disabil Rehabil*. 1997;19(2):47-55. doi:10.3109/09638289709166827.
74. Lloyd DG, Buchanan TS. Strategies of muscular support of varus and valgus isometric loads at the human knee. *J Biomech*. 2001;34(10):1257-1267. doi:10.1016/S0021-9290(01)00095-1.
75. Zhang LQ, Xu D, Wang G, Hendrix RW. Muscle strength in knee varus and valgus. *Med Sci Sports Exerc*. 2001;33(7):1194-1199. doi:10.1097/00005768-200107000-00018.
76. Knarr BA, Zeni JA, Higginson JS. Comparison of electromyography and joint moment as indicators of co-contraction. *J Electromyogr Kinesiol*. 2012;22(4):607-611. doi:10.1016/j.jelekin.2012.02.001.
77. Hubley-Kozey CL, Robbins SM, Rutherford DJ, Stanish WD. Reliability of surface electromyographic recordings during walking in individuals with knee osteoarthritis. *J Electromyogr Kinesiol*. 2013;23(2):334-341. doi:10.1016/j.jelekin.2012.12.002.
78. Rudolph KS, Schmitt LC, Lewek MD. Age-Related changes in strength, joint laxity, and walking patterns: Are they related to knee osteoarthritis? *Phys Ther*. 2007;81:1422-1432. doi:10.1111/j.1467-9639.1991.tb00167.x.
79. Lewek MD, Rudolph KS, Snyder-Mackler L. Quadriceps femoris muscle weakness and activation failure in patients with symptomatic knee osteoarthritis. *J Orthop Res*. 2004;22(1):110-115. doi:10.1016/S0736-0266(03)00154-2.

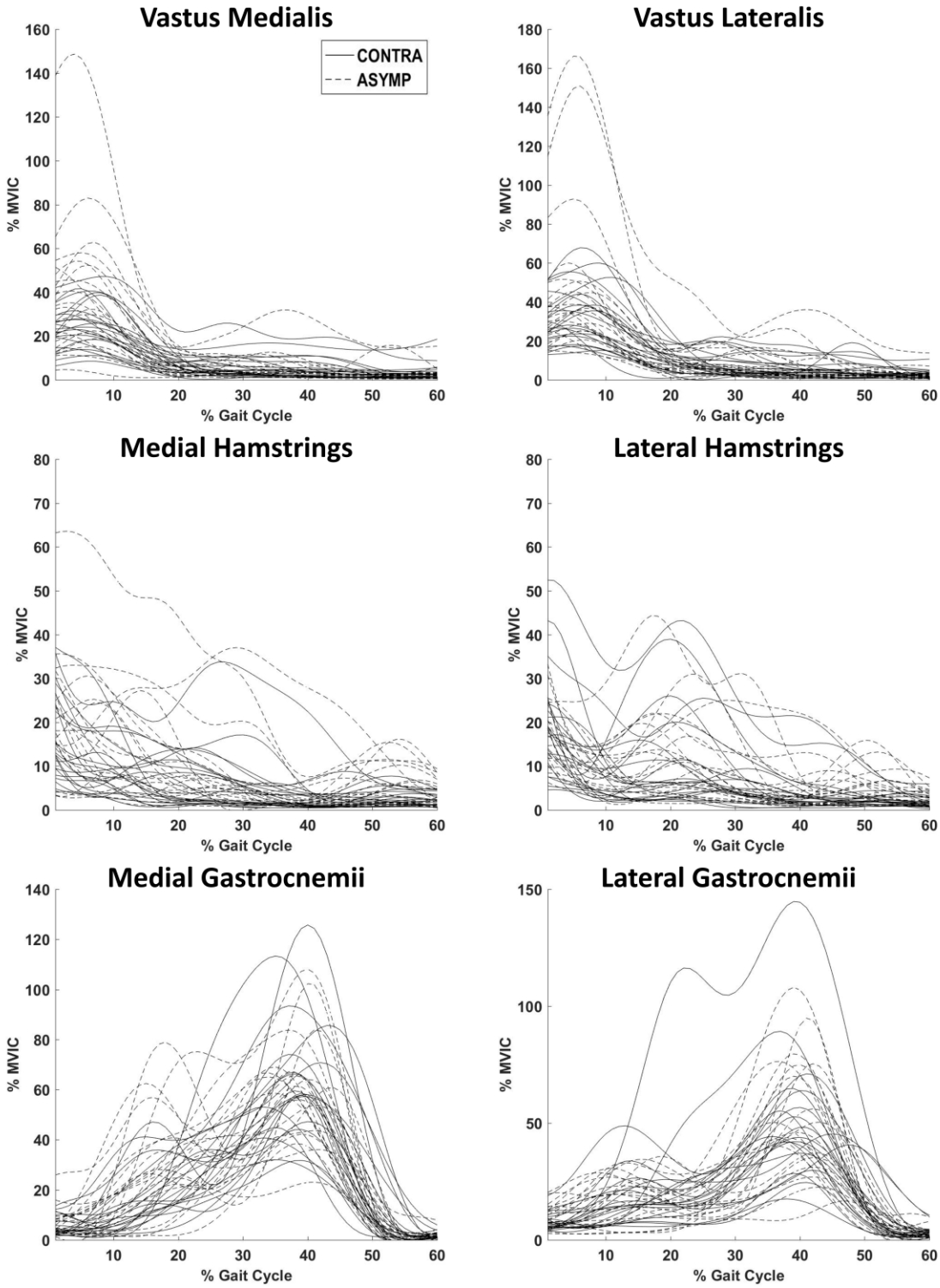
80. Mills K, Hettinga B a., Pohl MB, Ferber R. Between-limb kinematic asymmetry during gait in unilateral and bilateral mild to moderate knee osteoarthritis. *Arch Phys Med Rehabil*. 2013;94(11):2241-2247. doi:10.1016/j.apmr.2013.05.010.
81. Lathrop-Lambach RL, Asay JL, Jamison ST, et al. Evidence for joint moment asymmetry in healthy populations during gait. *Gait Posture*. 2013;40(4):526-531. doi:10.1016/j.gaitpost.2014.06.010.
82. Sadeghi H. Local or global asymmetry in gait of people without impairments. *Gait Posture*. 2003;17(3):197-204. doi:10.1016/S0966-6362(02)00089-9.
83. Worsley P, Stokes M, Barrett D, Taylor M. Joint loading asymmetries in knee replacement patients observed both pre- and six months post-operation. *Clin Biomech*. 2013;28(8):892-897. doi:10.1016/j.clinbiomech.2013.07.014.
84. Metcalfe A, Stewart C, Postans N, et al. Abnormal loading of the major joints in knee osteoarthritis and the response to knee replacement. *Gait Posture*. 2013;37(1):32-36. doi:10.1016/j.gaitpost.2012.04.018.
85. Birmingham TB, Giffin JR, Chesworth BM, et al. Medial opening wedge high tibial osteotomy: A prospective cohort study of gait, radiographic, and patient-reported outcomes. *Arthritis Care Res*. 2009;61(5):648-657. doi:10.1002/art.24466.
86. Rutherford DJ, Hubley-Kozey CL, Deluzio KJ, Stanish WD, Dunbar MJ. Foot progression angle and the knee adduction moment: a cross-sectional investigation in knee osteoarthritis. *Osteoarthr Cartil*. 2008;16(8):883-889. doi:10.1016/j.joca.2007.11.012.
87. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS)--development of a self-administered outcome measure. *J Orthop Sports Phys Ther*. 1998;28(2):88-96. doi:10.2519/jospt.1998.28.2.88.
88. McDonough AL, Batavia M, Chen FC, Kwon S, Ziai J. The validity and reliability of the GAITRite system's measurements: A preliminary evaluation. *Arch Phys Med Rehabil*. 2001;82(3):419-425. doi:10.1053/apmr.2001.19778.
89. Menz HB, Latt MD, Tiedemann A, Kwan MMS, Lord SR. Reliability of the GAITRite® walkway system for the quantification of temporo-spatial parameters of gait in young and older people. *Gait Posture*. 2004;20(1):20-25. doi:10.1016/S0966-6362(03)00068-7.
90. Winter DA, Fuglevand AJ, Archer SE. Crosstalk in surface electromyography: Theroretical and practical estimates. *J Electromyogr Kinesiol*. 1994;4(1)(1):15-26.
91. Zeni JA, Higginson JS. Gait parameters and stride-to-stride variability during familiarization to walking on a split-belt treadmill. *Clin Biomech*. 2010;25(4):383-386. doi:10.1016/j.clinbiomech.2009.11.002.
92. Rutherford D, Baker M, Wong I, Stanish W. Dual-belt treadmill familiarization: Implications for knee function in moderate knee osteoarthritis compared to asymptomatic controls. *Clin Biomech*. 2017;45(April):25-31. doi:10.1016/j.clinbiomech.2017.04.006.
93. Burden A. How should we normalize electromyograms obtained from healthy participants? What we have learned from over 25years of research. *J Electromyogr Kinesiol*. 2010;20(6):1023-1035. doi:10.1016/j.jelekin.2010.07.004.

94. Burden AM, Trew M, Baltzopoulos V. Normalisation of gait EMGs: A re-examination. *J Electromyogr Kinesiol*. 2003;13(6):519-532. doi:10.1016/S1050-6411(03)00082-8.
95. Rutherford DJ, Hubley-Kozey CL, Stanish WD. Maximal voluntary isometric contraction exercises: A methodological investigation in moderate knee osteoarthritis. *J Electromyogr Kinesiol*. 2011;21(1):154-160. doi:10.1016/j.jelekin.2010.09.004.
96. Raez MBI, Hussain MS, Mohd-Yasin F, Reaz M, Hussain MS, Mohd-Yasin F. Techniques of EMG signal analysis: detection, processing, classification and applications. *Biol Proced Online*. 2006;8(1):11-35. doi:10.1251/bpo115.
97. Soderberg GL. *Selected Topics in Surface Electromyography for Use in the Occupational Setting: Expert Perspectives*. Vol 24.; 1993. doi:10.1016/0003-6870(93)90098-T.
98. Konrad P. *The ABC of EMG*.; 2005. doi:10.1016/j.jacc.2008.05.066.
99. Astephen Wilson J, Hatfield G, Stanish WD, Hubley-Kozey C. Asymptomatic and symptomatic individuals with the same radiographic evidence of knee osteoarthritis walk with different knee moments and muscle activity. *J Orthop Res*. 2016. doi:10.1002/jor.23465.
100. Grood ES, Suntay WJ. A joint coordinate system for the clinical description of three-dimensional motions: application to the knee. *J Biomech Eng*. 1983;105(2):136-144. doi:10.1115/1.3138397.
101. Vaughan C, Davis B, O'Connor J. *Dynamics of Human Gait*. Second Edi. Capetown, South Africa: Kiboho Publishers; 1999.
102. Moisio KC, Sumner DR, Shott S, Hurwitz DE. Normalization of joint moments during gait: A comparison of two techniques. *J Biomech*. 2003;36(4):599-603. doi:10.1016/S0021-9290(02)00433-5.
103. Dunphy C, Casey S, Lomond A, Rutherford D. Contralateral pelvic drop during gait increases knee adduction moments of asymptomatic individuals. *Hum Mov Sci*. 2016;49:27-35. doi:10.1016/j.humov.2016.05.008.
104. Guillemin F, Rat AC, Mazieres B, et al. Prevalence of symptomatic hip and knee osteoarthritis: A two-phase population-based survey1. *Osteoarthr Cartil*. 2011;19(11):1314-1322. doi:10.1016/j.joca.2011.08.004.
105. Sharma L, Hurwitz DE, Thonar EJA, et al. Knee adduction moment, serum hyaluronan leve, and disease severity in medial tibiofemoral osteoarthritis. *Arthritis Rheum*. 1998;41(7):1233-1240.
106. Brandt K, Fife RS, Braunstein EM, Katz B. Radiographic grading of the severity of knee osteoarthritis: Relation of the kellgren and lawrence grade to a grade based on joint space narrowing, and correlation with arthroscopic evidence or articular cartilage degeneration. *Arthritis Rheum*. 1991;34(11):1381-1386.
107. Neogi T, Felson D, Niu J, et al. Association between radiographic features of knee osteoarthritis and pain: results from two cohort studies. *BMJ*. 2009;339(7719):b2844. doi:10.1136/bmj.b2844.

108. Bennell KL, Bowles K-A, Wang Y, Cicuttini F, Davies-Tuck M, Hinman RS. Higher dynamic medial knee load predicts greater cartilage loss over 12 months in medial knee osteoarthritis. *Ann Rheum Dis*. 2011;70(10):1770-1774. doi:10.1136/ard.2010.147082.
109. Mckean KA, Landry SC, Hubley-kozey CL, Dunbar MJ, Stanish WD, Deluzio KJ. Gender differences exist in osteoarthritic gait. *Clin Biomech*. 2007;22:400-409. doi:10.1016/j.clinbiomech.2006.11.006.
110. Miyazaki T, Wada M, Kawahara H, Sato M, Baba H, Shimada S. Dynamic load at baseline can predict radiographic disease progression in medial compartment knee osteoarthritis. *Ann Rheum Dis*. 2002;61:617-622. doi:10.1136/ard.61.7.617.
111. Tang ACW, Tang SFT, Hong WH, Chen HC. Kinetics features changes before and after intra-articular hyaluronic acid injections in patients with knee osteoarthritis. *Clin Neurol Neurosurg*. 2015;129(S1):S21-S26. doi:10.1016/S0303-8467(15)30007-X.
112. Phinyomark A, Osis ST, Hettinga BA, Kobsar D, Ferber R. Gender differences in gait kinematics for patients with knee osteoarthritis. *BMC Musculoskelet Disord*. 2016;17(1):157. doi:10.1186/s12891-016-1013-z.
113. Laxafoss E, Jacobsen S, Gosvig KK, Sonne-Holm S. Case definitions of knee osteoarthritis in 4,151 unselected subjects: Relevance for epidemiological studies: The copenhagen osteoarthritis study. *Skeletal Radiol*. 2010;39(9):859-866. doi:10.1007/s00256-009-0856-x.
114. Canadian Institute of Health Information. *Hip and Knee Replacements in Canada: Canadian Joint Replacement Registry 2015 Annual Report*.; 2015. https://secure.cihi.ca/free_products/CJRR_2015_Annual_Report_EN.pdf.

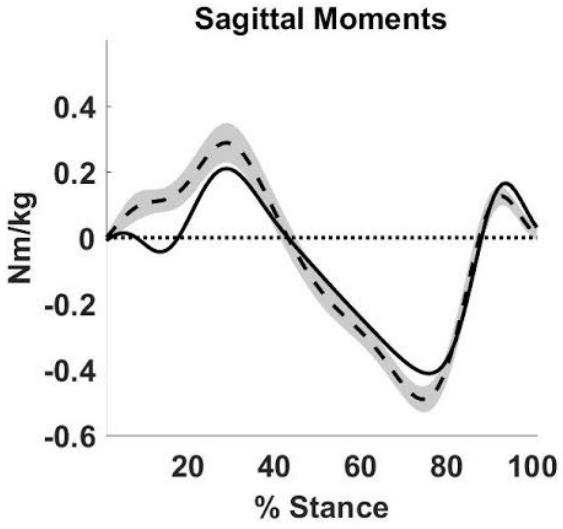
Appendix A – Inter-subject variability of processed and MVIC normalized EMG waveforms for the contra-lateral OA and random asymptomatic limbs.

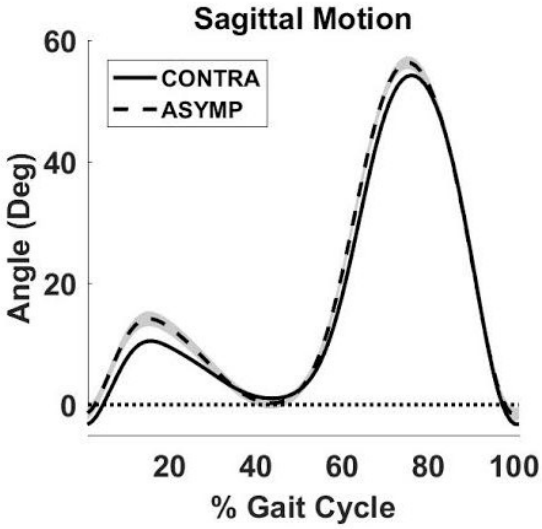
The waveforms provided in this appendix provide insight to the inter-subject variability of both the MOA and asymptomatic groups for each muscle through the individual subject waveforms.

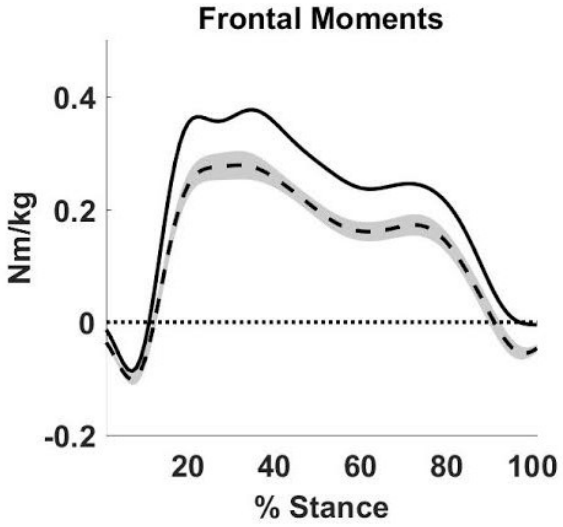

Vastus Medialis
CONTRA
ASYMP
% MVIC
% Gait Cycle
Vastus Lateralis
% MVIC
% Gait Cycle
Medial Hamstrings
% MVIC
% Gait Cycle
Lateral Hamstrings
% MVIC
% Gait Cycle
Medial Gastrocnemii
% MVIC
% Gait Cycle
Lateral Gastrocnemii
% MVIC
% Gait Cycle

Appendix B – Kinematic and external moment waveforms from the contra-lateral OA and random asymptomatic knees

Discrete features from sagittal kinematic and sagittal and frontal external moment waveforms are provided in Table 4.3, and significant differences were reported in several features. Ensemble averaged waveforms for sagittal kinematic and sagittal and frontal external moments aid to visually interpret the key biomechanical findings reported in this dissertation, including less dynamic flexion-extension angles and external moments during stance, and increased peak KAM and KAM impulse in the OA contra-lateral knee.

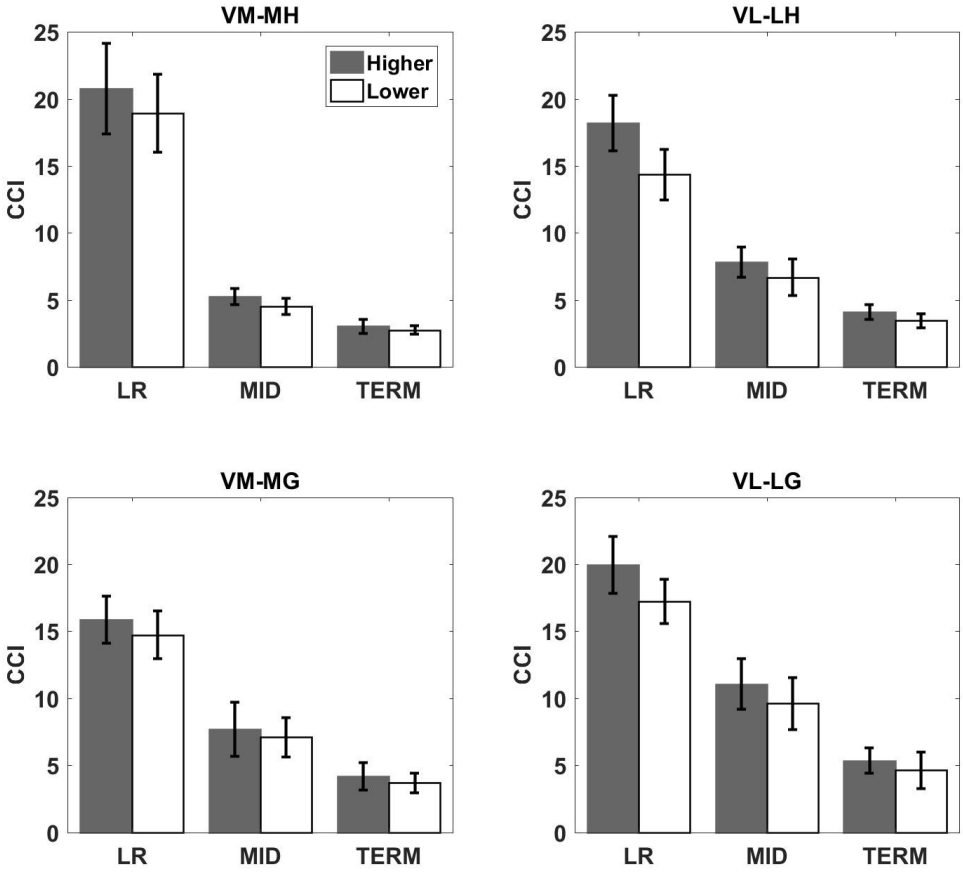

Sagittal Moments
0.4
0.2
0
-0.2
-0.4
-0.6
Nm/kg
20
40
60
80
100
% Stance


Sagittal Motion
CONTRA
ASYMP
60
40
20
0
Angle (Deg)
20
40
60
80
100
% Gait Cycle


Frontal Moments
0.4
0.2
0
-0.2
Nm/kg
20
40
60
80
100
% Stance

Appendix C – Inter-limb CCI differences in a healthy asymptomatic group

Chapter 5 quantified inter-limb RMS differences in four CCI pairs during loading response, mid-stance and terminal stance. The CCI bar graphs in this appendix try to aid with the interpretation of the inter-limb differences identified, however it does not provide information on individual subject between-limb differences. The bar graphs provided the average CCI magnitudes of the higher and lesser activated limbs during each phase.


VM-MH
Higher
Lower
CCI
25
20
15
10
5
0
LR
MID
TERM
VL-LH
CCI
25
20
15
10
5
0
LR
MID
TERM
VM-MG
CCI
25
20
15
10
5
0
LR
MID
TERM
VL-LG
CCI
25
20
15
10
5
0
LR
MID
TERM

Appendix D – Copyright Permissions Letters

The following are copyright permissions letters for images used from previous publications throughout this dissertation:

ELSEVIER LICENSE
TERMS AND CONDITIONS

Jun 15, 2017

This Agreement between Michelle Jones ("You") and Elsevier ("Elsevier") consists of your license details and the terms and conditions provided by Elsevier and Copyright Clearance Center.

License Number	4127740741855
License date	Jun 14, 2017
Licensed Content Publisher	Elsevier
Licensed Content Publication	Journal of Electromyography and Kinesiology
Licensed Content Title	Neuromuscular alterations during walking in persons with moderate knee osteoarthritis
Licensed Content Author	C.L. Hubley-Kozey,K.J. Deluzio,S.C. Landry,J.S. McNutt,W.D. Stanish
Licensed Content Date	Aug 1, 2006
Licensed Content Volume	16
Licensed Content Issue	4
Licensed Content Pages	14
Start Page	365
End Page	378
Type of Use	reuse in a thesis/dissertation
Portion	figures/tables/illustrations
Number of figures/tables/illustrations	1
Format	electronic
Are you the author of this Elsevier article?	No
Will you be translating?	No
Order reference number	
Original figure numbers	Figure 1
Title of your thesis/dissertation	CONTRA-LATERAL KNEE JOINT FUNCTION IN MODERATE KNEE OSTEOARHRITIS: AN ELECTROMYOGRAPHIC INVESTIGATION OF KNEE MUSCLE CO-CONTRACTION
Expected completion date	Aug 2017
Estimated size (number of pages)	130
Elsevier VAT number	GB 494 6272 12

ELSEVIER LICENSE
TERMS AND CONDITIONS

Jun 15, 2017

This Agreement between Michelle Jones ("You") and Elsevier ("Elsevier") consists of your license details and the terms and conditions provided by Elsevier and Copyright Clearance Center.

License Number	4127741147893
License date	Jun 14, 2017
Licensed Content Publisher	Elsevier
Licensed Content Publication	Journal of Electromyography and Kinesiology
Licensed Content Title	Changes in knee joint muscle activation patterns during walking associated with increased structural severity in knee osteoarthritis
Licensed Content Author	Derek J. Rutherford,Cheryl L. Hubley-Kozey,William D. Stanish
Licensed Content Date	Jun 1, 2013
Licensed Content Volume	23
Licensed Content Issue	3
Licensed Content Pages	8
Start Page	704
End Page	711
Type of Use	reuse in a thesis/dissertation
Intended publisher of new work	other
Portion	figures/tables/illustrations
Number of figures/tables/illustrations	2
Format	electronic
Are you the author of this Elsevier article?	No
Will you be translating?	No
Order reference number	
Original figure numbers	Figures 1F, 1G
Title of your thesis/dissertation	CONTRA-LATERAL KNEE JOINT FUNCTION IN MODERATE KNEE OSTEOARHRITIS: AN ELECTROMYOGRAPHIC INVESTIGATION OF KNEE MUSCLE CO-CONTRACTION
Expected completion date	Aug 2017
Estimated size (number of pages)	130
Elsevier VAT number	GB 494 6272 12

ELSEVIER LICENSE
TERMS AND CONDITIONS

Jun 15, 2017

This Agreement between Michelle Jones ("You") and Elsevier ("Elsevier") consists of your license details and the terms and conditions provided by Elsevier and Copyright Clearance Center.

License Number	4127750443784
License date	Jun 14, 2017
Licensed Content Publisher	Elsevier
Licensed Content Publication	Gait & Posture
Licensed Content Title	Stride-to-stride variability of knee motion in patients with knee osteoarthritis
Licensed Content Author	Michael D. Lewek,John Scholz,Katherine S. Rudolph,Lynn Snyder-Mackler
Licensed Content Date	Jun 1, 2006
Licensed Content Volume	23
Licensed Content Issue	4
Licensed Content Pages	7
Start Page	505
End Page	511
Type of Use	reuse in a thesis/dissertation
Intended publisher of new work	other
Portion	figures/tables/illustrations
Number of figures/tables/illustrations	1
Format	electronic
Are you the author of this Elsevier article?	No
Will you be translating?	No
Order reference number	
Original figure numbers	Figure 4
Title of your thesis/dissertation	CONTRA-LATERAL KNEE JOINT FUNCTION IN MODERATE KNEE OSTEOARHRITIS: AN ELECTROMYOGRAPHIC INVESTIGATION OF KNEE MUSCLE CO-CONTRACTION
Expected completion date	Aug 2017
Estimated size (number of pages)	130