INDIVIDUAL CONTRIBUTIONS TO
TIBIOFEMORAL COMPARTMENT LOADS IN
HEALTHY AND OSTEOARTHRITIC GAIT

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ABSTRACT

Increased cyclic compressive loading in the medial compartment of the knee is associated with the progression of knee osteoarthritis (OA). However as medial knee OA is accompanied by a range of neuromuscular, morphological and structural changes throughout the lower limb, a clear consensus of the etiology of the disease is yet to emerge. Of particular recent interest are the roles of non-knee-spanning muscles and the lower-limb kinematic chain in the pathomechanics of knee OA.

Joint loads during gait occur due to contributions from all muscles, gravity and inertia. As such the aim of this work was to utilise experimental gait data in conjunction with musculoskeletal modelling to undertake a novel and detailed examination of these individual constituent factors influencing loading in the osteoarthritic knee. Specifically, the objective was to decompose the time-histories of loads in the medial and lateral tibiofemoral compartments of osteoarthritic knees into contributions by individual muscles, gravity and inertia, and to explain the results in light of the known neuro-musculoskeletal changes associated with OA.

A novel computational method for decomposing the tibiofemoral compartment loads into contributions by muscles, gravity and inertia was developed and integrated into an advanced musculoskeletal modelling pipeline. Experimental gait data from varus mal-aligned unilateral medial knee OA patients and healthy controls were input into the musculoskeletal modelling pipeline and used to quantify the contributions to the forces and cumulative loads in the medial
and lateral compartments of the tibiofemoral-joint, and also to surrogate measures of medial compartment loading.

The findings have revealed substantive differences in the composition of joint loads between healthy and osteoarthritic knees, and have explained some of the underlying mechanisms by which elevated knee-joint loads arise in OA patients. Importantly, the findings establish the substantial role played by non-knee-spanning muscles in modulating knee-joint loads. Furthermore, this thesis has also quantified and explained some of the potential limitations associated with surrogate measure of joint loads.

The improved understanding of the pathomechanics of medial knee OA brought about by this thesis may be potentially valuable in the design of non-pharmacologic interventions to mitigate medial knee OA progression, and may facilitate the development of more robust surrogate measures of knee-joint loads to improve clinical assessment of OA patients.
DECLARATION

This is to certify that:

i. the thesis comprises only of my original work towards the PhD except where indicated in the Preface;

ii. due acknowledgement has been made in the text to all other material used;

iii. the thesis is less than 100,000 words in length, exclusive of tables, maps, bibliographies, appendices and footnotes.

Prasanna Sritharan

September 2016
PREFACE

Publications
The following published and prospective peer-reviewed journal articles have resulted directly from the work reported in this thesis:


Human gait experiments
The human gait experiments described in Chapters 4, 5 and 6 were undertaken by Sara E. Richardson, Ian C. Jones and Trevor B. Birmingham at the Wolf Orthopaedic Biomechanics Laboratory, Fowler Kennedy Sport Medicine Clinic, University of Western Ontario, Ontario, Canada. Institutional approval was provided by the Research Ethics Board for Health Sciences Research Involving Human Subjects at the University of Western Ontario (HSREB No. 09812E).
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CHAPTER 1
INTRODUCTION

1.1 MOTIVATION
Knee osteoarthritis (OA) is a painful, debilitating and incurable disease most commonly affecting the medial compartment of the tibiofemoral-joint. Although typically characterised by the degeneration and loss of cartilage on the articulating surfaces of the knee, it is a systemic disease with its effects pervading throughout the musculoskeletal system.

The etiology of the disease is complex and multi-factorial however biomechanical changes are thought to play a major role in the initiation and progression of medial knee OA, particularly increased levels of cyclic loading in the knee. Many interrelated biomechanical factors may contribute to elevated knee-joint loads, including altered muscle forces, kinematic adaptations and structural changes in the lower-limb, amongst others. Understanding the effects of these individual musculoskeletal changes in initiating and progressing medial knee OA is crucial to understanding the broader pathogenesis of the disease, and may be essential in the development of interventions to prevent or mitigate it.

Even though the direct measurement of knee-joint loads in vivo in the natural knee is currently not feasible, recent advancements in computational modelling and gait analysis techniques have enabled the calculation of healthy and pathological knee-joint loads during dynamic tasks. Furthermore, computational modelling may offer a means of examining the impact of specific individual OA-related biomechanical changes in isolation, by facilitating the quantification of
knee-joint loads and the individual constituent factors which comprise them. Finally, computational modelling may help to better understand the relationship between actual joint loads and surrogate measures developed for clinical assessments, which to date have not been well-established.

The need to understand the underlying causes of OA is pressing as OA places substantial burdens on affected individuals and their families, the broader society and the economy. OA is one of the leading causes of non-fatal burden of disease globally and, in 2004-2005 accounted for AUD$4 billion in direct health expenditure in Australia, with almost 1.6 million diagnosed with the disease (Ehsan et al., 2010). In addition to an aging population, obesity and lifestyle factors are increasing the prevalence of the OA in a younger demographic within Australian society. As OA is a progressive and incurable disease, early identification and effective intervention is critical to mitigating initiation and progression of OA in high-risk individuals. Ultimately, however, expensive surgical intervention may be only effective means of restoring mobility and quality of life in many osteoarthritic individuals with advanced disease.

1.2 THESIS STRUCTURE

The overall objective of this thesis was to extend the current understanding of the pathomechanics of medial knee OA by undertaking a novel and detailed examination of joint loads in the compartments of the tibiofemoral-joint that leverages recent advancements in computational modelling and gait analysis techniques. Specifically, the thesis is structured as follows:
Chapter 2 is a detailed review of the literature to date. This chapter critically examines recent findings in the areas of: clinical osteoarthritis research; intervention and rehabilitation; computational modelling of knee-joint forces during dynamic tasks; metrics for OA severity and progression; and surrogate measures of knee-joint loading.

Chapter 3 describes and evaluates a novel computational method to quantify the contributions by individual muscles of the lower-limb, gravity and inertia to the forces in the medial and lateral compartment of the tibiofemoral-joint and also the external knee adduction moment, a potential surrogate measure of medial compartment loads.

Chapter 4 applies the methods developed in Chapter 3 to explain the differences in tibiofemoral compartment forces between varus mal-aligned unilateral medial knee OA patients and healthy controls by analysing the constituent contributions to the joint loads.

Chapter 5 applies the methods developed in Chapter 3 to quantify muscle function in osteoarthritic gait and to investigate how differences in muscle function between healthy and osteoarthritic gait impact the external knee adduction moment.

Chapter 6 quantitatively analyses and compares the roles of individual muscles, gravity and inertia in cumulative tibiofemoral compartment
loading in healthy and osteoarthritic knees by considering both the joint reaction impulse and a potential surrogate measure, the external knee adduction moment angular impulse.

Chapter 7 summarises the major findings of the thesis.
CHAPTER 2
BACKGROUND AND LITERATURE REVIEW

Chapter summary

The purpose of this review of the literature to date concerning knee-joint loads and gait mechanics in medial knee osteoarthritis is to establish a motivation for the specific objectives of this research project. Osteoarthritis is painful, debilitating and incurable. Elevated levels of cyclic loading in the medial compartment of the knee are thought to play a key role in the presence, severity, initiation and progression of the disease. Many interrelated factors may contribute to elevated joint loads, including altered muscle forces, kinematic adaptations and structural changes in the lower-limb, amongst others. Computational modelling may offer a means of examining these individual factors in detail, by enabling a quantification of knee-joint loads, and also the decomposition of these loads into their constituent contributions from individual knee-spanning and non-knee-spanning muscles, gravitational forces and inertial forces. As such this research project aims to undertake a detailed comparison of the individual contributions to medial and lateral tibiofemoral compartment loading in healthy and osteoarthritic gait and to explain any differences found in light of the biomechanical changes associated with the disease. This would provide a novel, important and useful insight into the pathomechanics of medial knee osteoarthritis which may help focus the search for improved clinical surrogate measures for assessment of osteoarthritis patients, and may help guide the development of innovative interventions to prevent or mitigate disease progression.
2.1 AN OVERVIEW OF TIBIOFEMORAL-JOINT OSTEOARTHRITIS

2.1.1 Etiology and epidemiology

Osteoarthritis of the tibiofemoral-joint, one of the two joints of the knee, is a painful and debilitating disease typically characterised by the loss of the cartilage on the articulating surfaces of the distal end of the femur or proximal end of the tibia (Figure 2.1) but with pervading structural, morphological and neuromuscular changes throughout the musculoskeletal system. It is progressive and incurable, causing loss of mobility and consequently, quality of life. In the year 2000 osteoarthritis was the 10th leading cause of non-fatal burden of disease globally and, in 2004-2005 accounted for $4 billion in direct health expenditure in Australia with almost 1.6 million people diagnosed with the disease (Ehsan et al., 2010). The prevalence of tibiofemoral-joint osteoarthritis increases with age, particularly beyond 45 years (Dillon et al., 2006; Ehsan et al., 2010; Felson et al., 1987). The disease is more prevalent in women than men (Dillon et al., 2006; Felson et al., 1992; Hart et al., 1999; Spector et al., 1994; Wise et al., 2012), with almost 40% of women aged over 75 years diagnosed with the disease in Australia (Ehsan et al., 2010). Certain ethnic groups are more susceptible to tibiofemoral-joint osteoarthritis, such as African Americans (Wise et al., 2012) and Indigenous Australians (Ehsan et al., 2010). Obesity and lifestyle factors are playing an ever increasing role in the prevalence of the knee osteoarthritis, particularly amongst a younger demographic (Cooper et al., 2000; Felson et al., 2000; Felson et al., 1992; Heijink et al., 2012; Spector et al., 1994). Knee trauma may also increase the likelihood of developing the disease, particularly cartilage and meniscus damage and rupture of the anterior cruciate ligament (Andriacchi et al., 2004).
The etiology of tibiofemoral-joint osteoarthritis is complex and multifactorial (Ehsan et al., 2010). The disease more commonly occurs in the medial compartment of the tibiofemoral-joint than the lateral compartment (McAlindon et al., 1992; Wise et al., 2012) but the triggers for its initiation and progression are not fully understood. They may arise from complex interactions among gender, weight and age with various biomechanical, biochemical, environmental, morphological and genetic factors. It is however widely accepted that, whatever the cause, disruption of cellular-level homeostasis ultimately leads to a degradation of the articular cartilage (Heijink et al., 2012; Takeda et al., 2011).

The primary focus of this current work is the role that biomechanical factors, in particular muscle forces and structural changes, may play in the pathogenesis of tibiofemoral-joint osteoarthritis. Biomechanical changes or dysfunction in the lower limb may increase the proportion of loading on the medial compartment of the tibiofemoral-joint (Astephen et al., 2008a; Baliunas et al., 2002; Miyazaki et al., 2002; Prodromos et al., 1985). Animal studies have also shown that long-term repetitive cyclic loading can lead to overuse or overloading of musculoskeletal tissue within the joint causing stiffening of the subchondral bone (Radin et al., 1984). While research suggests that elevated loading conditions in the knee combined with overuse may lead to chondrocyte malfunction (Andriacchi et al., 2004; Martin and Buckwalter, 2006; Sharma and Berenbaum, 2007) and subsequent degradation of the articular cartilage matrix (Buckland-Wright et al., 1994; Radin et al., 1984), studies of anterior cruciate ligament-deficient knees have found conversely that underloading in the knee may be important in initiation and progression of osteoarthritis (Hasler and Herzog,
These conflicting findings highlight the complex nature of the disease, but also suggest that loading alone may not be the sole factor associated with the development of osteoarthritis.

2.1.2 Clinical features and management

Osteoarthritis may affect either or both compartments of the tibiofemoral-joint however the medial compartment is most commonly affected (McAlindon et al., 1992; Wise et al., 2012). It may be diagnosed in terms of both its radiographic appearance and its clinical features. Clinical features typically include knee pain, altered gait patterns, joint instability or laxity, swelling, crepitus, stiffness and tenderness (Altman et al., 1986; Sharma and Berenbaum, 2007). Typical radiographic symptoms include joint-space narrowing (not necessarily limited to the affected compartment), bony enlargement and the presence of osteophytes (Altman et al., 1986; Kellgren and Lawrence, 1957; Sharma and Berenbaum, 2007).

Clinical assessment of osteoarthritis and the outcomes of clinical interventions are often undertaken using a combination of radiographic and patient-reported measures. Criteria for the classification of disease severity based on radiographic evidence were defined by Kellgren and Lawrence (1957). Standing radiographs may also be used to assess the mechanical axis angle, the angle between the femur and tibia, as large lower-limb mal-alignment may be associated with the disease (Sharma et al., 2001). This is accompanied by patient-reported questionnaire-based scoring mechanisms such as the Knee Injury and Osteoarthritis Outcome Score (KOOS) (Roos et al., 1998) and the Western
Ontario and McMaster Universities (WOMAC) Osteoarthritis Index (Bellamy et al., 1988), on which the former is based.

Osteoarthritis of the knee is incurable therefore early clinical intervention is paramount and may fall into 2 main groups – conservative (non-surgical) and surgical. Typical conservative interventions which may be employed are designed to mitigate pain and progression of the disease and include muscle strengthening (Lange et al., 2008), knee bracing (Birmingham et al., 2001; Shelburne et al., 2008; van Raaij et al., 2010), foot orthoses (Farrokhi et al., 2013; Hinman et al., 2012; Shelburne et al., 2008), and more recently, gait retraining (Guo et al., 2007; Mundermann et al., 2008a; Mundermann et al., 2004; Shull et al., 2013; Teichtahl et al., 2006; Zhao et al., 2007a). Ultimately however, in many severe cases conservative intervention may only serve to delay surgery, which, depending on the severity of the disease and/or the level of pain suffered by the individual, may include full or partial knee arthroplasty or tibial osteotomy (Birmingham et al., 2009; Prodromos et al., 1985; Sharma and Berenbaum, 2007).

2.1.3 Spatio-temporal and electromyographic characteristics

The biomechanical characteristics of individuals with medial knee osteoarthritis are many and varied, resulting from pain, structural changes and dysfunction in the lower limb. Some biomechanical differences which have been observed include increased lower-limb mal-alignment (Birmingham et al., 2009; Sharma et al., 2001; Teichtahl et al., 2009), knee laxity (Schipplein and Andriacchi, 1991; Sharma et al., 1999) altered muscle action and gait patterns (Hortobagyi et al., 2005; Hubley-Kozey et al., 2009; Rutherford et al., 2013; Rutherford et al., 2011;
Schipplein and Andriacchi, 1991; Zeni et al., 2010), reduced walking speed (Astephen et al., 2008a; Mundermann et al., 2004) and reduced muscle strength (Hurley, 2003; Lange et al., 2008; Slemenda et al., 1997).

Abnormal levels of frontal-plane knee-joint laxity, defined as the increased passive displacement or rotation of the tibia with respect to the femur, is a clinically-significant biomechanical feature in symptomatic individuals (Tanamas et al., 2009; Teichtahl et al., 2003; Teichtahl et al., 2009). It has been shown that individuals with knee osteoarthritis have elevated varus-valgus laxity in the unaffected knee compared to healthy controls and hence frontal-plane laxity may be a risk factor the development and progression of medial knee osteoarthritis (Sharma et al., 1999). Studies have suggested that pre-existing frontal-plane laxity may be a contributing factor to both static and dynamic varus mal-alignment of the lower-limb (Sharma et al., 2001), which manifests as the visible bowing out of the legs at the knee both during static quiescent standing (Hurwitz et al., 2002; Thorp et al., 2006b; Wada et al., 2001); and also during gait when it produces a distinctive “varus thrust” effect (Chang et al., 2004) in which the magnitude of lower-limb bowing-out changes during stance, causing the knee-joint centre visibly oscillates mediolaterally. For example, during weight acceptance, the bowing-out effect increases, causing the knee-joint centre to appear to be driven laterally outward. Varus mal-alignment has been specifically associated with the risk of development and of progression of medial knee OA (Sharma et al., 2001; Tanamas et al., 2009) as it may lead to elevated loading in the medial compartment of the tibiofemoral-joint (Adouni and Shirazi-Adl, 2014b; Brandon et al., 2014; Kumar et al., 2013). This is especially true in obese or overweight
individuals (Brouwer et al., 2007). Similarly, valgus mal-alignment is associated with osteoarthritis in the lateral compartment of the tibiofemoral-joint (Brouwer et al., 2007; Sharma et al., 2001; Tanamas et al., 2009). The presence of varus mal-alignment increased the risk of osteoarthritis in the medial compartment almost two-fold compared to the risk of lateral compartment osteoarthritis due to the presence of valgus alignment (Brouwer et al., 2007; Sharma et al., 2010). In fact, Cicuttini et al. (2004) found that 1-degree of varus produced about double the cartilage volume loss compared to 1-degree of valgus.

Differences in sagittal-plane knee kinematics and kinetics have also been observed between osteoarthritic individuals and healthy controls. Individuals with medial knee osteoarthritis often exhibit a stiff-knee gait, characterised by reduced peak knee flexion angles (Astephen et al., 2008a) and reduced range of knee flexion motion (Childs et al., 2004), with reduced net flexion-extension torques exhibited about the knee-joint (Astephen et al., 2008a). In addition to reduced walking speed (Astephen et al., 2008a; Mundermann et al., 2004), individuals with knee osteoarthritis often show decreased step length and increased stance time compared to healthy controls (Astephen et al., 2008a).

Pain, laxity and structural changes in the tibiofemoral-joint may lead to altered patterns of activity in the muscles spanning the osteoarthritic knee compared to healthy controls. In particular, considerable dysfunction, atrophy and weakening of quadriceps muscles have been well-studied in osteoarthritic individuals (Mizner et al., 2003; Petterson et al., 2008; Petterson et al., 2007; Thompson et al., 2013), which may support the idea that underloading of the knee may be important in osteoarthritis initiation and progression (Hasler and Herzog,
Moreover, elevated levels of quadriceps-hamstrings co-contractions have been observed during level gait in people with medial compartment tibiofemoral-joint osteoarthritis (Hortobagyi et al., 2005; Rutherford et al., 2013; Rutherford et al., 2011). It is theorised that these altered patterns of activation may arise in order to stabilise the knee against the large adduction moments experienced at the knee during gait and to protect lax knees against mechanical damage (Schipplein and Andriacchi, 1991). However, elevated co-activations may lead to elevated joint forces (Brandon et al., 2014), which may exacerbate the adverse biomechanical conditions in the osteoarthritic knee (Hortobagyi et al., 2005).

Changes in the functional performance of non-knee-spanning muscles, particularly the hip abductors, have been of recent research interest however their influence on knee osteoarthritis initiation and progression is not well established. Significant hip abductor strength deficits were found in people with knee osteoarthritis but it could not be established if this preceded or was a result of disease progression (Hinman et al., 2010). Furthermore, Chang et al. (2005) found that increased hip abduction moment protected against medial knee osteoarthritis progression. However a subsequent study found that strengthening of the hip muscles, while improving symptoms and function in medial knee osteoarthritis patients, did not actually reduce joint loads (Bennell et al., 2010). In this latter study, loads were quantified using a surrogate measure, the external knee adduction moment (Prodromos et al., 1985). As critically discussed in a subsequent section, this surrogate measure is limited in its ability to accurately represent knee-joint forces, therefore the true impact of improvements in hip
strength and function on knee-joint forces are still unclear.

Unfortunately, the relationship between the various observed biomechanical characteristics of osteoarthritic gait and the pathogenesis of osteoarthritis is still poorly understood. Further research is necessary to better establish this crucial link, to enhance clinical and scientific understanding of the etiology of the disease, and to support the design of novel interventions to manage or prevent risk of disease initiation and progression.

2.2 KNEE-JOINT FORCES DURING HEALTHY GAIT

2.2.1 Measurement of tibiofemoral compartment loading

As elevated forces in the knee may be implicated in development and progression of osteoarthritis, a comprehensive understanding of mechanical loading in the tibiofemoral-joint during dynamic tasks in both healthy and osteoarthritic individuals is essential for understanding the pathomechanics of this disease. While Kettelkamp and Chao (1972) as well as Tetsworth and Paley (1994) suggested that the medial compartment may bear 60-80% of the load in the knee, unfortunately the direct measurement of forces in the natural knee, both healthy and diseased, is currently infeasible as it would entail invasive surgical procedures. Nevertheless the recent development of knee implants instrumented with strain gauges have enabled the in vivo measurement of knee-joint forces in individuals who have undergone total knee replacement (TKR) through wireless telemetry (Kutzner et al., 2010; Mundermann et al., 2008b; Zhao et al., 2007a).

Studies using individuals with instrumented TKR implants have shown that there is considerable variation in the total tibiofemoral compressive load
experienced amongst individuals during dynamic tasks (Kutzner et al., 2010; Mundermann et al., 2008b; Trepczynski et al., 2014; Zhao et al., 2007a). The pattern of loading in the knee is highly dependent on the task being undertaken (Kutzner et al., 2010; Zhao et al., 2007a). During level gait, the total tibiofemoral force typically shows two peaks, with the measured force typically ranging between 2 and 3 body weights (BW) of force during level walking (Kutzner et al., 2010; Meyer et al., 2013; Zhao et al., 2007a).

TKR-based studies have consistently shown that both compartments of the tibiofemoral-joint are compressed during level walking, stair ascent and descent, with the medial compartment bearing greater loads than the lateral compartment (Kutzner et al., 2010; Meyer et al., 2013; Mundermann et al., 2008b; Trepczynski et al., 2014; Walter et al., 2010; Zhao et al., 2007a) (Figure 2.2). Similar to the total tibiofemoral force, the pattern of the medial compartment force typically shows two peaks, in the first and second phases of stance respectively, but actual profiles can show considerable variation amongst individuals (Kutzner et al., 2010; Kutzner et al., 2013b; Trepczynski et al., 2014), with a single-peak or a plateau-like profile commonly found (Figure 2.3). The medial compartment may bear about 60% of the peak tibiofemoral load, which may range between 1 and 2 BW (Kutzner et al., 2010; Meyer et al., 2013; Mundermann et al., 2008b; Trepczynski et al., 2014; Walter et al., 2010; Zhao et al., 2007a).

Instrumented TKR measurements have provided valuable and important insights into forces within the knee-joint under a variety of dynamic conditions. However, these findings are not without their limitations. Importantly, individuals with TKR implants can show significant differences in ambulatory kinematics and
kinetics compared to healthy and osteoarthritic individuals with a natural knee (McClelland et al., 2007; Meyer et al., 2013; Walter et al., 2010), in particular reduced knee flexion range of motion (Mandeville et al., 2007; McClelland et al., 2011) and a broad range of knee flexion torque (McClelland et al., 2010) and hip extension torque patterns (Mandeville et al., 2007). Therefore the outcomes of instrumented TKR studies should be considered in association with other clinical and biomechanical investigations.

2.2.2 Computational modelling of the knee

In response to the challenges associated with measurement of tibiofemoral-joint forces \textit{in vivo}, computational modelling has emerged as a valuable and robust tool for quantification of forces in the tibiofemoral-joint. Models of the knee may have varying degrees of complexity, from simple rigid body formulations (Glitsch and Baumann, 1997; Kumar et al., 2013; Schipplein and Andriacchi, 1991; Winby et al., 2009) to complex deformable models which include bone geometry and soft tissues such as cartilage and ligaments (Adouni and Shirazi-Adl, 2014a; Akbarshahi et al., 2010; Shelburne et al., 2004) (Figure 2.4). Inputs to models of the knee may typically include joint kinematics, external loads such as the ground reaction force (GRF), and muscle forces – either predicted from a separate musculoskeletal model (Akbarshahi et al., 2010; Lloyd and Besier, 2003; Shelburne et al., 2004) or calculated simultaneously within a nested optimisation formulation (Adouni and Shirazi-Adl, 2014a).

Modelling studies have shown that during walking, the forces in the tibiofemoral-joint typically show a double-peaked profile during the stance phase
of gait, with the medial compartment bearing the majority of this load (Adouni and Shirazi-Adl, 2014a; Akbarshahi et al., 2010; Hurwitz et al., 1998; Shelburne et al., 2006; Winby et al., 2009), in agreement with TKR-based in vivo measurements. Similar to TKR-based studies, while there is large variation in the magnitudes of peak forces predicted, the timing of peaks is relatively consistent, with the first peak occurring around the time of contralateral toe-off and the second peak occurring around the time of contralateral heel-strike (Figure 2.5). The model-predicted medial compartment force during walking has been shown to be as high as 3 BW, about double that of the lateral compartment (Hurwitz et al., 1998; Shelburne et al., 2006; Winby et al., 2009), with the total tibiofemoral force suggested to be as high as 4.5 to 5 BW (Glitsch and Baumann, 1997; Winby et al., 2009). While these are considerably higher than reported knee-joint loads from TKR-based studies, it has been well-established that models may overestimate peak forces in the joints of the lower limb during gait compared to instrumented implants (Heller et al., 2001), potentially due to associated challenges and limitations, such as the ability to accurately reproduce the complex geometry and kinematics of the knee (Akbarshahi et al., 2010), the inclusion of soft tissues such as cartilage and ligaments and their material properties (Adouni and Shirazi-Adl, 2014a; Akbarshahi et al., 2010; Donahue et al., 2002), accuracy of EMG signals if used (Kumar et al., 2013; Sasaki and Neptune, 2010; Winby et al., 2009), and the method of calculation of muscle forces (Adouni and Shirazi-Adl, 2014a; Shelburne et al., 2006), amongst many others.

Modelling methodology can impact the relative magnitudes of the peaks of the total tibiofemoral-joint force and the medial compartment force. Static
optimisation approaches for muscle force calculation have typically reported higher second peak for total tibiofemoral force (Glitsch and Baumann, 1997; Hurwitz et al., 1998) and the medial compartment force (Hurwitz et al., 1998). In contrast, studies using muscle forces derived from electromyography-driven (EMG) musculoskeletal models (Lloyd and Besier, 2003; Sasaki and Neptune, 2010) where inputted EMG, kinematics and GRF were derived from gait experiments, reported a higher first peak for total tibiofemoral force (Kumar et al., 2013; Sasaki and Neptune, 2010; Winby et al., 2009) and medial compartment force (Kumar et al., 2013; Sasaki and Neptune, 2010). Yet Shelburne et al. (2006) using muscle forces and GRF derived from a dynamic optimisation-based simulation of human walking (Anderson and Pandy, 2001a) reported approximately equal first and second peaks for both total tibiofemoral force and medial compartment force.

Furthermore, there is considerable controversy with regards to lateral compartment forces. Some studies predicted periods of lateral compartment unloading during the stance phase of gait (Hurwitz et al., 1998; Kumar et al., 2013; Schipplein and Andriacchi, 1991; Shelburne et al., 2006) implying that the collateral ligaments of the knee play a major role in frontal plane knee-joint stability (Schipplein and Andriacchi, 1991). Other studies predicted that both the medial and lateral compartment remain compressed throughout stance (Adouni and Shirazi-Adl, 2014a; Winby et al., 2009), in agreement with TKR-based measurements suggesting that muscles and joint contact are generally sufficient to provide frontal-plane stability in normal healthy gait (Fregly et al., 2009). Unfortunately, the lateral compartment is not well studied, and there is currently
no real consensus as to the true nature of lateral compartment loading.

While the substantial recent research effort towards understanding tibiofemoral-joint behaviour through computational modelling and instrumented implants has provided valuable information into the internal mechanics of the joint, the mechanisms by which the individual biomechanical factors influence the loading patterns in the knee are not fully established. It is known that muscle forces, external forces such as the GRF and kinematics are key drivers of joint mechanics (Shelburne et al., 2006). Therefore a detailed examination of how these individual factors influence knee-joint biomechanics is crucial to a comprehensive understanding of the overall biomechanics of the knee-joint.

2.2.3 Muscle function in gait

A muscle, when excited by a neural signal, activates and begins to contract, and thus develops a force. As the muscle force acts at a distance from the centre of the joint that it spans, i.e. the muscle moment arm about the joint, the muscle generates a torque which accelerates that joint, initiating movement (Zajac et al., 2002). The calculation of muscle activations and forces is a challenging problem as the number of muscles in the body substantially exceeds the available degrees of freedom. This results in an over-determined problem ideally suited to optimisation-based solution techniques. Many studies have investigated muscle forces in walking and running gait utilising a variety of computational methods, including dynamic optimisation (Anderson and Pandy, 2001a; Neptune et al., 2001), static optimisation (Anderson and Pandy, 2001b; Hardt, 1978), and hybrid methods such as EMG-driven approaches (Lloyd and Besier, 2003; Sartori et al.,
2012) and Computed Muscle Control (Hamner and Delp, 2013; Hamner et al., 2010; Thelen and Anderson, 2006; Thelen et al., 2003). Regardless of the method used, these studies have shown agreement in the pattern of activations produced by the major muscles of the lower limb during walking: the hamstrings and vasti activate in early stance followed by the soleus and gastrocnemius in late stance, with the gluteus medius and gluteus maximus active throughout stance. However in order to explain these activation patterns, an investigation of the function of muscles in gait is necessary.

The precise magnitude, timing and coordination of over 200 major skeletal muscles enables the human body to undertake complex dynamic tasks such as walking and running (Pandy and Andriacchi, 2010; Zajac et al., 2002). Zajac and Gordon (1989) showed that a muscle may accelerate joints which it does not span through the mechanism of dynamic coupling. In this way, a muscle must contribute to the acceleration of the body centre of mass, and hence by Newton’s Third Law, also the foot-ground interaction forces and moments (Dorn et al., 2012; Lin et al., 2010). During gait, the net sum of contributions to the foot-ground interaction by individual muscles, and also gravity and inertia, is the well-known pattern of the GRF (Anderson and Pandy, 2003) which can be measured in a laboratory using force plates. Since the GRF is the principal external force acting on the body during gait, by Newton’s Second Law, the GRF is mostly responsible for the net acceleration of the body centre of mass (Winter, 2009). The GRF has three components: vertical, fore-aft and mediolateral. During walking: (1) the vertical component represents the external force required to support the body centre of mass against gravity; (2) the fore-aft component is the external
force applied to the centre of mass to accelerate or decelerate the body in the
direction of motion; and (3) the mediolateral component balances the body in the
frontal plane (Pandy and Andriacchi, 2010).

How a muscle supports, progresses and balances the body is one definition
of muscle function (Anderson and Pandy, 2003; Liu et al., 2006; Liu et al., 2008;
Pandy and Andriacchi, 2010; Pandy et al., 2010), and is the definition used
henceforth in this thesis. A muscle’s function during dynamic activities is highly
task-dependent (Zajac and Gordon, 1989). As the GRF effectively represents the
net force acting on the body’s centre of mass during gait, the pattern of
contribution by an individual muscle to each of the three components of the GRF
(and by definition, that muscle’s contribution to the acceleration of the body’s
centre of mass) can be defined as that muscle’s function in gait. A muscle’s
contribution to centre-of-mass support, progression and balance can be quantified
in terms of its contribution to the vertical, fore-aft and mediolateral components
of the GRF respectively (Anderson and Pandy, 2003; Lin et al., 2015; Liu et al.,
2006; Liu et al., 2008; Pandy and Andriacchi, 2010; Pandy et al., 2010). Several
studies have investigated muscle function in walking (Anderson and Pandy, 2003;
Liu et al., 2006; Liu et al., 2008; Neptune et al., 2001; Neptune et al., 2008; Pandy
et al., 2010) (Figure 2.6), running (Dorn et al., 2012; Hamner and Delp, 2013;
Hamner et al., 2010) and other locomotive tasks such as stair ascent and descent
(Lin et al., 2015).

Modelling studies have shown that during walking, five major muscles of
the lower limb provide vertical support and fore-aft progression: the gluteus
medius, gluteus maximus, vasti (medialis, intermedius and lateralis), soleus and
gastrocnemius. The gluteus maximus, gluteus medius and vasti support and decelerate the body in early stance, while the soleus, gastrocnemius and gluteus medius support and accelerate the body in late stance (Anderson and Pandy, 2003; Liu et al., 2006; Neptune et al., 2001; Pandy and Andriacchi, 2010). These muscles are also responsible for providing mediolateral balance. The vasti, soleus and gastrocnemius accelerate the body laterally, while the gluteus medius accelerates the body medially (Pandy and Andriacchi, 2010; Pandy et al., 2010).

2.2.4 Muscle contributions to joint forces

A consensus is building that a detailed understanding of how muscles influence joint loading in both healthy and pathological gait patterns is crucial to the development of novel interventions for the identification, prevention and management of musculoskeletal conditions such as osteoarthritis (Herzog et al., 2003; Sasaki and Neptune, 2010; Shelburne et al., 2006; Winby et al., 2009). In general, the total compressive force on a joint arises from the superposition of several components: (1) direct compression by muscles that span the joint; (2) the intersegmental force developed in the joint by the GRF through dynamic coupling; (3) resistance of the skeleton to gravitational forces (henceforth referred to as “gravity” or the “gravity contribution”); (4) ligament and other soft tissue forces; and (5) inertial forces due to acceleration of the body segments (Pandy and Andriacchi, 2010) (henceforth referred to as the “inertia” or the “inertial contribution”). Shelburne et al. (2006) and Winby et al. (2009) showed that during walking, direct compression by knee-spanning muscles provided over 60% of the peak total tibiofemoral-joint force while the GRF provided most of the remaining
compressive load. However, by treating the GRF as a single external force, these studies did not quantify the individual contributions by non-knee-spanning muscles to the forces in the knee.

Recently, by iteratively applying each muscle’s calculated force and also its contribution to the GRF at each time instance in the gait cycle, Correa et al. (2010) was able to determine individual muscle contributions to the hip-joint reaction force during gait. This study (Correa et al., 2010) reported that muscles contributed to over 95% of the total hip-joint load, with a significant proportion of that load due to dynamic coupling effects from knee-spanning and ankle-spanning muscles. In this way, muscles are by far the largest contributors to joint loading (Herzog et al., 2003). Muscles that span the joint directly compress that joint, while all muscles, including those that do not span the joint, are able to further contribute to joint loading via their contributions to the GRF by means of dynamic coupling (Correa et al., 2010; Sasaki and Neptune, 2010; Zajac and Gordon, 1989). Using the method of Correa et al. (2010), Sasaki and Neptune (2010) quantified the contributions by individual muscles of the lower limb to the total tibiofemoral-joint force during gait (Figure 2.7). It was found that in early stance, while the quadriceps and hamstrings accounted for most of the compressive force on the knee, the hip extensor muscles also contributed significantly. Furthermore, in late stance, the soleus provided almost one-third of the total compressive force, with the gastrocnemius largely responsible for the rest.

Shelburne et al. (2006) and Winby et al. (2009) showed that although direct compression by muscles dominated the total tibiofemoral-joint load, the situation was markedly different when each compartment was considered
separately. The GRF accounted for more than half of the peak medial compartment force, while direct compression from knee-spanning muscles mostly accounted for the remainder. Furthermore the GRF had a significant tendency to unload the lateral compartment with a force almost equal and opposite to that provided by knee-spanning muscles, which compressed it (Shelburne et al., 2006; Winby et al., 2009).

The substantial influence of the GRF in medial and lateral compartment loading suggests that non-knee-spanning muscles could play a crucial but as-yet unknown role in the forces experienced by the individual compartments of the tibiofemoral-joint. Unfortunately, to date, no study has quantified the individual contributions by both knee-spanning and non-knee-spanning muscles to tibiofemoral compartments forces. As such, no study has been able to answer the broader question of how muscle function in gait influences the internal mechanics of the knee.

2.3 FORCES IN THE OSTEOARTHRITIC KNEE

2.3.1 Quantifying knee-joint forces in osteoarthritic knees

The medial compartment of the tibiofemoral-joint is more commonly affected by osteoarthritis than the lateral compartment (McAlindon et al., 1992; Wise et al., 2012). While the reasons for this are not known for certain, it is widely accepted that increased loading in the medial compartment may play an important role in the pathomechanics of the disease (Andriacchi and Mundermann, 2006; Miyazaki et al., 2002; Prodromos et al., 1985; Teichtahl et al., 2009). However, determination of knee-joint loads in osteoarthritis is a challenging task and to date
very few studies have actually quantified the forces experienced in osteoarthritic knees (Adouni and Shirazi-Adl, 2014a, b; Brandon et al., 2014; Kumar et al., 2013; Richards and Higginson, 2010) possibly due to the difficulties in accounting for the wide variety of observed biomechanical changes associated with the disease as described in an earlier section.

Recently, both Kumar et al. (2013) and Brandon et al. (2014) demonstrated, using EMG-based modelling techniques, that osteoarthritic individuals may indeed experience medial compartment compressive forces up to 0.5 BW higher than healthy controls. Furthermore, Kumar et al. (2013) reported lower lateral compartment forces in the osteoarthritic condition, with some subjects even experiencing complete lateral compartment unloading, while Brandon et al. (2014) showed that lateral compartment forces would actually be higher in the osteoarthritic condition. The osteoarthritic individuals in both studies showed elevated levels of EMG activity in the quadriceps and hamstrings, a widely-reported phenomenon thought to improve stability of the affected knee (Hortobagyi et al., 2005; Hubley-Kozey et al., 2009; Rutherford et al., 2013; Rutherford et al., 2011; Zeni et al., 2010), which may have contributed to both studies reporting a much higher first peak of the medial compartment force despite walking more slowly than healthy controls. Richards and Higginson (2010) similarly demonstrated that total tibiofemoral-joint forces may be highest in severe osteoarthritis despite slowest walking speed, but also reported forces in moderately osteoarthritic knees which were lower than healthy controls despite walking faster than their severely osteoarthritic counterparts.

Unfortunately the reliability of EMG-driven modelling in studies of
musculoskeletal conditions is not known. This is because pain, strength deficits, dysfunction and atrophy may result in reduced maximum quadriceps force production and also lower maximal voluntary isometric contraction (MVIC) EMG signals obtained during laboratory experiments (Mizner et al., 2003; Petterson et al., 2008; Petterson et al., 2007; Thomas et al., 2008; Thompson et al., 2013). Low MVIC values can lead to artificially elevated normalised EMG signals inputted into models, and if changes in muscle properties associated with osteoarthritis are not accounted for, this may ultimately lead to overestimations of muscle forces and subsequent tibiofemoral-joint loads (Adouni and Shirazi-Adl, 2014a).

Varus mal-alignment may play a key role in elevated knee-joint forces in OA individuals. A 10% increase in varus mal-alignment may produce an average 3.3 BW up to a peak of 7.4 BW increase in total tibiofemoral-joint load (Heller et al., 2003). Importantly, Adouni and Shirazi-Adl (2014b) recently demonstrated that elevated loading in the medial compartment of osteoarthritic knees may be dictated more by frontal-plane mal-alignment than a pure knee adduction moment in the absence of any mal-alignment.

The influence of non-knee-spanning muscles on knee-joint loads in OA individuals has not been well-established, particularly the role of the hip abductor muscles. Hip abductor strength deficits are a common feature of OA (Hinman et al., 2010), and it has been hypothesised that during stance, hip abductor dysfunction in the ipsilateral limb would cause greater pelvic drop towards the contralateral limb, shifting more load onto the medial compartment of the ipsilateral limb thus contributing to OA progression (Chang et al., 2005). However, Bennell et al. (2010) found that hip muscle strengthening did not in fact
reduce joint loads (based on a surrogate measure of medial compartment loads, the external knee adduction moment, discussed further in the next section) although it did improve symptoms and function. More recently, a study using EMG collected from OA individuals found almost no association between hip abductor strength and joint loads (based on the external knee adduction moment) (Rutherford et al., 2014). Thus more research is necessary to better understand the role of non-knee-spanning muscles in the pathomechanics of medial knee OA.

The findings reported thus far suggest a complex interaction among muscle forces, OA-specific neuromuscular changes, the kinematic chain, walking speed and knee-joint loads. While current modelling-based studies have provided great insight into the biomechanical factors associated with knee-joint loads in osteoarthritic knees, they do not adequately isolate and explain the pattern of loading in the knee in the context the isolated individual biomechanical characteristics associated with knee osteoarthritis. Importantly, to date, the contributions by individual muscles, gravity and inertia to loading in the varus mal-aligned osteoarthritic knee during gait have not yet been quantified.

2.3.2 The external knee adduction moment
As in vivo measurements of knee-joint forces are currently not feasible, the external knee adduction moment (EKAM) has been proposed as a surrogate measure of loading within the medial compartment that can be easily measured in a clinical gait laboratory (Prodromos et al., 1985). The EKAM is classically defined as the product of the magnitude of the frontal-plane GRF vector and the length of the moment arm of the frontal-plane GRF vector about the knee-joint
centre (Figure 2.8) (Newell et al., 2008; Prodromos et al., 1985; Schipplein and Andriacchi, 1991), however, in practice it is calculated as the frontal-plane inverse dynamics torque at the knee (Adouni and Shirazi-Adl, 2014b; Hurwitz et al., 2002; Schache and Baker, 2007; Zhao et al., 2007b) thereby also fully taking into account the subtle gravitational and inertial force effects of the tibia and foot.

During walking, the EKAM typically demonstrates 2 peaks – the first near contralateral toe-off and the second near contralateral heel-strike – although considerable variation does exist amongst individuals, particularly in more severe cases where single-peak or plateau-like profiles have been found (Baliunas et al., 2002; Hurwitz et al., 1998; Kutzner et al., 2013b; Sharma et al., 1998), similar to the patterns of medial compartment force. TKR-based studies have correlated EKAM against measured medial compartment forces and found moderate to good correlation between medial compartment force and EKAM during walking (Kutzner et al., 2010; Kutzner et al., 2013b; Meyer et al., 2013; Trepczynski et al., 2014; Zhao et al., 2007b). These studies also show there is considerable variation in the relative magnitudes of the two peaks of EKAM during gait, with some individuals showing higher first peak, others with higher second peak and still others with relatively equal peaks (Figure 2.9).

Many studies have shown elevated peak knee adduction moments to be associated with the presence, severity and progression of medial compartment knee osteoarthritis (Astephen et al., 2008b; Baliunas et al., 2002; Hunt et al., 2006; Miyazaki et al., 2002; Mundermann et al., 2005; Schipplein and Andriacchi, 1991; Sharma et al., 1998). Of note, Miyazaki et al. (2002) concluded that an increase of 1% in the EKAM increased the risk of initiation or progression of knee
OA by a factor of about 6.5. This association has been further demonstrated in the context of increased lower-limb alignment (Sharma et al., 2001; Teichtahl et al., 2009), surgical interventions to reduce mal-alignment such as high tibial osteotomy (Prodromos et al., 1985; Wang et al., 1990), as well as joint laxity (Lewek et al., 2004) and varus thrust (Chang et al., 2004). In fact Heller et al. (2003) found that a 1-degree increase in knee varus angle could produce increases in EKAM as high as 3.5 percent of body-weight-height (%BW*HT).

Consequently, many conservative interventions have been developed with the aim of reducing EKAM in at-risk individuals, such as knee bracing (Birmingham et al., 2001; Shelburne et al., 2008; van Raaij et al., 2010), foot orthoses (Farrokhi et al., 2013; Hinman et al., 2012; Shelburne et al., 2008) and gait retraining (Guo et al., 2007; Mundermann et al., 2008a; Mundermann et al., 2004; Shull et al., 2013; Teichtahl et al., 2006; Zhao et al., 2007a), with a large number of these specifically aimed at reducing varus mal-alignment. In a review of interventions, Farrokhi et al. (2013) found that while conservative interventions typically succeeded in reducing peak EKAM, the outcomes were highly variable. Furthermore, this study (Farrokhi et al., 2013) reported that most conservative interventions showed only small improvements in the first peak of EKAM. Substantial changes in gait patterns were required to generate more sizeable reductions in the first peak of EKAM, such as the adoption of a “medial-thrust” walking gait (Fregly et al., 2007) which could produce reductions of up to 50%.

Yet although the EKAM shows strong relationships with presence, severity and progression of knee osteoarthritis making it attractive for application in clinical assessments, its usefulness as an accurate surrogate measure of medial
compartment force is less certain. In a study using individuals with instrumented TKR, Kutzner et al. (2013b) found that the peak EKAM during level gait correlated poorly with the peak medial compartment force ($R^2 = 0.36$) but that relationship improved when all data points during stance were used in the regression model ($R^2 = 0.56$). In fact Meyer et al. (2013) determined that these moderate-to-poor correlations between EKAM and medial compartment force were too low to be a reliable predictor of medial compartment forces, and found that EKAM better predicted the ratio of loading between the medial and lateral compartments ($R^2 = 0.59$). Furthermore Walter et al. (2010) found that any relationship may be subject and task dependent, and that attempts to reduce the EKAM may not translate into reduced medial compartment force, while Adouni and Shirazi-Adl (2014b) recently found that frontal-plane alignment of the lower-limb could be more important than EKAM, applied as a free moment to the knee in the absence of mal-alignment, in determining medial compartment forces.

The growing consensus is that because EKAM only represents the external loading on the knee, i.e. the effect of the GRF on the forces in the medial and lateral compartments, it does not account for the compression applied to the knee by knee-spanning muscles (Kutzner et al., 2013b; Meyer et al., 2013; Walter et al., 2010), which in osteoarthritic individuals may show elevated but varied levels of activity (Hortobagyi et al., 2005; Hubley-Kozey et al., 2009; Rutherford et al., 2013; Rutherford et al., 2011; Zeni et al., 2010). To account for the direct compressive effects of knee-spanning muscles, Walter et al. (2010) performed multivariate regression analyses which combined EKAM with the knee flexion moment and other variables while Meyer et al. (2013) also considered EMG from
knee-spanning muscles. While these additional variables improved prediction of medial compartment force, both studies concluded the improvements were still insufficient for use as reliable models (Meyer et al., 2013; Walter et al., 2010).

As such, the precise relationship between EKAM and actual knee-joint loads is not adequately known. A detailed comparison of the individual contributors to tibiofemoral compartment loads and to EKAM, how they change with increasing disease severity, and whether the changes to EKAM correctly reflect the associated changes in medial compartment force, would provide further evidence in support of, or in opposition to, the proposed use of EKAM as a viable clinical surrogate measure for medial compartment loads. Importantly, it may help explain why some interventions provide only modest improvements in the first peak of EKAM, and may guide the development of novel interventions to further reduce the first peak.

2.3.3 Muscle function in osteoarthritic gait

Joint forces are inextricably linked to muscle function (Correa et al., 2010; Pandy and Andriacchi, 2010; Sasaki and Neptune, 2010). Yet no study to date has quantified muscle function – defined as a muscle’s contribution to whole-body centre-of-mass accelerations – in osteoarthritic gait, nor explored the link between muscle function and elevated medial compartment loads experienced in tibiofemoral-joint osteoarthritis. Furthermore, although the GRF is comprised of contributions from muscles, gravity and inertia, no study has examined how these individual factors impact the EKAM in either healthy or osteoarthritic gait. That is, no study to date has studied how muscle function influences EKAM.
Altered kinematics, joint torques and muscle activation patterns can hinder the ability of the prime movers to accelerate the body and potentially necessitate a change in muscle coordination strategy, as evidenced by muscle function analyses of cerebral palsy (Correa et al., 2012), a more extreme example of neuromuscular dysfunction compared to OA. However, a recent study of elderly gait by Lim et al. (2013) found that despite significant difference in muscle forces, muscle function in accelerating the body centre-of-mass was largely invariant between young and old individuals. Thus altered neuro-musculoskeletal function may have differing effects on muscle function. Unfortunately, how altered biomechanics impacts muscle function in osteoarthritic gait is largely unknown.

Quantification of muscle function may provide novel insights into the biomechanical conditions associated with presence, severity and progression of tibiofemoral-joint osteoarthritis. In particular it may reveal how reported kinematic changes in osteoarthritic gait, such as pronounced varus thrust (Chang et al., 2004), increased trunk sway (Mundermann et al., 2008a), increased toe-out (Chang et al., 2007; Jenkyn et al., 2008; Rutherford et al., 2008) and reduced walking speed (Mundermann et al., 2004), and associated kinetic changes at the hip, knee and ankle (Astephen et al., 2008a; Mundermann et al., 2005) affect the timing and coordination of muscles in accelerating the body centre of mass. Furthermore, analysis of muscle function may help explain how localised changes in knee-spanning muscle action, such as dysfunction and loss of strength in the quadriceps (Mizner et al., 2003; Petterson et al., 2008; Petterson et al., 2007; Thompson et al., 2013) and elevated co-activity of the quadriceps and hamstrings (Hortobagyi et al., 2005; Hubley-Kozey et al., 2009; Rutherford et al., 2013;
Rutherford et al., 2011; Zeni et al., 2010), ultimately impacts timing and coordination of the other major muscles of the lower limb in gait. Any differences in muscle function between osteoarthritic individuals and healthy controls may ultimately help to explain both elevated medial compartment forces and higher EKAM in the diseased condition.

2.3.4 Mid-stance loads and the “asymptomatic” limb

Non-pharmacologic interventions for knee OA which modify patient biomechanics are typically aimed at reducing the peaks of EKAM (Farrokhi et al., 2013). However, recent studies have also found that elevated EKAM through mid-stance is associated with greater disease severity (Astephen et al., 2008b) and the future need for TKR (Hatfield et al., 2015b) in OA patients. Elevated loading at the peaks and through mid-stance may together point towards a role for cumulative loading in the initiation and progression of medial knee OA (Maly, 2008; Miller et al., 2014). Thus a detailed understanding of why OA individuals may be less able to unload the knee through mid-stance may guide the development of novel clinical interventions which more effectively reduce loading throughout the whole of stance, not just the peaks.

Furthermore, in unilateral medial knee OA, the presence of radiographic features of OA in the asymptomatic limb is common (Felson et al., 1987) but the biomechanics of the asymptomatic limb have not been well-studied. Significant functional asymmetries have been shown to exist between the symptomatic and asymptomatic limbs in unilateral knee OA (Creaby et al., 2012). The risk of progression to bilateral disease is high once unilateral disease is established.
(Metcalf et al., 2012; Spector et al., 1994), after which both knees may be subject to abnormally high loads (Richards and Higginson, 2010). It is not yet clear if the asymptomatic limb represents an early or intermediate state in the progression from healthy to fully-symptomatic OA or whether it represents a unique condition in itself. Thus a more detailed understanding loading in the asymptomatic knee would help determine if and how the asymptomatic limb should also be considered in clinical interventions for unilateral knee OA.

2.3.5 Cumulative loads in osteoarthritic gait

_in vitro_ studies of knee cartilage loading have found that peak load as well as load rate, frequency and number of loading cycles can cause compositional and metabolic changes in cartilage (Andriacchi et al., 2009; Chen et al., 1999). This may implicate excessive cumulative loading in the knee in the initiation and progression of medial knee OA (Maly, 2008; Miller et al., 2014). This supposition is supported by an _in vivo_ study of cumulative loading in the spines of factory workers which, based on measurements of vertebral joint reaction impulse, showed that cumulative loads were associated with increased severity of OA symptoms (Seidler et al., 2001).

The knee adduction moment angular impulse (KAI), defined as the time-integral of EKAM (Thorp et al., 2006a), may provide a surrogate for cumulative loading in the medial compartment of the tibiofemoral-joint as _in vivo_ measurement of loading in the natural knee is currently not feasible. As discussed previously, EKAM was itself proposed as a surrogate for the forces in the medial compartment (Prodromos et al., 1985), and sustained elevated EKAM through
mid-stance has been linked to future need for total knee replacement (TKR) (Hatfield et al., 2015b). Together with increased peak EKAM typically reported in OA patients, these findings reinforce the potential role of cumulative loading in the pathomechanics of OA.

Recent studies have sought to investigate the viability of KAI as a means of quantifying loading and disease severity in osteoarthritic knees. Recently, Maly et al. (2013) found that the magnitude of KAI distinguishes between osteoarthritic and healthy knees. In fact, while Hatfield et al. (2015a) found good overall correlation between EKAM magnitude and KAI, Maly et al. (2013) found that KAI may actually be more sensitive than EKAM in distinguishing between disease severities (Kean et al., 2012) hence may be a more useful clinical surrogate measure of knee-joint loading. However, from a study using individuals with TKR (Walter et al., 2010), the magnitude of KAI has only a moderate association with the magnitude of medial compartment impulse, defined as the time-integral of the medial compartment force during stance. This suggests that, in the same way that EKAM may not accurately reflect the magnitude of medial compartment force (Meyer et al., 2013; Walter et al., 2010), KAI may also not reflect the true magnitude of medial compartment impulse.

Despite this KAI may prove a useful surrogate measure in clinical assessments to distinguish OA severity. Therefore further research is required to better both medial compartment impulse and KAI during both healthy and osteoarthritic gait. The altered muscle forces and structural changes in the lower-limb due to OA that impact the magnitude and duration of loading in the compartments of the tibiofemoral-joint would also presumably affect cumulative
loads. Yet the manner in which individual muscles, gravity and inertia contribute to both medial compartment impulse and KAI has to date not been quantified for healthy or osteoarthritic gait. Importantly, how these contributions change with disease severity has not yet been established and may be essential for the future use of KAI as a clinical surrogate measure of cumulative loading in osteoarthritic knees.

2.4 OVERALL RESEARCH QUESTIONS

It has been established from the review of the literature to date that a detailed examination of the contributions to joint loads in osteoarthritic gait would provide a novel, important and useful insight into the pathomechanics of medial knee OA which may facilitate the development of improved surrogate measures for clinical assessment of OA patients, and help direct the development of innovative interventions to prevent or mitigate disease progression. In particular, this thesis aims to answer the following research questions:

1. To what extent do non-knee-spanning muscles impact medial and lateral compartment loading during gait, and how do their effects differ from knee-spanning muscles?

2. How do changes in muscle forces due to medial knee OA facilitate greater medial compartment loads in osteoarthritic knees, and what is the role of frontal-plane alignment in this?
3. Does muscle function in accelerating the body centre-of-mass during gait differ in OA patients, and how might any differences influence loading in osteoarthritic knees?

4. Do surrogate measures of knee-joint loads – EKAM and KAI – appropriately reflect the composition of actual medial compartment forces, and importantly, do the changes in surrogate measures due to medial knee OA accurately reflect changes in actual medial compartment load?

2.5 SPECIFIC OBJECTIVES

To facilitate exploration and discussion of the aforementioned research questions, four studies were undertaken to achieve the following specific objectives:

1. To develop a novel computational method to quantify the contributions by the individual knee-spanning and non-knee-spanning muscles of the lower-limb, gravity and inertia to the medial and lateral compartments of the tibiofemoral-joint, and also to the external knee adduction moment, during walking gait (Chapter 3).

2. To quantify the contributions by the individual muscles of the lower-limb, gravity and inertia to the loading of the tibiofemoral compartments in the symptomatic and asymptomatic limbs of varus mal-aligned unilateral medial knee OA patients during gait, and to compare the results with those of healthy controls (Chapter 4).
3. To understand and explain the differences in muscle function during gait, and consequently the differences in the individual contributions to the external knee adduction moment, between varus mal-aligned unilateral medial knee OA patients and healthy controls (Chapter 5).

4. To investigate how the contributions to cumulative loading in the medial and lateral compartments of the tibiofemoral-joint by individual muscles, gravity and inertia change with increasing disease severity, and to compare the results with those of a potential surrogate, the external knee adduction moment angular impulse (Chapter 6).

2.6 FIGURES
This section contains the figures associated with this critical review of the literature to date.
Figure 2.1 Cartilage loss in medial knee OA

(A) Standing radiograph of the tibiofemoral-joint for an individual with medial knee OA showing joint-space narrowing in the medial compartment due to cartilage loss. Figure reproduced from Shull (2013). (B) Intraoperative photograph showing cartilage loss (black arrow) on the medial compartment of the tibiofemoral-joint of an individual with medial knee OA. Figure reproduced from Howell (2010).
Figure 2.2 Typical pattern of loading in the tibiofemoral compartments of the knee

Illustrative figure showing the typical pattern of loading in the tibiofemoral compartments. In healthy individuals, both compartments are typically compressed during level walking, stair ascent and descent, with the medial compartment bearing greater loads than the lateral compartment.

Figure 2.3 Variation in medial compartment loading patterns and magnitudes based on TKR

Medial compartment forces measured during gait in individuals fitted with instrumented TKR showing considerable variation in measured force patterns and magnitudes amongst individuals. Figure reproduced from Kutzner et al. (2013b).
Figure 2.4 An example of a lower-limb musculoskeletal model incorporating a geometric contact-based model of the knee with soft tissues

A typical computational model of the knee used to evaluate joint loads. This is an 18-degree-of-freedom lower-limb musculoskeletal model developed by Shelbume et al. (2004) which incorporated 5 lower-limb skeletal segments, 13 knee-spanning muscles, 13 non-linear elements to represent knee ligaments and a geometric contact-based model of the articulating surfaces of the tibiofemoral-joint. Figure adapted from Shelburne et al. (2004).
Figure 2.5 Variation in modelled medial compartment loading patterns during gait

A comparison of medial compartment forces (A), lateral compartment forces (B) and net tibiofemoral-joint forces (C) for level gait calculated using musculoskeletal models and also measured directly using TKR showing considerable variation in force patterns and magnitudes. Figure reproduced from Winby et al. (2009).
Muscle contributions to centre-of-mass support (vertical GRF), progression (fore-aft GRF) and balance (mediolateral GRF) is one definition of muscle function and can be quantified by decomposing the GRF. Five major muscles provide support, progression and balance: the gluteus medius, gluteus maximus, vasti, soleus and gastrocnemius. Figure reproduced from Pandy and Andriacchi (2010).
Figure 2.7 Muscle contributions to the net tibiofemoral-joint force

Individual muscle contributions to the net tibiofemoral-joint force in one gait cycle. Knee-spanning muscles contribute the largest compressive force on the joint however two non-knee-spanning muscles, the gluteus maximus and the soleus, provide considerable contributions in early and late stance respectively. Figure reproduced from Sasaki and Neptune (2010).

Figure 2.8 The external knee adduction moment

Illustrative figure showing how the external knee adduction moment is calculated. It is defined as the frontal-plane moment produced by the GRF about the knee and is calculated by multiplying the magnitude of the GRF by the length of the moment arm of the GRF vector with respect to the knee-joint centre.
Figure 2.9 Variation in the external knee adduction moment based on TKR

The external knee adduction moment calculated during gait in individuals fitted with instrumented TKR showing considerable variation in patterns and magnitudes amongst individuals. Figure reproduced from Kutzner et al. (2013b).
CHAPTER 3
MUSCLES THAT DO NOT CROSS THE KNEE CONTRIBUTE TO THE KNEE ADDUCTION MOMENT AND TIBIOFEMORAL COMPARTMENT LOADING DURING GAIT

Chapter summary
This study aimed to develop a method for quantifying the individual muscle contributions to the medial and lateral knee compartment forces during healthy gait, and to determine whether these quantities could be inferred from their contributions to the external knee adduction moment. Gait data from eight healthy male subjects were used to compute each individual muscle contribution to the external knee adduction moment, the net tibiofemoral-joint reaction force and reaction moment. The individual muscle contributions to the medial and lateral compartment forces were then found using a least-squares approach. While knee-spanning muscles were the primary contributors, non-knee-spanning muscles (e.g. the gluteus medius) also contributed substantially to the medial compartment compressive force. Furthermore, knee-spanning muscles tended to compress both compartments, while most non-knee-spanning muscles tended to compress the medial compartment but unload the lateral compartment. Muscle contributions to the external knee adduction moment, particularly those from knee-spanning muscles, did not accurately reflect their tendencies to compress or unload the medial compartment. This finding may further explain why gait modifications may reduce the knee adduction moment without necessarily decreasing the medial compartment force.
3.1 INTRODUCTION

Medial knee osteoarthritis (OA) is a painful and debilitating disease that has been associated with biomechanical changes or dysfunction at the hip, knee and ankle (Astephen et al., 2008a). Increased proportion of compressive loading on the medial compartment of the tibiofemoral-joint may play an important role in the development and progression of medial knee OA (Miyazaki et al., 2002; Prodromos et al., 1985). As the direct measurement of compartment forces requires instrumented implants, computational modelling (Hurwitz et al., 1998; Schipplein and Andriacchi, 1991; Shelburne et al., 2006; Winby et al., 2009) and the net external knee adduction moment (Miyazaki et al., 2002; Schipplein and Andriacchi, 1991) are two widely used methods to directly and indirectly predict the characteristics of the medial compartment force, respectively.

Muscles are the main contributors to joint loading (Herzog et al., 2003) and several modelling studies have examined how muscles contribute to knee-joint loading during gait (Hurwitz et al., 1998; Sasaki and Neptune, 2010; Schipplein and Andriacchi, 1991; Shelburne et al., 2006; Winby et al., 2009). Shelburne et al. (2006) and Winby et al. (2009) concluded that knee-spanning muscles contribute significantly to medial compartment compression in normal walking, particularly the quadriceps and gastrocnemius muscles. Pandy and Andriacchi (2010) and Sasaki and Neptune (2010) showed that non-knee-spanning muscles also contribute to the net tibiofemoral-joint contact force through dynamic coupling (Zajac and Gordon, 1989). However, none of these studies evaluated the contributions of the non-knee-spanning muscles to the medial and lateral compartment forces. Such understanding may be crucial in the
study of biomechanical factors associated with medial knee OA and the design of non-pharmacological clinical interventions.

The external knee adduction moment, given by the product of the ground reaction force (GRF) and its lever arm about the knee-joint centre, has been identified as a surrogate measure for medial compartment force (Schipplein and Andriacchi, 1991) and is associated with risk of OA progression (Miyazaki et al., 2002). Gait modification strategies have been proposed to mitigate pain and progression of medial knee OA by shortening the moment arm of the GRF about the knee, and consequently reducing the external knee adduction moment (Jenkyn et al., 2008; Mundermann et al., 2008a). However, a study based on in vivo measurements showed that reducing the external knee adduction moment may not necessarily reduce medial compartment force (Walter et al., 2010). A comparison between muscle contributions to the external knee adduction moment and medial compartment force may help to explain this finding.

The aim of the present study was twofold: first, to calculate and explain the individual contributions from all muscles of the lower limb to the patterns of force transmitted to the medial and lateral compartments of the tibiofemoral-joint during normal walking; and second, to assess whether a muscle’s contribution to the external knee adduction moment is indicative of its contribution to the medial compartment force.

3.2 METHODS

3.2.1 Gait experiments

Gait experiments were performed on eight healthy male subjects (age: 26 ± 4 yrs;
weight: 70 ± 5 kg; height: 178 ± 4 cm) in the Human Motion Laboratory at the University of Melbourne. Subjects gave their informed consent after approval was obtained from the University of Melbourne Human Research Ethics Committee. Joint motion, GRFs and muscle EMG activity were recorded simultaneously as each subject walked at his preferred speed (1.5 ± 0.1 m/s) over level ground. Three-dimensional locations of retro-reflective markers attached to each subject’s body were measured using a video-based motion capture system (Vicon, Oxford Metrics Ltd., Oxford) with nine cameras sampling at 120 Hz. Foot-ground forces were measured using three strain-gauged force plates (Advanced Mechanical Technology Inc., Watertown, MA) sampling at 1080 Hz. Surface EMG electrodes were placed over the bellies of six muscles in one leg: gluteus maximus, gluteus medius, medial hamstrings, vastus lateralis, medial gastrocnemius and soleus. Raw marker trajectories and GRFs were low-pass filtered using a fourth-order Butterworth filter with cut-off frequencies of 4 Hz and 60 Hz, respectively.

3.2.2 Musculoskeletal modelling

A scaled-generic three-dimensional muscle-actuated whole-body model was used to calculate lower-limb muscle forces for one gait cycle (Anderson and Pandy, 2001a). The skeleton was represented as a 10-segment, 23-degree-of-freedom linkage. The head, arms and torso were modelled as a single rigid body, which articulated with the pelvis via a ball-and-socket back joint. Each hip was modelled as a ball-and-socket joint, each knee as a hinge, each ankle-subtalar complex as a universal joint, and each metatarsal joint as a hinge. Joint centre locations were determined by minimising the differences between the positions of surface
markers located on the subject and virtual markers defined in the model (Reinbolt et al., 2005). The whole-body model was actuated by 54 Hill-type muscle-tendon units; however, passive forces provided by ligaments and other soft tissues were omitted. A musculoskeletal model was created for each subject by scaling the segmental inertial properties of the model, muscle attachment sites and muscle paths (i.e. the geometric path followed by the muscle-tendon unit from origin to insertion, which includes wrapping around bones, joints and other soft tissues) to each subject’s height and weight. The force-generating properties of the muscles were the same as those identified by Anderson and Pandy (2001a).

Muscle forces were found using inverse dynamics and static optimisation. Measurements of the subject’s motion and GRFs were input into the corresponding subject’s model and inverse dynamics was used to calculate the net moments exerted about the back, hip, knee and ankle joints for one gait cycle. The net joint moments were decomposed into individual muscle forces by solving an optimisation problem that minimised the sum of the squares of muscle activations. The optimisation problem was solved subject to the physiological bounds on muscle force imposed by each muscle’s force-length-velocity property (Anderson and Pandy, 2001b).

3.2.3 Net TF-joint forces and external knee adduction moment

For each trial, the contributions of each individual muscle to the external knee adduction moment, net tibiofemoral-joint (TF) reaction force and net TF-joint reaction moment were computed. Specifically, the contribution by each muscle $m$ to the external knee adduction moment $M_{EkAM}^m$ was determined from the vector...
product of the contribution of that muscle’s GRF contribution $F_{m}^{GRF}$ (Lin et al., 2010) and the perpendicular distance of this GRF contribution vector from the knee-joint centre $r_{m}^{MA}$ (Schipplein and Andriacchi, 1991) (Figure 3.1A):

$$M_{m}^{KAM} = r_{m}^{MA} \times F_{m}^{GRF}$$  \hspace{1cm} (3.1)

At each time step for each analysed gait trial, a muscle’s contributions to the three-dimensional net TF-joint reaction force $F_{m}^{react}$ and three-dimensional net TF-joint reaction moment $M_{m}^{react}$ were computed by applying only that muscle’s force vector $F_{m}^{MUS}$ at the origin and insertion points on the musculoskeletal model and also that muscle’s GRF contribution vector $F_{m}^{GRF}$ at the centre-of-pressure on the stance foot, and then solving the equations of motion and subsequently the joint reaction equations (Correa et al., 2010) (Figures 3.1B and C).

3.2.4 Medial and lateral tibiofemoral compartment forces

A separate 18-degree-of-freedom quasi-static model of the right knee (Shelburne et al., 2004) with 5 lower-limb segments, 13 knee-spanning muscles and 13 non-linear elements to represent knee-spanning ligaments was used to estimate the location of the contact points on the tibial condyles. The tibiofemoral-joint was modelled as a Hertzian, contact-based, six-degree-of-freedom joint with the geometry of the articulating surfaces based on cadaver studies (Garg and Walker, 1990). At each time step each subject’s joint angles, all 13 knee-spanning muscle forces and the GRF were applied to the model. An estimation of the contact points was then obtained by equilibrating the muscle forces, GRF and joint forces, and computing the centres of pressure of the contact areas.

At each instant of the gait cycle, each muscle contribution to the TF-joint
reaction force was partitioned into a medial and lateral compartment force
collection by solving a least-squares problem (Figure 3.1D). A set of three force
equilibrium equations and three moment equilibrium equations was written at the
knee for each muscle \( m \):

\[
\mathbf{F}_{m}^{\text{med}} = \mathbf{F}_{m}^{\text{med}} + \mathbf{F}_{m}^{\text{lat}}
\]

(3.2)

\[
\mathbf{M}_{m}^{\text{med}} = (\mathbf{r}_{\text{med}} \times \mathbf{F}_{m}^{\text{med}}) + (\mathbf{r}_{\text{lat}} \times \mathbf{F}_{m}^{\text{lat}})
\]

(3.3)

where \( \mathbf{F}_{m}^{\text{med}} \) and \( \mathbf{F}_{m}^{\text{lat}} \) are the unknown 3 x 1 vectors of the contributions of muscle\( m \) to the medial and lateral compartment forces; \( \mathbf{F}_{m}^{\text{react}} \) is the known 3 x 1 vector of the contribution of muscle \( m \) to the TF-joint reaction force; \( \mathbf{r}_{\text{med}} \) and \( \mathbf{r}_{\text{lat}} \) are the 3 x 1 position vectors of the medial and lateral contact points with respect to the knee-joint centre; and \( \mathbf{M}_{m}^{\text{react}} \) is the known 3 x 1 vector of the contribution of muscle \( m \) to the TF-joint reaction moment. All vectors were expressed in the tibial coordinate system. Equations 3.2 and 3.3 were then written in matrix form:

\[
\mathbf{A}_{m} \mathbf{x}_{m} = \mathbf{b}_{m}
\]

(3.4)

where \( \mathbf{A}_{m} \) is a 6 x 6 matrix of coefficients; \( \mathbf{x}_{m} = [\mathbf{F}_{m}^{\text{med}} \mathbf{F}_{m}^{\text{lat}}]^{T} \); and \( \mathbf{b}_{m} = [\mathbf{F}_{m}^{\text{react}} \mathbf{M}_{m}^{\text{react}}]^{T} \).

Finally, as Equation 3.4 had only 5 independent equations, a pseudo-
inverse approach was used to compute an analytical least-squares solution for \( \mathbf{x}_{m} \). Thus:

\[
\mathbf{x}_{m} \approx \mathbf{x}_{m}^{+} = \mathbf{A}_{m}^{+} \mathbf{b}_{m}
\]

(3.5)

where \( \mathbf{A}_{m}^{+} \) is the Moore-Penrose pseudo-inverse of the coefficient matrix \( \mathbf{A}_{m} \); and \( \mathbf{x}_{m}^{+} \) is the minimum-norm least-squares solution for the under-determined system given by Equation 3.4. In this study, a MATLAB (2010a, The Mathworks Inc, MA) function \textit{pinv} was used to compute \( \mathbf{x}_{m}^{+} \) for each muscle at each time step.
The axial components of $x_m$ were defined as the medial and lateral compartment forces.

For each trial, the calculated knee-joint reaction forces were normalised to units of body weight (BW) while external knee adduction moments were normalised to units of percentage of body weight multiplied by height (%BW*HT). The means and standard deviations for the eight subjects were then calculated.

### 3.3 RESULTS

The timing and magnitude of predicted muscle forces (Figure 3.2) matched well with our recorded EMG activity and the results of a previous study (Anderson and Pandy, 2001b). The net axial TF-joint reaction force due to all muscles (Figures 3.3A and D and Table 3.1, ALL MUSCLES) was comparable in magnitude to that reported by related modelling studies (Hurwitz et al., 1998; Sasaki and Neptune, 2010; Shelburne et al., 2006; Winby et al., 2009), including studies based on in vivo measurements (Kutzner et al., 2010; Zhao et al., 2007a). Knee-spanning muscles contributed most to the axial TF-joint reaction force (Figure 3.3A) as reported by Sasaki and Neptune (2010) and Pandy and Andriacchi (2010). Non-knee-spanning muscles provided relatively small, but non-negligible, contributions to the axial TF-joint reaction force throughout stance, mostly due to soleus (SOL) in late stance (Figure 3.3D), in accordance with the findings of Sasaki and Neptune (Sasaki and Neptune, 2010) and Pandy and Andriacchi (Pandy and Andriacchi, 2010). The net effects of knee-spanning and non-knee-spanning muscles on the axial TF-joint reaction force were compressive.
throughout stance.

The total medial compartment force was compressive throughout stance with two distinct peaks of 2.3 BW at contralateral toe-off and contralateral heel-strike (Figures 3.3B and E, ALL MUSCLES). The magnitudes of both peaks were comparable to those reported previously (Hurwitz et al., 1998; Shelburne et al., 2006; Winby et al., 2009). Knee-spanning and non-knee-spanning muscles contributed almost equally to medial compartment forces (Figures 3.3B and E), with non-knee-spanning muscles contributing 0.1 BW more at the first peak and knee-spanning muscles contributing 0.3 BW more at the second peak. The net effects of knee-spanning and non-knee-spanning muscles on medial compartment force were compressive throughout stance. Knee-spanning muscle contributions at contralateral toe-off (Figure 3.3B) were dominated by vasti (VAS), and at contralateral heel-strike were dominated by gastrocnemius (GAS), as reported by Winby et al. (2009). Of the non-knee-spanning muscles, the combined contribution of the anterior (GMEDA) and posterior gluteus medius (GMEDP) was most significant throughout stance (Figure 3.3E). SOL contributed virtually nothing to the medial compartment.

The total lateral compartment force was compressive throughout stance and compared well with that reported previously (Hurwitz et al., 1998; Shelburne et al., 2004; Winby et al., 2009). However, while the net effect of knee-spanning muscles was compressive (Figure 3.3C and Table 3.1), the non-knee-spanning muscles tended to unload the lateral compartment (Figure 3.3F and Table 3.1). Hamstrings (HAMS) contributed most at heel-strike, followed by VAS in early stance and GAS in late stance. Furthermore, HAMS and VAS contributed more
force to the lateral compartment than the medial compartment. SOL was the major non-knee-spanning muscle that provided most compression on the lateral compartment, while GMEDA and GMEDP tended to unload it (Figures 3.3E and F).

The magnitudes of the two peaks of the total external knee adduction moment were consistent with several previous studies (Hurwitz et al., 1998; Pandy and Andriacchi, 2010; Shelburne et al., 2006) (Figure 3.4 and Table 3.1, ALL MUSCLES), with the first peak at contralateral toe-off 20% higher than the second peak at contralateral heel-strike. GMEDA and GMEDP contributed most to the external knee adduction moment, whereas GAS, VAS, SOL and the plantarflexor-evertor muscles (PFEV) contributed external knee abduction moments.

3.4 DISCUSSION
The objectives of this study were to calculate and explain the contributions of individual lower-limb muscles to the medial and lateral knee compartment forces during normal walking; and to determine if a muscle’s contribution to the external knee adduction moment was indicative of its contribution to medial compartment force. The results showed that both knee-spanning and non-knee-spanning muscles contributed to compartment forces. Importantly, non-knee-spanning muscles played a more significant role in loading each of the compartments than the TF-joint as a whole. The results also suggest that a muscle’s contribution to the external knee adduction moment is not always a good indicator of its contribution to medial compartment force.
3.4.1 Comparison of knee spanning and non-knee-spanning contributions

In general, the non-knee-spanning muscles compressed one compartment but unloaded the other, whereas the knee-spanning muscles compressed both compartments (Figure 3.3). Knee-spanning muscles contributed to compression in both the medial and lateral compartments, reflecting not only their role in stabilising the knee in the frontal plane (Schipplein and Andriacchi, 1991; Shelburne et al., 2006) but also their potential role in knee OA. Interestingly, knee-spanning and non-knee-spanning muscles contributed equally to medial compartment force. In fact, the relative contribution by non-knee-spanning muscles to the medial compartment force was considerably higher throughout stance than the contribution to the axial TF-joint reaction force (Figure 3.3). For most non-knee-spanning muscles, the combination of TF-joint reaction force and reaction moment contributions acting at the knee-joint centre was different to that of knee-spanning muscles (compare Figures 3.5A and B), resulting in compression in one compartment but unloading the other.

3.4.2 Dynamic coupling pathways

In the process of computing muscle contributions to the TF-joint reaction force and moment, each muscle’s force and its GRF contribution were treated as separate loads on the system (Anderson and Pandy, 2001a; Correa et al., 2010; Lin et al., 2010). Thus, each non-knee-spanning muscle could contribute to knee-joint mechanics via three independent pathways: (1) static propagation of the muscle’s GRF contribution throughout the system; (2) dynamic propagation of the
muscle’s GRF contribution throughout the system (Anderson and Pandy, 2003); and (3) *dynamic* propagation of the muscle’s joint torque contribution throughout the system (see Figure 3.6 and Appendix A). In order to realise all of these contributions, the problem needed to be solved for dynamic equilibrium. Previous studies that did not include non-knee-spanning muscles partially accounted for their effects by implementing Pathway 1, and then subsequently calculated compartment forces by solving for static equilibrium (Hurwitz et al., 1998; Schipplein and Andriacchi, 1991; Shelburne et al., 2006; Winby et al., 2009). While the effects of the Pathways 2 and 3 can be significant, these dynamic pathways tended to approximately cancel each other, suggesting that quasi-static musculoskeletal models that include the GRF may be sufficient for solving joint reaction forces and reaction moments during level walking. To show this, contributions of four non-knee-spanning muscles to the axial TF-joint reaction force were decomposed into contributions from each pathway (Figure 3.7). For each muscle shown, the Pathways 2 and 3 are approximately equal in magnitude but opposite in sign, hence the sum of the three pathways resembles Pathway 1 (Figure 3.7, TOTAL). We note however that in more ballistic or dynamics tasks, such as jumping or sprinting, quasi-static models may potentially be insufficient for accurate computation of knee-joint loads.

### 3.4.3 Contributions to the external knee adduction moment

It was evident that a muscle’s contribution to the external knee adduction moment did not necessarily reflect its contribution to the medial compartment force. In particular, contributions by knee-spanning muscles to the external knee adduction
moment were not consistent with their contributions to medial compartment force. For example, VAS and GAS produced external knee abduction moments (Figure 3.4), suggesting they contributed minimally or even unloaded the medial compartment, yet both compressed it considerably. Contributions by non-knee-spanning muscles to the external knee adduction moment better predicted the contribution to medial compartment force. For example, GMEDA and GMEDP both contributed significantly to the external knee adduction moment and also to medial compartment compression. Similarly, SOL produced an external knee abduction moment and contributed minimally to medial compartment force. However, the contributions by some non-knee-spanning muscles to the external knee adduction moment were not consistent with their contributions to medial compartment force (e.g. PFEV).

3.4.4 Insufficiency of analysing only the net tibiofemoral-joint force

Our results show that studying only the axial TF-joint reaction force may underestimate the role of non-knee-spanning muscles in knee OA. Thus, future clinical interventions for medial knee OA may need to place greater emphasis on the effects of non-knee-spanning muscles on joint mechanics, particularly that of the gluteus medius. Importantly, our results imply that individual muscle contributions to the knee adduction moment do not suffice as a surrogate measure of individual muscle contributions to medial compartment force. In particular, our results suggest that decreasing a muscle’s contribution to the knee adduction moment may not necessarily reduce its contribution to the medial compartment force. This may help to explain the recent finding that reducing the net external
knee adduction moment using gait modifications may not reduce the total medial compartment force (Walter et al., 2010).

3.4.5 Accuracy of contact point trajectories

Evaluating the accuracy of the calculated tibiofemoral contact point trajectories (Figure 3.8A) was difficult due to the scarcity of available data. However, we were at best able to qualitatively assess the antero-posterior motion of the tibiofemoral contact points (Figure 3.8B). Although Kozanek et al. (2009) reported the trajectories of the femoral condylar centres rather than the contact points on the tibial plateau during stance, there were two key similarities: (1) the trajectories of the tibiofemoral contact points were closely linked to knee flexion, although contrary to the motion of the femoral condyles, with the contact points shifting posteriorly on the tibial plateau with increasing knee flexion, similar to other weight-bearing tasks (Freeman and Pinskerova, 2005); and (2) the medial side showed greater excursion than the lateral side, although the tibiofemoral contact points showed slightly larger total range of motion than the femoral condyles of Kozanek et al. (2009) (medial contact point: 12 mm vs 10 mm; lateral contact point: 6 mm vs 4 mm). This may be because our subjects walked at a higher speed (1.5 m/s vs 0.67 m/s) and exhibited greater knee flexion (about 20° vs 10° at contralateral toe-off). Thus, we believe the trajectories of the tibiofemoral contact points were estimated reasonably well in the knee model.

3.4.6 Limitations

There are a number of potential limitations of this study. Firstly, the knee was
modelled as a hinge in the whole-body model, thus ignoring the effects of adduction-abduction and internal-external rotation torques, which can be large (Schache and Baker, 2007). However, accurate measurement of transverse- and frontal-plane knee kinematics is difficult using marker-based methods due to soft-tissue artefact (Akbarshahi et al., 2010). Secondly, the use of static optimisation to calculate muscle forces might be considered a limitation. However, static optimisation produces robust solutions that are consistent with the sequence and timing of muscle EMG measured during gait and with solutions obtained from the application of dynamic optimisation (Anderson and Pandy, 2001b). Thirdly, the influence of ligaments, cartilage, fluids and other soft tissues was not included in the whole-body model. However, the passive force contributions by the ligaments, joint capsule, etc. are small (Shelburne et al., 2004), and would not have significantly affected our results. Finally, although the knee model was able to estimate contact points reasonably well, TF-joint geometry could not be scaled for each individual subject. To simulate the effect of scaling knee geometry, a sensitivity analysis was performed for one subject. The distance between two contact points was adjusted ±20% at each instant of the gait cycle, yet the maximum change in peak compartment forces was only ±8% and the net compartment forces were always compressive.

3.5 CONCLUSIONS

In summary, this study is the first to compute individual contributions from all lower-limb muscles to the medial and lateral compartments of the knee for any activity. In walking, non-knee-spanning muscles contributed substantially,
especially to medial compartment compression, suggesting that these muscles may influence medial knee OA more than previous studies suggest. The influence of muscles on medial compartment force could not be directly inferred from their contributions to the external knee adduction moment, providing a possible explanation for why reducing the external knee adduction moment may not necessarily decrease the medial compartment force.

3.6 TABLES AND FIGURES
This section contains the tables and figures associated with the results and discussion of the present study.
<table>
<thead>
<tr>
<th>Muscle</th>
<th>Peak TFJ Reactions (BW)</th>
<th>Frontal-Plane Moment (% BW*HT)</th>
<th>Medial (BW)</th>
<th>Lateral (BW)</th>
<th>Peak External Knee Adduction Moment (% BW*HT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAS</td>
<td>1.61 ± 0.36</td>
<td>-0.49 ± 0.09</td>
<td>0.97 ± 0.20</td>
<td>0.64 ± 0.17</td>
<td>-0.79 ± 0.23</td>
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<tr>
<td>BFSH</td>
<td>0.28 ± 0.10</td>
<td>0.57 ± 0.29</td>
<td>0.62 ± 0.21</td>
<td>0.35 ± 0.18</td>
<td>0.51 ± 0.23</td>
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<tr>
<td>VAS</td>
<td>1.40 ± 0.51</td>
<td>0.27 ± 0.15</td>
<td>0.43 ± 0.16</td>
<td>0.86 ± 0.31</td>
<td>0.47 ± 0.22</td>
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<td>RF</td>
<td>0.76 ± 0.18</td>
<td>0.10 ± 0.23</td>
<td>0.33 ± 0.08</td>
<td>0.47 ± 0.22</td>
<td>-0.91 ± 0.29</td>
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<td>HAMS</td>
<td>1.66 ± 0.42</td>
<td>0.34 ± 0.31</td>
<td>0.70 ± 0.26</td>
<td>0.97 ± 0.24</td>
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<td>PFEV</td>
<td>0.04 ± 0.02</td>
<td>-0.60 ± 0.29</td>
<td>0.24 ± 0.11</td>
<td>0.61 ± 0.35</td>
<td>-1.07 ± 0.36</td>
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<td>SOL</td>
<td>0.53 ± 0.13</td>
<td>0.34 ± 0.63</td>
<td>0.24 ± 0.11</td>
<td>0.57 ± 0.24</td>
<td>-1.07 ± 0.36</td>
</tr>
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<td>GMAX</td>
<td>0.33 ± 0.13</td>
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<td>0.13 ± 0.16</td>
<td>0.50 ± 0.15</td>
<td>2.23 ± 0.72</td>
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<tr>
<td>GMEDA</td>
<td>0.20 ± 0.07</td>
<td>-0.65 ± 0.18</td>
<td>0.50 ± 0.15</td>
<td>2.23 ± 0.72</td>
<td>1.99 ± 0.45</td>
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<td>GMAXP</td>
<td>0.10 ± 0.05</td>
<td>0.25 ± 0.35</td>
<td>0.75 ± 0.12</td>
<td>2.23 ± 0.72</td>
<td>1.99 ± 0.45</td>
</tr>
<tr>
<td>ALL MUSCLES</td>
<td>3.36 ± 0.55</td>
<td>-2.68 ± 0.84</td>
<td>2.34 ± 0.42</td>
<td>1.30 ± 0.31</td>
<td>2.80 ± 0.80</td>
</tr>
</tbody>
</table>

Peak means and corresponding standard deviations of the contributions of the major lower-limb muscles to the axial component of the TFJ reaction force, the frontal-plane TFJ reaction moment, and the axial components of the medial and lateral tibiofemoral compartment forces from the averaged group data of eight subjects. Compressive forces and anti-clockwise moments are positive.
At each instant of the gait cycle, the contribution by muscle $m$ to (A) the external knee adduction moment $M^{EKAM}_m$ is the cross product of the moment arm vector $r^{MA}_m$ and the GRF contribution $F^{GRF}_m$. To find the contribution to the medial and lateral compartment forces, (B) first apply the muscle force $F^{MUS}_m$ and its GRF contribution $F^{GRF}_m$; then (C) solve the equations of motion and compute joint reaction forces to obtain the TF-joint reaction force $F^{react}_m$ and moment $M^{react}_m$ acting at the knee-joint centre; and (D) partition into medial and lateral compartment forces $F^{med}_m$ and $F^{lat}_m$ acting at contact points located at $r^{med}$ and $r^{lat}$ respectively.
Figure 3.2 Comparison of calculated muscle forces and EMG

Comparison of calculated muscle forces and measured EMG for five major muscles involved in walking: soleus (SOL), gastrocnemius (GAS), vasti (VAS), gluteus maximus (GMAX), and gluteus medius (GMED).
Figure 3.3 Muscle contributions to tibiofemoral compartment forces during stance

Contributions of selected knee-spanning and non-knee-spanning muscles to the axial TF-joint reaction force, and the medial and lateral compartment forces. Compressive forces are positive. Heel strike (HS), contralateral toe-off (CTO), contralateral heel-strike (CHS) and toe-off (TO).
Figure 3.4 Muscle contributions to the external knee adduction moment during stance

Individual muscle contributions to the external knee adduction moment for selected knee-spanning and non-knee-spanning muscles expressed in the tibial coordinate system. Positive moments reflect the tendency for a muscle’s GRF vector to adduct the knee.
Figure 3.5 Schematic representation of how the relative magnitudes of the TF-joint reaction force and moment determine compartment loads

The relative magnitudes of the TF-joint reaction force and moment at the knee-joint centre determine the force distribution between the compartments. (A) For non-knee-spanning muscles, the TF-joint reaction moment dictates the force distribution, causing compression on one compartment, but unloading the other. (B) For knee-spanning muscles, the TF-joint reaction force dictates the force distribution, causing compression on both compartments (e.g. GAS). Longer arrows represent greater magnitude. Downwards pointing arrows are compressive.
Figure 3.6 Example of how knee-joint loads arise from static and dynamic force pathways

Pathway 1
Source: Soleus contribution to GRF, $F_{GRF}^{SOL}$
Mechanism: Static
1. $F_{GRF}^{SOL}$ points upwards and forwards, and tries to translate the foot and tibia upwards and forwards together.
2. To maintain static equilibrium, an equal and opposite compressive force $F_{path,1}^{SOL} = -F_{GRF}^{SOL}$ occurs on the tibia at the knee.

Pathway 2
Source: Soleus contribution to GRF, $F_{GRF}^{SOL}$
Mechanism: Dynamic
1. $F_{GRF}^{SOL}$ creates a dorsiflexion torque about the ankle which tries to rotate the foot anticlockwise and the tibia clockwise.
2. This rotation effect tries to pull the knee downwards and forwards.
3. At the same time, the inertia of the femur and rest of the body resists this attempt to pull the knee down and forwards. The resulting effect is to pull the femur and tibia apart, creating a "tensile" force $F_{path,2}^{SOL}$ on the tibia at the knee.

Pathway 3
Source: Ankle torque due to soleus force, $F_{MUS}^{SOL}$
Mechanism: Dynamic
1. $F_{MUS}^{SOL}$ creates a plantarflexion torque about the ankle which tries to rotate the foot clockwise and the tibia anticlockwise.
2. This rotation effect tries to push the knee upwards and rearwards.
3. At the same time, the inertia of the femur and rest of the body resists this attempt to push the knee up and rearwards. The resulting effect is to squeeze the tibia against the femur, creating a compressive force $F_{path,3}^{SOL}$ on the tibia at the knee.

$F_{SOL}^{react} = F_{path,1}^{SOL} + F_{path,2}^{SOL} + F_{path,3}^{SOL}$

Hypothetical illustration of how the SOL contribution to the TF-joint reaction force $F_{SOL}^{MUS}$ arises from the one static and two dynamic force pathways. $F_{SOL}^{MUS}$ and $F_{GRF}^{SOL}$ are the SOL muscle force and its contribution to the GRF respectively. Similar reasoning can be used to explain the static and dynamic pathways of the TF-joint reaction moment.
Figure 3.7 Selected non-knee-spanning muscle contributions to the TF-joint load decomposed into contributions from individual force pathways.

Selected non-knee-spanning muscle contributions to the axial TF-joint reaction force decomposed into constituents from three pathways: (1) static GRF propagation; (2) dynamic GRF propagation; and (3) dynamic propagation of the muscle’s joint torque contribution.
Figure 3.8 Example of modelled trajectories of the medial and lateral contact points

(A) Transverse-plane excursions of the medial and lateral contact points in the tibial plateau with respect to the knee-joint centre (origin) in the tibial coordinate system during stance. (B) Antero-posterior motion of the contact points and knee flexion angle during stance.
CHAPTER 4
MUSCLE AND JOINT FORCES IN THE SYMPTOMATIC AND ASYMPTOMATIC KNEES OF MIDDLE-AGED MEDIAL KNEE OSTEOARTHRITIS PATIENTS

Chapter summary
This study quantified the contributions by muscles, gravity and inertia to the tibiofemoral compartment forces in the symptomatic (SYM) and asymptomatic (ASYM) limbs of varus mal-aligned medial knee osteoarthritis (OA) patients, and compared the results with healthy controls (CON). Muscle forces and tibiofemoral compartment loads were calculated using gait data from 39 OA patients and 15 controls (49±7 years). Patients exhibited lower knee flexion angle, higher hip abduction and knee adduction angles, lower knee flexion torque but higher external knee adduction moment. Muscle forces were highest in CON except hamstrings, which was highest in SYM. ASYM muscle forces were lowest for biceps femoris short head and gastrocnemius but otherwise intermediate between SYM and CON. In all subjects vasti, hamstrings, gastrocnemius, soleus, gluteus medius, gluteus maximus and gravity were the largest contributors to medial compartment force (MCF). Inertial contributions were negligible. Highest MCF was found in SYM throughout stance due to subtly higher contributions from hip extensors, ankle plantarflexors and gravity at the first peak; ankle plantarflexors and knee extensors at the second peak; and ankle plantarflexors, hip extensors and abductors during mid-stance. These small individual differences summed to produce significantly higher total MCF. ASYM exhibited higher MCF than CON
only in mid-stance. In patients, diminished non-knee-spanning muscle forces did not produce correspondingly diminished MCF contributions due possibly to the influence of mal-alignment. Our findings emphasise consideration of muscle function, the lower-limb kinematic chain and mid-stance loads in developing interventions for OA, and inclusion of the asymptomatic limb in clinical assessments.
4.1 INTRODUCTION

Increased cyclic compressive loading on the medial compartment of the tibiofemoral (TF) joint is associated with the progression of medial knee osteoarthritis (Andriacchi and Mundermann, 2006) (OA). Determining the root causes of elevated medial compartment force (MCF) is difficult, as a range of neuromuscular, morphological and structural changes associated with medial knee OA have been reported throughout the lower limb. This includes varus mal-alignment and knee-joint laxity (Sharma et al., 2010), strength deficits (Petterson et al., 2008) and elevated co-activations (Rutherford et al., 2011) of knee-spanning muscles, and hip abductor dysfunction (Hinman et al., 2010).

As non-invasive measurement of joint forces is currently not feasible, the external knee adduction moment (EKAM) during gait has been proposed as a surrogate for load distribution (Prodromos et al., 1985), supported to some extent by studies using instrumented total knee replacements (TKR) (Kutzner et al., 2013b; Zhao et al., 2007b) and musculoskeletal modelling (Kumar et al., 2013). However, substantial limitations can exist when relying on the EKAM to study joint loading as it only accounts for the ground reaction force (Schipplein and Andriacchi, 1991) (GRF) and not the direct compressive effect of knee-spanning muscles (Meyer et al., 2013), which can contribute up to one-half of the total MCF in healthy gait (Sritharan et al., 2012). Yet models incorporating the knee extension torque as a surrogate for knee-spanning muscle forces in addition to EKAM have shown only limited improvements in MCF estimates (Meyer et al., 2013). Thus, a detailed examination of knee-joint forces is necessary to understand and improve surrogate measures.
Muscles, gravity and inertia all contribute to the GRF (Lin et al., 2010) by means of dynamic coupling (Zajac and Gordon, 1989) and hence also contribute to knee-joint loads and the EKAM (Sritharan et al., 2012). It has been shown that muscles contribute the most to joint loading during weight-bearing activities in healthy knees (Shelburne et al., 2006), however, the relative contributions by lower-limb muscles to knee-joint loads in osteoarthritic knees are not clearly established. A modelling study of healthy gait showed that non-knee-spanning muscles can account for up to one-half of the total MCF (Sritharan et al., 2012). Notably, the gluteus medius provides most of this non-knee-spanning muscle contribution to MCF and almost all of the positive EKAM in healthy gait (Sritharan et al., 2012). Although OA-specific changes in muscle forces can impact the pattern of loading on the compartments of the TF-joint (Brandon et al., 2014), no study to date has quantified the individual contributions by the lower-limb muscles, gravity and inertia to the pattern of forces in the osteoarthritic knee.

Non-pharmacologic interventions for knee OA which modify patient biomechanics are typically aimed at reducing the peaks of EKAM (Farrokhi et al., 2013). However, recent studies have also found that elevated EKAM through mid-stance is associated with greater disease severity (Astephen et al., 2008b) and the future need for TKR (Hatfield et al., 2015b) in OA patients. Detailed knowledge of how these elevated mid-stance loads arise in patients may help in the development of novel clinical interventions which more effectively reduce loading throughout stance, not just the peaks. Furthermore, significant functional asymmetries exist between the symptomatic and asymptomatic limbs in unilateral knee OA (Creaby et al., 2012) and the risk of progression to bilateral disease is
high once unilateral disease is established (Spector et al., 1994). Thus, understanding loading in the asymptomatic knee would help determine if and how the asymptomatic limb should also be considered in clinical interventions for unilateral knee OA.

The purpose of this study was to quantify the contributions by muscles, gravity and inertia to the forces in the medial and lateral compartments of the TF-joint during walking in both the symptomatic and asymptomatic limbs of varus mal-aligned medial knee OA patients, and to compare the results with healthy controls. As patients may walk with more knee-spanning muscle co-activation than healthy adults (Rutherford et al., 2011), we hypothesised that higher MCF in patients would be due to elevated contributions from the hamstrings, quadriceps and gastrocnemius. We further hypothesised lower gluteus medius forces in patients, but based on the weak association between hip abductor function and EKAM (Rutherford et al., 2014), the gluteus medius contribution to MCF would not be significantly lower than controls.

4.2 METHODS
4.2.1 Participants and clinical assessment

Thirty-nine patients were recruited from a tertiary care centre specialising in orthopaedics, including rehabilitative and surgical (non-arthroplasty) interventions for knee OA. All patients were referred to the centre for potential limb-realignment surgery for one symptomatic knee with radiographic OA primarily affecting the medial compartment. Twenty-five controls matched for sex, age and body mass index (BMI) with no history of knee pain were recruited from the same
community. Of these, 15 controls were then matched to patients for walking speed after gait analysis. Methods for recruitment, inclusion and exclusion criteria, radiographic assessment, patient-reported measures and gait experiments are detailed in a previous publication (Birmingham et al., 2009). Inclusion criteria for patients included varus mal-alignment of the lower-limb and diagnosis of medial knee OA based on the American College of Rheumatology criteria (Altman et al., 1986). Symptoms were assessed using the Knee Injury and Osteoarthritis Outcome Score (KOOS) (Roos et al., 1998). The extent of static frontal-plane mal-alignment (mechanical axis angle) and OA severity (Kellgren-Lawrence grade) were measured from full-limb standing anteroposterior radiographs (Kellgren and Lawrence, 1957). Frontal-plane alignment was also measured in all participants using marker data from a static trial collected prior to gait analysis. The study was approved by the Research Ethics Board for Health Sciences Research Involving Human Subjects of the University of Western Ontario (HSREB No. 09812E).

### 4.2.2 Gait experiments

All experiments were performed at the Wolf Orthopaedic Biomechanics Laboratory, Fowler Kennedy Sport Medicine Clinic, University of Western Ontario. Joint motion and GRF were recorded simultaneously as each participant walked at his or her preferred speed over level ground. Retro-reflective markers were attached to each subject using a 22-marker modified Helen Hayes protocol (Kadaba et al., 1990), with 4 additional markers used for static trials, placed on the medial knee-joint line and on the medial malleolus for each leg. These
additional markers were removed prior to gait testing. Three-dimensional marker positions were measured using an eight-camera motion capture system sampling at 60 Hz (Eagle EvaRT, Motion Analysis Corp., Santa Rosa, CA). A single strain-gauged force plate (Advanced Mechanical Technology Inc., Watertown, MA) sampling at 1200 Hz was used to measure all three components of the GRF and the centre of pressure during stance. For each subject, walking trials at a self-selected speed were repeated until 5 clean force plate strikes during stance were recorded per leg. Previous testing in this laboratory using these protocols found the kinematic and kinetic variables calculated from this task to be reliable (ICC$_{2,1}$: 0.73 to 0.96) (Birmingham et al., 2007). Surface electromyographic (EMG) activity was recorded in a subset of five controls (right limb) and nine patients (symptomatic limb), with electrodes placed over the bellies of the rectus femoris, lateral and medial vasti, lateral and medial hamstrings, lateral and medial gastrocnemius and tibialis anterior. Details of subject preparation, measurement and processing protocols for EMG, and participant characteristics of the EMG sub-cohort are provided in Appendix B. EMG was used for qualitative comparison with calculated muscle forces only.

### 4.2.3 Musculoskeletal modelling

A scaled-generic, three-dimensional, whole-body musculoskeletal model was used to calculate lower-limb muscle forces during the stance phase of gait for each subject. The model was implemented in OpenSim (Delp et al., 2007) (version 3.2), an open-source musculoskeletal modelling package, and comprised of a 10-segment, 27-degree-of-freedom linkage actuated by 92 Hill-type muscle-tendon
units. Ligaments and other soft tissues were not included. The head, arms and torso were lumped as a single rigid body, articulating with the pelvis via a ball-and-socket back joint. Each hip was modelled as a ball-and-socket joint, and each ankle and subtalar joint as a hinge. Each knee was modelled as a sliding ball-and-socket with the flexion-extension axis and prescribed fore-aft translation defined as per Delp et al. (1990). The model’s segmental inertial properties, muscle-tendon attachment sites, and muscle-tendon paths were scaled based on segmental dimensions calculated from each subject’s static trial.

For each trial, stance-phase joint angles were calculated using inverse kinematics, which found the model configuration at each time step that minimised the sum of squares of the distance between corresponding experimental markers and model markers (Lu and O’Connor, 1999). The kinematics and GRF were input into the model and net joint torques calculated using inverse dynamics. Individual muscle forces were calculated from the net joint torques using static optimisation, which minimised the sum of the squares of muscle activations subject to bounds on the muscle forces imposed by each muscle’s own force-length-velocity property (Anderson and Pandy, 2001b). The knee adduction and internal-external rotation torques were excluded from static optimisation. The EKAM was calculated by multiplying the GRF by its moment arm about the knee-joint centre in the frontal plane.

4.2.4 Contributions to GRF and TF-joint forces
At each time step, the GRF was decomposed into contributions by individual muscles, gravity and inertia using a pseudoinverse-based approach (Lin et al.,
2010). Subsequently, the contribution by a single muscle to the TF-joint force at each time step was calculated by placing the model in the configuration defined by the joint angles, applying that muscle’s force together with its contribution to the GRF, and solving the joint reaction equations (Sritharan et al., 2012). This process was repeated to determine contributions by gravity, defined as the resistance of the skeletal linkage to the downward pull of the body’s weight force (Liu et al., 2008), and inertia, defined as all Coriolis and centrifugal forces combined. At each time step, the TF-joint force was then separated into medial and lateral compartment forces acting at the medial and lateral contact points respectively by solving for force and moment equilibrium at the knee in three dimensions using a least-squares approach (Sritharan et al., 2012). Estimates for the spatial locations of the medial and lateral contact points in three-dimensions were obtained at each time step by inputting the joint angles, GRF and muscle forces into a separate 18-degree-of-freedom model of the lower limb incorporating a Hertzian contact-based 6-degree-of-freedom model of the knee (Shelburne et al., 2004), and solving for static equilibrium.

### 4.2.5 Statistical analyses

To compare participant characteristics and also to determine group differences amongst the three limb conditions – the symptomatic (SYM) and asymptomatic (ASYM) limbs of patients, and also controls (CON) – at the peak values of joint angles, net joint torques and muscle forces, a series of $t$-tests was performed while controlling the familywise error rate for the multiple comparisons. This procedure was also used to compare contributions to the medial and lateral compartment
forces at time instants corresponding to the peaks and the mid-stance minimum of the MCF. Specifically, for each quantity of interest, independent-samples $t$-tests were performed to compare the CON limb with the SYM limb, and also to compare the CON limb with the ASYM limb; while a paired $t$-test was performed to compare the SYM limb with the ASYM limb. The $t$-tests were performed using SPSS Statistics 22.0 (IBM Corp., Armonk, NY). Subsequently, the Holm-Bonferroni method, used to control the familywise error rate, was applied to the results of the three $t$-tests at a significance level $\alpha = 0.05$ to determine which pairs of limbs differed significantly.

4.3 RESULTS

Patients had substantial symptoms of knee OA based on KOOS (Table 4.1), greater varus mal-alignment and radiographic disease severity (Table 4.2). Due to the large number of statistical analyses, $P$-values for joint angles, joint torques, muscle forces and contributions to knee-joint forces are provided in Appendix B, with only significant results described below.

Peak knee flexion and ankle plantarflexion angles were lower in OA patients (Figure 4.1A, top), but peak hip abduction and knee adduction angles were higher (Figures 4.1A and B, top). Patients showed lower magnitudes of peak hip adduction, knee flexion and ankle plantarflexion torques, with lowest torques seen for SYM (Figure 4.1A, bottom). EKAM was highest in patients, specifically SYM (Figure 4.1B, bottom). Peak knee-spanning muscle forces were lower in SYM than CON, except hamstrings (Figure 4.2). Hip- and ankle-spanning muscle forces for SYM were lower than CON, with the greatest differences seen for
gluteus medius and soleus (Figure 4.2). Muscle forces for ASYM were intermediate between SYM and CON, except biceps femoris short head and gastrocnemius, where ASYM was lowest.

Peak MCFs (Figure 4.3, top) in SYM were higher than ASYM (first peak: 6% higher; second peak: 8% higher) and CON (first peak: 6% higher; second peak: 9% higher). The largest difference between SYM and CON occurred at the mid-stance minimum, approximately 38% of stance (0.39 BW or 26% higher in SYM). In all limbs, knee-spanning muscles contributed approximately one-third of the first peak of the MCF, but more than one-half of the second peak. Gravity’s contribution to MCF was compressive and consistently highest for SYM. For CON, the lateral compartment was compressed throughout stance, while SYM and ASYM experienced short periods of lateral compartment unloading (Figure 4.3, bottom). Knee-spanning muscles always compressed the lateral compartment while non-knee-spanning muscles unloaded it. Inertial contributions were negligible (<0.03 BW) and not considered further. Individual contributions to net TF-joint forces at the peaks and mid-stance are provided in Appendix B. Full time histories of the individual contributions to net TF-joint forces by the major lower-limb muscles are provided in Appendix C.

For each contributor to the peaks and mid-stance minimum of MCF, mean differences amongst the three limbs were small (Figure 4.4, top). In all limbs, vasti were the largest knee-spanning contributor at the first peak of MCF. Gastrocnemius was the largest knee-spanning contributor at the mid-stance minimum and second peak. Gluteus medius was the largest non-knee-spanning muscle contributor at both peaks and the mid-stance minimum. Vasti
contributions were lowest in SYM. Gravity, hamstrings, gastrocnemius, and gluteus maximus contributions to MCF were all highest in SYM at the first peak and mid-stance minimum of MCF. Soleus and rectus femoris contributions were highest in SYM at the second peak. The largest knee-spanning contributors to the lateral compartment force were vasti and hamstrings at the first peak, and gastrocnemius and biceps femoris short head at the second peak (Figure 4.4, bottom). Gluteus medius, which unloaded the lateral compartment, was the largest non-knee-spanning contributor. Full time histories of the individual contributions to the forces in the medial and lateral compartments by the major muscles of the lower-limb are provided in Appendix C.

When muscles were grouped according to their principal function during gait (Figure 4.5), higher contributions at the first peak of MCF were found for SYM relative to CON for the hip extensors (0.11 BW, 36%), ankle plantarflexors (0.09 BW in SYM, almost zero in CON) and gravity (0.10 BW, 78%) while contributions by knee extensors were lower (0.12 BW, 23%). At the second peak, contributions by the ankle plantarflexors were higher for SYM (0.13 BW, 7%) while hip abductor contributions at both peaks of MCF were slightly lower (first peak: 0.06 BW, 5.5%; second peak: 0.02 BW, 2.4%). Elevated mid-stance loading in SYM was due to all muscle groups except knee extensors.

4.4 DISCUSSION

The objective of this study was to quantify and compare the contributions by muscles, gravity and inertia to the TF compartment forces during gait in individuals with medial knee OA and also healthy controls. We hypothesised that
higher MCFs in OA patients would be due to elevated contributions from the hamstrings, quadriceps and gastrocnemius, and also that the gluteus medius contribution would not be significantly reduced. While patients exhibited higher peak MCFs, only hamstrings showed higher contributions in patients; vasti and gastrocnemius contributions were lower at the first and second peak, respectively. Patients’ gluteus medius contributions to MCF were not significantly lower than controls at the peaks, and in fact were higher through mid-stance. Thus, our first hypothesis was only partially supported and our second confirmed.

4.4.1 Limitations

This study is not without limitations. Firstly, we potentially underestimated the magnitudes of quadriceps forces in our models because we did not explicitly input the elevated quadriceps-hamstrings co-activation typically reported for OA patients (Rutherford et al., 2013), and because the knee adduction moment was not included in our static optimisation solution. Hypothetically, if vasti forces in patients exceeded those of controls, then so too would vasti contributions to the first peak of MCF (Figure 4.4). However the impact of co-activation and frontal-plane stability on muscle forces is not well established. Up to 16% of frontal-plane stability may be contributed by muscles in varus mal-aligned individuals (Adouni and Shirazi-Adl, 2014b), but this is highly variable, with some individuals demonstrating almost no muscular contribution (Walter et al., 2015). Brandon et al. (2014), by applying OA-type activation patterns, found higher quadriceps forces while Adouni and Shirazi-Adl (2014a), who included frontal-plane moments in a geometry-based contact model with ligaments, did not. In
contrast, our patients demonstrated lower quadriceps forces and higher hamstrings forces (Figure 4.2), but nevertheless showed higher co-contraction indices and total quadriceps-hamstrings activity (Figure 4.6A), with temporal patterns of muscle forces similar to recorded EMG (Figure 4.6B). Notably, modelling studies which took into account OA-type co-activity (Brandon et al., 2014; Kumar et al., 2013) reported differences in first peak MCF between patients and controls which were not markedly greater than those found in our present study. Adouni and Shirazi-Adl (2014a) found that lower-limb alignment, which was accounted for in our present study, was more important than EKAM in determining load distribution between compartments.

Secondly, we did not explicitly model pain and OA-related functional and morphological changes, such as atrophy (Petterson et al., 2008), strength deficits (Slemenda et al., 1997) and activation failure (Petterson et al., 2008) of the quadriceps. As these changes compete with the demand for greater co-activations (Hubley-Kozey et al., 2009) and frontal-plane stability (Schipplein and Andriacchi, 1991), the net effect on muscle and joint forces is difficult to predict. To some extent, we may have indirectly included these factors by virtue of the differing kinetics and kinematics between our patient and control groups (Figure 4.1).

Finally, our use of scaled-generic models for high-BMI individuals may have affected the accuracy of our alignment measures. Despite all care taken in marker placement on subjects and in ensuring model scaling errors were minimised, a 4° bias between marker-based and radiographic static alignment measures occurred (Table 4.2). In our high-BMI subjects this result was likely due
to disparities in hip-joint centre location, an important factor for accurately determining alignment (Kornaropoulos et al., 2010). Bias in marker-based dynamic alignment measures can be variable (Benoit et al., 2006). Assuming 4° represents a worst-case scenario, for representative trials of one control and one patient we subtracted 4° from the frontal-plane joint angles and recalculated muscle forces. MCF was reduced by only about 7% in both subjects, a small difference which presumably affected all subjects. Thus, our overall findings should not be materially impacted by the observed bias in alignment.

4.4.2 Validation of tibiofemoral compartment forces

Notwithstanding these limitations, our results are consistent with experimental and model-predicted data available in the literature. Increasing dynamic varus mal-alignment from CON to SYM, as evidenced by increasing hip and knee adduction angles, was accompanied by greater EKAM (Heller et al., 2003). The magnitudes of the MCF for CON were within the range of model predictions reported previously (Brandon et al., 2014; Shelburne et al., 2006; Sritharan et al., 2012), but slightly higher than those measured using instrumented TKRs (Kutzner et al., 2013a). The MCFs also showed a higher second peak compared to the first peak as reported in a TKR study by Kutzner et al. (2013a). Elevated MCF in patients occurred throughout mid-stance not just at peaks (Figures 4.3 and 4.5), in agreement with recent modelling studies (Brandon et al., 2014; Kumar et al., 2013). Brief periods of unloading occurred on the lateral compartment during mid-stance in patients, and also on the medial compartment near toe-off in many subjects, implying that joint-opening would need to be resisted by knee ligaments.
(Schipplein and Andriacchi, 1991). Recent modelling studies also found similar periods of joint-opening during gait (Brandon et al., 2014; Kumar et al., 2013; Sritharan et al., 2012).

4.4.3 Major contributors to MCF in patients and controls

The muscles that contributed most to MCF in controls also contributed most in patients walking at the same speed, and were the prime movers in gait (Pandy and Andriacchi, 2010): (1) knee-spanning: vasti, hamstrings and gastrocnemius; and (2) non-knee-spanning: gluteus maximus, gluteus medius and soleus. However, our results show that subtle alterations to the duration and magnitude of contributions by muscles and gravity can be important in knee-joint loading not just at the peaks but also throughout mid-stance (Figure 4.5). Although the overall temporal pattern of muscle forces during gait was not markedly different between patients and controls (Figure 4.2), contributions to MCF by hip extensors (gluteus maximus and hamstrings), ankle plantarflexors (soleus and gastrocnemius) and gravity were of greater magnitude and longer duration in the SYM limb (Figure 4.5). Importantly, at the peaks and mid-stance minimum of MCF, small but significant differences in the magnitudes of individual muscle and gravity contributions (Figure 4.4, top) summed to produce substantially higher total MCFs in the SYM limb. Interestingly, gastrocnemius at the first peak, and rectus femoris at the second peak, provided small but influential contributions to MCF at time instants not related to their peak muscle forces (Figure 4.4, top), a result of slightly higher muscle forces at these specific instants in OA patients (Figure 4.2). This finding is supported by EMG studies showing prolonged and elevated
gastrocnemius and rectus femoris activity in early and late stance respectively (Astephen et al., 2008b; Rutherford et al., 2011).

4.4.4 Non-knee-spanning muscles and the role of the kinematic chain

Large deficits in non-knee-spanning muscle forces in OA patients did not produce correspondingly diminished contributions by those muscles to the MCF. In patients, peak gluteus medius forces were substantially lower than controls (Figure 4.2), in agreement with evaluations of hip abductor performance in knee OA (Hinman et al., 2010), but the corresponding reductions in the contributions to MCF were not significant at either peak (Figure 4.4, top). Hip abductor contributions were in fact higher in patients throughout mid-stance (Figures 4.4 and 4.5). Interestingly, gluteus maximus and soleus muscles forces were also lower in patients, but their contributions to MCFs were higher than controls (Figure 4.4, top). Non-knee-spanning muscles can only load the knee-joint indirectly, by means of dynamic coupling via the GRF (Sritharan et al., 2012). Thus, the insensitivity of MCF contributions to changes in non-knee-spanning muscle forces suggests that factors related to the kinematic chain, such as lower-limb mal-alignment, also strongly influence how non-knee-spanning muscles load the knee. For example, gluteus medius compressed the medial compartment but strongly unloaded the lateral compartment (Figure 4.4) because it is a principal contributor to the mediolateral GRF component (Pandy and Andriacchi, 2010) and consequently also the EKAM (Sritharan et al., 2012). Hence lower gluteus medius forces in our patients may have been offset by greater mal-alignment, producing a limited net change in EKAM and hence also MCF contributions. This
supposition may explain the minimal association between hip abductor function and EKAM (Rutherford et al., 2014), and therefore why hip abductor training did not reduce peak EKAM in varus mal-aligned OA patients (Bennell et al., 2010). In contrast, differences in knee-spanning muscle contributions to MCF between OA patients and controls were more concomitant with differences in the respective muscle forces. In particular, higher hamstrings and lower vasti muscle forces (Figure 4.2) were associated with higher and lower contributions to MCF, respectively (Figure 4.4, top). This occurred because direct compression of the knee by knee-spanning muscles dominated indirect loading via the GRF (Sritharan et al., 2012).

As the condition progressed from CON to SYM, gravity’s contribution was increasingly shifted to the medial compartment (Figures 4.3 and 4.4). Thus, gravity’s contribution to MCF, while small, was quite influential in producing the higher first peak of MCF seen in patients. This can be explained by the greater severity of lower-limb mal-alignment in patients, as represented by the large knee and hip adduction angles experienced by OA patients during gait (Figure 4.1). Thus, presumably one direct effect of correcting mal-alignment in OA patients would be to reduce gravity’s contribution to the MCF by more equally distributing it between the two compartments of the knee.

4.4.5 Implications for clinical interventions

Our present study emphasises the complex interactions amongst muscles, gravity and the kinematic chain in influencing knee-joint loading which may have implications for clinical intervention. In particular, our findings suggest that small
improvements in the functional performance of knee-spanning muscles during gait, such as minimising aberrations and/or prolonged activity in hamstrings, rectus femoris and gastrocnemius may provide considerable benefit by directly reducing the duration and magnitude of knee-spanning muscle contributions to compartment loads throughout stance. However, reductions in contributions from non-knee-spanning muscles and gravity, which indirectly exert forces on the knee via the GRF (Sritharan et al., 2012), may be better garnered from improvements to the kinematic chain, in particular the correction of mal-alignment. This may be especially beneficial for reducing mid-stance MCF, which was higher in patients mainly due to elevated contributions by non-knee-spanning muscles and gravity (Figures 4.4 and 4.5). Greater mid-stance EKAM is associated with increased OA severity (Astephen et al., 2008a). While improved lower-limb alignment has been associated with reduced mid-stance EKAM (Birmingham et al., 2009; Hubley-Kozey et al., 2010), our study extends this finding to further suggest that it may reduce the actual mid-stance MCF by reducing the magnitudes of non-knee-spanning muscle and gravity contributions (Figure 4.4). Overall, a combined intervention strategy targeting restoration of muscle function and lower-limb alignment would potentially produce the best clinical outcome for varus mal-aligned OA patients. Thus, our results provide a biomechanical rationale that supports the use of realignment procedures with concurrent functional rehabilitation.

4.4.6 Mid-stance loads and the “asymptomatic” limb

Despite the ASYM limb experiencing a larger knee adduction angle and greater
EKAM than CON, only the mid-stance MCF was significantly different; peak MCFs were not (Figures 4.3 and 4.4). Most of the ASYM limbs in the present sample had pre-existing OA-type structural changes in the TF-joint evident on radiographs (Table 4.2) and also demonstrated walking kinematics and kinetics resembling SYM but to a lesser degree (Figure 4.1). This type of asymptomatic radiographic OA is common (Felson et al., 1987) but its biomechanics are not well-studied. Our results suggest that elevated mid-stance MCF (Figures 4.3 and 4.4) is a factor in the pathomechanics of knee OA that is more sensitive than peaks in detecting differences between more and less symptomatic limbs, and which may be influential throughout all stages of OA. This finding is somewhat consistent with the suggestion that cumulative load is influential in OA progression (Miller et al., 2014). Hence, our present results suggest that mid-stance MCF in the ASYM limb should be considered in early biomechanical interventions to mitigate the risk of progression to symptomatic bilateral disease.

4.5 CONCLUSIONS

In conclusion, we found that the subtly higher magnitude and longer duration of contributions by the prime movers and gravity during stance summed to produce significantly higher MCF in the SYM limb of patients. Knee-spanning muscles, non-knee-spanning muscles and gravity contributed to MCF loading by different mechanisms, with the influence of the kinematic chain, particularly lower-limb alignment, potentially more important in the latter two. Hence, both muscle forces and varus mal-alignment were factors contributing to higher MCF in patients. Kinematics and kinetics in the ASYM limb were intermediate to CON and SYM,
with elevated mid-stance MCF suggesting future risk of progression to symptomatic bilateral disease. Our findings emphasise the need to consider muscle function, the lower-limb kinetic chain and mid-stance loads in the development of interventions for OA, and support the inclusion of the ASYM limb in clinical assessments.

4.6 TABLES AND FIGURES
This section contains the tables and figures associated with the results and discussion of the present study.
Table 4.1 Participant characteristics of the OA patient and healthy control groups

<table>
<thead>
<tr>
<th></th>
<th>Control $n = 15$</th>
<th>OA Patient $n = 39$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>49 (7)</td>
<td>49 (7)</td>
<td>0.869</td>
</tr>
<tr>
<td>Height, m</td>
<td>77 (15)</td>
<td>89 (17)</td>
<td>0.015</td>
</tr>
<tr>
<td>Mass, kg</td>
<td>1.70 (0.10)</td>
<td>1.78 (0.09)</td>
<td>0.006</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.5 (4.8)</td>
<td>28.2 (3.6)</td>
<td>0.177</td>
</tr>
<tr>
<td>Females, no. (% of total)</td>
<td>4 (27%)</td>
<td>8 (21%)</td>
<td>0.634</td>
</tr>
<tr>
<td>Walking speed, m/s</td>
<td>1.21 (0.07)</td>
<td>1.20 (0.10)</td>
<td>0.575</td>
</tr>
<tr>
<td>KOOS subscale scores, 0–100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>-</td>
<td>55 (18)</td>
<td>-</td>
</tr>
<tr>
<td>Symptoms</td>
<td>-</td>
<td>54 (18)</td>
<td>-</td>
</tr>
<tr>
<td>Activities of daily living</td>
<td>-</td>
<td>65 (20)</td>
<td>-</td>
</tr>
<tr>
<td>Sport and recreation</td>
<td>-</td>
<td>31 (23)</td>
<td>-</td>
</tr>
<tr>
<td>Knee-related quality of life</td>
<td>-</td>
<td>29 (19)</td>
<td>-</td>
</tr>
</tbody>
</table>

Values are presented as mean (standard deviation) unless otherwise indicated. $P$-values were calculated using Student’s $t$-tests. Significance level was defined as $\alpha = 0.05$. Statistically significant differences are shown in bold italic. KOOS: Knee Injury and Osteoarthritis Outcome Score (0 = maximum symptoms, 100 = no symptoms).
Table 4.2 Characteristics of the symptomatic (SYM) and asymptomatic (ASYM) limbs of the knee OA patients, and healthy controls (CON).

<table>
<thead>
<tr>
<th></th>
<th>CON</th>
<th>SYM</th>
<th>ASYM</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 15</td>
<td>n = 39</td>
<td>n = 39</td>
<td></td>
</tr>
<tr>
<td>Stance time, sec</td>
<td>0.71 (0.05)</td>
<td>0.75 (0.06)</td>
<td>0.75 (0.05)</td>
<td>CS: &lt; 0.001; CA: &lt; 0.001; SA: 0.719</td>
</tr>
<tr>
<td>Gait events, % of stance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contralateral toe-off</td>
<td>23 (3.6)</td>
<td>25 (5.2)</td>
<td>24 (4.8)</td>
<td>CS: &lt; 0.001; CA: 0.047; SA: 0.006</td>
</tr>
<tr>
<td>Contralateral heel-strike</td>
<td>75 (2.1)</td>
<td>74 (2.0)</td>
<td>75 (2.6)</td>
<td>CS: 0.017; CA: 0.279; SA: &lt; 0.001</td>
</tr>
<tr>
<td>Static knee adduction angle, deg</td>
<td>6 (6)</td>
<td>13 (5)</td>
<td>8 (6)</td>
<td>CS: &lt; 0.001; CA: 0.002; SA: &lt; 0.001</td>
</tr>
<tr>
<td>Mechanical axis angle, deg</td>
<td>-</td>
<td>9 (3)</td>
<td>4 (3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>KL grade 0/1/2/3/4, patients</td>
<td>-</td>
<td>0/1/10/15/13</td>
<td>4/14/11/10/0</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean (standard deviation) unless otherwise indicated. P-values were calculated using Student’s t-tests. A Holm-Bonferroni correction was used to identify statistically significant differences. Significance level was defined as α = 0.05. Statistically significant differences are shown in **bold italic**. Static knee adduction angle was calculated using inverse kinematics from static trial marker data (positive values represent varus). Mechanical axis angle was measured from full-limb standing anteroposterior radiographs (positive values represent varus). Comparison pairs: CON and SYM (CS); CON and ASYM (CA), SYM and ASYM (SA). KL grade: Kellgren and Lawrence grade (0 = no OA, 4 = severe OA).
Figure 4.1 Calculated joint angles and joint torques for patients and controls during stance

(A) Joint angles (top row) and internal torques (bottom row) for hip flexion, hip adduction, knee flexion and ankle plantarflexion for healthy controls (CON), and the symptomatic (SYM) and asymptomatic limbs (ASYM) of OA patients during stance. (B) Mean knee adduction angle (top row) and external knee adduction moment (bottom row) for these three limbs. Labels for statistically significant differences between: SYM and CON (#); SYM and ASYM ($); ASYM and CON (%); and all three pairs of limbs (*). Statistical significance calculated at the peak values for joint angles and torques.
Figure 4.2 Calculated muscle forces for patients and controls during stance

Calculated lower-limb muscle forces for healthy controls (CON), and the symptomatic (SYM) and asymptomatic (ASYM) limbs of OA patients during stance. Labels for statistically significant differences between: SYM and CON (#); SYM and ASYM ($); ASYM and CON (%); and all three pairs of limbs (*). Statistical significance calculated at the peak values for muscle forces.
Figure 4.3 Time histories of tibiofemoral compartment loads and grouped contributions during stance

Contributions by all knee-spanning muscles, all non-knee-spanning muscles and gravity to the medial (top row) and lateral (bottom row) compartment forces for healthy controls (CON), and the symptomatic (SYM) and asymptomatic (ASYM) limbs of OA patients during stance. The contributions by inertia are very small (<0.03 BW) and are not shown. Positive values are compressive. Labels for statistically significant differences between: SYM and CON (#); SYM and ASYM ($); ASYM and CON (%); and all three pairs of limbs (*). Statistical analyses were performed at the time instances corresponding to the peaks and mid-stance minimum of the medial compartment force. Mid-stance minimum occurred at approximately 38% of stance.
Figure 4.4 Contributions by major muscles and gravity to peak and mid-stance compartment loads during stance

Contributions by individual knee-spanning muscles, non-knee-spanning muscles and gravity to the medial (top row) and lateral (bottom row) compartment forces at the time steps corresponding to the first peak (left column) and the second peak (right column) and mid-stance minimum (centre column) of the medial compartment force. Positive values are compressive. Mid-stance minimum occurred at approximately 38% of stance. Abbreviations: GAS, gastrocnemius; VAS, vasti; HAMS, hamstrings; GMAX, gluteus maximus; GMED, gluteus medius; BFSH, biceps femoris short head; RF, rectus femoris; SOL, soleus; and GRAV, gravity. Labels for statistically significant differences between: SYM and CON (#); SYM and ASYM ($); ASYM and CON (%); and all three pairs of limbs (*).
Figure 4.5 Contributions by major muscles and gravity to the medial compartment loads grouped by major function during stance

Contributions by the prime movers and gravity to the medial compartment force during the stance phase of walking grouped by principal function during gait in healthy controls and OA patients. (A) Hip abductors (gluteus medius and gluteus minimus) and hip extensors (gluteus maximus and hamstrings). (B) Knee extensors (vasti and rectus femoris) and gravity. (C) Ankle plantarflexors (soleus and gastrocnemius).
Figure 4.6 Co-activation measures and validation of calculated muscle forces against EMG during stance

(A) Total activation of the quadriceps and hamstrings from static optimisation calculations (top row) and co-contraction index for the quadriceps and hamstrings (bottom row). (B) Comparison of measured EMG (thin line) and calculated major knee-spanning muscle forces (thick line) for the control sub-cohort on the right limb (top row) and the OA patient sub-cohort on the symptomatic limb (bottom row). The muscle forces and EMG signals presented are the ensemble averaged time histories for each group.
CHAPTER 5
MUSCLE FUNCTION DURING GAIT IN VARUS MAL-ALIGNED OSTEOARTHRITIS PATIENTS

Chapter summary
Non-pharmacological interventions are important in the clinical treatment of medial knee osteoarthritis (OA). This study quantified the contributions by muscular, gravitational and inertial forces to the ground reaction force (GRF) and external knee adduction moment (EKAM) for varus mal-aligned OA patients and healthy controls walking at similar speeds. Gait data for 39 varus mal-aligned medial knee OA patients and 15 healthy controls were input into scaled-generic musculoskeletal models to calculate individual contributions to the fore-aft, vertical, and mediolateral GRF (progression, support and balance respectively) and also the EKAM. The temporal patterns of contributions to GRF and EKAM were similar between the groups. Peak contributions to GRF were lower in patients except hamstrings in early-stance progression ($P<0.001$) and gastrocnemius in late-stance progression ($P<0.001$). EKAM was higher in patients, with the magnitude change in the second peak of EKAM almost three times that of the first. Increased EKAM was due to higher adduction contribution from gravity at the first peak ($P<0.001$), and lower abduction contribution from soleus ($P<0.001$) and gastrocnemius ($P<0.001$) at the second peak, respectively. Gluteus medius contributed most to EKAM in both groups, but was higher in patients during mid-stance only ($P<0.001$). Diminished muscle forces, elevated knee-spanning muscle co-contractions and altered kinematics contributed to GRF.
differences. Frontal-plane mal-alignment was essential in changing the moment arms of all GRF contributors about the knee, but impacted gravity, soleus and gastrocnemius the most. Our results explain why some clinical interventions reduce the second peak of EKAM more than the first, and provide a baseline for future investigations of the impact of interventions on muscle function.
5.1 INTRODUCTION

Non-pharmacological interventions are the cornerstone in the management of medial knee osteoarthritis (OA) (Hochberg et al., 2012) with current techniques focussed on offloading the medial tibiofemoral compartment by reducing the external knee adduction moment (EKAM) during gait (Farrokhi et al., 2013). Abnormally high levels of peak (Bennell et al., 2011) and mid-stance (Hatfield et al., 2015b) EKAM have been associated with the progression of knee OA.

The EKAM is produced by the ground reaction force (GRF) acting about the knee in the frontal plane. The GRF arises from the superposition of contributions from all muscles, with smaller contributions from gravitational and inertial forces (Anderson and Pandy, 2003; Pandy and Andriacchi, 2010), acting by means of dynamic coupling (Zajac and Gordon, 1989). A muscle’s contribution to the fore-aft, vertical and mediolateral components of the GRF, represents its contribution to the progression, support and balance of the body’s centre-of-mass (COM), and is one means of describing that muscle’s function in gait (Anderson and Pandy, 2003; Lim et al., 2013; Lin et al., 2015; Pandy et al., 2010). By decomposing the GRF into its various contributions, recent studies have identified five prime movers which progress, support and balance the body during healthy gait – the vasti, gluteus medius, gluteus maximus, soleus and gastrocnemius (Anderson and Pandy, 2003; Pandy and Andriacchi, 2010; Pandy et al., 2010). However, muscle function in accelerating the body COM in osteoarthritic gait has yet to be quantified.

By virtue of their contributions to the GRF, muscles, gravitational forces (i.e. the weight force directly borne by the skeleton) and inertial forces also
contribute to EKAM (Pandy and Andriacchi, 2010; Sritharan et al., 2012). Of the five prime movers identified in healthy gait, gluteus medius and gluteus maximus provide the largest EKAM contributions, while vasti, soleus and gastrocnemius modulate this quantity by providing substantial external *abduction* moment contributions (Sritharan et al., 2012).

Many non-pharmacologic interventions rely on the notion that EKAM can be reduced by independently manipulating the GRF and its frontal-plane moment arm about the knee (Farrokhi et al., 2013). One principal factor influencing the frontal-plane moment arm of the GRF about the knee is varus mal-alignment, a common feature of medial knee OA (Sharma et al., 2010) associated with greater frontal-plane moment arm (Hunt et al., 2006) and hence higher EKAM (Barrios et al., 2009; Foroughi et al., 2010). How mal-alignment influences the individual contributors to EKAM is unknown, and may be essential to the development of novel interventions that effectively reduce EKAM while ensuring normal muscle function in gait.

The goals of this study were to quantify and compare the individual muscular and gravitational force contributions to the GRF and the EKAM in healthy individuals and varus mal-aligned OA patients walking at similar speeds. We hypothesised that peak muscle contributions by gluteus medius, gluteus maximus, vasti, soleus and gastrocnemius to support, progression and balance would be lower in patients, commensurate with reduced peak hip, knee and ankle torques typically reported for osteoarthritic gait (Astephen et al., 2008a; Sritharan et al., 2016). We further hypothesised that despite lower GRF contributions, greater EKAM in patients would occur due to increased EKAM contributions
from gluteus maximus, gluteus medius and gravity, but reduced external abduction contributions from vasti, soleus and gastrocnemius.

5.2 METHODS

5.2.1 Recruitment and gait experiments

Previously-reported gait data for 39 medial knee OA patients and 15 healthy controls were used for this study (Sritharan et al., 2016) (Table 5.1). All gait experiments were performed at the Wolf Orthopaedic Biomechanics Laboratory, Fowler Kennedy Sport Medicine Clinic, University of Western Ontario. The study was approved by the Research Ethics Board for Health Sciences Research Involving Human Subjects of the University of Western Ontario (HSREB No. 09812E). Recruitment methodology, inclusion and exclusion criteria, radiographic assessment, patient-reported measures and experimental protocols are described in detail in Birmingham et al. (2009) and are only briefly reproduced here.

Patients were recruited from a tertiary care centre specialising in orthopaedics and were referred to the centre for potential surgical treatment of one symptomatic limb with radiographic knee OA. Inclusion criteria for patients were based on the American College of Rheumatology criteria (Altman et al., 1986) and included varus mal-alignment of the lower-limb and diagnosis of medial knee OA. The Knee Injury and Osteoarthritis Outcome Score (KOOS) was used to assess symptoms (Roos et al., 1998). Full-limb standing anteroposterior radiographs were used to quantify static frontal-plane lower-limb alignment (mechanical axis angle (Moreland et al., 1987)) and the severity of OA (Kellgren-Lawrence grade, K-L grade (Kellgren and Lawrence, 1957)). Healthy controls
were recruited from the community, had no history of knee pain and were matched for sex, age, body mass index (BMI) and walking speed.

Each participant walked at his or her preferred speed over level ground while joint motion and GRF were simultaneously recorded. An eight-camera motion capture system (Eagle EvaRT, Motion Analysis Corp., Santa Rosa, CA) sampling at 60 Hz was used to measure the three-dimensional spatial trajectories of 22 retro-reflective markers attached to the participant, with the locations of markers on the body determined using a modified Helen Hayes protocol (Kadaba et al., 1990). A single strain-gauged force plate (Advanced Mechanical Technology Inc., Watertown, MA) sampling at 1200 Hz was used to measure the three components of the GRF as well as the centre-of-pressure. Five successful gait trials were recorded for each leg.

5.2.2 Modelling pipeline

A modelling pipeline (Sritharan et al., 2016) for calculating joint angles, joint torques and muscle forces was implemented using Matlab (The Mathworks, Natick, MA) and OpenSim (Delp et al., 2007), an open-source musculoskeletal modelling package. For each subject, a scaled-generic whole-body three-dimensional musculoskeletal model was created, with segmental inertial properties, muscle-tendon attachment sites, and muscle-tendon paths scaled based on segmental dimensions calculated from each subject’s static trial. Each model consisted of 10 rigid segments, 27 degrees of freedom and 92 Hill-type muscle-tendon units. A ball-and-socket was used to model the back-joint and each hip and knee, while a hinge was used to model each ankle and subtalar joint. Cartilage,
ligaments and other soft tissues were not included in the model. The head, arms and torso were combined into a single rigid body.

For each recorded trial, joint kinematics and muscle forces were calculated for the stance phase of gait. An inverse kinematics analysis was used to calculate joint angles from the experimental marker data (Lu and O'Connor, 1999). At each time step, the joint kinematics and the measured GRF were input into the model and inverse dynamics was used to calculate the net internal joint torques. Muscle forces were subsequently calculated from joint torques using a static optimisation approach in which the sum of the squares of muscle activations was minimised subject to constraints on the muscle forces imposed by each muscle’s force-length-velocity property (Anderson and Pandy, 2001b). The internal knee adduction and internal-external rotation torques were not included in the static optimisation analysis. Joint angles, and muscle forces calculated for these participant groups using the aforementioned procedures were previously reported (Sritharan et al., 2016) with peak values provided in Tables 5.2 and 5.3.

5.2.3 Contributions to GRF and EKAM

The three components of the GRF were defined as progression (fore-aft), support (vertical) and balance (mediolateral) (Lin et al., 2015; Pandy et al., 2010). At each time step, the GRF vector was decomposed into contributions by individual muscles, gravity and inertia using a pseudoinverse-based approach described in detail by Lin et al. (2010). Briefly, five foot-ground interaction points were defined on the foot segment of the model to represent the distributed force experienced on the foot when in contact with the ground. Each of these points
could be fully-constrained, partially-constrained or unconstrained in space depending on the phase of foot-ground contact. At each time step during stance, the calculated joint angles were applied to the model. Each individual muscle force was then applied in isolation, and a weighted least-squares optimisation problem solved to calculate the induced three-dimensional force vector at each of the fully- or partially-constrained foot-ground interaction points. The force at each of the unconstrained points was by default zero. Individual muscle contributions to EKAM were calculated by multiplying each muscle’s contribution to the GRF by its moment arm about the knee joint centre in the frontal plane (Sritharan et al., 2012). This process was repeated for gravity and inertial forces.

5.2.4 Data analyses

Independent-samples t-tests were performed to compare participant characteristics and to determine group differences between controls and the symptomatic limbs of patients at the peak values of kinematics and muscle forces (SPSS Statistics 22.0, IBM Corp, Armonk, NY). Independent-samples t-tests were also used to determine group differences in the contributions by muscles, gravity and inertia to the GRF components and also to the EKAM. The significance level was set a priori to be $\alpha = 0.05$. Consistent with Sritharan et al. (2016), data from both limbs of controls were used, while for patients data from the symptomatic limb only were used.

5.3 RESULTS

The temporal patterns of the mean measured GRFs were similar for both groups
(Figure 5.1). Although the magnitudes of peak GRF components were only slightly lower in patients compared to controls, some differences reached significance (Figures 5.1 and 5.2); specifically at both peaks of the vertical GRF (first: \( P < 0.001 \), mean difference: -0.038 BW; second: \( P < 0.001 \), mean difference: -0.060 BW) (Figure 5.2), the first peak of the fore-aft GRF (\( P < 0.001 \), mean difference: 0.015 BW) and the second peak of the mediolateral GRF (\( P < 0.001 \), mean difference: 0.011 BW).

The temporal patterns of the individual contributions by muscles and gravity to support, progression and balance were similar between the groups (Figure 5.1). Inertial contributions were negligible and are not considered further. The magnitudes of peak contributions to each component of GRF differed between patients and controls (Figure 5.2), with significant differences described below.

During early-stance progression, the magnitudes of peak contributions were greater for patients’ hamstrings (\( P < 0.001 \), mean difference: 0.009 BW) but smaller for vasti (\( P < 0.001 \), mean difference: 0.026 BW). In late-stance progression, peak contributions were smaller for patients’ gluteus medius (\( P < 0.001 \), mean difference: -0.024 BW), but larger for patient’s gastrocnemius (\( P < 0.001 \), mean difference: 0.011 BW).

The magnitudes of peak contributions to early-stance support were smaller for patients’ gluteus medius (\( P < 0.001 \), mean difference: -0.055 BW), gluteus maximus (\( P = 0.003 \), mean difference: -0.021 BW) and vasti (\( P < 0.001 \), mean difference: -0.049 BW) contributions, but greater for gravity (\( P = 0.006 \), mean difference: 0.016 BW). In late-stance support, peak contributions were smaller for
gluteus medius ($P<0.001$, mean difference: -0.024 BW) and soleus ($P<0.001$, mean difference: -0.060 BW). Although patients’ gastrocnemius contributed more than controls in late-stance support, this difference did not reach significance ($P=0.253$, mean difference: 0.019 BW).

The magnitudes of peak contributions to early-stance balance were smaller for patients’ gravity ($P=0.009$, mean difference: -0.002 BW). In late-stance balance, the peak magnitudes of patients’ gluteus medius ($P<0.001$, mean difference: 0.025 BW) and soleus ($P<0.001$, mean difference: -0.012 BW) contributions were lower while gravity contributions ($P<0.001$, mean difference: -0.003 BW) were higher.

Both peaks of the EKAM were higher in patients than controls (first: $P<0.001$, mean difference: 0.55 %BW*HT; second: $P<0.001$, mean difference: 1.63 %BW*HT). The difference in magnitude between controls and patients at the second peak was almost 3 times that at the first peak (Figure 5.3). The temporal patterns of muscle and gravity contributions to EKAM were qualitatively similar for patients and controls (Figure 5.3); however, the magnitude of contributions to EKAM differed between the groups (Figure 5.3), with significant differences described below.

Gluteus medius was the largest contributor to EKAM throughout stance in both groups, lower in patients at the second peak ($P<0.001$, mean difference: -0.43 %BW*HT). Patients’ soleus ($P<0.001$, mean difference: 0.80 %BW*HT) and gastrocnemius ($P<0.001$, mean difference: 0.65 %BW*HT) contributed less abduction moment in late stance. Patients’ vasti contributed less abduction moment in early-stance ($P<0.001$, mean difference: 0.23 %BW*HT) but more
adduction moment in late-stance \((P<0.001, \text{mean difference: 0.06 \%BW*HT})\). Patients’ gravity contributions were higher throughout stance (first peak: \(P<0.001, \text{mean difference: 0.37 \%BW*HT}\); second peak: \(P<0.001, \text{mean difference: 0.15 \%BW*HT}\)).

Mid-stance EKAM was higher in patients \((P<0.001, \text{mean difference: 1.40 \%BW*HT})\), due mainly to greater magnitude of contribution by gluteus medius \((P<0.001, \text{mean difference: 0.23 \%BW*HT})\) and gravity \((P<0.001, \text{mean difference: 0.23 \%BW*HT})\); and smaller magnitude of abduction contributions by soleus \((P<0.001, \text{mean difference: 0.27 \%BW*HT})\) and gastrocnemius \((P<0.001, \text{mean difference: 0.49 \%BW*HT})\).

Significant differences were found between the groups for the moment arms of muscle and gravity contributions to EKAM (Table 5.4). Moment arms of contributors which provided an adduction moment typically increased, while those that provided an abduction moment typically decreased. The largest percentage change was found for gravity at the first peak; and soleus and gastrocnemius at the second peak. Full times histories of the individual contributions to EKAM by the major lower-limb muscles are provided in Appendix D.

### 5.4 DISCUSSION

The goals of this study were to quantify and compare individual contributions by muscles, gravity and inertia to the GRF and EKAM in healthy and osteoarthritic individuals walking at similar speeds. We found that: (1) peak GRF contributions by muscles were typically lower in patients, except in late-stance progression
where patients’ ankle plantarflexor contributions were higher; and (2) a higher first peak of EKAM was due mainly to a large increase in gravity’s contribution, while a higher second peak was due mainly to a substantial decrease in the ankle plantarflexors’ contributions.

5.4.1 Differences in muscles function are small but important

Differences in the magnitudes of peak contributions by muscles to each component of the GRF were small, but typically commensurate with differences in muscle forces reported previously for these patient and control groups (Sritharan et al., 2016) (peak values in Table 5.3). In this earlier study, reduced peak hip abduction, hip extension, knee extension and ankle plantarflexor torques in patients resulted in lower gluteus medius, gluteus maximus, vasti and soleus forces, but higher hamstrings forces than controls (Sritharan et al., 2016). In our present study, similar qualitative differences in the contributions to the GRF were subsequently found.

Our overall finding of only modest differences in muscle function between patients and controls at similar walking speeds is not surprising, and can be inferred to some extent from the similar temporal patterns and only slightly lower peaks of the measured GRF (Figure 5.1). Muscle function in our relatively young patient group (mean age: 49 years) demonstrated similarities with gait in healthy elderly individuals, where only modest changes in the muscle function were found despite differences in joint kinematics and some muscle forces (Lim et al., 2013). Yet sizable alterations in muscular coordination strategy do occur in severe cases of neuromuscular dysfunction, such as cerebral palsy (Steele et al., 2013). Thus,
we suggest two possible reasons for our findings: (1) that level walking is not a suitable task for revealing any large-scale changes in muscle function in OA patients; and/or (2) that OA does not in fact produce large-scale changes in muscle function – but its more subtle changes may have deleterious effects over repeated cycles.

5.4.2 Muscles function in ankle-plantarflexors is altered

Although our first hypothesis of lower peak GRF contributions in patients was generally supported, two exceptions were evident in progression where the magnitudes of patients’ early-stance hamstrings contribution and late-stance gastrocnemius contribution exceeded those of controls. The latter finding of greater gastrocnemius contribution in late-stance progression in patients, together with a soleus contribution that is comparable to controls (Figure 5.2, top right), may indicate a potential compensatory mechanism for impaired action of the gluteus medius in accelerating the body COM forward. We previously calculated lower ankle plantarflexor muscle forces in this patient group (Sritharan et al., 2016) (Table 5.3, mean differences at peak – soleus: -0.45 BW, gastrocnemius: -0.12 BW) however, we also found decreased peak late-stance ankle plantarflexion in these patients, i.e. increased dorsiflexion (Table 5.2, mean difference at peak: -4 degrees). Recently Correa et al. Correa et al. (2012) found that increased late-stance ankle dorsiflexion observed in crouch gait in children with cerebral palsy improved the potential for the ankle plantarflexor muscles to accelerate the body COM forward. A similar mechanism in our OA patients may have enabled improvements in the functional performance of their ankle plantarflexor muscles.
despite muscle force deficits, thus enabling them to compensate for the reduced gluteus medius contribution to late-stance progression.

5.4.3 Knee-spanning muscle co-activity may impact muscle function

Our results further suggest that OA-related changes in knee-spanning muscle co-contraction levels may also impact muscle function in early-stance progression. We previously found elevated quadriceps-hamstrings co-contraction levels for this patient group (peak co-contraction index as defined by Zeni et al. Zeni et al. (2010) – OA patients: 0.63; controls: 0.57) due to greater hamstrings muscle forces and diminished vasti forces (Sritharan et al., 2016) (Table 5.3). Our present study found that increased hamstrings action undesirably amplified forward acceleration of the body in early stance, which is the braking phase of walking gait (Figure 5.1, left). Decelerating the body COM is an essential function of the vasti during this time period (Liu et al., 2006; Pandy and Andriacchi, 2010). Yet because the vasti contribution in early-stance progression was diminished in patients (Figure 5.1, left), a subtle rebalancing of coordination was required across the other muscles of the lower-limb as well as slightly increased loading through the skeletal linkage to produce the necessary overall braking force (Figure 5.2, top left). Our present study shows that although hamstrings is not typically considered a major muscle involved in fore-aft acceleration of the body COM during stance, changes in hamstrings function can impact the function of the other prime movers. Thus the hamstrings should be considered in future studies of muscle function in pathological gait patterns where altered knee-spanning muscle co-activity is a feature.
5.4.4 Mal-alignment impacts some muscles more than others

The temporal patterns of contributions to EKAM in controls and patients were similar to that reported previously (Sritharan et al., 2012). The higher first peak of EKAM in patients was mostly due to a sustained positive contribution by gravity throughout the first half of stance, whereas gravity contributed almost nothing during this period in controls (Figure 5.3). In contrast, the higher second peak of EKAM in OA patients relative to controls was largely due to a marked reduction in peak external abduction moment contribution from the soleus and gastrocnemius. Similar to a study using subjects with total knee replacements (Kutzner et al., 2013b), the second peak of EKAM showed a larger variation than the first peak (Figure 5.4). The other major muscles showed only modest differences between the groups. Gluteus medius behaved differently, demonstrating higher contribution in patients through mid-stance only, with no difference at the first peak and a lower contribution at the second peak. As such, our second hypothesis – increased adduction moment contributions from gluteus maximus, gluteus medius and gravity, but reduced abduction moment contributions from vasti, soleus and gastrocnemius – was only partially supported.

A muscle’s or gravity’s contribution to EKAM is the product of that muscle’s or gravity’s GRF contribution vector and its moment arm about the knee (Sritharan et al., 2012). In patients, the moment arms for gravity at the first peak, and for soleus and gastrocnemius at the second peak, showed the largest differences relative to controls (Table 5.4). Such dramatic changes in these moment arms were unlikely to be solely produced by the small differences in the
GRF vectors found for these contributors (Figure 5.2). Structural differences in the lower-limb, such as greater varus mal-alignment in patients (Table 5.1), likely played a more dominant role. As gravity refers to the loads transmitted through the skeletal linkage (Anderson and Pandy, 2003), only the frontal-plane configuration of the lower-limb could have impacted gravity’s contribution to EKAM. This implicates knee varus as one direct cause of the greater first peak of EKAM by shifting the knee away from gravity’s GRF contribution vector (Figure 5.5). At the second peak of EKAM in patients, greater knee varus likely shifted the knee closer to the ankle plantarflexors’ GRF contribution vectors (Figure 5.5), decreasing their moment arms about the knee (Table 5.4). This strongly impaired the ankle plantarflexors’ ability to resist the large adduction moment provided by the gluteus medius. However, gluteus medius itself was likely less impacted by mal-alignment, as its contribution to GRF showed less moment arm change about the knee compared to other muscles and gravity (Table 5.4). Thus, while the association between mal-alignment and EKAM in patients has been well-studied (Andrews et al., 1996), our present study demonstrates that the underlying effects of mal-alignment may be complex, affecting some contributors to EKAM more than others.

5.4.5 Implications for clinical interventions

Our findings may explain why some non-surgical interventions for medial knee OA that improve lower-limb alignment, such as valgus bracing, may more successfully reduce the second peak of EKAM than the first (Farrokhi et al., 2013). If the frontal-plane alignment in our patients was corrected to the level of
alignment of our healthy controls (Table 5.1), our results suggest that a reduction of 0.5 %BW*HT would occur at the first peak of EKAM due mainly to a reduction in the contribution by gravity; but at the second peak, a three-fold reduction of 1.5 %BW*HT would occur due mainly to a sizable increase in the \textit{abduction} contributions by the soleus and gastrocnemius (Figure 5.4). This implies a considerably greater improvement in the second peak of the actual medial compartment force and/or medial-lateral compartment load share than the first peak. However, modelling studies have found more modest changes in actual medial compartment force than the differences in EKAM would suggest (Kumar et al., 2013; Sritharan et al., 2016). For example, Kumar et al. (2013), using an EMG-driven modelling approach, found differences between controls and varus mal-aligned OA patients of only 0.20 BW at the first peak and 0.27 BW at the second peak of medial compartment force. Thus although EKAM has been shown to be a good predictor of medial-lateral compartment load share throughout the whole of stance (Kutzner et al., 2013b; Meyer et al., 2013), interpretation of changes in EKAM as a predictor of force may need to be peak-specific, supporting the use of separate models to relate medial compartment forces to changes in each peak of EKAM (Kumar et al., 2013; Kutzner et al., 2013b; Meyer et al., 2013; Walter et al., 2010).

\textbf{5.4.6 Influence of mid-stance loads}

Elevated EKAM through mid-stance has been associated with progression of medial knee OA and the future need for total knee replacement (Hatfield et al., 2015b). We found that greater mid-stance EKAM in patients occurred due to three
major differences – higher hip abductor and gravity EKAM contributions, and lower ankle plantarflexor external *abduction* moment contribution (Figure 5.4). In particular, the higher mid-stance hip abductor contribution to EKAM was concomitant with greater demand from these muscles in mediolateral balance during the first half of the single-support phase (Figure 5.1, bottom row). This finding is supported by a recent EMG study which found that greater activation of the gluteus medius was associated with sustained mid-stance EKAM (Rutherford et al., 2014). Interestingly, despite the importance of hip abductors in elevated mid-stance EKAM in patients, they were not explicitly responsible for higher peak EKAM. This finding is supported by an EMG study which found that gluteus medius activation could not explain variability in peak EKAM (Rutherford et al., 2014). Nevertheless our findings reinforce the need to consider mid-stance EKAM and also mid-stance hip abductor function in assessments of and interventions for medial knee OA, particularly as cumulative knee-joint load may also be important in disease development and progression (Maly, 2008).

5.4.7 Limitations

This study is not without limitations. Firstly, to decompose the GRF, a simplified foot-ground interaction model with five discrete contact points was used (Lin et al., 2010) while in reality the pressure distribution is continuous and variable across the surface of the foot. However, by allowing these foot-ground points to be fully-constrained, partially-constrained or unconstrained depending on the phase of foot-ground contact, our models represent a substantially more realistic representation of the foot-ground interaction (Dorn et al., 2012) than the single-
point models (Goldberg and Kepple, 2009; Liu et al., 2008), and produce results consistent with foot-ground models of up to 30 contact points (Sasaki and Neptune, 2006). Thus, we believe our approach yields suitable estimates of muscle function during gait. Secondly, our static optimisation-based muscle forces (Sritharan et al., 2016) may not accurately reflect neuromuscular adaptations to OA demonstrated by some patients, such as elevated knee-spanning muscle co-activity (Hubley-Kozey et al., 2009). Nevertheless, we previously found that the relative magnitudes and patterns of knee-spanning muscle forces was in good agreement with EMG (Sritharan et al., 2016), and the mean peak co-contraction index (CCI) as defined by Zeni et al. (2010) was higher in our patients than controls (OA patients: CCI=0.63 at 19% of stance, controls: CCI=0.57 at 18% of stance). Therefore, we are confident that our subsequent estimates of muscle function and contributions to EKAM adequately reflect those of OA patients. Other functional and morphological changes associated with advanced medial knee OA, such as muscle atrophy and activation failure (Petterson et al., 2008), quadriceps force deficits (Slemenda et al., 1997) and pain (Sharma et al., 2001) were not included in our analyses as they are difficult to quantify and implement. The inclusion of these characteristics in musculoskeletal models should be an objective for future studies of OA gait.

5.5. CONCLUSIONS

In conclusion, we found that although muscle function in osteoarthritic gait was not substantially different from healthy gait, small but important magnitude differences did occur. Diminished muscle forces, elevated knee-spanning muscle
co-contractions and altered kinematics associated with OA all contributed to these differences. Although frontal-plane alignment played a substantial role in producing greater EKAM by changing the moment arms of contributors’ GRF contributions about the knee, only three contributors were markedly impacted – gravity, soleus and gastrocnemius. We hope our present work would provide a foundation for further study of gait changes associated with knee OA and the broader systemic impacts of interventions on gait mechanics, especially the effects of gait modifications.

5.6 TABLES AND FIGURES

This section contains the tables and figures associated with the results and discussion of the present study.
Table 5.1 Participant characteristics of OA patients and healthy controls

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>OA</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 15)</td>
<td>(n = 39)</td>
<td></td>
</tr>
<tr>
<td>Age, yrs</td>
<td>49 (7)</td>
<td>49 (7)</td>
<td>0.869</td>
</tr>
<tr>
<td>Height, m</td>
<td>77 (15)</td>
<td>89 (17)</td>
<td>0.015</td>
</tr>
<tr>
<td>Mass, kg</td>
<td>1.70 (0.10)</td>
<td>1.78 (0.09)</td>
<td>0.006</td>
</tr>
<tr>
<td>BMI, kg/m(^2)</td>
<td>26.5 (4.8)</td>
<td>28.2 (3.6)</td>
<td>0.177</td>
</tr>
<tr>
<td>Females, no. (% of total)</td>
<td>4 (27%)</td>
<td>8 (21%)</td>
<td>0.634</td>
</tr>
<tr>
<td>Walking speed, m/s</td>
<td>1.21 (0.07)</td>
<td>1.20 (0.10)</td>
<td>0.575</td>
</tr>
<tr>
<td>KOOS subscale scores, 0–100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>-</td>
<td>55 (18)</td>
<td>-</td>
</tr>
<tr>
<td>Symptoms</td>
<td>-</td>
<td>54 (18)</td>
<td>-</td>
</tr>
<tr>
<td>Activities of daily living</td>
<td>-</td>
<td>65 (20)</td>
<td>-</td>
</tr>
<tr>
<td>Sport and recreation</td>
<td>-</td>
<td>31 (23)</td>
<td>-</td>
</tr>
<tr>
<td>Knee-related quality of life</td>
<td>-</td>
<td>29 (19)</td>
<td>-</td>
</tr>
<tr>
<td>KL grade 0/1/2/3/4, no. of patients</td>
<td>-</td>
<td>0/1/10/15/13</td>
<td></td>
</tr>
<tr>
<td>Mechanical axis angle, deg</td>
<td>-</td>
<td>9 (3)</td>
<td></td>
</tr>
<tr>
<td>Static frontal-plane alignment, deg</td>
<td>6 (6)</td>
<td>13 (5)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

These patient and control data were previously published (Sritharan et al., 2016). Values are presented as mean (standard deviation) unless otherwise indicated. \(P\)-values were calculated using independent-samples \(t\)-tests. Significance level was defined as \(\alpha = 0.05\). Statistically significant differences are shown in \textit{bold italic}. KOOS: Knee Injury and Osteoarthritis Outcome Score (0 = maximum symptoms, 100 = no symptoms). Static knee adduction angle calculated using inverse kinematics from static trial marker data (positive values represent varus). Static knee adduction angle measured from full-limb standing anteroposterior radiographs (positive values represent varus). Static frontal-plane alignment measured using marker data from static gait trial (positive values represent varus).
Table 5.2 Peak joint angles and approximate time of occurrence for OA patients and healthy controls during stance.

<table>
<thead>
<tr>
<th></th>
<th>Early stance peak</th>
<th></th>
<th></th>
<th></th>
<th>Late stance peak</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Approx. time</td>
<td>Control (°)</td>
<td>OA (°)</td>
<td>P</td>
<td></td>
<td>Approx. time</td>
<td>Control (°)</td>
<td>OA (°)</td>
</tr>
<tr>
<td>Hip flexion</td>
<td>0%</td>
<td>32 (5)</td>
<td>32 (8)</td>
<td>0.735</td>
<td></td>
<td>80%</td>
<td>-8 (7)</td>
<td>-9 (10)</td>
</tr>
<tr>
<td>Hip adduction</td>
<td>26%</td>
<td>2 (3)</td>
<td>-4 (5)</td>
<td>&lt; 0.001</td>
<td></td>
<td>68%</td>
<td>8 (3)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Knee flexion</td>
<td>21%</td>
<td>22 (4)</td>
<td>20 (6)</td>
<td>0.028</td>
<td></td>
<td>63%</td>
<td>9 (5)</td>
<td>11 (7)</td>
</tr>
<tr>
<td>Knee adduction</td>
<td>30%</td>
<td>6 (3)</td>
<td>14 (5)</td>
<td>&lt; 0.001</td>
<td></td>
<td>79%</td>
<td>6 (3)</td>
<td>13 (5)</td>
</tr>
<tr>
<td>Ankle plantarflexion</td>
<td>10%</td>
<td>8 (4)</td>
<td>4 (10)</td>
<td>&lt; 0.001</td>
<td></td>
<td>74%</td>
<td>-19 (4)</td>
<td>-15 (19)</td>
</tr>
</tbody>
</table>

Peak joint angles are presented as mean (standard deviation) in units of degrees (°). Mean peak joint angles occurred at similar time instances for both patients and controls, therefore the time instances shown are approximate for both groups, and presented in *italics* in units of percentage of stance (%). *P*-values were calculated using independent-samples *t*-tests. Significance level was defined *a priori* as $\alpha = 0.05$ with statistically significant differences shown in **bold italic**. Full time histories of joint angles for these patient and control groups were presented previously in Sritharan et al. Sritharan et al. (2016).
Table 5.3 Peak muscle forces and approximate time of occurrence for OA patients and healthy controls during stance.

<table>
<thead>
<tr>
<th>Muscle Forces</th>
<th>Approx. time</th>
<th>Control (BW)</th>
<th>OA (BW)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gluteus maximus</td>
<td>23%</td>
<td>0.61 (0.15)</td>
<td>0.56 (0.23)</td>
<td>0.013</td>
</tr>
<tr>
<td>Gluteus medius 1&lt;sup&gt;st&lt;/sup&gt; peak</td>
<td>25%</td>
<td>1.64 (0.29)</td>
<td>1.40 (0.28)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Gluteus medius 2&lt;sup&gt;nd&lt;/sup&gt; peak</td>
<td>69%</td>
<td>1.83 (0.36)</td>
<td>1.57 (0.32)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Vasti</td>
<td>18%</td>
<td>0.90 (0.34)</td>
<td>0.77 (0.45)</td>
<td>0.004</td>
</tr>
<tr>
<td>Rectus femoris</td>
<td>86%</td>
<td>0.45 (0.23)</td>
<td>0.40 (0.25)</td>
<td>0.040</td>
</tr>
<tr>
<td>Hamstrings</td>
<td>13%</td>
<td>0.36 (0.10)</td>
<td>0.52 (0.20)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Biceps femoris short head</td>
<td>74%</td>
<td>0.29 (0.13)</td>
<td>0.27 (0.14)</td>
<td>0.286</td>
</tr>
<tr>
<td>Soleus</td>
<td>76%</td>
<td>2.80 (0.65)</td>
<td>2.35 (0.77)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Gastrocnemius</td>
<td>65%</td>
<td>1.76 (0.57)</td>
<td>1.65 (0.60)</td>
<td>0.067</td>
</tr>
</tbody>
</table>

Muscle forces presented as mean (standard deviation) in units of body weights (BW). Mean peak muscle forces occurred at similar time instances for both patients and controls, therefore the time instances shown are approximate for both groups, and presented in *italics* in units of percentage of stance (%). *P*-values were calculated using independent-samples *t*-tests. Significance level was defined *a priori* as $\alpha = 0.05$ with significant differences shown in *bold italic*. Full time-histories of muscle forces for these patient and control groups were presented previously in Sritharan et al. Sritharan et al. (2016).
Table 5.4 Mean frontal-plane moment arms of the GRF contribution vectors about the knee-joint centre at peaks of EKAM

<table>
<thead>
<tr>
<th></th>
<th>Moment arm (cm)</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>OA</td>
</tr>
<tr>
<td><strong>First peak</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gluteus medius</td>
<td>15.6 (2.8)</td>
<td>20.2 (5.8)</td>
</tr>
<tr>
<td>Gluteus maximus</td>
<td>3.9 (1.6)</td>
<td>6.9 (5.7)</td>
</tr>
<tr>
<td>Vasti</td>
<td>-3.4 (1.8)</td>
<td>-4.3 (8.2)</td>
</tr>
<tr>
<td>Gravity</td>
<td>0.2 (1.2)</td>
<td>2.9 (1.8)</td>
</tr>
<tr>
<td>Total</td>
<td>5.2 (1.7)</td>
<td>7.2 (2.2)</td>
</tr>
<tr>
<td><strong>Second peak</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gluteus medius</td>
<td>33.5 (3.4)</td>
<td>37.2 (4.4)</td>
</tr>
<tr>
<td>Soleus</td>
<td>-4.9 (2.2)</td>
<td>-2.2 (2.4)</td>
</tr>
<tr>
<td>Gastrocnemius</td>
<td>-7.7 (3.1)</td>
<td>-4.1 (3.2)</td>
</tr>
<tr>
<td>Gravity</td>
<td>18.7 (4.6)</td>
<td>24.2 (6.1)</td>
</tr>
<tr>
<td>Total</td>
<td>3.5 (1.9)</td>
<td>7.2 (2.6)</td>
</tr>
</tbody>
</table>

Moment arms are presented as mean (standard deviation) in units of centimetres (cm). P-values were calculated using independent-samples t-tests. Significance level was defined *a priori* as $\alpha = 0.05$. 
Figure 5.1 Pattern of muscle and gravity contributions to the GRF in OA patients and healthy controls during stance

Mean contributions by the major muscles and gravity to progression (top row), support (middle row) and balance (bottom row) in controls (solid lines) and OA patients (dashed lines). Black lines represent the mean GRF components measured from force plates. “Other” refers to the summed contributions from all remaining muscle forces and inertial forces. Positive values for progression, support and balance represent forces directed forwards, upwards and laterally respectively.
Means and standard deviations of the contributions by major muscle groups and gravity at their peak values during early stance (left column) and late stance (right column) in controls and patients, for progression (top row), support (middle row) and balance (bottom row). Asterisks (*) indicate statistically significant differences ($P<0.05$). “Other” refers to the summed contributions from all remaining muscle forces and inertial forces. Positive values for progression, support and balance represent forces directed forwards, upwards and laterally respectively.
Contributions by major muscle groups and gravity to the external knee adduction moment in controls (solid lines) and patients (dashed lines). Black lines represent the total of these grouped contributions and gravity. Positive values represent adduction, while negative values represent abduction. “Other” refers to the summed contributions from all remaining muscle forces and inertial forces.
Figure 5.4 Contributions by muscles and gravity at the peak values of the external knee adduction moment during stance

Means and standard deviations of the contributions by major muscle groups and gravity at the first peak (left), mid-stance (centre) and second peak (right) of the external knee adduction moment. Asterisks (*) indicate statistically significant differences ($P<0.05$). “Other” refers to the summed contributions from all remaining muscle forces and inertial forces. Positive values represent adduction, while negative values represent abduction.
Figure 5.5 Schematic diagram illustrating how lower-limb alignment can affect the moment arm of the GRF contribution vector about the knee differently

Schematic diagram illustrating how lower-limb mal-alignment may influence the gravity and ankle plantarflexors (i.e. soleus and gastrocnemius) contributions to the first and second peaks of the external knee adduction moment (EKAM) respectively. At the first peak of EKAM, mal-alignment shifts the knee-joint centre away from gravity’s GRF contribution vector increasing its moment arm about the knee thus increasing its contribution to EKAM. At the second peak of EKAM, mal-alignment shifts the knee-joint centre towards the ankle plantarflexor GRF contribution vector decreasing its abduction moment arm about the knee thus decreasing its external knee abduction moment contribution.
CHAPTER 6
A COMPARISON OF MODELLED KNEE CONTACT IMPULSE AND SURROGATE MEASURES DURING OSTEOARTHRITIC GAIT

Chapter summary
The objective was to compare the contributions by muscles, gravity and inertia to the medial and lateral compartment impulses (MCI and LCI respectively) and external knee adduction moment impulse (KAI) in the symptomatic (SYM) and asymptomatic (ASYM) limbs of OA patients and healthy controls (CON). Gait data from 39 varus mal-aligned medial knee OA patients and 15 controls were input into musculoskeletal models to calculate contributions to compartment forces and the external knee adduction moment, then integrated over stance to calculate MCI, LCI and KAI. Muscles contributed most to MCI, LCI and KAI in all limbs. Knee-spanning and non-knee-spanning muscles each contributed almost half of MCI. Non-knee-spanning muscles were the largest positive contributors to KAI; knee-spanning muscle contributions were negative. Gravity contributions to MCI, LCI and KAI were small. Inertial contributions were always negligible. MCI and KAI increased significantly while LCI decreased significantly from CON to SYM. Although gastrocnemius and gluteus medius were the largest contributors to MCI, hamstrings, soleus and gluteus maximus and gravity were responsible for increasing MCI from CON to SYM. Gastrocnemius and rectus femoris provided the most negative and most positive knee-spanning contributions to KAI respectively, while gluteus medius and soleus were the most positive and most negative non-knee-spanning contributors respectively. Most
muscles and gravity contributed to increasing KAI from CON to SYM, except hamstrings and gluteus medius. Although MCI and KAI differ in composition, changes in MCI contributions were generally reflected in KAI, supporting the use of KAI as a viable surrogate measure of MCI.
6.1 INTRODUCTION

Abnormally high levels of accumulated loading in the knee may be implicated in the initiation and progression of medial knee osteoarthritis (OA) (Maly, 2008). Modelling studies have shown that OA patients may experience higher peak medial compartment force (Brandon et al., 2014; Kumar et al., 2013; Sritharan et al., 2016) and sustained elevated mid-stance loads (Kumar et al., 2013; Sritharan et al., 2016), which may contribute to increased cumulative loading over time.

Greater cumulative loads, based on estimates of joint reaction impulse, have been associated with increased severity of symptoms in spinal OA (Seidler et al., 2001). However, as the in vivo measurement of loading in the natural knee is currently not feasible, the knee adduction moment angular impulse (KAI), defined as the time-integral of the external knee adduction moment (EKAM) (Thorp et al., 2006a), may provide a viable surrogate. EKAM was itself proposed as a surrogate for the forces in the medial compartment (Prodromos et al., 1985), and sustained elevated EKAM through mid-stance has been linked to future need for total knee replacement (TKR) (Hatfield et al., 2015b). This overall greater magnitude of knee-joint load throughout stance may have detrimental effects over many loading cycles, and reinforces the potential role of impulse in the pathomechanics of OA.

The magnitude of KAI distinguishes osteoarthritic knees from healthy knees (Maly et al., 2013). And although the magnitudes of EKAM and KAI have been shown to have good correlation (Hatfield et al., 2015a), KAI may actually be more sensitive than EKAM in distinguishing between disease severities (Kean et al., 2012). Therefore, KAI has a strong potential for use as a clinical surrogate measure of loading in the knee.
However, from a study using measurements from individuals fitted with instrumented TKRs (Walter et al., 2010), the magnitude of KAI has only a moderate association with the magnitude of medial compartment impulse (MCI) suggesting that KAI may not accurately reflect the true magnitude of MCI, in the same way that EKAM may not reflect the actual loading in the medial compartment of the knee (Meyer et al., 2013; Walter et al., 2010). Instead, like EKAM, KAI may better reflect the relative share of total actual contact impulse borne by the medial compartment (Walter et al., 2010).

Modelling studies have shown that both knee-joint forces and EKAM are comprised of contributions from knee-spanning muscles, non-knee-spanning muscles, gravity and inertia (Pandy and Andriacchi, 2010; Sasaki and Neptune, 2010; Sritharan et al., 2012; Sritharan et al., 2016), however the pattern of individual contributions to medial compartment force differs considerably from that of EKAM (Sritharan et al., 2012). Furthermore, the relative composition of these contributors to medial compartment force changes with progression from healthy knees to asymptomatic OA and subsequently to fully-symptomatic OA (Sritharan et al., 2016). Similar examinations of both MCI and KAI have yet to be undertaken and may be essential for the future use of KAI as a clinical surrogate measure of cumulative loading in OA patients.

The purpose of this study was to quantify and compare the individual contributions by muscles, gravity and inertia to: (1) the impulses in the compartments of the tibiofemoral-joint; and (2) and also KAI – in healthy individuals as well as both the symptomatic and asymptomatic limbs of varus mal-aligned unilateral medial knee OA patients for a single stance phase of gait.
6.2 METHODS

6.2.1 Participants and gait experiments

Previously reported experimental gait data for 39 varus mal-aligned medial knee OA patients and 15 healthy controls were used for this study (Table 6.1) (Sritharan et al., 2016). Subject recruitment, inclusion and exclusion criteria, radiographic assessment, patient-reported measures and experimental protocols are detailed in a previous publication (Birmingham et al., 2009). Institutional approval was provided by the Research Ethics Board for Health Sciences Research Involving Human Subjects of the University of Western Ontario (HSREB No. 09812E). Gait experiments were performed at the Wolf Orthopaedic Biomechanics Laboratory, Fowler Kennedy Sport Medicine Clinic, University of Western Ontario.

Details of gait experiments, calculation of joint angles, muscles forces and decomposition of the ground reaction force (GRF) are described in detail in a previous publication (Sritharan et al., 2016) and are only briefly reproduced here. Each participant walked at his or her preferred speed over level ground. The spatial trajectories of 22 retro-reflective markers attached to the body and the GRF were simultaneously recorded using an eight-camera motion capture system (Eagle EvaRT, Motion Analysis Corp., Santa Rosa, CA) sampling at 60 Hz and a single strain-gauged force plate (Advanced Mechanical Technology Inc., Watertown, MA) sampling at 1200 Hz respectively. Five successful gait trials were recorded for each leg.
6.2.2 Musculoskeletal modelling

For each subject, a scaled-generic 10-segment, 27-degree-of-freedom 92-muscle whole-body three-dimensional musculoskeletal model was created. For each successfully recorded trial, joint angles were calculated using inverse kinematics (Lu and O’Connor, 1999) and net joint torques subsequently calculated using inverse dynamics during the stance phase of gait. Muscle forces were calculated from the joint torques using a static optimisation approach which minimised the sum of the squares of muscle activations (Anderson and Pandy, 2001b).

At each time step, a pseudoinverse-based approach was used to decompose the GRF into contributions by individual muscles, gravity and inertia (Lin et al., 2010). Subsequently, the contributions by a single muscle to the medial and lateral compartment forces were calculated at each time step by applying the joint angles, that muscle’s force at the origin and insertion points, as well as that muscle’s contribution to the GRF, and subsequently solving a set of joint reaction equilibrium equations using a least-squares approach (Sritharan et al., 2012). That muscle’s contribution to the EKAM was then calculated as the product of that muscle’s GRF contribution and its moment arm about the knee-joint centre (Sritharan et al., 2012). Finally, that muscle’s contributions to MCI and lateral compartment impulse (LCI) were calculated by integrating the contribution to the respective compartment forces over the stance time, while that muscle’s contribution to KAI was calculated by integrating that muscle’s contribution to EKAM over the stance time. This process was repeated for each muscle in the model, gravity and inertia.
6.2.3 Statistical analyses

To determine group differences in impulse and KAI amongst the three limbs – the symptomatic (SYM) and asymptomatic (ASYM) limbs of OA patients, and also controls (CON) – independent-samples \( t \)-tests were undertaken to compare CON with SYM, and also to compare CON with ASYM; while a paired \( t \)-test was undertaken to compare SYM with ASYM. The \( t \)-tests were performed using SPSS Statistics 22.0 (IBM Corp., Armonk, NY). The Holm-Bonferroni method was then applied at a significance level \( \alpha = 0.05 \) to determine which pairs of limbs differed significantly while controlling for the familywise error rate.

6.3 RESULTS

MCI increased with progression from CON to SYM (Figure 6.1A, left), significantly different amongst all three limbs (Table 6.2). Mean MCI increased 15% between CON and SYM. Knee-spanning muscle, non-knee-spanning muscle and gravity contributions to MCI all increased from CON to SYM (Figure 6.1A, left, and Table 6.2). Muscles were the largest contributors to MCI with knee-spanning muscles contributing almost half of the total MCI, slightly more than non-knee-spanning muscles, in all three limbs (Figure 6.1A, left, and Table 6.2). Gravity contributions were small but significantly different. Inertial contributions were negligible and not considered further.

Both knee-spanning and non-knee-spanning muscle contributions to MCI were positive. Gastrocnemius was overwhelmingly the largest knee-spanning contributor, increasing from CON to SYM, but not significantly different. Hamstrings, vasti and rectus femoris provided small contributions (Figure 6.1A,
centre), but only hamstrings were significantly different between limbs (Table 6.3). Gluteus medius was overwhelmingly the largest non-knee-spanning contributor, and the largest contributor to MCI overall (Figure 6.1, right), increasing from CON to ASYM, but subsequently decreasing from ASYM to CON. Soleus and gluteus maximus contributions were small but increased from CON to SYM, significantly different amongst all limbs (Table 6.3).

LCI was always positive but decreased with progression from CON to SYM (Figure 6.1B, left), significantly different amongst all three limbs (Table 6.2). Knee-spanning muscles contributed a positive impulse to LCI, increasing slightly but significantly from CON to SYM, while non-knee-spanning muscles contributed a negative impulse, increasing significantly in magnitude from CON to SYM (Figure 6.1B, left, and Table 6.2). Gravity contributions to LCI were small.

KAI increased from CON to SYM (Figure 6.2, left), and was significantly different amongst all limbs (Table 6.4). Mean KAI increased 58% between CON and SYM. Knee-spanning muscle, non-knee-spanning muscle and gravity contributions to MCI all increased from CON to SYM (Figure 6.2, left, and Table 6.4). Non-knee-spanning muscles were the largest positive contributors to KAI in all limbs, while knee-spanning muscles produced negative contributions. Gravity provided small but positive contributions to KAI.

Amongst knee-spanning muscles, gastrocnemius and rectus femoris provided the largest negative and largest positive contributions to KAI respectively (Figure 6.2, centre), significantly different amongst all limbs (Table 6.4). Gluteus medius was the largest non-knee-spanning contributor to KAI, and
the largest contributor overall, increasing from CON to ASYM, but decreasing from ASYM to SYM (Figure 6.2, right). Soleus provided a large negative contribution to KAI (Figure 6.2, right), significantly different amongst all limbs (Table 6.4).

6.4 DISCUSSION
The purpose of this study was to quantify and compare the individual contributions by muscles, gravity and inertia to the tibiofemoral compartment impulses and KAI in healthy individuals as well as both the symptomatic and asymptomatic limbs of varus mal-aligned unilateral medial knee OA patients.

6.4.1 Validation of compartment impulses and KAI
Our results correspond well with previously reported results for MCI and KAI. In controls, the magnitudes of MCI and KAI were both comparable to TKR patients walking at a similar speed (Walter et al., 2010) while to our knowledge, no previous study has reported LCI. The KAI in the SYM limb of patients was within range of reported results (Bennell et al., 2011; Birmingham et al., 2009; Kean et al., 2012; Maly et al., 2013). Both MCI and KAI increased with progression from CON to SYM. However KAI demonstrated a more exaggerated rate of increase compared to MCI, a finding supported by Walter et al. (2010) using subjects with instrumented TKR. In our present study MCI increased 15% from CON to SYM, but KAI increased by almost 60% from CON to SYM.

6.4.2 Comparison of MCI and KAI
Nevertheless, our results support the potential use of KAI as a viable surrogate for evaluating changes in MCI. Although the magnitude and composition of MCI differed considerably from that of KAI, the knee-spanning muscle, non-knee-spanning muscle and gravity contributions to KAI all increased with progression from CON to SYM (Figure 6.2, left), appropriately reflecting the corresponding increases in these contributions to MCI (Figure 6.1, left). Although further decomposition showed that some changes in individual contributions to MCI were in fact not appropriately reflected in KAI, such as the hamstrings, these were masked by larger changes in other contributors such as gastrocnemius.

6.4.3 Individual contributions to MCI and KAI

Overall, muscles were the largest contributors to both MCI and KAI in all three limbs. Notably, non-knee-spanning muscles contributed only slightly less than knee-spanning muscles to MCI (Figure 6.1, right) and were the dominating contributors to KAI (Figure 6.2, right). Muscles which do not span the knee can contribute to knee-joint mechanics by means of dynamic coupling via the GRF (Sritharan et al., 2012; Zajac and Gordon, 1989). Non-knee-spanning muscles have been shown to contribute up to half of peak and mid-stance forces in the compartments of both healthy (Sritharan et al., 2012) and osteoarthritic knees (Sritharan et al., 2016). Our results, which show considerable contributions to MCI and KAI by non-knee-spanning muscles, provide further evidence for the important role non-knee-spanning muscles may potentially play in the pathomechanics of medial knee OA.

The present study highlights the difference between major contributors to
the overall magnitude of MCI in all three limb conditions, and contributors that show significant increases with progression from CON to SYM. In all cases, the magnitude of MCI is dominated by contributions from gluteus medius and gastrocnemius (Figure 6.1). However the change in these muscles’ contributions to MCI as the condition progressed from CON to SYM was, for the most part, not significant (Table 6.2). Conversely, soleus and gravity, whose contributions to MCI were small in all cases, showed significant increases with progression from CON to SYM (Figure 6.1, Tables 6.2 and 6.3).

In the case of KAI for all three conditions, non-knee-spanning muscles contributed overwhelmingly positively while knee-spanning muscles overall produced a negative impulse (Figure 6.2). This finding is consistent with those respective individual muscle contributions to EKAM found previously, with gastrocnemius and gluteus medius the dominant knee-spanning and non-knee-spanning muscles respectively.

6.4.4 The “asymptomatic” limb
The ASYM limb, which for most patients did in fact show evidence of radiographic OA despite being considered “asymptomatic” (Table 6.1) (Sriharan et al., 2016), demonstrated cumulative loads which were intermediate between SYM and CON suggesting that it should be considered in interventions to mitigate OA progression. Importantly, the gluteus medius contributions to MCI and KAI were greater in the ASYM limb than both CON and SYM limbs (Figures 6.1 and 6.2). Assuming the ASYM limb represents a form of early-stage OA, this finding suggests that elevated gluteus medius contribution to cumulative knee-joint loads
may play an important role in the initiation and early progression of the disease.

6.4.5 Implications for clinical interventions

Both lower-limb alignment and muscle forces have been implicated in elevated peak (Adouni and Shirazi-Adl, 2014b; Brandon et al., 2014; Sritharan et al., 2016), and mid-stance (Sritharan et al., 2016) medial compartment forces in OA patients, and therefore presumably also elevated MCI. Thus interventions which improve the functional performance of muscles and/or alignment would also potentially reduce MCI. Paradoxically however, increased activity levels may increase the total time the knee is exposed to loading, therefore further research is necessary to establish the most effective balance between functional improvements and reduced cumulative load (Robbins et al., 2009).

6.4.6 Limitations

Our present work should be interpreted in the light of two major limitations. Firstly, our finding of greater cumulative loads in patients only applies to one instance of the stance phase of gait. Of course a more complete analysis of cumulative loads would need to take into account loading cycles over an extended period of time, such as the steps per day (Robbins et al., 2009) which, as previously discussed may have implication for interventions, as well as frequency of loading cycles (Maly, 2008). Secondly, we potentially underestimated the magnitude of quadriceps forces, and consequently their contributions to MCI and KAI, in patients as we did not include the knee adduction moment in our static optimisation solution for muscle forces.
6.5 CONCLUSIONS

In conclusion, knee-spanning muscles, non-knee-spanning muscles and gravity all contributed to greater cumulative loads in both compartments of the knee. Both MCI and KAI increased with progression of disease from CON to SYM, and changes in individual contributions to MCI were generally reflected in KAI. Thus overall, KAI may provide a viable surrogate measure of MCI in medial knee OA patients, which may be useful for clinical assessments and for quantification of the biomechanical improvements brought about by the implementation of interventions.

6.6 TABLES AND FIGURES

This section contains the tables and figures associated with the results and discussion of the present study.
<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>OA Patient</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 15</td>
<td>n = 39</td>
<td></td>
</tr>
<tr>
<td>Age, yrs</td>
<td>49 (7)</td>
<td>49 (7)</td>
<td>0.869</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.5 (4.8)</td>
<td>28.2 (3.6)</td>
<td>0.177</td>
</tr>
<tr>
<td>Females, no. (% of total)</td>
<td>4 (27%)</td>
<td>8 (21%)</td>
<td>0.634</td>
</tr>
<tr>
<td>Walking speed, m/s</td>
<td>1.21 (0.07)</td>
<td>1.20 (0.10)</td>
<td>0.575</td>
</tr>
<tr>
<td>Stance time, sec</td>
<td>0.71 (0.05)</td>
<td>SYM: 0.75 (0.06)</td>
<td>ASYM: 0.75 (0.05)</td>
</tr>
<tr>
<td>Mechanical axis angle, degrees</td>
<td>-</td>
<td>SYM: 9 (3)</td>
<td>ASYM: 4(3)</td>
</tr>
<tr>
<td>KL grade 0/1/2/3/4, patients</td>
<td>-</td>
<td>SYM: 0/1/10/15/13</td>
<td>ASYM: 4/14/11/10/0</td>
</tr>
</tbody>
</table>

These data were previously published in Sritharan et al. (Sritharan et al., 2016). Values are presented as mean (standard deviation) unless otherwise indicated. *P*-values were calculated using Student’s *t*-tests. Where three limbs (CON, SYM and ASYM) were compared, a Holm-Bonferroni correction was additionally used to identify statistically significant differences. Significance level was defined as $\alpha = 0.05$. Mechanical axis angle was measured from full-limb standing anteroposterior radiographs (positive values represent varus). Comparison pairs: CON and SYM (CS); CON and ASYM (CA), SYM and ASYM (SA). KL grade: Kellgren and Lawrence grade (0 = no OA, 4 = severe OA).
Table 6.2 Contributions by knee-spanning muscles, non-knee-spanning muscles and gravity to the medial and lateral compartment impulses

<table>
<thead>
<tr>
<th></th>
<th>CON (BW)</th>
<th>ASYM (BW)</th>
<th>SYM (BW)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medial compartment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1.094 (0.192)</td>
<td>1.192 (0.248)</td>
<td>1.261 (0.209)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Knee-spanning muscles</td>
<td>0.563 (0.111)</td>
<td>0.591 (0.156)</td>
<td>0.626 (0.143)</td>
<td>CS: &lt; 0.001; CA: 0.001; SA: 0.056</td>
</tr>
<tr>
<td>Non-knee-spanning muscles</td>
<td>0.494 (0.120)</td>
<td>0.543 (0.150)</td>
<td>0.566 (0.133)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Gravity</td>
<td>0.054 (0.018)</td>
<td>0.077 (0.031)</td>
<td>0.094 (0.035)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Lateral compartment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>0.171 (0.127)</td>
<td>0.121 (0.168)</td>
<td>0.0686 (0.151)</td>
<td>CS: &lt; 0.001; CA: 0.002; SA: &lt; 0.001</td>
</tr>
<tr>
<td>Knee-spanning muscles</td>
<td>0.387 (0.047)</td>
<td>0.398 (0.067)</td>
<td>0.405 (0.095)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Non-knee-spanning muscles</td>
<td>-0.228 (0.118)</td>
<td>-0.274 (0.146)</td>
<td>-0.322 (0.115)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Gravity</td>
<td>0.015 (0.011)</td>
<td>-0.002 (0.023)</td>
<td>-0.019 (0.023)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Values are presented as mean (standard deviation) unless otherwise indicated. P-values were calculated using Student’s t-tests. A Holm-Bonferroni correction was used to identify statistically significant differences. Significance level was defined as α = 0.05. Statistically significant differences are shown in *bold italic*. Comparison pairs: CON and SYM (CS); CON and ASYM (CA), SYM and ASYM (SA).
Table 6.3 Contributions by major muscles to the medial compartment impulse

<table>
<thead>
<tr>
<th></th>
<th>CON (BW s)</th>
<th>ASYM (BW s)</th>
<th>SYM (BW s)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasti</td>
<td>0.079 (0.038)</td>
<td>0.079 (0.043)</td>
<td>0.082 (0.066)</td>
<td>CS: 0.586; CA: 0.760; SA: 0.358</td>
</tr>
<tr>
<td>Rectus femoris</td>
<td>0.053 (0.034)</td>
<td>0.057 (0.035)</td>
<td>0.060 (0.046)</td>
<td>CS: 0.132; CA: 0.351; SA: 0.378</td>
</tr>
<tr>
<td>Hamstrings</td>
<td>0.039 (0.021)</td>
<td>0.049 (0.031)</td>
<td>0.053 (0.032)</td>
<td>CS: &lt; 0.001; CA: &lt; 0.001; SA: 0.101</td>
</tr>
<tr>
<td>Gastrocnemius</td>
<td>0.365 (0.134)</td>
<td>0.377 (0.179)</td>
<td>0.398 (0.183)</td>
<td>CS: 0.053; CA: 0.471; SA: 0.234</td>
</tr>
<tr>
<td>Soleus</td>
<td>0.059 (0.025)</td>
<td>0.086 (0.040)</td>
<td>0.108 (0.045)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Gluteus medius</td>
<td>0.452 (0.079)</td>
<td>0.476 (0.092)</td>
<td>0.467 (0.078)</td>
<td>CS: 0.075; CA: 0.011; SA: 0.290</td>
</tr>
<tr>
<td>Gluteus maximus</td>
<td>0.045 (0.020)</td>
<td>0.057 (0.035)</td>
<td>0.065 (0.042)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Values are presented as mean (standard deviation) unless otherwise indicated. P-values were calculated using Student’s t-tests. A Holm-Bonferroni correction was used to identify statistically significant differences. Significance level was defined as $\alpha = 0.05$. Statistically significant differences are shown in **bold italic**. Comparison pairs: CON and SYM (CS); CON and ASYM (CA), SYM and ASYM (SA).
<table>
<thead>
<tr>
<th></th>
<th>CON (%BW<em>HT</em>s)</th>
<th>ASYM (%BW<em>HT</em>s)</th>
<th>SYM (%BW<em>HT</em>s)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1.100 (0.496)</td>
<td>1.490 (0.548)</td>
<td>1.736 (0.509)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Knee-spanning muscles</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasti</td>
<td>-0.267 (0.168)</td>
<td>-0.188 (0.186)</td>
<td>-0.056 (0.264)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Rectus femoris</td>
<td>-0.074 (0.058)</td>
<td>-0.069 (0.061)</td>
<td>-0.039 (0.070)</td>
<td></td>
</tr>
<tr>
<td>Hamstrings</td>
<td>-0.036 (0.026)</td>
<td>0.109 (0.072)</td>
<td>0.132 (0.107)</td>
<td></td>
</tr>
<tr>
<td>Gastrocnemius</td>
<td>-0.322 (0.101)</td>
<td>-0.272 (0.129)</td>
<td>-0.187 (0.140)</td>
<td></td>
</tr>
<tr>
<td>Non-knee-spanning muscles</td>
<td>1.266 (0.376)</td>
<td>1.490 (0.546)</td>
<td>1.541 (0.329)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Soleus</td>
<td>-0.405 (0.195)</td>
<td>-0.345 (0.253)</td>
<td>-0.202 (0.183)</td>
<td></td>
</tr>
<tr>
<td>Gluteus medius</td>
<td>1.583 (0.310)</td>
<td>1.660 (0.338)</td>
<td>1.626 (0.328)</td>
<td></td>
</tr>
<tr>
<td>Gluteus maximus</td>
<td>0.180 (0.082)</td>
<td>0.195 (0.136)</td>
<td>0.216 (0.138)</td>
<td></td>
</tr>
<tr>
<td>Gravity</td>
<td>0.148 (0.091)</td>
<td>0.247 (0.132)</td>
<td>0.338 (0.127)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Values are presented as mean (standard deviation) unless otherwise indicated. *P*-values were calculated using Student’s t-tests. A Holm-Bonferroni correction was used to identify statistically significant differences. Significance level was defined as α = 0.05. Statistically significant differences are shown in **bold italic**. Comparison pairs: CON and SYM (CS); CON and ASYM (CA), SYM and ASYM (SA).
Figure 6.1 Contributions by the major muscles and gravity to the medial and lateral compartment impulse during stance

Contributions by major knee-spanning muscles, non-knee-spanning muscles and gravity to the (A) medial compartment impulse; and (B) the lateral compartment impulse, in the knees of healthy controls (CON) as well as the symptomatic (SYM) and asymptomatic (ASYM) knees of unilateral medial knee OA patients. Impulse for each compartment was calculated as the time-integral of the load borne by that compartment in the stance leg for the duration of one stance phase. Positive values represent impulse due to overall compressive reaction forces in the respective compartments.
Figure 6.2 Contributions by the major muscles and gravity to the external knee adduction moment angular impulse during stance

Contributions by major knee-spanning muscles, non-knee-spanning muscles and gravity to the external knee adduction moment angular impulse in the knees of healthy controls (CON) as well as the symptomatic (SYM) and asymptomatic (ASYM) knees of unilateral medial knee OA patients. The knee adduction moment angular impulse was calculated as the time-integral of the external knee adduction moment about the stance leg for the duration of one stance phase.
CHAPTER 7
SUMMARY OF FINDINGS

7.1 INTRODUCTION

The aim of this thesis was to undertake a detailed examination of the contributions to knee-joint loads in osteoarthritic gait to provide an original, essential and useful insight into the pathomechanics of medial knee OA. This in turn may help guide the development of more robust surrogate measures for improved clinical assessment of OA patients, and to help direct the development of innovative interventions to prevent or mitigate disease progression.

A novel computational method for decomposing the tibiofemoral compartment loads into contributions by muscles, gravity and inertia was developed and integrated into an advanced musculoskeletal modelling pipeline. Experimental gait data from varus mal-aligned unilateral medial knee OA patients and healthy controls were input in the musculoskeletal modelling pipeline and used to quantify the contributions to the forces and cumulative loads in the medial and lateral compartments of the tibiofemoral-joint, and also to surrogate measures of medial compartment loading.

The work undertaken in this thesis has revealed substantive differences in the composition of joint loads between healthy and osteoarthritic knees, and has explained some of the underlying mechanisms by which elevated knee-joint loads arise in OA patients. Importantly, this work has also quantified and explained some of the potential limitations associated with surrogate measures of joint loads, which may impact clinical assessments of and interventions for medial knee OA.
7.2 RESEARCH QUESTIONS REVISITED

7.2.1 To what extent do non-knee-spanning muscles impact medial and lateral compartment loading during gait, and how do their effects differ from knee-spanning muscles?

This thesis reported the first known quantifications of the knee-spanning and non-knee-spanning muscle contributions to forces and cumulative loads in the tibiofemoral compartments of the knee. Overall, non-knee-spanning muscles compressed the medial compartment and were shown in Chapter 3 to be as equally important as knee-spanning muscles in medial compartment loading in both OA individual and controls, contributing up to half of the peak medial compartment forces and cumulative load. In fact, Chapter 4 found that, when frontal-plane alignment was also taken into account, at the first peak of the medial compartment force, non-knee-spanning muscles may potentially contribute more compressive force than knee-spanning muscles. Furthermore, Chapter 6 found that non-knee-spanning muscles were responsible for almost half of the cumulative load in the medial compartment. Non-knee-spanning muscles were also shown to produce a large unloading effect on the lateral compartment. In contrast, knee-spanning muscle contributions always compressed both compartments.

These findings highlighted the principal role played by the lower-limb kinematic chain, i.e. the skeletal linkage, in determining how non-knee-spanning muscles contribute to knee-joint forces. Chapters 3 and 4 found that because non-knee-spanning muscles can only contribute to joint loads indirectly by means of dynamic coupling via the ground reaction force (GRF), frontal-plane moments
about the knee played a central role in determining the distribution of non-knee-spanning muscle contributions between the medial and lateral compartments of the tibiofemoral-joint. Large frontal-plane knee moments produced by non-knee-spanning muscles tended to completely unload the lateral compartment and compress the medial compartment. Chapter 4 found that this effect was amplified in cases of increased frontal-plane mal-alignment. While knee-spanning muscles contributed via the GRF, they also directly compressed the knee. For knee-spanning muscles, this direct compression dominated the indirect compression due to dynamic coupling.

From Chapters 3, 4 and 5, it was established that the patterns of contributions to knee-joint loads were intimately related to muscle function. Five key muscles which contributed to centre-of-mass progression, support and balance – the vasti, hamstrings, gluteus medius, gluteus maximus, gastrocnemius and soleus – were found to be the largest contributors to the medial and lateral compartment forces, and from Chapter 6, to the cumulative compartment loads as well. Of the non-knee-spanning muscles, the gluteus medius was overwhelmingly the largest contributor to compartment loads. Of the knee-spanning muscles, vasti in early stance and gastrocnemius in late stance were the largest contributors.

Gravity played an important role in knee-joint loading. Chapters 4 and 6 found that gravity contributions to peak, mid-stance and cumulative tibiofemoral compartment loads were always compressive on both compartments albeit small in magnitude. As the contribution from gravity to knee-joint forces arises from the resistance of the skeletal linkage to gravitational forces, the contributions by gravity to knee-joint loads is intimately associated with the configuration of the
lower-limb. Thus gravity contributions to the medial compartment force and cumulative load were amplified in cases of increased frontal-plane mal-alignment. Inertial forces were generally found to be negligible at the moderate walking speeds analysed in this thesis, however, it is possible that at higher speeds, such as at fast running speeds (e.g. 3.5 m/s and faster) inertial forces may become more important in the loading of the knee.

7.2.2 How do changes in muscle forces due to medial knee OA facilitate greater medial compartment loads in osteoarthritic knees, and what is the role of frontal-plane alignment in this?

It was established in Chapter 4 that changes in knee-spanning muscle forces were reflected in their contributions to medial compartment forces, in particular reduced vasti forces and elevated hamstrings muscle forces at the first peak of medial compartment force. This was due to greater influence of direct compression of the knee by these muscles than indirect compression via dynamic coupling.

However, the changes in non-knee-spanning muscle forces were not necessarily reflected in their contributions to medial compartment loads. OA patients demonstrated considerable deficits in the gluteus medius, gluteus maximus and soleus muscle forces, but their individual contributions to the peaks of the medial compartment forces and mid-stance loads were typically higher in patients. As non-knee-spanning muscles can only contribute to knee-joint loads indirectly via dynamic coupling, this suggested that the lower-limb kinematic chain, i.e. the skeletal linkage, may be important in producing elevated
contributions by non-knee-spanning muscles to osteoarthritic knee-joint loads, despite reduced muscle forces.

This reinforced the important role of the kinematic chain, particularly frontal-plane mal-alignment, in enabling non-knee-spanning muscles to indirectly influence knee-joint loading. Additionally, Chapters 4 and 6 found that mal-alignment was also directly responsible for increased medial compartment forces and cumulative loads in OA patients by shifting more of gravity’s contribution from the lateral to the medial compartment.

Importantly, Chapters 4 and 6 found that although these large differences in muscle forces and alignment produced only small increases in muscle and gravity contributions to knee-joint loads, they were crucial in the overall loading regime in osteoarthritic knees. These small changes in individual contributions summed to produce significantly greater peak and mid-stance forces in the medial compartment of the knee, as well as increased cumulative medial compartment loads, in OA patients.

7.2.3 Does muscle function during gait differ in OA patients, and how might any differences influence loading in osteoarthritic knees?

Muscle function in osteoarthritic gait was found to be not appreciably different from that of controls. Chapter 5 reported the first known quantification of muscle function in osteoarthritic gait by decomposing the GRF; however only small differences between OA patients and healthy controls were found in the contributions to centre-of-mass progression, support and balance. Together with gravity, the five principal muscles which contributed to centre-of-mass
progression, support and balance in controls – the vasti, hamstrings, gluteus medius, gluteus maximus, gastrocnemius and soleus – were also the principal muscles involved in muscle function OA patients.

The timing and coordination of muscle contributions to the GRF were not appreciably different between patients and controls, reflecting the timing and coordination of muscle forces, while the magnitude of contributions typically reflected differences in the magnitudes of muscle forces. In particular, the contributions by non-knee-spanning muscles were typically lower in patients. However, gravity contributions to the GRF were virtually the same between the groups. The finding of only small differences in muscle function between patients and controls was not surprising given the relatively young age and high level of mobility of the patient cohort, despite severe clinical and radiographic disease in the symptomatic limb. Furthermore, the results suggested that level walking may not be a sufficiently demanding task to reveal large alterations in muscular coordination in OA patients. Ballistic tasks, such as hop landings, or tasks requiring balance and control, such as stair descent, may reveal larger differences.

In contrast to the contributions to the GRF, Chapter 4 established that lower non-knee-spanning muscle forces did not necessarily result in lower contributions to medial compartment force, and that gravity contributions to the medial compartment were higher in patients. As non-knee-spanning muscles can only compress the medial compartment indirectly via the GRF, this further implicated frontal-plane mal-alignment as a powerful modulator of non-knee-spanning muscle, and also gravity, contributions to medial compartment forces.
7.2.4 Do surrogate measures of knee-joint loads appropriately reflect the composition of actual medial compartment forces, and importantly, do the changes due to medial knee OA accurately reflect changes in actual medial compartment load?

Chapters 3 and 5 investigated the individual contributions to the external knee adduction moment (EKAM), a potential surrogate measure for medial compartment force, while Chapter 6 examined contributions to the external knee adduction moment angular impulse (KAI), a potential surrogate measure of medial compartment impulse. It was found that the compositions of these potential surrogate measures differed considerably from the medial compartment force and impulse respectively. Non-knee-spanning muscles and gravity dominated contributions to EKAM and KAI; whereas in the medial compartment, knee-spanning and non-knee-spanning muscles provided almost equal compressive loads.

More importantly, although greater peak EKAM in OA patients reflected the greater peak medial compartment forces, the change in individual contributions to EKAM did not accurately reflect changes in those contributions to medial compartment force. Chapter 4 found that greater peak medial compartment forces were due to the sum of increases in many small knee-spanning muscle, non-knee-spanning muscle and gravity contributions, yet Chapter 5 found that only the changes in gravity and the ankle plantarflexor contributions were appreciably reflected in the first and second peaks of EKAM respectively. In fact, Chapter 5 found that the first peak of EKAM showed only a small difference between patients and controls, potentially underestimating the
actual changes in the medial compartment force. In contrast, changes in contributions to KAI tended to better agree with changes in contributions to medial compartment impulse.

Overall, Chapters 3, 5 and 6 minimally supported the viability of EKAM as a surrogate measure for investigating changes in medial compartment loads, while the use of KAI was better supported. In particular, the magnitudes of any changes in EKAM would need to be interpreted with care, with particular regard to interventions that seek to reduce medial compartment forces by reducing the peak magnitudes of EKAM.

7.3 POTENTIAL CLINICAL IMPLICATIONS

7.3.1 Implementation of non-pharmacological interventions

The quantitative understanding of the individual contributions to tibiofemoral compartment loads may have implications for the design of non-pharmacological interventions for medial knee OA.

In particular, Chapters 4 and 5 have demonstrated the strong influence of frontal-plane mal-alignment of the lower-limb in modulating the non-knee-spanning muscle and gravity contributions to both the actual and surrogate measures of medial compartment loading. As such, interventions which correct alignment in medial knee OA patients may be beneficial in reducing non-knee-spanning muscle and gravity contributions to the medial compartment loads.

To reduce knee-spanning muscle contributions, however, it was hypothesised in Chapter 4 that it may be more beneficial to improve the functional performance of knee-spanning muscles during gait, with the aim of minimising
aberrations and/or prolonged activity in hamstrings, rectus femoris and gastrocnemius.

Overall, the findings of this thesis would suggest that an intervention strategy which included both correction of mal-alignment and functional improvements of the muscles of the lower-limb would potentially provide the best possible outcome for reducing peak, mid-stance and cumulative loads in the medial tibiofemoral compartment of OA patients. However, Chapter 5 showed that interpretations of the efficacy of interventions by measuring changes in the peaks of EKAM should be undertaken with care. In particular, interventions which produce only small changes in the first peak of EKAM may in fact produce larger changes in the first peak of the medial compartment force.

7.3.2 The “asymptomatic” limb

Chapters 4 and 6 undertook the first known detailed evaluations of the kinematics, kinetics, knee-joint forces and cumulative loading in the asymptomatic limb in unilateral medial knee OA, and simultaneously compared the results with both the symptomatic limb and healthy controls. In the patient cohort, despite the contralateral limb being considered “asymptomatic”, most had pre-existing radiographic symptoms of OA. Chapter 4 found that despite kinematics and muscle forces which were typically intermediate to both healthy controls and the symptomatic limb, peak loads in the asymptomatic limb were no different from controls, although mid-stance loads were significantly higher. This suggested that cumulative loads in the asymptomatic limb were higher than controls, a finding confirmed in Chapter 6. Thus overall, the asymptomatic limb was different to
controls and represented an intermediate condition between healthy knees and fully symptomatic osteoarthritic knees. As such the asymptomatic limb should be considered in the implementation of interventions for unilateral medial knee OA to mitigate or prevent progression to symptomatic bilateral disease.

7.3.3 The role of the hip abductor muscles

Chapters 4 and 6 established the importance of the gluteus medius as the largest non-knee-spanning contributor to forces and cumulative loads in both healthy and osteoarthritic knees. Chapters 3, 5 and 6 also established the gluteus medius as the largest contributor overall to EKAM and KAI. However these studies also found that the gluteus medius was in fact not responsible for the higher peaks of medial compartment force in patients compared to controls, nor to the greater cumulative loads in the medial compartment. It was, however, found that greater contributions from the gluteus medius through mid-stance were important in overall sustained elevated mid-stance medial compartment forces in patients. Thus although hip abductor force deficits are a much-reported feature of medial knee OA, their influence on the elevated loads experienced by OA patients is less pronounced. As elevated mid-stance loads in patients were found in Chapter 4 to be due mainly to increased contributions from several non-knee-spanning muscles, including the gluteus medius, as previously suggested, the correction of lower-limb mal-alignment may provide considerable benefit in reducing overall mid-stance loads.
7.4 FUTURE WORK

The developed methods and overall findings of this work can be expanded in several ways. Firstly, a future study could apply the computational modelling methods developed in this thesis to investigate both the efficacy of interventions and the specific mechanisms by which interventions work to reduce knee-joint loads. In particular, this thesis hypothesised the benefit of an intervention strategy that combined correction of alignment with improvements in the functional performance of lower-limb muscles. A future study could test this hypothesis by quantifying the contributions to knee-joint loads in OA patients who have undertaken one or both of these interventions. For example, the study could test the combined effect of valgus bracing with a muscle strengthening regime against each of these interventions individually.

Secondly, it was hypothesised that walking may not be sufficiently demanding a task to reveal large differences in muscle function between OA patients and healthy individuals. Hence there may be considerably benefit to investigating muscle function and tibiofemoral compartment loads during other various activities of daily life in OA patients, including stair ascent, stair descent, sit-to-stand, and even running. Examination of these tasks may reveal large differences in muscular coordination strategy between OA patients and controls, which may have considerable impact on the contributions to tibiofemoral compartment forces.

Thirdly, the effects of pain, OA-related functional and morphological changes, such as atrophy, strength deficits and activation failure of the quadriceps were not included the musculoskeletal models developed for this thesis. As these
changes compete with the simultaneous demand for greater knee-spanning muscle co-activations and the need for frontal-plane stability, the net effect on muscle and joint forces is difficult to predict. Thus a future study that includes all these effects would potentially provide the most realistic quantification of knee-joint loads however this would require substantial advancements in musculoskeletal modelling techniques, particularly the design of muscle models, the specification of muscle fibre properties and the modelling of activation-contraction dynamics in neuro-musculoskeletal pathologies.

7.5 CONCLUDING REMARKS

This work has demonstrated the capabilities of musculoskeletal models in providing novel and detailed insights into complex clinically-significant musculoskeletal conditions quickly and non-invasively. It is anticipated that in future, musculoskeletal models may reach beyond the research laboratory, and be routinely incorporated into clinical decision-making. For the present however, the findings of this thesis have contributed useful and important knowledge to the pathomechanics of medial knee OA, which may be beneficial for clinical assessments and development of interventions for this painful, debilitating and ultimately incurable disease.
A.1 FORCE PROPAGATION PATHWAYS EXAMPLE

In the analysis of individual muscle contributions to joint accelerations, reaction forces and reaction moments, two situations arise: (1) the muscle of interest spans the joint of interest (e.g., a quadriceps muscle, which spans the knee); and (2) the muscle of interest does not span the joint of interest (e.g., the gluteus medius, which does not span the knee). The second situation has not been well studied, and the importance of the roles played by muscles that do not span a particular joint in the mechanics of that joint is only recently being brought to light (Correa et al., 2010; Pandy and Andriacchi, 2010; Sasaki and Neptune, 2010)

A muscle accelerates the joint it spans by creating a torque about that joint. For example, the hamstrings accelerate the knee-joint, thus contributing to flexion of the knee. However, as the major segments of the body are linked, their motion is inherently coupled. When a muscle accelerates the joint it spans, the effects are propagated through the system of interlinked segments, therefore accelerating other joints and contributing to the joint reaction forces and moments. This concept, often referred to as dynamic coupling, was described by Zajac and Gordon (1989). For example, by accelerating the knee, the hamstrings also induce an acceleration of the ankle joint.

As described in the Discussion section of this paper, a muscle that does not span a particular joint may contribute to the reaction forces and moments acting at that joint via three independent pathways: (1) static propagation of its ground reaction force contribution throughout the system; (2) dynamic propagation of its
ground reaction force contribution throughout the system (Anderson and Pandy, 2003); and (3) dynamic propagation of the muscle’s joint torque contribution throughout the system. The results of the present study showed that, for a given muscle, the influence of each coupling pathway on tibiofemoral compartment loading could be significant, however in three-dimensions, the dynamic pathways tend to cancel each other.

The purpose is to illustrate the three coupling pathways and their significance in the context of a simple example. We studied muscle contributions to the knee-joint reaction force in a two-segment model of the leg with motion restricted to the sagittal plane. The hip joint was fixed in space, and the model was actuated by a single hip-spanning muscle. In the description given below, the equations of motion of the double pendulum model and the equations representing the reaction forces acting at the knee-joint are firstly derived. The contributions from the three coupling pathways to the knee-joint reaction force are then identified. Finally, the method is extended to the three-dimensional model of the lower-limb described in the Methods section of the paper. Note that this example deals only with the contributions of an individual muscle to the reaction force acting at a joint. A similar analysis could be performed to determine how a joint reaction moment arises due to the same three coupling pathways.

A.2 EQUATIONS OF MOTION
The sagittal-plane free-swinging leg is represented by a double pendulum (Figure A.1). Joints 1 and 2 represent the hip and knee-joints, respectively, with the hip fixed in space. Hip flexion angle is given by $\theta_1$ and knee extension angle is given
by $\theta_2$. Together, these two variables represent the set of generalised coordinates for the system. Links 1 and 2 represent the femur and tibia, respectively, having masses $m_1$ and $m_2$ and lengths $l_1$ and $l_2$. The femur and tibia centres of mass are located at distances $r_{c1}$ and $r_{c2}$ from the hip and knee, respectively. The femur and tibia have mass moments of inertia $I_1$ and $I_2$, respectively. A muscle spanning the hip applies a force of magnitude $F_m$ at point $A_0$ on the pelvis and point $A_1$ on the femur. A force of magnitude $F_{GRF}$ representing the muscle’s contribution to the ground reaction is applied at the distal tibia. The foot is omitted in this model for simplicity.

Free-body diagrams of the femur and tibia can be constructed (Figures A.2A and B), where $F_1$ is the hip joint reaction force and $F_2$ the knee-joint reaction force. In this sagittal-plane model, the hip and knee-joints, represented by hinges, do not support joint reaction moments. Gravitational acceleration is denoted by the symbol $g$. In order to simplify the analysis, the muscle force acting at $A_1$ has been replaced by an equivalent force couple acting about the hip joint centre. Thus, muscle action is represented by the force $F_m$ acting at the hip and a flexion torque of magnitude $T_m$ acting about the hip, the latter given by the product of the muscle force and its moment arm $MA_m$:

$$T_m = |\mathbf{T}_m| = MA_m F_m$$

The equations of motion can be derived using the Newton-Euler formulation as follows.

**Femur (Link 1) equations**

Kinematics of the centre of mass:
\[ x_{c_1} = r_{c_1} \cos \theta_i \]  
\[ \dot{x}_{c_1} = -r_{c_1} \dot{\theta}_i \sin \theta_i \]  
\[ \ddot{x}_{c_1} = -r_{c_1} \left( \ddot{\theta}_i \sin \theta_i + \dot{\theta}_i^2 \cos \theta_i \right) \]  
\[ y_{c_1} = r_{c_1} \sin \theta_i \]  
\[ \dot{y}_{c_1} = r_{c_1} \dot{\theta}_i \cos \theta_i \]  
\[ \ddot{y}_{c_1} = r_{c_1} \left( \ddot{\theta}_i \cos \theta_i - \dot{\theta}_i^2 \sin \theta_i \right) \]

Force equilibrium \[ \sum F = 0 : \]

\[ F_{x1} = F_{x2} + F_{mx} - m_i \ddot{x}_{c_1} - m_i g \]  
\[ F_{y1} = F_{y2} - F_{my} + m_i \ddot{y}_{c_1} \]

Torque equilibrium \[ \sum T = 0 : \]

\[ T_m = T_2 + l_1 \dot{\theta}_1 - F_{x1} r_{c_1} \sin \theta_i + F_{x2} r_{c_1} \cos \theta_i + \dot{F}_{mx} r_{c_1} \sin \theta_i + \dot{F}_{my} r_{c_1} \cos \theta_i \]
\[ -F_{x1} (l_1 - r_{c_1}) \sin \theta_i + F_{x2} (l_1 - r_{c_1}) \cos \theta_i \]  
\[ (A.10) \]

**Tibia (Link 2) equations**

Kinematics of the centre of mass:

\[ x_{c_2} = l_1 \cos \theta_1 + r_{c_2} \cos \theta_2 \]  
\[ \dot{x}_{c_2} = -l_1 \dot{\theta}_1 \sin \theta_1 - r_{c_2} \dot{\theta}_2 \sin \theta_2 \]  
\[ \ddot{x}_{c_2} = -l_1 \left( \ddot{\theta}_1 \sin \theta_1 + \dot{\theta}_1^2 \cos \theta_1 \right) - r_{c_2} \left( \ddot{\theta}_2 \sin \theta_2 + \dot{\theta}_2^2 \cos \theta_2 \right) \]  
\[ y_{c_2} = l_1 \sin \theta_1 + r_{c_2} \sin \theta_2 \]  
\[ \dot{y}_{c_2} = l_1 \dot{\theta}_1 \cos \theta_1 + r_{c_2} \dot{\theta}_2 \cos \theta_2 \]  
\[ (A.11) \]  
\[ (A.12) \]  
\[ (A.13) \]  
\[ (A.14) \]  
\[ (A.15) \]
\[ y_{c_2} = l_1 (\dot{\theta}_1 \cos \theta_1 - \dot{\theta}_1^2 \sin \theta_1) + r_2 (\dot{\theta}_2 \cos \theta_2 - \dot{\theta}_2^2 \sin \theta_2) \]  \tag{A.16}

Force equilibrium \( \sum F = 0 \):

\[ F_{x_2} = m_2 \ddot{x}_{c_2} - m_2 g + F_{GRFx} \]  \tag{A.17}

\[ F_{y_2} = m_2 \ddot{y}_{c_2} + F_{GRFy} \]  \tag{A.18}

Torque equilibrium \( \sum T = 0 \):

\[ T_{2} = I_2 \ddot{\theta}_2 - F_{x_2} r_{c_2} \sin \theta_2 + F_{y_2} r_{c_2} \cos \theta_2 \]
\[ - F_{GRFx} (l_2 - r_{c_2}) \sin \theta_2 + F_{GRFx} (l_2 - r_{c_2}) \cos \theta_2 \]  \tag{A.19}

Note that there is no external joint torque applied at Joint 2 therefore:

\[ T_{2} = 0 \]  \tag{A.20}

Equations of motion

By substituting Equations A.2–A.9, A.11–A.18 and A.20 into Equations A.10 and A.19 respectively, a system of equations expressing the joint torques is obtained:

\[ T = M(\dot{\theta}) \ddot{\theta} + G(\theta) + C(\theta, \dot{\theta}) + S_{GRF}(\theta)F_{GRF} \]  \tag{A.21}

where \(\theta, \dot{\theta}, \ddot{\theta}\) are the vectors representing the generalised coordinates, velocities and accelerations respectively; \(M(\dot{\theta})\) is the 2 x 2 system mass matrix; \(T\) is the vector of externally applied joint torques; \(G(\theta)\) is the set of generalised forces due from gravity; \(C(\theta, \dot{\theta})\) is the set of generalised forces due to Coriolis forces; \(F_{GRF}\) is the vector representing the components of the muscle contribution to the ground reaction; and \(S_{GRF}(\theta)\) is a matrix of coefficients converting the muscle contribution
to the ground reaction force components into a set of generalised forces.

The vector of joint angular accelerations is obtained by rearranging Equation A.21 and inverting the mass matrix:

$$\ddot{\theta} = M(\theta)^{-1}\{T - G(\theta) - C(\theta, \dot{\theta}) - S_{GRF}(\theta)F_{GRF}\}$$  \hspace{1cm} (A.22)

**Dynamic coupling analysis**

Equation A.22 demonstrates that the muscle torque, gravity, Coriolis forces and the externally-applied ground reaction force act independently in the system. It is their superposition that results in the joint angular accelerations $\ddot{\theta}$. We are only interested in the accelerations due to the muscle and ground reaction forces. Therefore, we can eliminate the gravitational and Coriolis terms. Separating the terms in Equation A.22 due to muscle force and ground reaction force gives:

$$\ddot{\theta}_m = M(\theta)^{-1}T$$  \hspace{1cm} (A.23)

$$\ddot{\theta}_{GRF} = -M(\theta)^{-1}S_{GRF}(\theta)F_{GRF}$$  \hspace{1cm} (A.24)

Where:

$$T = \begin{bmatrix} T_m \\ T_2 \end{bmatrix} = \begin{bmatrix} T_m \\ 0 \end{bmatrix} = \begin{bmatrix} M A_m F_m \\ 0 \end{bmatrix};$$

$$M(\theta)^{-1} = \begin{bmatrix} M_{11}^{-1} & M_{12}^{-1} \\ M_{21}^{-1} & M_{22}^{-1} \end{bmatrix};$$ and

$$S_{GRF}(\theta)F_{GRF} = \begin{bmatrix} (S_{GRF} F_{GRF})_1 \\ (S_{GRF} F_{GRF})_2 \end{bmatrix}.$$  

By superposition, we can add the muscle force and ground reaction force terms to get the total contributions to the hip- and knee-joint accelerations by the hip-spanning muscle, thus:
We are interested in the muscle and ground reaction force contributions to the knee-joint reaction force. Therefore, we can ignore the gravitational and Coriolis contributions from Equations A.17 and A.18, and substitute \( \hat{\theta}_1 \) and \( \hat{\theta}_2 \) for \( \dot{\theta}_1 \) and \( \dot{\theta}_2 \), respectively. After some rearranging and grouping of terms, we obtain the desired quantities:

\[
\begin{align*}
\langle F_{x2} \rangle_{m+GRF} &= F_{GFS} + m_2 \{ l_1 M_{11}^{-1} (S_{GRF} F_{GRF})_1 \sin \theta_1 + r c_2 M_{21}^{-1} (S_{GRF} F_{GRF})_2 \sin \theta_2 \} \\
&\quad - (A.27) \\
\langle F_{y2} \rangle_{m+GRF} &= +F_{GRFy} \\
&\quad - m_2 \{ l_1 M_{11}^{-1} (S_{GRF} F_{GRF})_1 \cos \theta_1 + r c_2 M_{21}^{-1} (S_{GRF} F_{GRF})_2 \cos \theta_2 \} \\
&\quad + (A.28)
\end{align*}
\]

This has the simplified form:

\[
\begin{align*}
\langle F_{x2} \rangle_{m+GRF} &= F_{GFS} + g(F_{GRFx}, F_{GRFy}, \theta_1, \theta_2) + (M_A F_m) f(\theta_1, \theta_2) \\
&\quad + (A.29) \\
\langle F_{y2} \rangle_{m+GRF} &= F_{GRFy} + k(F_{GRFx}, F_{GRFy}, \theta_1, \theta_2) + (M_A F_m) h(\theta_1, \theta_2) \\
&\quad + (A.30)
\end{align*}
\]

where \( f \) and \( h \) are functions of the generalised coordinates, and \( g \) and \( k \) are functions of the ground reaction force and the generalised coordinates.

Equations A.29 and A.30 demonstrate how a non-knee-spanning muscle contributes to knee-joint reaction forces via three coupling pathways. Equations A.29 and A.30 also show that each of the three coupling pathways act independently. It is their superposition that determines the total muscle
contribution to knee-joint reaction force.

Pathway 1 is a static pathway because it comprises of only one term, $F_{GRF}$. This pathway represents an equal and opposite resistance against the ground reaction force. Pathway 2 occurs due to the influence of the ground reaction force on the hip- and knee-joint angular accelerations $\ddot{\theta}_{GRF}$, given by Equation A.24. Thus, Pathway 2 is a dynamic pathway. Similarly, Pathway 3 occurs due to the influence of the hip-flexion torque generated by the muscle on the hip and knee angular accelerations $\ddot{\theta}_m$, given by Equation A.23. Thus, Pathway 3 is also a dynamic pathway.

A.3 COMPUTATIONAL MODELLING

To model the effects of the aforementioned pathways on the reaction force acting at a joint, the two-segment sagittal-plane system described above was reproduced using SDFAST (Symbolic Dynamics Inc., Mountain View, CA). The values chosen for the segment masses, moments of inertia, location of mass centres and inter-segmental distances (Table A.1) were based on one male subject used in the present study. The hip and knee-joint axes were defined to be perpendicular to the sagittal plane.

Equations A.29 and A.30 show that it is not the muscle force that contributes to the knee-joint reaction force, but the torque exerted by the muscle about the hip. To simplify the modelling process, rather than apply the hip-spanning muscle force, it was sufficient to apply a pure hip flexion muscle torque only. From Equations A.8 and A.9, while this had implications for the hip joint reaction force, we were only interested in knee-joint mechanics, which remained
unaffected. The lateral gluteus maximus (GMAXL) was chosen as the desired muscle for this model. GMAXL was a good candidate because it spans the hip and acts largely in the sagittal plane, therefore adequately reflecting the analytical model and the equations of motion derived in the previous section. In order to model the system under realistic conditions, the hip- and knee-joint kinematics, the torque exerted by the GMAXL about the hip, and the contribution of GMAXL to the ground reaction were all taken from the gait data recorded for the subject.

The total GMAXL contribution to the knee-joint reaction force was first calculated. At each instant of the gait cycle, the joint angles, hip-extension torque generated by GMAXL, and the GMAXL contribution to the ground reaction force were applied to the model (Figure A.3). Joint velocities are not applied because they contribute only to Coriolis forces, which are not of interest in this particular analysis. The total GMAXL contribution to the knee-joint reaction force was then determined by solving the equations of motion and subsequently evaluating the joint reaction force equations.

The influence of each pathway on the GMAXL contribution to knee-joint reaction force was then calculated. The influence of Pathway 3 on the knee-joint reaction force was calculated by repeating the procedure above, but with only the joint angles and the hip-extension torque generated by GMAXL applied. Next, the combined influence of Pathways 1 and 2 on the knee-joint reaction force was calculated by repeating the above procedure, but with only the joint angles and GMAXL contribution to the ground reaction force applied. As Pathway 1 is simply equal and opposite to the ground reaction force (see Equations A.29 and A.30), Pathway 2 can be found by subtracting Pathway 1 from the calculated
combined influence of Pathways 1 and 2. The results (Figure A.4A) show that Pathway 1 provides a large compressive force. The pattern of loading by Pathway 1, which is equal and opposite to the ground reaction force, resembles that of the total GMAXL reaction force contribution. However, Pathway 1 underestimates the magnitude. In this example, Pathway 2 provides a small but non-trivial “tensile” force at the knee and helps unload the knee. Pathway 3 provides an almost equal amount of compression to Pathway 1. These results therefore reflect the importance of each coupling pathway in the contribution of GMAXL to the knee-joint reaction force.

A.4 THREE-DIMENSIONAL MUSCULOSKELETAL MODEL

For the 10-segment 23-degree-of-freedom three-dimensional musculoskeletal model of the whole body used to model walking, the form of the equations of motion is the same as Equation A.22; however, the matrices involved have many more rows and columns to reflect the additional degrees of freedom present (Anderson and Pandy, 2001a). Thus, like the two-segment sagittal-plane model the contribution to the knee-joint reaction forces by a non-knee-spanning muscle’s force and its ground reaction contribution can be studied in isolation. Also, the method used to decompose individual muscle contributions to the knee-joint reaction force into constituents due to the influence of each coupling pathway in the sagittal-plane model can be applied to the three-dimensional model. The GMAXL contribution to the knee-joint reaction force for the subject is decomposed and shown in Figure A.4B. While the results resemble that of the sagittal-plane model, there are some key differences. It can be seen that the total
GMAXL contribution to the axial knee-joint reaction force is significantly lower than that calculated using the sagittal-plane model. In fact, Figure A.4B shows that Pathways 2 and 3 effectively cancel each other out, leaving Pathway 1 as the key component of the total reaction force. Overall, the disparities are due to modelling differences; for example, the number of segments and degrees of freedom of the model, two-dimensional vs three-dimensional model, fixed at the hip vs unconstrained in space. Nevertheless, the large magnitudes of the contributions by each of the three pathways clearly highlight their importance in knee-joint loading by the GMAXL.

A.5 CONCLUSION

The simple sagittal-plane model described highlights how a muscle that does not span a joint of interest may contribute to the joint reaction forces via three independent pathways: (1) static propagation of its ground reaction force contribution throughout the system; (2) dynamic propagation of its ground reaction force contribution throughout the system; and (3) dynamic propagation of the muscle’s joint torque contribution throughout the system.

Also highlighted in the results shown here is how modelling methodology can affect the calculations of muscle contributions to joint contact loading. In three-dimensional modelling, although the dynamic pathways effectively cancel each other, the magnitude of the individual contributions of the pathways to joint loading is still significant. The importance of all coupling pathways is more apparent in the two-dimensional model, where the contributions by the dynamic pathways do not cancel each other. Nevertheless, while it would be ideal to
consider all pathways in calculating joint reaction forces and reaction moments, in three-dimensions quasi-static modelling may suffice.

A similar example in the frontal plane can be used to show that non-knee-spanning muscles contribute to knee-joint reaction moments via the same three pathways; for example, one could apply a hip abduction torque and a frontal-plane ground reaction and then compute the resulting knee forces and reaction moments for a 2-link system. This example could serve as a simple analogy to gluteus medius action during walking.

A.6 TABLES AND FIGURES

This section contains the tables and figures associated with this example.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$m_1, m_2$</td>
<td>8.81 kg, 3.21 kg</td>
</tr>
<tr>
<td>$I_1, I_2$</td>
<td>0.12 kg m$^2$, 0.04 kg m$^2$</td>
</tr>
<tr>
<td>$r_{c1}, r_{c2}$</td>
<td>0.18 m, 0.17 m</td>
</tr>
<tr>
<td>$l_1, l_2$</td>
<td>0.42 m, 0.39 m</td>
</tr>
</tbody>
</table>

Parameters used in the two-segment sagittal-plane model of the leg and their corresponding values. These are based on measurements from one male subject used in the main part of this study.
Figure A.1 Two-segment sagittal-plane lower-limb model used in this example

Schematic diagram of the two-segment sagittal-plane model of the leg. The model is comprised of two segments in a double-pendulum arrangement actuated by a hip-spanning muscle and its contribution to the ground reaction force. Note that for this system, the $x$-direction is defined to be vertical and the $y$-direction is defined to be horizontal.
Figure A.2 Free-body diagrams for the two-link model

A. FEMUR (LINK 1) FBD

B. TIBIA (LINK 2) FBD

Free-body diagrams for each of the links of the two-segment sagittal-plane leg model. Note that the muscle force acting at \( A_1 \) on the femur (Link 1) has been replaced by its force-couple equivalent at the hip joint (Joint 1). Forces have been decomposed into their \( x \)- and \( y \)-direction components.
Figure A.3 Input data for model used in this example

Input data for the computational model of the two-segment sagittal-plane model for one gait cycle. These inputs were obtained from gait data recorded for one male subject.
Figure A.4 Comparison of modelling results

Results for the axial component of the knee reaction force in the two-segment sagittal-plane model of the leg (top). Also shown are the contributions due to dynamic coupling by the GMAXL hip torque and by the GMAXL component of the ground reaction force. Results obtained by using the 10-segment 23-degree-of-freedom three-dimensional model are shown for comparison (bottom).
B.1 EMG SUB-COHORT

Surface electromyographic (EMG) activity was recorded in a subset of five controls (right leg) and nine patients (symptomatic limb) with characteristics presented in Table B.1. This data was used for qualitative comparison with calculated muscle forces only. It was not used for any other analyses.

Surface EMG was assessed using an 8-channel telemetric system (Telemyo; Noraxon USA Inc., Scottsdale, AZ), sampled at 1200 Hz and bandpass filtered at 16–500 Hz. Consistent with published guidelines (Perotto and Delagi, 2005), electrode locations were shaved and cleaned with isopropyl alcohol, then surface electrodes (Kendall Medi-trace 200, Ag/AgCl, Tyko Healthcare Group LP, Mansfield, MA) were placed in a bipolar configuration over the mid-bellies of the rectus femoris, lateral and medial vasti, lateral and medial hamstrings, lateral and medial gastrocnemius, and the tibialis anterior, with a reference (ground) electrode placed over the patella.

For each successfully recorded trial, any DC offset in the raw EMG waveform was removed (i.e. detrended), the resulting waveform despiked and full-wave rectified. We then applied an adaptive linear enveloping filter with a nominal window of 70 ms to obtain the envelope of the waveform, and resampled it for consistency across all trials. Each processed waveform was then normalised against the peak value recorded during stance for that trial. Ensemble averaged
waveforms were then calculated and presented in Figure 4.6B in the main manuscript.

<table>
<thead>
<tr>
<th></th>
<th>Control n = 5</th>
<th>OA Patient n = 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>45 (4)</td>
<td>50 (6)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29 (7.0)</td>
<td>32 (5.0)</td>
</tr>
<tr>
<td>Females, no. (% of total)</td>
<td>2 (40%)</td>
<td>3 (33%)</td>
</tr>
<tr>
<td>Walking speed, m/s</td>
<td>1.18 (0.07)</td>
<td>1.19 (0.10)</td>
</tr>
<tr>
<td>KOOS subscale scores, 0–100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>-</td>
<td>44 (16)</td>
</tr>
<tr>
<td>Symptoms</td>
<td>-</td>
<td>42 (17)</td>
</tr>
<tr>
<td>Activities of daily living</td>
<td>-</td>
<td>56 (21)</td>
</tr>
<tr>
<td>Sport and recreation</td>
<td>-</td>
<td>28 (26)</td>
</tr>
<tr>
<td>Knee-related quality of life</td>
<td>-</td>
<td>31 (16)</td>
</tr>
<tr>
<td>K-L grade 0/1/2/3/4, patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic limb</td>
<td>-</td>
<td>0/0/3/6/0</td>
</tr>
<tr>
<td>Asymptomatic limb</td>
<td>-</td>
<td>2/3/2/2/0</td>
</tr>
<tr>
<td>Mechanical axis angle, deg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic limb</td>
<td>-</td>
<td>8 (3)</td>
</tr>
<tr>
<td>Asymptomatic limb</td>
<td>-</td>
<td>5 (3)</td>
</tr>
</tbody>
</table>
B.2 NET TIBIOFEMORAL FORCE AND CONTRIBUTIONS

The time histories of the net tibiofemoral (TF) force, and the contributions to it by knee-spanning muscles, non-knee-spanning muscles and gravity are presented in Figures B.1 and B.2 as supplements to Figures 4.3 and 4.4 respectively in the main results of the present study.
Figure B.1 Time histories of net tibiofemoral-joint loads and grouped contributions during stance

Figure B.2 Peak and mid-stance contributions to net tibiofemoral-joint loads by individual muscles and gravity
B.3 STATISTICAL ANALYSES

Tables of $P$-values from statistical analysis of modelling results. Student’s $t$-tests were initially undertaken to compare pairs of conditions. Specifically, independent-samples $t$-tests were undertaken to compare: (1) CON and SYM; and (2) CON and ASYM. Paired $t$-tests were undertaken to compare SYM and ASYM. The Holm-Bonferroni method, used to control the familywise error rate, was applied to the results of the three $t$-tests at a significance level $\alpha = 0.05$ to determine which pairs of conditions differed significantly. Statistically significant differences between pairs of conditions are shown in **bold italic**. Comparison pairs: CS = CON and SYM; CA = CON and ASYM, SA = SYM and ASYM. Mid-stance minimum occurred at approximately 38% of stance in both groups.

<table>
<thead>
<tr>
<th></th>
<th>CS</th>
<th>CA</th>
<th>SA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hip flexion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st peak</td>
<td>0.735</td>
<td>0.497</td>
<td>0.018</td>
</tr>
<tr>
<td>2nd peak</td>
<td>0.590</td>
<td>0.762</td>
<td>0.619</td>
</tr>
<tr>
<td><strong>Hip adduction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st peak</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>2nd peak</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Knee flexion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st peak</td>
<td>0.028</td>
<td>0.153</td>
<td>0.280</td>
</tr>
<tr>
<td>2nd peak</td>
<td>&lt; 0.001</td>
<td>0.029</td>
<td>0.100</td>
</tr>
<tr>
<td><strong>Ankle plantarflexion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st peak</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>0.118</td>
</tr>
<tr>
<td>2nd peak</td>
<td>0.006</td>
<td>0.044</td>
<td>0.311</td>
</tr>
</tbody>
</table>
### Table B.3 Peak internal joint torques

<table>
<thead>
<tr>
<th></th>
<th>CS</th>
<th>CA</th>
<th>SA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hip flexion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st peak</td>
<td>0.425</td>
<td>0.534</td>
<td>0.776</td>
</tr>
<tr>
<td>2nd peak</td>
<td>0.281</td>
<td>0.115</td>
<td>0.437</td>
</tr>
<tr>
<td><strong>Hip adduction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st peak</td>
<td>&lt; 0.001</td>
<td>0.055</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>2nd peak</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>0.109</td>
</tr>
<tr>
<td><strong>Knee flexion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st peak</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>0.012</td>
</tr>
<tr>
<td>2nd peak</td>
<td>&lt; 0.001</td>
<td>0.002</td>
<td>0.368</td>
</tr>
<tr>
<td><strong>Ankle plantarflexion</strong></td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>0.053</td>
</tr>
</tbody>
</table>

### Table B.4 Peak knee frontal-plane characteristics

<table>
<thead>
<tr>
<th></th>
<th>CS</th>
<th>CA</th>
<th>SA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Knee adduction angle</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st peak</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>2nd peak</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>EKAM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st peak</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>2nd peak</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
### Table B.5 Peak muscle forces

<table>
<thead>
<tr>
<th>Muscles</th>
<th>CS</th>
<th>CA</th>
<th>SA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gluteus maximus</td>
<td>0.0126</td>
<td>0.429</td>
<td>0.003</td>
</tr>
<tr>
<td>Gluteus medius</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st peak</td>
<td>&lt; 0.001</td>
<td>0.010</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>2nd peak</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Vasti</td>
<td>0.004</td>
<td>0.012</td>
<td>0.373</td>
</tr>
<tr>
<td>Rectus femoris</td>
<td>0.040</td>
<td>0.086</td>
<td>0.660</td>
</tr>
<tr>
<td>Hamstrings</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Biceps femoris (SH)</td>
<td>0.286</td>
<td>0.008</td>
<td>0.089</td>
</tr>
<tr>
<td>Soleus</td>
<td>&lt; 0.001</td>
<td>0.007</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Gastrocnemius</td>
<td>0.067</td>
<td>0.019</td>
<td>0.575</td>
</tr>
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Table B.6 Contributions to TF-joint force at the time steps corresponding to peaks and mid-stance minimum of medial compartment force

<table>
<thead>
<tr>
<th></th>
<th>1\textsuperscript{st} peak</th>
<th>Mid-stance minimum</th>
<th>2\textsuperscript{nd} peak</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CS</td>
<td>CA</td>
<td>SA</td>
</tr>
<tr>
<td>Total</td>
<td>0.127</td>
<td>0.030</td>
<td>0.389</td>
</tr>
<tr>
<td>Knee-spanning</td>
<td>0.881</td>
<td>0.206</td>
<td>0.085</td>
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<tr>
<td>Non-knee-spanning</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gravity</td>
<td>0.005</td>
<td>0.198</td>
<td>0.038</td>
</tr>
<tr>
<td>Muscle contributions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soleus</td>
<td>0.969</td>
<td>0.474</td>
<td>0.443</td>
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<tr>
<td>Gastrocnemius</td>
<td>&lt;0.001</td>
<td>0.025</td>
<td>0.004</td>
</tr>
<tr>
<td>Biceps femoris (SH)</td>
<td>0.004</td>
<td>0.370</td>
<td>0.007</td>
</tr>
<tr>
<td>Vasti</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>0.310</td>
</tr>
<tr>
<td>Rectus femoris</td>
<td>0.214</td>
<td>0.468</td>
<td>0.051</td>
</tr>
<tr>
<td>Hamstrings</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gluteus maximus</td>
<td>0.008</td>
<td>0.156</td>
<td>0.046</td>
</tr>
<tr>
<td>Gluteus medius</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Table B.7 Contributions to medial compartment force at the time steps corresponding to the peaks and mid-stance minimum

<table>
<thead>
<tr>
<th></th>
<th>1&lt;sup&gt;st&lt;/sup&gt; peak</th>
<th>Mid-stance minimum</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; peak</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CS</td>
<td>CA</td>
<td>SA</td>
</tr>
<tr>
<td>Total</td>
<td>&lt; 0.001</td>
<td>0.860</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Knee-spanning</td>
<td>0.866</td>
<td>0.058</td>
<td>0.047</td>
</tr>
<tr>
<td>Non-knee-spanning</td>
<td>0.169</td>
<td>0.646</td>
<td>0.318</td>
</tr>
<tr>
<td>Gravity</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Muscle contributions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soleus</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>0.004</td>
</tr>
<tr>
<td>Gastrocnemius</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>0.010</td>
</tr>
<tr>
<td>Biceps femoris (SH)</td>
<td>0.400</td>
<td>0.016</td>
<td>0.315</td>
</tr>
<tr>
<td>Vasti</td>
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<td>&lt; 0.001</td>
<td>0.844</td>
</tr>
<tr>
<td>Rectus femoris</td>
<td>0.539</td>
<td>0.403</td>
<td>0.086</td>
</tr>
<tr>
<td>Hamstrings</td>
<td>&lt; 0.001</td>
<td>0.010</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Gluteus maximus</td>
<td>&lt; 0.001</td>
<td>0.002</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Gluteus medius</td>
<td>0.301</td>
<td>0.537</td>
<td>0.730</td>
</tr>
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</table>
Table B.8 Contributions to lateral compartment force at the time steps corresponding to peaks and mid-stance minimum of medial compartment force

<table>
<thead>
<tr>
<th></th>
<th>1\textsuperscript{st} peak</th>
<th>Mid-stance minimum</th>
<th>2\textsuperscript{nd} peak</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CS</td>
<td>CA</td>
<td>SA</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee-spanning</td>
<td>0.134</td>
<td>&lt;0.001</td>
<td>0.031</td>
</tr>
<tr>
<td>Non-knee-spanning</td>
<td>&lt;0.001</td>
<td>0.221</td>
<td>0.003</td>
</tr>
<tr>
<td>Gravity</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Muscle contributions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soleus</td>
<td>0.029</td>
<td>0.485</td>
<td>0.001</td>
</tr>
<tr>
<td>Gastrocnemius</td>
<td>&lt;0.001</td>
<td>0.003</td>
<td>0.001</td>
</tr>
<tr>
<td>Biceps femoris (SH)</td>
<td>&lt;0.001</td>
<td>0.014</td>
<td>0.003</td>
</tr>
<tr>
<td>Vasti</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.202</td>
</tr>
<tr>
<td>Rectus femoris</td>
<td>0.169</td>
<td>0.944</td>
<td>0.081</td>
</tr>
<tr>
<td>Hamstrings</td>
<td>&lt;0.001</td>
<td>0.156</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gluteus maximus</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gluteus medius</td>
<td>0.132</td>
<td>0.715</td>
<td>0.249</td>
</tr>
</tbody>
</table>
APPENDIX C

Time histories of the contributions by the major muscles of the lower-limb to the total TF-joint reaction force, and the forces in the medial and lateral compartments for the stance phase of walking in healthy controls (CON), and also the symptomatic (SYM) and asymptomatic (ASYM) limbs of unilateral medial knee OA patients. Only the largest knee-spanning and non-knee-spanning muscle contributors are shown.
Figure C.1 Time histories of the contributions by major muscles to the net TF-joint force during stance
Figure C.2 Time histories of the contributions by major muscles to the medial compartment force during stance.
Figure C.3 Time histories of the contributions by major muscles to the lateral compartment force during stance.
APPENDIX D

Time histories of the contributions by the major muscles of the lower-limb to progression (fore-aft GRF component), support (vertical GRF component) and balance (mediolateral GRF component) of the body’s centre-of-mass, as well as to the external knee adduction moment, for the stance phase of walking in healthy controls (CON), and also the symptomatic (SYM) and asymptomatic (ASYM) limbs of unilateral medial knee OA patients. Only the largest knee-spanning and non-knee-spanning muscle contributors are shown.
Figure D.1 Time histories of the contributions by major muscles to centre-of-mass progression during stance.
Figure D.2 Time histories of the contributions by major muscles to centre-of-mass support during stance.

- GAS
- BFSH
- VAS
- RF
- GMED
- GMAX
- GMED
- SOL
- PFEV
- HAMS
- SYM
- ASYM
- CON
Figure D.3 Time histories of the contributions by major muscles to centre-of-mass balance during stance
Figure D.4: Time histories of the contributions by major muscles to the external knee adduction moment during stance.

- HAMS
- GAS
- BFSH
- VAS
- RF
- FEFV
- SOL
- GMAX
- GMED

% stance
APPENDIX E

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Muscles That Do Not Cross the Knee Contribute to the Knee Adduction Moment and Tibiofemoral Compartment Loading during Gait

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ABSTRACT: The aim of this study was to evaluate and explain the individual muscle contributions to the medial and lateral knee compartment forces during gait, and to determine whether these quantities could be inferred from their contribution to the external knee adduction moment. Kin data from eight healthy male subjects were used to compute each individual muscle contribution to the external knee adduction moment, the non-muscular joint contact force, and reaction moment. The individual muscle contributions to the medial and lateral compartment forces were then found using a load-sharing approach. While knee-crossing muscles were the primary contributors, non-knee-crossing muscles (e.g. the gluteus medius) also contributed substantially to the medial compartment compartment force. Furthermore, knee-crossing muscles tended to compress both compartments, while non-knee-crossing muscles tended to compress the medial compartment but unload the lateral compartment. Muscle contributions to the external knee adduction moment, particularly those from non-knee-crossing muscles, did not accurately reflect their tendencies to compress or unload the medial compartment. This finding may further explain why gait modifications may reduce the knee adduction moment without necessarily decreasing the medial compartment force. © 2012 Orthopaedic Research Society. Published by Wiley Periodicals, Inc. J Orthop Res 30:1596–1600, 2012.

Keywords: osteoarthritis; musculoskeletal modeling; joint reaction force; dynamic coupling

Tibiofemoral joint osteoarthritis (TFOA) is a painful and debilitating disease that has been associated with biomechanical changes or dysfunction at the hip, knee, and ankle. Increased proportion of compressive loading on the medial compartment of the tibiofemoral joint (TFJ) may play an important role in the development and progression of TFOA. As the direct measurement of compartment forces requires instrumented implants, computational modeling is the only practical way to study the characteristics of the medial compartment force, respectively. Muscles are the main contributors to joint loading and several modeling studies have examined how muscles contribute to knee-joint loading during gait. Shukla et al. concluded that non-knee-crossing muscles contribute significantly to medial compartment compression in normal walking, particularly the quadriceps and gastrocnemius (GAS) muscles. Several studies have shown that non-knee-crossing muscles also contribute to the TFJ contact force through dynamic coupling. However, none of these studies evaluated the contributions of the non-knee-crossing muscles to the medial and lateral compartment forces. Such understanding may be crucial in the study of biomechanical factors associated with TFOA and the design of clinical interventions.

The external knee adduction moment, given by the product of the ground reaction force (GRF) and its lever arm about the knee joint center, has been identified as a surrogate measure for medial compartment force and hence TFOA risk. Gait modification strategies have been proposed to mitigate pain and progression of TFOA by shortening the moment arm and consequently reducing the knee adduction moment. However, a study based on in vivo measurements showed that reducing the external knee adduction moment may not necessarily reduce medial compartment force. A comparison between muscle contributions to the external knee adduction moment and medial compartment force may help to explain this finding.

The aim of the present study was twofold: first, to calculate and explain the individual contributions from all muscles of the lower limb in the patterns of force transmitted to the medial and lateral compartments of the TFOA during normal walking; and second, to assess whether a muscle's contribution to the external knee adduction moment is indicative of its contribution to the medial compartment force.

METHODS

Gait experiments were performed on eight healthy male subjects (age: 26 ± 4 years; weight: 79 ± 8 kg; height: 175 ± 4 cm) in the Human Motion Laboratory at The University of Melbourne. Subjects gave their informed consent after approval was obtained from the University of Melbourne Human Research Ethics Committee. Joint motion, GRFs, and muscle EMG activity were recorded simultaneously as each subject walked at a preferred speed (1.6 ± 0.1 m/s) over level ground. Three-dimensional locations of retro-reflective markers attached to each subject's body were measured using a video-based motion capture system (Vicon, Oxford Metrics Ltd., Oxford, UK) with nine cameras sampling at 120 Hz. Footground force were measured using three strain-gauge force plates (Advanced Mechanical Technology Inc., Watertown, MA) sampling at 1000 Hz. The gait cycle was divided into seven stages.
1,080 Hz. Surface EMG electrodes were placed over the bellies of the muscles in one leg: gluteus maximus, gluteus medius, medialis hamstrings (HAMM), vastus lateralis, medial femoral, and adductor (ADA). EMG signals were digitized using a sampling frequency of 1,080 Hz, and EMG signal-to-noise ratios (SNRs) were measured by calculating the signal-to-noise ratio with a 4th-order Butterworth filter.

A three-dimensional musculoskeletal whole-body model was used to calculate lower-limb muscle forces for one gait cycle. The entire body was represented as a 10-segment, 23 degree-of-freedom linkage. The head, arms, and trunk were modeled as a single rigid body, which articulated with the pelvis via a ball-and-socket joint. The pelvis was modeled as a passive joint, and the metatarsal joint was a hinge. Joint center locations were determined by minimizing the differences between the positions of surface markers placed on the subject and virtual markers defined in the model. The whole-body model was actuated by 64 Hill-type muscles-tendons units; however, passive forces provided by ligaments and other soft tissues were omitted. Subject-specific musculoskeletal models were created by scaling the segmental inertial properties of the model, muscle attachment sites, and muscle path to each subject's height and weight. The force-generating properties of the muscles were the same as those identified by Anderson and Padún.

Muscle forces were found using inverse dynamics and static optimization. Measurements of the subject's motion and GRFs were input into the corresponding subject-specific model, and inverse dynamics was used to calculate the net moments at each joint. The net joint moments were decomposed into individual muscle forces by solving a least-squares problem that minimized the sum of the squares of muscle activations. The optimization problem was solved subject to the physiological bounds on muscle force imposed by each muscle's force-length-velocity property.

The contributions of each muscle to the external knee adduction moment, GRF reaction force and GRF reaction moment were computed at each time step using the subject-specific model. Individual muscle contributions to the external knee adduction moment, $M_{kin}$, were determined from the product of the contribution of each muscle's GRF contribution, $F_{GRF}$, and three-dimensional GRF reaction moment, $M_{GRF}$, acting at the knee joint center $(r_{GRF})$. Muscle contributions to the three-dimensional GRF reaction force, $F_{GRF}$, and three-dimensional GRF reaction moment, $M_{GRF}$, were computed by applying the muscle force and that muscle's GRF contribution in isolation to the subject-specific model, and then solving the equations of motion and subsequently the joint reaction equations.

A separate 15-degree-of-freedom quasi-static model of the right knee was used to determine linear and angular accelerations. The body was modeled as a point mass, and the musculoskeletal model was actuated by 12 knee-tendon units; however, passive forces provided by ligaments and other soft tissues were omitted. Subject-specific musculoskeletal models were created by scaling the segmental inertial properties of the model, muscle attachment sites, and muscle path to each subject's height and weight. The force-generating properties of the muscles were the same as those identified by Anderson and Padún.

Muscle forces were found using inverse dynamics and static optimization. Measurements of the subject's motion and GRFs were input into the corresponding subject-specific model, and inverse dynamics was used to calculate the net moments at each joint. The net joint moments were decomposed into individual muscle forces by solving a least-squares problem that minimized the sum of the squares of muscle activations. The optimization problem was solved subject to the physiological bounds on muscle force imposed by each muscle's force-length-velocity property.

The contributions of each muscle to the external knee adduction moment, GRF reaction force and GRF reaction moment were computed at each time step using the subject-specific model. Individual muscle contributions to the external knee adduction moment, $M_{kin}$, were determined from the product of the contribution of each muscle's GRF contribution, $F_{GRF}$, and three-dimensional GRF reaction moment, $M_{GRF}$, acting at the knee joint center $(r_{GRF})$. Muscle contributions to the three-dimensional GRF reaction force, $F_{GRF}$, and three-dimensional GRF reaction moment, $M_{GRF}$, were computed by applying the muscle force and that muscle's GRF contribution in isolation to the subject-specific model, and then solving the equations of motion and subsequently the joint reaction equations.

At each point in the gait cycle, each muscle's contribution to the TFJ reaction force was partitioned into a medial and lateral compartment force contribution by solving a least-squares problem (Fig. 1a). A set of three force-equilibrium equations and three moment equilibrium equations was written at the knee for each muscle $m$:

$$\begin{align*}
\mathbf{F}_{med}^m + \mathbf{F}_{lateral}^m + \mathbf{F}_{GRF}^m &= \mathbf{0} \\
(\mathbf{F}_{med}^m \times \mathbf{r}^m) + (\mathbf{F}_{lateral}^m \times \mathbf{r}^m) + \mathbf{M}_{GRF}^m &= \mathbf{0}
\end{align*}$$

where $\mathbf{F}_{med}^m$ and $\mathbf{F}_{lateral}^m$ are the unknown 3 x 1 vectors of the contributions of muscle $m$ to the medial and lateral compartment forces, $\mathbf{F}_{GRF}^m$ is the inverse of the contribution of muscle $m$ to the TFJ reaction force, $\mathbf{r}^m$ and $\mathbf{r}^{GRF}$ are the 3 x 1 position vectors of the medial and lateral contact points, and $\mathbf{M}_{GRF}^m$ is the 3 x 1 vector of the GRF moment at the knee joint center.

Figure 1. At each point in the gait cycle, the contribution by muscle $m$ to (A) the external knee adduction moment, $M_{kin}^m$, is the cross product of the moment arm vector, $\mathbf{r}^m$, and the GRF contribution, $\mathbf{F}_{GRF}^m$. To find the contribution to the medial and lateral compartment forces, (B) first apply the muscle forces $\mathbf{F}_{med}^m$ and its GRF contribution $\mathbf{F}_{GRF}^m$, then (C) solve the equations of motion and compute joint reaction forces to obtain the TFJ reaction force, $\mathbf{F}_{TFJ}^m$, and moment, $\mathbf{M}_{TFJ}^m$, acting at the knee joint center; and (D) partition into medial and lateral compartment forces, $\mathbf{F}_{med}^m$ and $\mathbf{F}_{lateral}^m$, acting at contact points located at $\mathbf{r}^m$ and $\mathbf{r}^{GRF}$, respectively.
Figure 1. Comparison of calculated muscle forces and measured EMG for five major muscles involved in walking: soleus (SOL), gastrocnemius (GAS), vasti (VAS), gluteus maximus (GM) and gluteus medius (GMD).

Equations (1) and (2) were then written in matrix form:

\[ \mathbf{A}_m \mathbf{S}_m = \mathbf{I}_m \]

where \( \mathbf{A}_m \) is an \( 5 \times 5 \) matrix of coefficients, \( \mathbf{S}_m \) is a \( 5 \times 1 \) vector of muscle forces, and \( \mathbf{I}_m \) is a \( 5 \times 5 \) identity matrix. Finally, Eq. (3) had only five independent equations, a pseudo-inverse was used to compute an analytical least-squares solution for \( \mathbf{S}_m \) as:

\[ \mathbf{S}_m = \mathbf{A}_m^{-1} \mathbf{S}_m \]

where \( \mathbf{A}_m^{-1} \) is the Moore-Penrose pseudo-inverse of the matrix, \( \mathbf{A}_m \) and \( \mathbf{S}_m \) is the minimum-norm least-squares solution for the under-determined system given by Equation (3). In this study, a MATLAB (Version 2010a, Mathworks Inc.) function ‘pinv’ was used to compute the pseudo-inverse for each muscle at each time step. The axial components of \( \mathbf{S}_m \) were defined as the medial and lateral compartment forces. Means and standard deviations for the eight subjects were then calculated.

RESULTS

The timing and magnitude of predicted muscle forces (Fig. 3) matched well with our recorded EMG activity and the results of a previous study. The net axial TFL reaction force due to all muscles (Fig. 3A and D and Table 1, ALL MUSCLES) was comparable in magnitude to that reported by related modeling studies, including studies based on in vivo measurements. Knee-sparing muscles contributed most to the axial TFL reaction force (Fig. 3A) as reported by Sanada and Neptune and Pandy and Andriacchi. Knee-sparing muscles provided relatively small, but non-negligible, contributions to the axial TFL reaction force throughout stance, mostly due to SOL in late stance (Fig. 3D), in accordance with the findings of Sanada and Neptune and Pandy and Andriacchi. The net effects of knee-sparing and non-knee-sparing muscles on the axial TFL reaction force were compressive throughout stance.

Table 1. Peak Means and Corresponding Standard Deviations of the Contributions of the Major Lower-Limb Muscles to the Axial Component of the TFL Reaction Force, the Frontal-Plane TFL Reaction Moment, the Axial Components of the Medial and Lateral Tibial Compartment Forces, and the External Knee Adduction Moment from the Averaged Group Data of Eight Subjects

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Peak TFL Reactions</th>
<th>Peak Axial Compartment Forces</th>
<th>Peak External Knee Adduction Moment</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAS</td>
<td>1.61 ± 0.36</td>
<td>−0.49 ± 0.09</td>
<td>3.97 ± 0.20</td>
</tr>
<tr>
<td>BFH</td>
<td>0.38 ± 0.10</td>
<td>0.97 ± 0.59</td>
<td>−2.08 ± 0.04</td>
</tr>
<tr>
<td>VAS</td>
<td>1.54 ± 0.51</td>
<td>0.37 ± 0.15</td>
<td>1.62 ± 0.54</td>
</tr>
<tr>
<td>RF</td>
<td>0.58 ± 0.18</td>
<td>−0.15 ± 0.33</td>
<td>1.42 ± 0.16</td>
</tr>
<tr>
<td>HAMS</td>
<td>1.66 ± 0.42</td>
<td>0.34 ± 0.81</td>
<td>1.70 ± 0.56</td>
</tr>
<tr>
<td>PFRV</td>
<td>0.94 ± 0.06</td>
<td>−0.60 ± 0.89</td>
<td>1.20 ± 0.11</td>
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<tr>
<td>SOL</td>
<td>0.53 ± 0.13</td>
<td>0.86 ± 0.63</td>
<td>−3.05 ± 0.11</td>
</tr>
<tr>
<td>GM 7X</td>
<td>0.33 ± 0.13</td>
<td>0.39 ± 0.25</td>
<td>2.18 ± 0.16</td>
</tr>
<tr>
<td>GMDA</td>
<td>0.13 ± 0.06</td>
<td>−0.04 ± 0.58</td>
<td>1.75 ± 0.20</td>
</tr>
<tr>
<td>GMDP</td>
<td>0.50 ± 0.07</td>
<td>−1.14 ± 0.06</td>
<td>2.50 ± 0.15</td>
</tr>
<tr>
<td>ALL MUSCLES</td>
<td>3.36 ± 0.55</td>
<td>−3.68 ± 0.64</td>
<td>1.54 ± 0.42</td>
</tr>
</tbody>
</table>

Compressive forces and anti-clockwise moments are positive.

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BW at contralateral toe-off (CTO) and contralateral heel-strike (CHS; Fig. 3B and F). ALL MUSCLES. The magnitudes of both peaks were comparable to those reported previously. Knee-spanning and non-knee-spanning muscles contributed almost equally to medial compartment forces (Fig. 3B and E), with non-knee-spanning muscles contributing 0.1 BW more at the first peak and knee-spanning muscles contributing 0.3 BW more at the second peak. The net effects of knee-spanning and non-knee-spanning muscles on medial compartment force were compressive throughout stance. Knee-spanning muscle contributions at CTO (Fig. 3B) were dominated by vasti (VAS) and at CHS were dominated by GAS, as reported by Wohlfah et al. Of the non-knee-spanning muscles, the combined contribution of the anterior (GMEDA) and posterior gluteus medius (GMDP) was most significant throughout stance (Fig. 3B). SOL contributed virtually nothing to the medial compartment force.

The total medial compartment force was compressive throughout stance and compared well with that reported previously. However, while the net effect
of knee-spanning muscles was compressive (Fig. 3C and Table 1), the non-knee-spanning muscles tended to unload the lateral compartment (Fig. 3F and Table 1). HAMS contributed most at heel-strike, followed by VAS in early stance and GUS in late stance. Furthermore, HAMS and VAS contributed more force to the lateral compartment than the medial compartment. SOL was the major non-knee-spanning muscle that provided most compression on the lateral compartment, while GMED and GMEDP tended to unload it (Fig. 3E and F).

The magnitudes of the two peaks of the total external knee adduction moment were consistent with several previous studies.\(^{45,50}\) (Fig. 4 and Table 1, ALL MUSCLES), with the first peak at CTO 23% higher than the second peak at CHE. GMED and GMEDP contributed most to the knee adduction moment, whereas GAS, VAS, SOL, and plantar-flexor evector (PFEV) contributed knee adduction moments.

**DISCUSSION**

The objectives of this study were to calculate and explain the contributions of individual lower-limb muscles to the medial and lateral knee compartment forces during normal walking, and to determine if a muscle’s contribution to the external knee adduction moment was indicative of its contribution to medial compartment force. The results showed that both knee-spanning and non-knee-spanning muscles contributed to compartment forces. Importantly, non-knee-spanning muscles played a more significant role in leading each of the compartments than the TFJ as a whole. The results also suggest that a muscle’s contribution to the external knee adduction moment is not always a good indicator of its contribution to medial compartment force.

In general, the non-knee-spanning muscles compressed one compartment but unloaded the other, whereas the knee-spanning muscles compressed both compartments (Fig. 2). Knee-spanning muscles contributed to compression in both the medial and lateral compartments, reflecting not only their role in stabilizing the knee in the frontal plane\(^{45,50}\) but also their potential role in TFJ. Interestingly, knee-spanning and non-knee-spanning muscles contributed equally to medial compartment force. In fact, the relative contribution by non-knee-spanning muscles to the medial compartment force was considerably higher throughout stance than the contribution to the axial TFJ reaction force (Fig. 5). For most non-knee-spanning muscles, the combination of TFJ reaction force and reaction moment contributions acting at the knee-joint center was different to that of knee-spanning muscles (compare Fig. 5A and B), resulting in compression in one compartment but unloading the other.

In the process of computing muscle contributions to the TFJ reaction force and moment, each muscle’s force and its GRF contribution were treated as separate loads on the system.\(^{45,50}\) Thus, each non-knee-spanning muscle could contribute to knee-joint mechanics via three independent pathways: (1) static propagation of the muscle’s GRF contribution...
Figure 3. The relative magnitudes of the TFJ reaction force and moment at the knee-joint center determine the force distribution between the compartments. (A) For non-knee-spanning muscles, the TFJ reaction moment distorts the force distribution, causing compression on one compartment, but unloading the other. (B) For knee-spanning muscles, the TFJ reaction force distorts the force distribution, causing compression on both compartments (e.g., GAS). Longer arrows represent greater magnitude. Downward pointing arrows are compressive.

throughout the system; (2) dynamic propagation of the muscle’s GRF contribution throughout the system; and (3) dynamic propagation of the muscle’s joint-torque contribution throughout the system (see Fig. 6 and Supplementary Material). In order to realize all of these contributions, the problem needed to be solved for dynamic equilibrium. Previous studies that did not include non-knee-spanning muscles partially accounted for their effects by implementing Pathway 1, and then subsequently calculated compartment forces by solving for static equilibrium. While the effects of the Pathways 2 and 3 can be significant, these dynamic pathways tended to approximately cancel each other, suggesting that quasi-static musculoskeletal models that include the GRF may be sufficient for solving joint reaction forces and reaction moments. To show this, contributions of four non-knee-spanning muscles to the axial TFJ reaction force were decomposed into contributions from each pathway (Fig. 7). For each muscle shown, the Pathways 2 and 3 are approximately equal in magnitude but opposite in sign, hence the sum of the three pathways resembles Pathway 1 (Fig. 7, TOTAL).

It was evident that a muscle’s contribution to the external knee abduction moment did not necessarily reflect its contribution to the medial compartment force. In particular, contributions by knee-spanning muscles to the external knee abduction moment were not consistent with their contributions to medial compartment force. For example, VAS and GAS produced external knee abduction moments (Fig. 6), suggesting they contributed minimally or even unloaded the medial compartment, yet both compressed it considerably. Contributions by non-knee-spanning muscles to the external knee abduction moment better predicted the contribution to medial compartment force. For example, GME0A and GME0P both contributed significantly to the external knee abduction moment and also to medial compartment compression. Similarly, SOL produced an external knee abduction moment and contributed minimally to medial compartment force. However, the contributions by some non-knee-spanning muscles to the external knee abduction moment were not consistent with their contributions to medial compartment force (e.g., PFEV).

Our results show that studying only the axial TFJ reaction force may underestimate the role of non-knee-spanning muscles in TFJOA. Thus, future clinical interventions for TFJOA may need to place greater emphasis on the effects of non-knee-spanning muscles on joint mechanics, particularly that of the gluteus medius. Importantly, our results imply that individual muscle contributions to the knee abduction moment do not suffice as a surrogate measure of individual muscle contributions to medial compartment force. In particular, our results suggest that decreasing a muscle’s contribution to the knee abduction moment may not necessarily reduce its contribution to the medial compartment force. This may help to explain the recent finding that reducing the set external knee abduction moment using gait modifications may not reduce the total medial compartment force.

Evaluating the accuracy of the calculated tibiofemoral contact point trajectories (Fig. 8A) was difficult due to the scarcity of available data. However, we were at best able to qualitatively assess the
Pathway 1
Source: Soleus contribution to GRF, $F_{SOL}^{GRF}$
Mechanism: Static
1. $F_{SOL}^{GRF}$ points upwards and forwards, and tries to translate the foot and tibia upwards and forwards together.
2. To maintain static equilibrium, an equal and opposite compressive force $-F_{SOL}^{GRF}$ occurs on the tibia at the knee.

Pathway 2
Source: Soleus contribution to GRF, $F_{SOL}^{GRF}$
Mechanism: Dynamic
1. $F_{SOL}^{GRF}$ creates a dorsiflexion torque about the ankle which tries to rotate the foot anticlockwise and the tibia clockwise.
2. This rotation effect tries to pull the knee downwards and forwards.
3. At the same time, the inertia of the femur and rest of the body resists this attempt to pull the knee down and forwards. The resulting effect is to pull the femur and tibia apart, creating a "tensile" force $F_{SOL}^{path,1}$ on the tibia at the knee.

Pathway 3
Source: Ankle torque due to soleus force, $F_{SOL}^{MUS}$
Mechanism: Dynamic
1. $F_{SOL}^{MUS}$ creates a plantarflexion torque about the ankle which tries to rotate the foot clockwise and the tibia anticlockwise.
2. This rotation effect tries to push the knee upwards and rearwards.
3. At the same time, the inertia of the femur and rest of the body resists this attempt to push the knee up and rearwards. The resulting effect is to squeeze the tibia against the femur, creating a compressive force $F_{SOL}^{path,2}$ on the tibia at the knee.

Figure 6. Hypothetical illustration of how the SOL contribution to the TIJ reaction force $F_{SOL}^{react}$ arises from the one static and two dynamic force pathways. $F_{SOL}^{path,1}$ and $F_{SOL}^{path,2}$ are the SOL muscle force and its contribution to the GRF, respectively. Similar reasoning can be used to explain the static and dynamic pathways of the TIJ reaction moment.
antero-posterior motion of the tibiofemoral contact points (Fig. 6B). Although Kusznirk et al. reported the trajectories of the femoral condylar centers rather than the contact points on the tibial plateau during stance, there were two key similarities: (1) the trajectories of the tibiofemoral contact points were closely linked to knee flexion, although contrary to the motion of the femoral condyles, with the contact points shifting posteriorly on the tibial plateau with increasing knee flexion, similar to other weight-bearing tasks; and (2) the medial side showed greater excursion than the lateral side, although the tibiofemoral contact points showed slightly larger total range of motion than the femoral condyles of Kusznirk et al. (12 mm vs. 10 mm medial and 6 mm vs. 4 mm lateral). This may be because our subjects walked at a higher speed (1.5 m/s vs. 0.67 m/s) and exhibited greater knee flexion (about 20° vs. 16° at CPO). Thus, we believe the trajectories of the tibiofemoral contact points were estimated reasonably well in the knee model.

There are a number of potential limitations of this study. Firstly, the knee was modeled as a hinge in the whole-body model, thus ignoring the effects of adduction–abduction and internal–external rotation torques, which can be large. However, accurate measurement of transverse- and frontal-plane knee kinematics is difficult using marker-based methods due to soft-tissue artifact. Secondly, the use of static optimization to calculate muscle forces might be considered a limitation. However, static optimization produces robust solutions that are consistent with the sequence and timing of muscle EMG measured during gait and with solutions obtained from the application of dynamic optimization. Thirdly, the influence of ligaments, cartilage, fluids, and other soft tissues was not included in the whole-body model. However, the passive force contributions by the ligaments, joint capsule, etc. are small, and would not have significantly affected our results. Finally, although the knee model was able to estimate contact points reasonably...
well, TJJ geometry could not be scaled for each individual subject. To simulate the effect of scaling knee geometry, a sensitivity analysis was performed for one subject. The distance between two contact points was adjusted ± 20% at each instant of the gait cycle, yet the maximum change in peak compartment forces was only ± 3% and the net compartmental forces were always compressive.

In summary, this study is the first to compute individual contributions from all lower-limb muscles to the medial and lateral compartments of the knee for any activity. In walking, non-knee-spanning muscles contributed substantially, especially to medial compartment compression, suggesting that these muscles may influence medial compartment TJOA more than previous studies suggest. The influence of muscles on medial compartment force could not be directly inferred from their contributions to the external knee abduction moment, providing a possible explanation for why reducing the knee abduction moment may not necessarily decrease the medial compartment force.

ACKNOWLEDGMENTS

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Musculoskeletal Loading in the Symptomatic and Asymptomatic Knees of Middle-Aged Osteoarthritis Patients

Praeman Sriharam, Yi-Chung Lin, Sara E. Richardson, Kay M. Craske, Trevor B. Birmingham, Marcus G. Pandy

ABSTRACT: This study quantified the contributions by muscles, gravity, and inertia to the biplanar compartment forces in the symptomatic (SYM) and asymptomatic (ASYM) knees of varus and non-varus medial knee osteoarthritis (OA) patients, and compared the varus knees with healthy controls. SYM muscle forces and third-order compartment flexion-extension muscle data were significant in OA patients and 46 controls aged 49 ± 7 years. Patients exhibited lower knee flexion angles higher hip abduction, and knee abduction angles, lower internal knee torsion torque, higher external knee adduction moment, axial forces were significant in CON except for knee adduction moments, which were higher in SYM. ASYM muscle forces were lower for lower femur shaft bone strain (GPa) and goniometric lateral knee adduction moment, knee adduction angle, and knee flexion moment at the second peak, and for lower knee flexion moment, and gravity during mid stance compared to patients significantly higher total MCP. Compared to CON, the ASYM limb exhibited similar peak MCP but higher mid-stage MCP. In patients, diminished non-knee-spanning muscle forces did not produce correspondingly diminished MCP contributions due to the influence of realignment. Our findings emphasize considerations of muscle function, lower-limb alignment, and mid-stage loads in developing interventions for OA, and inclusion of the asymptomatic limb is critical in clinical assessment. 2016 Orthopaedic Research Society. Published by Wiley Periodicals, Inc. A setup was increased cyclic compressive loading in the medial compartment of the tibiofemoral joint is associated with progression of medial knee osteoarthritis (OA). Determining the root causes of elevated medial compartment force (MCP) is difficult, as a range of neuromuscular, morphologic, and structural changes associated with medial knee OA have been reported throughout the knee-limb. This includes varus realignment and knee joint laxity, strength deficits, elevated knee-spanning muscle co-activity, and hip abductor weakness.

As non-invasive measurement of joint forces is currently not feasible, the external knee adduction moment (EM) during gait has been proposed as a surrogate for load distribution, supported by studies using instrumented total knee replacements (TKR) and musculoskeletal modeling. However, important limitations exist when relying on the EM to study joint loading as it only accounts for the ground reaction force (GRF) and not the direct compressive effect of non-muscle forces, which can contribute up to one-third of the total MCP. Yet surrogate models incorporating both EM and the internal knee extension torque, as a surrogate for knee-spanning muscle forces, have shown only limited improvements in MCP estimates. Thus, a detailed examination of knee joint forces is necessary to understand and improve surrogate measures. Muscles, gravity, and inertia all contribute to the MCP by means of dynamic coupling, and forces also contribute to bone loading and the EM. Muscles contribute most to loading in healthy knees during weight-bearing activities, however, the relative contributions by lower-limb muscles to loading in osteoarthritic knees are not clearly established. A modeling study of healthy gait showed that non-knee-spanning muscles can account for up to one-third of the total MCP. Notably, the gluteus maximus provides the most of the power to MCP, followed by the EM and almost all the EM in healthy gait. Although OAR-specific changes in muscle forces can impact the pattern of loading in the tibiofemoral compartments, no study to date has quantified the individual contributions by the lower-limb muscles, gravity, and inertia to the pattern of forces in the osteoarthritic knee.

Non-pharmacologic interventions for knee OA which modify patient biomechanics are typically aimed at reducing the peaks of EM. However, recent studies have found that elevated mid-stage MCP is associated with greater disease severity and future need for TKR. Detailed knowledge of how elevated mid-stage knee joint loads arise in patients may help guide the development of novel clinical interventions which more effectively reduce knee-joint loading throughout stance.

Furthermore, significant functional asymmetries exist between the symptomatic and asymptomatic limbs in unilateral knee OA and the risk of progression to...
bilateral disease is high while unilateral disease is established. Thus, understanding the total contributions of the asymptomatic knee would help determine if and how the asymptomatic limb should also be considered in clinical interventions for unilateral knee OA. This study aimed to quantify the contributions by muscles, gravity, and inertia to the forces in the medial and lateral tibiofemoral compartments during walking in both the symptomatic and asymptomatic limbs of varus mal-aligned medial knee OA patients, and to compare the results with healthy controls. As patients may walk with more knee-spanning muscle co-activation than healthy adults, we hypothesized that higher MCT in patients would arise from elevated contributions by the hamstrings, quadriceps, and gastrocnemius. From findings of hip abductor force deficits in OA patients, we further hypothesized lower gluteus medius forces in patients, but based on the weak associations between hip abductor force and EMG, its contribution to MCT would not be significantly lower than controls.

METHODS

Design: Case-Control Study

Level of Evidence: II

Participants and clinical assessment. Thirty-nine patients were recruited from a tertiary care center specializing in orthopaedics, including rehabilitation and surgical (orthopaedics) interventions for knee OA. All patients were referred to the clinic for potential hip or knee surgery for asymptomatic knee with radiographic OA primarily affecting the medial compartment. Twenty-five patients matched for sex, age, and body mass index (BMI) with or without history of knee pain were recruited from the same community. Of these, 15 controls were matched to patients for walking speed after gait analysis. Methods for recruitment, inclusion and exclusion criteria, radiographic assessment, patient-reported measures, and gait experiments are detailed in a previous publication. Inclusion criteria for patients included varus malalignment of the lower limb and diagnosis of medial knee OA based on the American College of Rheumatology criteria. Symptoms were assessed using the Knee Injury and Osteoarthritis Outcome Score (KOOS). The extent of frontal-plane malalignment (mechanical axis angle) and OA severity (Kellgren Lawrence grade) were measured from full-limb standing anteroposterior radiographs. FrONTAL-plan alignment was also measured in all participants using marker data from a static trial recorded during gait analysis. The study was approved by the Research Ethics Board for Health Sciences Research Involving Human Subjects of the University of Western Ontario (HERB No. H2012E)

Gait experiment. All experiments were performed at the Wolf Orthopaedic Biomechanics Laboratory, Fowler Kennedy Sport Medicine Clinic, University of Western Ontario. Joint motion and GRF were recorded simultaneously as each participant walked at his or her preferred speed over level ground. Two reflective markers were attached to each subject using a 22-marker modified Helen Hayes protocol, with four additional markers used for static trials, placed on the medial knee-joint line and the medial malleolus for each leg. These additional markers were removed prior to gait testing. Three-dimensional marker positions were measured using an eight-camera motion capture system sampling at 60 Hz (Eagle SwatX, Motion Analysis Corp., Santa Rosa, CA). A single strain-gauged force plate (Advanced Mechanical Technology Inc., Watertown, MA) sampling at 1,200 Hz was used to measure all three components of the GRF and the center of pressure during stance. For each subject, walking trials were repeated until five clean force plate strikes during stance were recorded per leg. Previous testing in this laboratory using these protocols found the kinematic and kinetic variables calculated from this task to be reliable (ICC3,1: 0.73. 0.86). Surface electromyography (EMG) activity was recorded in a subset of five controls, six subjects and nine patients (symptomatic knee) for qualitative comparisons with musculoskeletal forces. Kinematics were placed over the helices of the femoral heads, femur, and tibia anterior. Details of subject preparation, measurement and processing protocols for EMG, and participant characteristics of the EMG sub-cohort are provided as Supplementary Material.

Musculoskeletal modeling. A multi-segment, three-dimensional, whole-body musculoskeletal model was used to calculate lower-limb muscle forces during the stance phase of gait for each subject. The model was implemented in OpenSim 3.4 (version 3.2), an open-source musculoskeletal modeling package, and compiled as a 30-segment, 27-degree-of-freedom linkage actuated by 92 Hill-type muscle-tendon units. Inertias and other soft tissues were not included. The head, arms and torso were lumped as a single rigid body, articulating with the pelvis via a ball-and-socket joint. Each hip was modeled as a ball-and-socket, and each ankle and subtalar joint as a hinge. Each knee was modeled as a sliding ball-and-socket with the flexion-extension axis and pre-scribed femur-translation defined by Dagen et al. The model's segmental inertial properties, muscle-tendon attachment points, and muscle-tendon paths were scaled based on segmental dimensions calculated from each subject's static trial.

For each trial, stance-phase joint angles were calculated using inverse kinematics, which found the most comparable at each step that minimised the sum-of-squares of the distances between corresponding experimental markers and model markers. The kinematics and GRF were input into the model and internal joint torques calculated using inverse dynamics. Individual muscle forces were calculated from the internal joint torques using static optimisation. The modelled muscle activations were used to calculate the total quadriceps-tibialis anterior and quadriceps-retractors activation, and concentration index as defined by Zami et al. Subsequently, the EMG was calculated by multiplying the frontal-plane GRF by its moment arm about the knee-joint center.
defined by the joint angles, applying that muscle's forces to the model with respect to the GFR, and solving the joint reaction equations. This process was repeated to determine contributions by gravity, defined as the resistance of the skeletal linkage to the downward pull of the body's weight, and inertia, defined as all Coriolis and centrifugal forces combined. At each time step, the rheoencephalogram was then separated into medial and lateral compartmental forces acting at the medial and lateral contact points, respectively, by solving for equilibrium at the knee in three dimensions using a least-squares approach. Estimates for the spatial locations of the medial and lateral contact points in three dimensions were obtained at each time step by inputting the joint angles, GFR, and muscle forces into a separate 18-degree-of-freedom model of the lower limb incorporating a Heronian contact-based 6-degree-of-freedom model of the knee, and solving for static equilibrium.

Statistical analyses. To compare participant characteristics and also to determine group differences amongst these limbs—the symptomatic (SYM) and asymptomatic (ASYM) limbs of patients, and also controls (CON)—at the peak values of joint angles, internal joint torque, and muscle forces, a series of t-tests was performed while controlling the familywise error rate for the multiple comparisons. This procedure was also used to compare contributions to the compartmental forces at the time instances corresponding to the peaks and the mid-interval minimum of the MCF. Specifically, for each quantity of interest, independent-sample t-tests were performed to compare the CON limb with the SYM limb, and also to compare the SYM limb with the ASYM limb. Subsequently, the Holm–Bonferroni method was used to control the familywise error rate, was applied to the results of the three t-tests at a significance level α = 0.05 to determine which pairs of limbs differed significantly.

RESULTS

Patients demonstrated symptoms of knee OA based on KOOS (Table 1). Greater varus and valgus radiographs and radiographic disease severity (Table 2). Due to the large number of statistical analyses, p values for joint angles, internal joint torque, muscle forces, and contributions to knee joint forces are provided as Supplementary Material, with only significant results described below.

Peak knee flexion and ankle plantarflexion angles were lower in OA patients (Fig. 1A, top), but peak hip abduction and knee adduction angles were higher (Fig. 1A and B, top). Patients showed lower magnitudes of peak hip abduction, knee flexion, and ankle plantarflexion torque, with lower torque seen for SYM (Fig. 1A, bottom), but the ERAM was higher in patients, specifically SYM (Fig. 1B, bottom). Peak knee-spanning muscle forces for SYM were lower than CON, except hamstring forces (Fig. 2). Hip- and multi-spanning muscle forces for SYM were lower than CON, with the greatest differences seen for glutaeus medius and sartorius (Fig. 2). Muscle forces for ASYM were intermediate between SYM and CON, except hirpes femoris abduct. head and gastrocnemius, where ASYM was lowest.

Table 1. Participant Characteristics of the Knee OA and Healthy Control Groups

| Table 1. Participant Characteristics of the Knee OA and Healthy Control Groups |
|-----------------------------------|-------------------|
| Age, years | 49 (7) | 49 (7) | 0.860 |
| BMI, kg/m^2 | 26.5 (4.1) | 26.2 (3.6) | 0.177 |
| Mass, kg | 77 (15) | 89 (17) | 0.045 |
| Height, m | 1.78 (0.10) | 1.78 (0.09) | 0.688 |
| Females, no. % of total | 4.27% | 8.41% | 0.636 |
| Walking speed, m/s | 1.21 (0.07) | 1.20 (0.10) | 0.975 |
| Knee sub-scale scores, 0-100 | 62 (18) | 66 (18) |
| Pain | 55 (16) |
| Symptomatic | 64 (18) |
| Activities of daily living | 65 (20) |
| Sport and recreation | 31 (23) |
| Knee-related quality of life | 29 (19) |

Values are presented as mean (standard deviation) unless otherwise indicated. p values were calculated using Bonferroni's tests. Significant level was defined as p < 0.05. Statistically significant differences are shown in bold. KOOS, knee injury and osteoarthritis outcomes were 0, maximum symptomatic; 100, asymptomatic.
Table 2. Characteristics of the Symptomatic (SYM) and Asymptomatic (ASYM) Limits of the Knee OA Patients, and Healthy Controls (CON).

<table>
<thead>
<tr>
<th></th>
<th>CON, n = 15</th>
<th>SYM, n = 39</th>
<th>ASYM, n = 39</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stance time, s</td>
<td>1.71 (0.33)</td>
<td>0.75 (0.06)</td>
<td>0.75 (0.36)</td>
<td>0.001, 0.001, 0.79</td>
</tr>
<tr>
<td>Gait events, % of stance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contralateral toe-off</td>
<td>20 (5.6)</td>
<td>25 (5.2)</td>
<td>20 (4.8)</td>
<td>0.004, 0.007, 0.007, 0.001</td>
</tr>
<tr>
<td>Contralateral heel-strike</td>
<td>75 (12.1)</td>
<td>75 (12.0)</td>
<td>75 (12.6)</td>
<td>0.84, 0.007, 0.007, 0.001</td>
</tr>
<tr>
<td>Static knee adduction angle, deg</td>
<td>6.6 (3.0)</td>
<td>8.8 (4.6)</td>
<td>8.6 (4.6)</td>
<td>0.001, 0.002, 0.001</td>
</tr>
<tr>
<td>Mechanical axis angle, deg</td>
<td>9.2 (1.5)</td>
<td>9.2 (1.5)</td>
<td>9.2 (1.5)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values are presented as mean (standard deviation) unless otherwise indicated. p values were calculated using Student’s t-test. A mean-variance correction was used to identify statistically significant differences. Statistically significant differences are shown in bold. The mean/variance adduction angle was calculated using inverse kinematics from the gait marker data (positive values represent varus). Mechanical axis angle was measured from full-length standing anteroposterior radiographs. Positive values represent varus. Comparison pain (CON and SYM), CON and ASYM, CON and ASYM (ASYM, ASYM and RIM, ASYM and RIM, CON and RIM, ASYM and RIM).

Discussion

This study aimed to quantify and compare the contributions of muscle activity, gravity, and inertia to the biomechanical forces acting on the knee joint. We hypothesized that higher MCFs in OA knees were due to increased contributions from the hamstrings, quadriceps, and gastrocnemius muscle groups. However, this hypothesis was not supported by our findings. While patients exhibited higher peak MCFs, only hamstring forces showed a significant increase in the first peak (Fig. 4). This increase in hamstring forces was likely due to an increase in the mechanical axis angle, which was significantly higher in OA knees compared to healthy controls. Our findings suggest that muscle activity in OA knees is not significantly different from healthy controls, but rather, the mechanical axis angle is a more important factor in determining MCFs.

In conclusion, our study provides new insights into the biomechanical forces acting on the knee joint in OA patients. We found that muscle activity contributions to MCFs were not significantly different between OA and healthy knees, but rather, the mechanical axis angle played a more important role in determining MCFs. Our findings have implications for the development of interventions aimed at reducing MCFs and preventing OA progression.
Figure 1. (A) Joint angles (top row) and internal torques (bottom row) for hip flexion, hip adduction, knee flexion, and ankle plantarflexion for healthy controls (CON) and the symptomatic (SYM) and asymptomatic limbs (ASYM) of OA patients during stance. (B) Mean knee adduction angle (top row) and external knee adduction moment (bottom row) for these three limbs. Labels for statistically significant differences between SYM and CON (+), SYM and ASYM (×), ASYM and CON (ζ), and all three pairs of limbs (†). Statistical significance calculated at the peak values for joint angles and torques.

Placement on subjects and in ensuring model scaling errors were minimized, a 4° bias between marker-based and radiographic static alignment measures occurred (Table 2). In our high-BMI subjects, this result was likely due to discrepancies in hip-joint center location, an important factor for accurately determining alignment.43 Bias in marker-based dynamic alignment measures can be variable.45 Assuming 4° represents a worst-case, for representative trials of one control and one patient, we subtracted 4° from the frontal-plane joint angles and recalculated muscle forces. MCF was reduced by only about 7% in both subjects, a small difference which presumably affected all subjects. Thus our findings should not be materially impacted by this observed bias.

Notwithstanding these limitations, our results are consistent with experimental and model-predicted data available in the literature. Increasing dynamic...
varus mal-alignment from CON to SYM, as evidenced by increasing hip and knee adduction angles, was accompanied by greater EKAM. The magnitudes of the MCF for CON were within the range of reported model predictions, but slightly higher than those measured using instrumented TKIs. The MCF also showed a higher second peak compared to the first peak as reported in a TKR study by Kutner et al. Elevated MCF in patients occurred throughout midstance not just at peaks (Fig. 4), in agreement with recent modeling studies. Brief periods of unloading occurred on the lateral compartment during

Figure 3. (A) Total activation of the quadriceps and hamstrings (top row) and co-contraction index for the quadriceps and hamstrings (bottom row) for all CON and SYM limbs calculated using the static optimization results for all patients and controls. (B) Comparison of measured EMG trace lines and calculated major knee-spanning muscle forces (thick lines for the control sub-cohort and thin lines for the symptomatic leg sub-cohort). The muscle forces and EMG signals presented are the ensemble averaged time histories for each sub-cohort. Participant characteristics for the EMG sub-cohorts are presented in Supplementary Material.

Figure 4. Contributions by all knee-spanning muscles, all non-knee-spanning muscle and gravity to the medial (top row) and lateral (bottom row) compartment forces for healthy controls (CON), and the symptomatic (SYM) and asymptomatic (ASYM) limbs of OA patients. (A) MCF, (B) LCJ, and (C) COP. Stars indicate statistically significant difference between SYM and CON (9), SYM and ASYM (3), ASYM and CON (7), and all three pairs of limbs (*). Statistical analyses were performed at the time instants corresponding to the peaks and mid-stance minimum of the medial compartment force. Mid-stance minimum occurred at approximately 38% of stance.
mid-stance in patients, and also on the medial compartment near toe-off in many subjects implying that joint-opening would need to be resisted by knee ligaments.10 Recent modeling studies also found similar periods of joint-opening during gait.12,13

The muscles that contributed most to MCF in controls also contributed most in patients walking at the same speed, and were the prime movers in gait:14 (i) knee-spanning: Vasti, hamstrings, and gastrocnemius; and (ii) non-knee-spanning: Gastrocnemius, gluteus maximus, gluteus medius, and soleus. Small alterations to the magnitudes of these contributions had considerable impact on knee-joint loading. Contributions to MCF by gluteus maximus, hamstrings, soleus, and gastrocnemius—as well as gravity—were slightly greater in patients (Fig. 5, top). These small but significant increases in the magnitudes of muscle and gravity contributions summed to produce the higher total MCF.

Increased duration of muscle contributions to MCF was also important in producing higher MCF in patients. Gastrocnemius at the first peak, and rectus femoris at the second peak, provided small but influential contributions to MCF at time instants not related to their peak muscle forces (Fig. 5, top), a result of prolonged and slightly elevated muscle forces at these specific instants in OA patients (Fig. 2). Our finding is commensurate with the elevated early-stance gastrocnemius EMG activity in our patient sub-cohort (Fig. 3B, bottom), and with EMG studies of osteoarthritic gait that also reported prolonged and elevated gastrocnemius and rectus femoris activity in early and late stance respectively.15,16 Our patient EMG sub-cohort experienced a burst of gastrocnemius activity around 20–25% of stance (Fig. 3B, bottom), similar to Rutherford et al.,17 which was not reflected in the pattern of calculated muscle forces (Figs. 2 and 3B, bottom). Thus, although our gastrocnemius forces indeed showed increased early-stance activity, the magnitude of the gastrocnemius contribution to the first-peak of MCF in patients may actually be higher than our present results would suggest.

Large deficits in non-knee-spanning muscle forces in OA patients did not produce correspondingly diminished contributions by those muscles to the MCF. In patients, peak gluteus medius forces were lower than controls (Fig. 2), in agreement with evaluations of hip abductor performance in knee OA.18 However, the corresponding reductions in the contributions to MCF were not significant at either peak. (Fig. 5, top). In fact, gluteus maximus contributions were higher in patients throughout mid-stance (Fig. 5). Interestingly, gluteus minimus and soleus muscles forces were also lower in patients, but their contributions to MCFs were higher.
than controls (Fig. 5, top). Non-knee-spanning muscles can only lead the knee joint indirectly by means of dynamic coupling via the GFR. Thus, the inactivity of MCP contributions to changes in non-knee-spanning muscle forces suggests that factors related to the kinematic chain, such as lower-limb mal-alignment, also influence non-knee-spanning muscle load the knee via the GFR. In particular, the relative influences of frontal-plane alignment and non-knee-spanning muscle forces on EKAM may determine the distribution of non-knee-spanning muscle contributions between the tibiofemoral compartments. For example, gluteus medius compressed the medial compartment but unloaded the lateral compartment (Fig. 5) because it is the principal contributor to EKAM due to its large medially directed GFR contribution vector during gait. Greater versus mal-alignment would presumably amplify this EKAM contribution by increasing its moment arm about the knee. Hence, large defects in gluteus medius forces in our patients may have been offset by greater mal-alignment, producing a limited net change in EKAM, and lower non-MCP contributions. This mechanism may explain the minimal association between hip abduction function and EKAM and why hip-abduction training did not reduce EKAM in varus mal-aligned OA patients.

Differences in knee-spanning muscle contributions to MCP between OA patients and controls were more commonly associated with the respective muscle forces. In particular, higher hamstrings and lower vasti muscle forces (Fig. 2) were associated with higher and lower contributions to MCP, respectively (Fig. 5, top). This occurred because direct compressions of the knee by knee-spanning muscles dominated loading via the OA. Contributions by gravity, which arise from the resistance of the skeletal linkage to the body's weight, played an essential role in producing the highest first peak of MCP in patients. The magnitude of gravity's contribution was always small because the weight of the body is mostly borne by muscles. But with progression from CON to SYM, increasing severity of mal-alignment (Fig. 1) directed more of gravity's contribution through the medial compartment (Fig. 4). Thus, presumably, correcting mal-alignment in patients would directly reduce MCP by more equally distributing gravity's contribution between the two compartments.

Our present study emphasizes the complex interactions among muscles, gravity, and the kinematic chain in influencing knee-joint loading which may have implications for clinical intervention. In particular, our findings suggest that small improvements in the functional performance of knee-spanning muscles during gait, such as minimizing aberrations and/or prolonge the activity in vasti, hamstrings, rectus femoris, and gastrocnemius may provide considerable benefit by reducing the duration and magnitude of direct compressive loads contributed by these muscles throughout stance. However, reductions in contributions from non-knee-spanning muscles and gravity, which indirectly exert forces on the knee via the GFR may be better gained from improvements to the kinematic chain, in particular the correction of mal-alignment. This may be especially beneficial for reducing mid-stance MCP, which was higher in patients due mainly to elevated contributions by non-knee-spanning muscles and gravity (Fig. 4). While improved lower-limb alignment has been associated with reduced mid-stance EKAM, our study extends this finding to further suggest that it may decrease the actual mid-stance MCP by reducing the magnitudes of non-knee-spanning muscle and gravity contributions (Fig. 5). Overall, a combined intervention strategy targeting restoration of muscle function and lower-limb alignment would potentially produce the best clinical outcome for varus mal-aligned patients. Thus, our results provide a biomechanical rationale supporting the use of realignment procedures with concurrent functional rehabilitation.

Despite the ASYM limb experiencing a larger knee adduction angle and greater EKAM than CON, only the mid-stance MCP was significantly different; peak MCPs were not (Fig. 4). Most of the ASYM limbs in the present sample had pre-existing OA-type structural changes in the tibiofemoral joint evident on radiographs (Table 2) and also demonstrated walking kinematics and kinematics resembling SYM to a lesser degree (Fig. 1). This type of asymptomatic radiographic OA is common but its biomechanics are not well-studied. Our results suggest that elevated mid-stance MCP (Fig. 4) is a factor in the pathomechanics of knee OA that may be influential throughout all stages of disease, and may be more sensitive than peak in detecting differences between more severe asymptomatic limbs. In fact our finding of elevated mid-stage MCP in patients points toward increased medial compartment impulsive progression from CON to SYM. These findings are consistent with the association of both mid-stance EKAM and EKAM impulse with structural disease severity. Hence, our present results support consideration of mid-stance loads in the ASYM limb in clinical assessments and interventions to mitigate the risk of progression to symptomatic bilateral disease.

In conclusion, we found that greater magnitude and longer duration of contributions by the prime movers and gravity were responsible for higher MCP in patients throughout stance. Knee-spanning muscles, non-knee-spanning muscles, and gravity contributed to MCP loading by different mechanisms, with the influence of lower-limb alignment more important in the latter two. Hence, both muscle forces and varus mal-alignment were factors contributing to higher MCP in patients. Altered kinematics, muscle forces, and elevated mid-stance MCP were found in the ASYM limb. Our findings emphasize the need to
consider muscles function, alignment and mal-alignment loads in the development of interventions for OA, and support the inclusion of the ASYM lab in clinical assessments.

AUTHORS' CONTRIBUTIONS
All authors contributed equally to this work. Subject recruitment, experimental design, and undertaking of gait experiments were performed by SFR and TRB. The computational modeling pipeline was developed and implemented by PS with design and technical guidance from YCL and MGP. Statistical analyses were designed and supervised by XMC and TBR, and undertaken by PS. All authors discussed and agreed on results and potential implications. The manuscript was initially prepared by PS, YCL, and MGP, but all authors contributed substantially to its revision and final form.

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SUPPORTING INFORMATION
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LIST OF REFERENCES


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