



Muscle Strategies and Mechanical Loading in Patients with Osteoarthritis

**Thesis submitted in fulfilment of the requirement for the degree of
Doctor of Philosophy in biomedical engineering**

By

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2017

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ABSTRACT

Osteoarthritis (OA) is a chronic degenerative joint disease frequently affecting the knee. The cause of OA remains unclear. It is known that mechanical loading is a key contributing factor to the initiation and progression of knee OA. The overall aim of this work was to investigate mechanical loading at the knee in terms of external moments, muscle co-ordination, muscle forces and knee contact forces (KCF) during gait in Non-pathological subjects (NP), subjects with medial knee OA listed for high tibial osteotomy surgery (pre-HTO), and subjects with late-stage OA listed for total knee replacement (pre-TKR) using musculoskeletal modelling and dynamic simulations of motion. This was achieved through four objectives.

Objective 1: Examine alternative methods of normalization that effectively reflect muscle activity as compared to Maximal Voluntary Contraction (MVC). **Rationale:** Patients with compromised function due to disease or injury are unable to maximally contract their muscles during MVC tasks. The current study finds an alternative method that is comparable to the MVC in reflecting muscle activity for level gait, whilst having good repeatability. **Hypothesis:** Activities of daily living (ADL) give a representative and repeatable measure of muscle activity during different ranges of motion. **Methods:** EMG data were recorded from knee muscles in 10 NP subjects during ADL and different methods of normalization were tested. Intra- and inter-individual variability were calculated to determine reliability. **Results:** ADLs are proposed and demonstrated in this work as a useful measure in EMG normalization.

Objective 2: Determine if there is a trend in co-contraction index and OA progression. **Rationale:** People with OA tend to walk with high muscle co-contraction to compensate for joint instability. For long-term joint integrity, this could increase in the net knee compressive contact load and may contribute to the progression of OA. The current study explores how the coordination between quadriceps, hamstrings and gastrocnemii are affected in pre-HTO and pre-TKR compared to NP. **Hypothesis:** Increased co-contraction of knee muscles to compensate for joint laxity in OA patients. **Methods:** EMG signals from seven peri-articular knee muscles were processed to create a linear envelope. The co-contraction index (CCI) was calculated for muscle pairs across the knee. **Results:** CCI was a useful marker of OA progression, where an increase in lateral CCI reflected progression from NP to pre-HTO. Increase in medial CCI could potentially differentiate the severity of knee OA.

Objective 3: Examine if activation patterns, used to stabilize the knee joint, change with OA progression. **Rationale:** Varying individual muscular control strategies depend on strength and coordination, and contribute to joint stability and loading. It is important to understand the changing role of muscles in the mechanical loading of joints with degenerative joint disease. The purpose of this study was to estimate quadriceps, hamstrings and gastrocnemius forces in patients with OA progression. **Hypothesis:** The knee joint is stabilized by the external knee adduction moment (KAM) that should be balanced by the internal moment produced by muscle forces and joint loading. In OA, lateral and medial muscles use different strategies to

counterbalance the high external KAM. Methods: An EMG-driven model was used to estimate muscle forces. Results: Compared to NP, OA subjects exhibited altered muscle forces in relation to applied external moments at the knee joint.

Objective 4: Estimate knee contact force (KCF) in patients with OA progression. Rationale: Assessment of muscle forces and joint loading is essential to fully understand altered loading mechanisms associated with the progression of OA. Hypothesis: Changes in muscle strategies would be different between groups and can have a significant effect on the magnitude of the knee joint loading. Methods: Gait biomechanics (moments, muscle forces and joint loading) were calculated by OpenSim. Results: Differences in the patterns and magnitudes of the KCF waveforms provide information on gait changes associated with the progression of knee OA.

ACKNOWLEDGEMENTS

The work for this dissertation was carried out at the Institute of Medical Engineering and Medical Physics (IMEMP), Cardiff University. I would like to express my gratitude to my supervisors, Dr. Gemma Whatling and Prof. Cathy Holt for their encouragement, patience, mentorship and support from start to finish. I would have never embarked on the journey of a PhD without their enthusiasm and dedication for the subject. As a member of the biomechanical research group in Arthritis Centre, I would like to say a special thank you to all my colleagues from the Arthritis Research UK Biomechanics and Bioengineering Centre (ARUKBBC) for making me feel so welcomed and at home right from the start and providing such a strong interdisciplinary network.

Thanks to all the colleagues, especially David Williams, Nidal Khatib, Dr Paul Biggs, Dr Sarah Forrest, and Dr Philippa Jones that contributed to the friendly atmosphere at the Biomedical Engineering Research Group. Thanks for assisting in data collection and for the numerous interesting and helpful discussions concerning programming, statistics, and mechanics.

My appreciation goes to my funding sources as well: The Higher Committee for Education Development in Iraq (HCED). Further, I would like to acknowledge that part of the data used in this work was previously collected under EPSRC funding [EP/J010111/1].

Finally, I wish to thank my parents (Mom and Dad), my sister (Amal), my lovely sister and brother-in-law (Areej & Bassam), and my brothers (Nabeel & Mohanned) for always being there for me, supported me unwaveringly and believed in me, for that I am indebted to you and eternally grateful.

"Opportunity to find deeper powers within ourselves comes when life seems most
challenging" - Joseph Campbell

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LIST OF ABBREVIATIONS

- ABSD – Absolute Difference
- ACL – Anterior Cruciate Ligament
- ADLs – Activities of Daily Living
- A/P – Anterior-Posterior
- ASIS – Anterior Superior Iliac Spine
- BMI – Body Mass Index
- BW – Body Weight
- CHS – Contralateral Heel Strike
- CCI – Co-Contraction Index
- CMC – computed muscle control
- CTO – Contralateral Toe Off
- CV – Coefficient of Variation
- %D – Percentage Difference
- EKAM – External Knee Adduction Moment
- EMG – Electromyographic
- F Max –Maximum Isometric Force
- Fmed – Medial Knee Contact Force
- GCS – Global Coordinate System
- GRF – Ground Reaction Force
- GS – Gastrocnemius-Soleus
- HS – Heel Strike
- ID – Inverse Dynamics
- IK – Inverse Kinematics
- JRF – Joint Reaction Force

KAAI – Knee Adduction Angular Impulse
KAM – Knee Adduction Moment
KCF – Knee Contact Force
KFM – Knee Flexion Moment
KL – Kellgren-Lawrence Scale
KOS – Knee Outcome Survey
MFR – Medial Force Ratio
MDM – Mean Dynamic Method
M/L – Medial-Lateral
MOT – Motion
MSK – Musculoskeletal
MTU – Musculo Tendon Unit
MVC – Maximum Voluntary Contraction
NP – Non-Pathological
OA – Osteoarthritis
OFL – optimal fibre length
OKS – Oxford Knee Score
PDM – Peak Dynamic Method
PSIS – Posterior Superior Iliac Spine
QTM – Qualysis Tracker Manager
RMSD Root Mean Square Difference
ROM – Range of Motion
RTL – Resting Tendon Length
SLS – Single Leg Stance
SO – Static optimization
STD – Standard Deviation

TKR – Total Knee Replacement

TRC – Track Row Column

VLLG – Vastus Lateralis- Lateral Gastrocnemius

VLLH – Vastus Lateralis-Lateral Hamstring

VMMG – vastus medialis-medial gastrocnemius

VMMH – Vastus Medialis -Medial Hamstring

VR – Variance Ratio

WOMAC – The Western Ontario and McMaster Universities Osteoarthritis Index

WTN – Different Walking Trial

Chapter 1

Introduction

1.1 What is Osteoarthritis?

Osteoarthritis (OA) is a chronic joint disease associated with cartilage and bone damage and general joint degeneration; leading to joint pain, stiffness and functional disability (Lane et al., 2011). The commonly affected joints are the hands, knees, hips, and spine, where the knee is the most frequently affected joint (Oliveria et al., 1995). In the UK, 4.71 million people have sought treatment for osteoarthritis of the knee (ARUK, 2013). Estimates suggest that the number of people with knee OA will increase from 4.71 million in 2010, to 5.4 million in 2020, and reaching 6.4 million by 2035 (ARUK, 2013). The progression of OA is often accompanied by pain and may result in changes in gait and neuromuscular function, which may in turn lead to increased wear on the joint and further progression of the disease (Asthephen et al., 2008).

The diagnosis of OA has most often been based on radiographic appearance. Radiographic criteria were proposed by Kellgren and Lawrence in 1957 (Kellgren and Lawrence, 1957), then accepted later by the World Health Organization at a symposium held in Milan in 1961 (Ball et al., 1963). According to Kellgren and Lawrence (KL) system, OA is divided into five stages. Stage 0 is assigned to a normal, healthy knee. The highest stage, 4, is assigned to severe OA.

Considering the risk factors of OA, it has been shown that women are more severely impacted by knee OA than men (Blagojevic et al., 2010). Increasing the risk of OA has also been found among people with previous knee injury (Thelin et al., 2006) and people aged 45 and over. Close to 1 in 5 people aged 45 and over have sought treatment for knee osteoarthritis (ARUK, 2013). OA increase with age from 27 % in subjects younger than 70, to 44 % in subjects age 80 or older (Felson et al. 1987).

Obesity is a strong risk factor for knee OA, obese individuals with a body mass index (BMI) of 36 or more have a 14 times more risk of knee OA compared to those within the healthy BMI range (Coggon et al., 2001). As the UK population ages and becomes more obese (UKHF, 2014), it is expected to see more patients with OA, which has its negative impact on their physical functioning and quality of life. Therefore, means that identifying approaches to prevention should be a public health priority. In addition, OA can cause a phenomenal negative impact on the economy (Bitton, 2009).

Total knee replacement (TKR) is widely accepted as one of the most effective interventions for OA, it is commonly used to correct end stage of knee OA. However, high tibial osteotomy (HTO) is increasingly being recognised as a good alternative surgical procedure for younger, more active patients who suffer from early to moderate stage of uni-compartmental OA (Sabzevari et al. 2016).

The onset of OA is a complex multifactorial problem and requires careful examination of both patient specific mechanical and mechano-biological contributing factors. These include mechanical considerations, such as the altered axis alignment, contact areas, load distribution across the joint, gait pattern, and biological considerations associated with the altered mechanical factors, such as whether the new stresses experienced in the tissues promote turnover of the cartilage matrix to prevent further degeneration of the tissue (Fujisawa et al., 1979). It is therefore, believed that the altered mechanical loading patterns due to the incidence of OA introduce changes in the biology of the tissue (Andriacchi and Mündermann, 2006). By understanding the relationship between altered loading and biological changes in OA patients, it will correspondingly provide a better insight into the relationship between altered loading and cartilage degeneration in OA patients.

The Arthritis Research UK Biomechanics and Bioengineering Centre (ARUKBBC) combines interdisciplinary research across surgeons, engineers, biomedical scientists, and physiotherapists to investigate relationships between mechanical loading, joint function, pain, and inflammation. This PhD research was run in parallel with other projects to address one of the many centre scientific objectives to achieve the ultimate aim, which is “to investigate NP joint biomechanics and neuromuscular control strategies, and determine how this is influenced by OA severity, and hence inform clinical intervention”.

1.2 Introduction

Mechanical factors play an important role in the development of OA (Andriacchi, 2006). Excessive knee contact force is believed to contribute to the development of medial compartment knee OA with an abnormally large peak value of the external knee adduction moment (KAM) linked to increased pain and rate of disease progression (Hurwitz et al., 2002; Amin et al., 2004). Typically, total knee joint loading is influenced by ground reaction, joint contact, muscle and soft tissue forces. The net moment resulting from the ground reaction force is counterbalanced by the moment produced by muscles and contact forces. 60-80% of total intrinsic knee load, which is primarily produced by muscle forces (Sasaki and Neptune, 2010; Taylor et al., 2004), is distributed through the medial compartment of the tibio-femoral joint (Andriacchi, 1994). This percentage varies between activities (Kutzner et al., 2017), as shown in Figure 1.1, with the highest percentages of medial force ratio (MFR) (up to 88%) found during activities that include single-limb support. Whereas, an MFR < 50% was found during most activities with double-limb support. This was also confirmed by (Trepczynski et al., 2014), revealing that activities with a

one legged stance phase had generally larger KAMs and medial forces than activities where both feet remained on the ground.

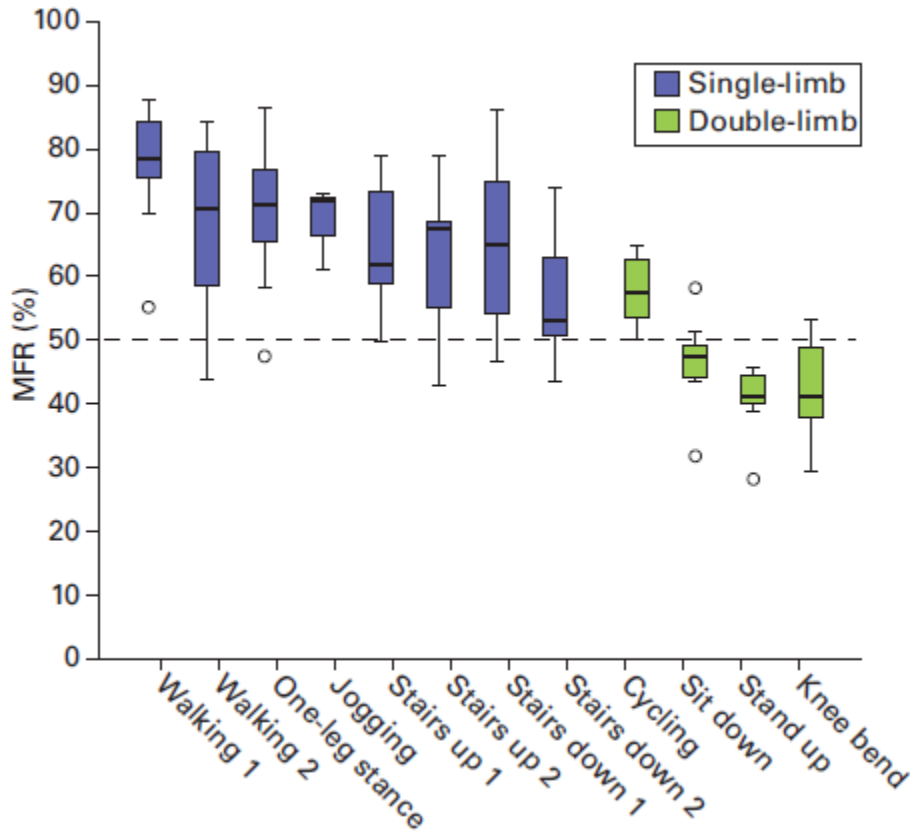


Figure 1.1: Box and whisker plots of medial force ratio (MFR), where MFR represents the percentage of the axial force that is transferred via the medial compartment of the knee joint, during various activities of daily living. Values taken at peak resultant forces (the transverse line shows the median value, with the box representing the 25th to 75th percentile range. 1 and 2 were referred to peak 1 and peak 2 for the corresponding activity, respectively) (Kutzner et al., 2017).

The pattern and magnitude of knee contact forces are directly affected by the way that individuals activate their muscles, as shown in Figure 1.2. Therefore, assessment of muscle forces and joint moments is essential to fully understand altered loading mechanisms associated with the incidence and progression of OA.

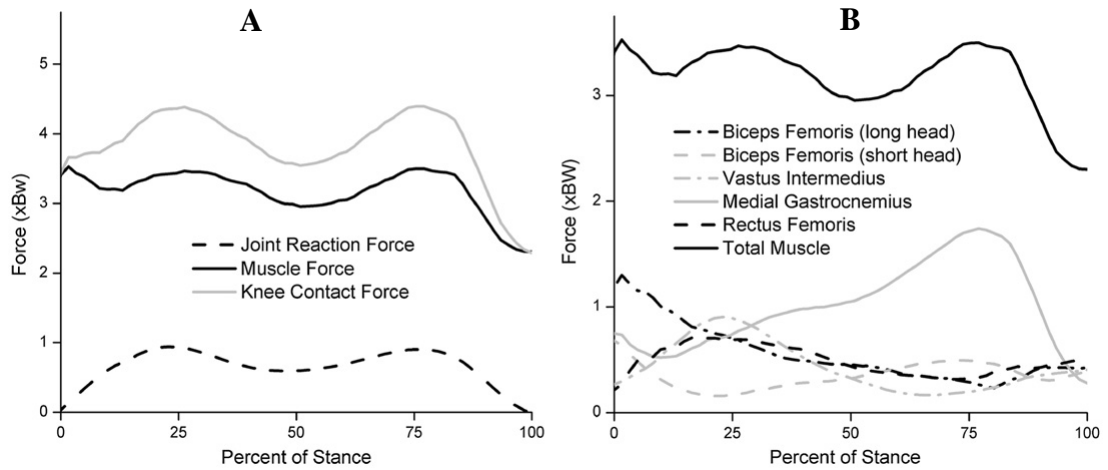


Figure 1.2: (A) Muscle force and external moment (presented here as joint reaction force) contributions to the knee contact force. (B) Individual muscle contributions to the total muscle force component of the knee contact force (Richards and Higginson, 2010).

Most gait studies have focussed their investigations on knee kinematics and kinetics (Astefhen et al., 2008; Sharma et al., 1998; Zeni and Higginson, 2011), muscle activations (Childs et al., 2004; Heiden et al., 2009; Hodges et al., 2016; Hortobagyi et al., 2005; Hubley-Kozey et al., 2008; Hubley-Kozey et al., 2006; Hubley-Kozey et al., 2010; Hubley-Kozey et al., 2009; Kumar et al., 2012; Lloyd and Buchanan, 2001b; Maria Grazia Benedetti et al., 1999; Rutherford et al., 2011; Schmitt and Rudolph, 2007b; Zeni et al., 2010), and muscle forces (Brandon et al., 2014; Herzog et al., 2003; Kim et al., 2009; Shull et al., 2015). In contrast, a limited number of studies have investigated all these variables together and correlate it with the degree of OA severity. Furthermore, joint loading is of great interest to be examined with the aforementioned parameters and how the mechanical loading is implicated with the OA progression.

Knee adduction moment (KAM) has received attention as an important surrogate measure of OA severity (Mundermann et al., 2004; Sharma et al., 1998) and has been used to evaluate joint loading, with peak KAM providing a strong predictor of

medial knee contact force (Zhao et al., 2007). A simplified illustration of how the KAM is calculated during walking is presented in Figure 1.3. The ground reaction force passes medially to the centre of knee causing a moment in the frontal plane about the knee, this moment is called the KAM. For the right leg, it acts anticlockwise about tibia, potentially causing increased loading on the knee joint, especially on the medial compartment of the knee. It is thought that an increased ground reaction force (GRF), combined with an increased lever arm distance between the knee joint centre and the GRF vector, due to mal-alignment, results in higher KAMs in OA subjects. However, whether or not increased KAM is involved in the initiation of OA remains a topic of debate. A previous study reported that increased KAM has been correlated with a reduction in pain (Hurwitz et al., 2000), indicating that higher KAMs are a consequence of pain reduction induced by pain relief medication.

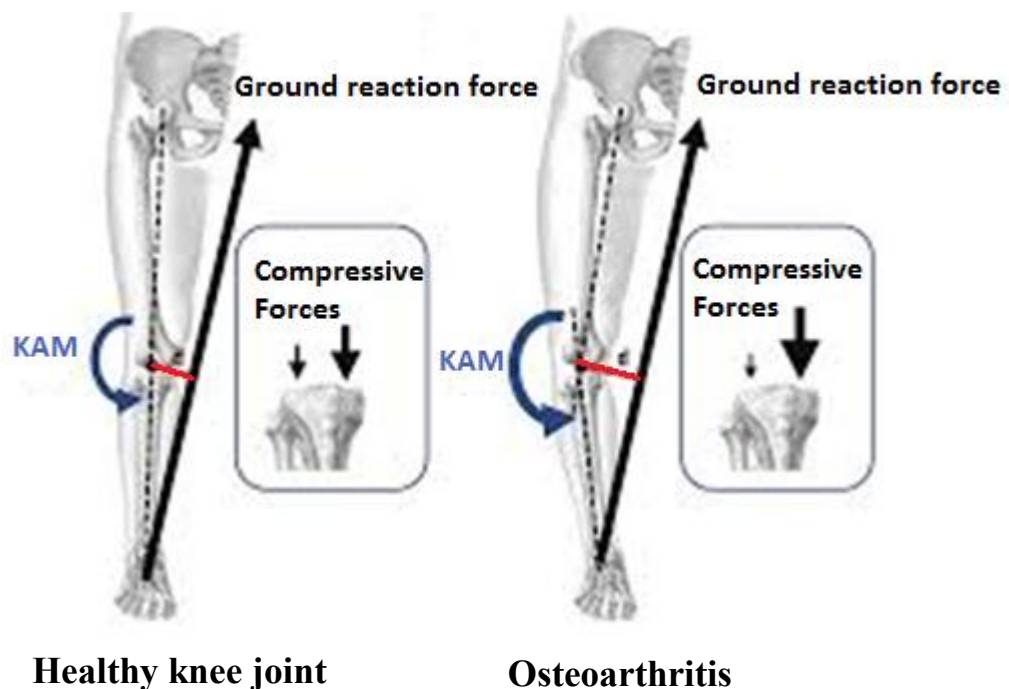


Figure 1. 3: Schematic illustration of Knee adduction moment for healthy and OA patient that produces medial tibiofemoral compartment loading.

Sharma et al. (1998) has reported knee adduction moment in knees with Kellgren-Lawrence (KL) grades of 0-2 to be 3.0 ± 1.1 %Wt*Ht, while those with KL grades of 3-4 had a higher adduction moment (5.1 ± 0.9 %Wt*Ht). Manal et al. (2015) reported that a combination of peak KAM and peak knee flexion moment (KFM) provides more accurate estimates of peak medial knee contact force compared to peak KAM alone. Moreover, knee adduction angular impulse (KAAI), which is the time integral of the knee adduction moment for the overall stance phase, provides additional information of knee joint loading beyond that available from KAM as it accounts for both the load magnitude and duration (Thorp et al., 2006). Two studies carried out by (Thorp et al., 2006; Thorp et al., 2007) have found that KAAI can differentiate between mild and moderate OA and symptoms of OA. As shown in figure 1.4, the KAAI, but not KAM, differed between individuals with mild OA and those with moderate OA.

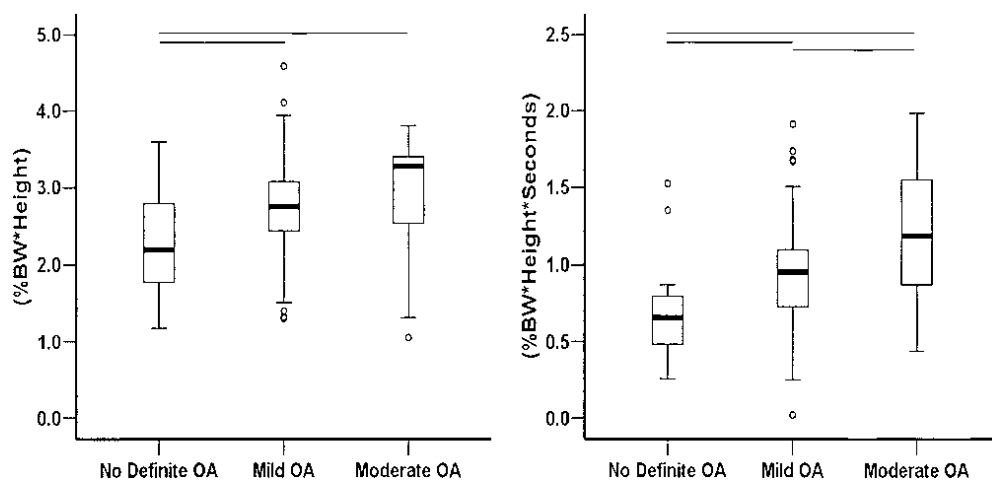


Figure 1. 4: Magnitude of the KAM (left) and KAAI (right) as a function of OA severity. Horizontal lines above the graphs indicate significant differences between groups ($P < 0.05$). %BW = percent body weight. (Thorp et al., 2006)

A case study carried out by (Walter et al., 2010), using in vivo gait data collected from a subject with a force-measuring knee implant, has shown that a reduction in

first peak KAM does not guarantee a reduction in medial contact load. Furthermore, being a net moment, it does not explicitly account for individual muscle activation patterns as well as muscle co-contractions.

Kutzner et al. (2013) examined the relationship between the external knee adduction moment and the medial knee contact force (F_{med}) for nine subjects with telemetric knee implants and found a significant correlation between peak values of F_{med} and the corresponding KAM values at early and late stance phase. Kutzner et al. (2010) measured loads on the knee joint using instrumented implants for most activities during daily life, and they found that the resultant forces lay typically in the range 107–346% BW. During level walking, the force measured on the knee joint was 261% BW. This is smaller than those determined analytically, 7x BW (Seireg and Arvikar, 1975). Two main force peaks occurred at the instant of contralateral toe off (CTO) and shortly before contralateral heel strike (CHS). An exemplary trial from one patient is presented in Figure 1.5.

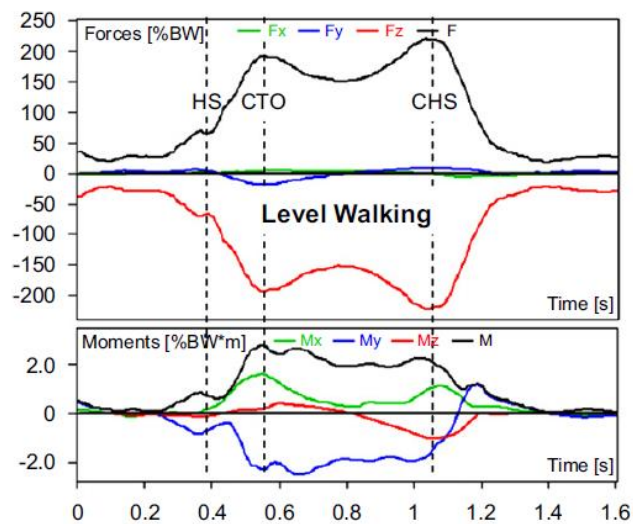


Figure 1.5: Load patterns during walking. Upper diagram=forces, lower diagram=moments. $-F_z$ =tibiofemoral axial force. $-M_y$ =adduction moment. HS: heel strike; CTO: contralateral toe off; CHS: contralateral heel strike; CSC: contralateral stair contact (Kutzner et al., 2010).

For gait analysis studies, it is important to understand neuromuscular activation and how it contributes to external forces to stabilize joints and distribute joint loading.

Muscle electromyography (EMG) has been used for decades to evaluate neuromuscular responses in Non-pathological subjects (Burden and Bartlett, 1999; Norcrossa et al., 2010) and to investigate alterations due to pathology (Benoit et al., 2003). To allow comparison of activity between different muscles, across time, and between individuals, the EMG signal should be normalized, i.e. expressed in relation to a reference value obtained during standardized and reproducible conditions. However normalization by using Maximum voluntary contraction (MVC) is considered as a gold standard for normalizing EMG (Burden et al., 2003; DeLuca, 1997; Sousa and Tavares, 2012), this method is not appropriate for patients with neurologic disorders. Notwithstanding the importance of the EMG normalization in the accuracy of the estimated muscle forces and joint loading, EMG based studies do not seem to show a uniform methodology. Taking this into account, the next Chapter will discuss different normalization procedures to relate the most appropriate method for OA patients, based on how the normalization method might influence data interpretation.

Muscle activation features play an important role in understanding the effects of longitudinal progression or interventions for knee OA. Hubley-Kozey et al. (2013) showed that reliable EMG characteristics can be captured for subjects with moderate knee OA. Lloyd and Buchanan (2001) investigated the activation strategies used by individuals to support adduction/abduction moments and the muscle loading patterns that result from these activation schemes during highly controlled isometric tasks. They found that activation of the gracilis and tensor fascia lata increased with the

increasing magnitude of the adduction and abduction moments. These two activation patterns provided positive support of lateral and medial loads at the knee. The sartorius appears to be activated to provide positive support of lateral loads, whereas during adduction moment this muscle increases the medial load on the knee, i.e. provides negative support.

In another study, Wilson et al. (2012) associated EMG patterns of the knee periarticular musculature with post-operative tibial implant migration. They found that a prolonged muscle activation pattern for both the lateral gastrocnemius and vastus medialis muscles, during the stance phase, was related to increased posterior migration of the tibial component. Moreover, higher muscle co-contractions have been linked to OA severity (Hubley-Kozey et al., 2009; Metcalfe et al., 2013; Ramsey et al., 2007; Schmitt and Rudolph, 2007), presumed to be linked with higher muscle forces (Hubley-Kozey et al., 2008; Schmitt and Rudolph, 2008), to compensate for joint instability.

Measuring the forces applied to a joint and estimating how these forces are partitioned with respect to surrounding muscles, ligaments, and articular surfaces is fundamental to understanding joint function, injury, and disease. Muscle forces have been proposed as the primary determinants of joint contact forces (Herzog et al., 2003; Sasaki and Neptune, 2010), with correctly predicted muscle forces assuming to result in sensible estimates of joint contact loads. However, to date, accurate measurement and prediction of individual muscle forces are still a major challenge.

Advances in musculoskeletal (MSK) modelling and computation power have enabled researchers to generate gait simulations in efforts to estimate joint moments, muscle forces (e.g., (Lloyd and Besier, 2003; Winby et al., 2009; Kim et al., 2009)) and, subsequently, joint loading, for patient populations that used altered neuromuscular

activation patterns (e.g., (Besier et al., 2009; Manal and Buchanan, 2013; Winby et al., 2009)). Four prominent methods exist in muscle modelling to estimate muscle forces: EMG-driven models were introduced by (White and Winter, 1993) to estimate periarticular knee muscle forces, Static optimization (SO), computed muscle control (CMC) (Thelen and Anderson, 2006) and DeVita model (DeVita and Hortobagyi, 2001). These models will be explained in details in the next chapter.

Although biomechanical evaluations of people with OA are frequently performed to identify gait impairments; little attention has been paid to the provision of quantitative information regarding the function of individual muscles. Adouni and Shirazi-Adl (2014) developed a gait-data driven MSK model of the lower extremity to estimate muscle forces and knee joint stresses-strains during the stance phase of the walking cycle in a subject with knee OA and a non-pathologic (NP) subject. They found individual with OA adopted reduced muscle forces through stance phase, except at mid stance, compared to NP subjects. However, (Kumar et al., 2009) demonstrated that OA patients had higher hamstring and gastrocnemius muscle forces at both loading response and mid-stance phases of gait cycle.

Varying individual muscular control strategies depends on muscle coordination and contributes to joint stability and loading. It is important to understand the changing role of muscles in the mechanical loading of joints with OA. Previous studies have found that patients with OA increased their muscle activations. These studies have been based on EMG data when normalization had relied on the use of MVC, which introduces limitations to the results as it is inconsistent and unreliable across the OA patient cohort. Literature have presented results for joint loading and muscle forces in OA however these are not reported together for the same patient or across two different patient groups, i.e. pre-HTO and pre-TKR.

Combining results for the same patient to provide information on corresponding joint forces, muscle forces and co-contractions could provide a novel and additional insight into the effects of OA for two patient groups, HTO patients with medial OA and varus deformity, and TKR patients with OA affecting the whole of the joint, as compared to people with healthy knees. Additionally, new approaches to EMG normalisation should be explored and optimised to provide consistency when comparing within and across the OA patient groups.

Addressing these important factors will add to the current understanding the adaptations strategies in the underlying neuromuscular mechanisms during gait for NP, pre-HTO and pre-TKR subjects. The studies described in this thesis have been undertaken to address the above factors and investigate altered muscle forces in relation to applied external moments at the knee joint in knee OA gait. In terms of how they align with clinical translation, the outputs would help multidisciplinary researchers to answer three key questions:

- I. Do OA subjects adopt different muscle coordination strategies across stance?
- II. Do modified activation patterns act to stabilize the knee joint, in line with the changes that might be seen in the biomechanical variables that are affected by OA progression?
- III. Can the knee loading patterns in OA subjects be used to characterize OA as it progresses from medial OA to all of the joint?

The results of this study have important implications for OA research. Identifying a linkage between joint loading and the compensatory strategies of the neuromuscular system (muscle coordination and muscle forces) as OA progresses across the joint, is a critical step in better understanding and intervening for patients with OA.

1.3 Delimitations

Non-pathological subject recruitment:

The recruitment of NP volunteers was approved by the Research Ethics Committee for Wales and Cardiff University Health Board. Volunteers were recruited via email and poster advertisements throughout Cardiff University and the wider South Wales community. The criteria for inclusion in the study as a NP volunteer was as follows:

- No self-reported OA, or pain in the foot, ankle, knee, hip or back.
- No known difficulty performing ADLs.
- No history of any major lower extremity injuries/surgeries.
- No other musculoskeletal, neurological or visual condition which might affect the way they move.
- An ability to give informed consent.

Any volunteers who expressed an interest in participating were given an information sheet. If the volunteer understood the information sheet and was happy to proceed, they were asked to sign a consent form.

Osteoarthritic patient recruitment:

The recruitment of NHS patients with OA was approved by the Research Ethics Committee for Wales and Cardiff and Vale University Health Board. Two patients groups were recruited: The first group is patients with medial knee OA listed for high tibial osteotomy surgery (pre-HTO). The second group is patients with late stage OA listed for total knee replacement (pre-TKR).

Where pre-HTO group represent patients with medial OA while pre-TKR represent patients having OA on the whole joint.

The criteria for inclusion in the study as a patient volunteer was as follows:

- An ability to walk 10m without a walking aid.
- An ability to give informed consent.
- No unrelated musculoskeletal, neurological or visual condition which might severely affect the way they move.

Before taking part in any aspect of the study, patient volunteers were given a patient information sheet. If the patient volunteer was still interested in taking part, they were asked to sign a patient consent form.

1.4 Aim and Objectives of the Study

The aim of this study was to investigate muscle coordination, muscle forces, joint forces and moments acting in knee for NP and patients with OA, based on musculoskeletal modelling and determine how these parameters are correlated with OA progression.

1.5 Focus of the thesis

The focus of this study was to investigate altered muscle forces and joint loading in relation to applied external moments at the knee joint in patients with knee OA progression. For gait analysis studies, it is important to understand neuromuscular activation during walking and how it contributes to the external forces to stabilize joints and distribute joint loading. The ideal strategy to understand this scenario is to explore muscle activation patterns, muscle coordination, muscle forces, and joint moment profiles during activities of daily living (ADLs). During ADLs, subjects adopt individual strategies to muscle coordination. However what is important is that these values are repeatable and give a representative measure of muscle activity during different ranges of motion. Consequently muscle activity

during ADLs is explored as an alternative method of EMG normalization. An EMG-driven model was used to estimate muscle forces. Further, subject specific computer simulation was generated for each participant and then the knee contact forces were subsequently calculated. Results were compared across groups (NP, pre-HTO, and pre-TKR) in an effort to better understand the effects of OA as it progresses across the joint. The overall objectives of the study are presented in five chapters as:

Chapter 2: Literature Review

Review the related researches and describe the background of this study.

Chapter 3: Can Activities of Daily Living Contribute to EMG Normalization for Gait Analysis?

This study examines alternative methods of normalization that effectively reflect muscle activity as compared to Maximal Voluntary Contraction (MVC). EMG data recorded from knee flexion-extension muscles in 10 control subjects during the stance phase of gait cycle were examined by adopting different approaches of normalization: MVC, Mean and Peak Dynamic during gait cycles, (MDM and PDM, respectively), Peak Dynamic during ADLs, (*PDM), and a combination of ADLs and MVC(**PDM). Intra- and inter-individual variability were calculated to determine reliability and similarity to MCV.

Chapter 4: The Importance of Knee Muscle Coordination in patients with OA

The normalization methods recommended in the previous chapter, *PDM and **PDM, will be used to study how the muscles changing their coordination across NP, pre-HTO, and pre_TKR subjects, by calculating co-contraction index (CCI).

This study has four objectives: First, determine whether a strategy of generalized increased co-contraction can be seen in patients with OA. Second, to test which time interval should be used for calculating CCI for OA subjects: stance phase or gait cycle. Third, to test the impact of using different methods of normalization for calculating co-contraction index. Fourth, to determine whether a positive relationship exists between OA progression and muscular co-contraction.

Chapter 5: Muscles Strategies in patients with OA

The purpose of this study is to estimate quadriceps, hamstrings and gastrocnemius forces in NP, pre-HTO, and pre-TKR subjects by using EMG-driven model, where the EMG data are normalized by using the approach recommended in Chapter Three. Lower limb kinematics and electromyography (EMG) data for subjects walking at self-selected speeds, are driven to an EMG-driven musculoskeletal (MSK) knee model, which is scaled and calibrated to each individual. Two different questions are posed. First, does the neuromuscular system modify their activation patterns to stabilize knee joint, in line with the changes that might be seen in the biomechanical variables, which are affected by OA progression? Second, do muscle force patterns change for pathological gait?

Chapter 6: Alterations in Knee Loading and Neuromuscular Activity in patients with OA

The purpose of this study is to estimate joint loading and the corresponding muscle forces in NP, pre-HTO, and pre-TKR. Static optimization simulations are used to estimate muscle forces in OpenSim (Delp et al., 2007). Knee contact forces are calculated by using joint reaction force (JRF) function in OpenSim. It is hypothesized that loading patterns in OA subjects can be used to characterize the progression of OA. the second hypothesis is that muscle strategies would be different across NP and those pre-HTO and pre-TKR subjects, and have a significant effect on the magnitude of the knee joint loading.

Chapter 7: Conclusion and Future work

Summarizes the key contributions of this study and identifies the direction of future works.

Chapter 2

Literature Review

2.1 Literature review

For gait analysis studies, it is important to understand neuromuscular activation and how it contributes to external forces to stabilize joints and distribute joint loading. Surface electromyography (EMG) has been used to evaluate muscle activation patterns, where EMG signals are used most often to represent neural drive. The EMG signal is highly variable and is dependent upon many factors. To allow comparison of activity between different muscles, across time, and between individuals, the EMG signal should be normalized; section 2.1.1 will summarize literature on different methods of normalization in terms of inter- and intra-subject variability in pathologic and non-pathologic subjects, providing the rationale for the method of normalization used in this study. After normalizing the EMG signals, muscle co-contractions need to be calculated to provide a detailed description on how the muscles are coordinated through the disease progression. Section 2.1.2 will provide an investigation of co-contraction strategies which may contribute to the progression of OA. Knowledge of the internal forces (muscle forces and joint loading) and external moments during movement is important for developing better rehabilitation programs for this population. Section 2.1.3 will cover a detailed description on the different methods used to estimate muscle forces and joint loading.

2.1.1 EMG Normalization

Surface electromyography (EMG) has been used for decades to evaluate neuromuscular responses during a range of activities, in non-pathological subjects (Burden and Bartlett, 1999; Norcrossa et al., 2010) and to investigate alterations due to pathology (Benoit et al., 2003) and rehabilitation. The EMG signal amplitude and frequency components are affected by many factors: electrode placement and

orientation (Jensen et al., 1993), subcutaneous fat thickness, muscle fiber type, and crosstalk from nearby muscles (McGill and Norman, 1986). Normalization of the EMG signal reduces the negative impact of the aforementioned variables and facilitates the comparison of EMG across muscles, between subjects, or between days for the same subject (DeLuca, 1997; Halaki and Gi, 2012; Kamen and Gabriel, 2010 ; Burnfield, 2010).

Different methods of normalization have been introduced and are in current practice, each with advantages and limitations related to inter-subject variability and the clinical interpretation of muscle activity. The peak dynamic method (PDM) was first introduced by Eberhart et al.(Eberhart et al., 1954), which expresses EMG data from a muscle as a ratio of the peak value acquired from the same muscle during gait. For the mean dynamic method (MDM), each data-point of the processed EMG signal is divided by an average of both quiet and active periods during the gait cycle. Both PDM and MDM produce good reliability between sessions and between subjects (Bolgla and Uhl, 2007; Burden et al., 2003; Yang and Winter, 1984), reduce inter-subject variability by 12-72% (Yang and Winter, 1984) in comparison to un-normalized EMG and give a representation of coordinated muscle activity (Benoit et al., 2003) by indicating the period at which the muscle is most active (Sousa and Tavares, 2012). The third method of normalization is the maximum voluntary contraction (MVC) (Dubo et al., 1976). Each data point is divided by the peak value recorded from an isometric maximal voluntary contraction of the same muscle. The reference value used for normalization (the denominator), called the normalization factor (Burden, 2010), should be processed in an identical manner as the task EMG. Although EMGs normalized by MVC have been shown to display poor reliability (Clarys, 2000; DeLuca, 1997; Yang and Winter, 1983), MVC is highly

recommended by many reported studies as it reflects a true increase or decrease in the neural drive, if it is performed under isometric conditions (Burden et al., 2003; DeLuca, 1997; Sousa and Tavares, 2012).

The question “What is the best method of normalization?” initiated an ongoing discussion at the beginning of the eighties. Researchers attempted to answer this question by taking into account that the reference value should be reliable across time and between subjects. It should also be meaningful by reflecting the muscle activity and timing of activation.

In 1983, Yang and Winter (Yang and Winter, 1983) tested the MVC reliability within subjects, within day and between days, using the submaximal isometric contraction methods of normalization. They concluded that using submaximal MVC values are more reliable than using MVCs. In 1984, Yang and Winter (Yang and Winter, 1984) determined the reliability between subjects by adopting different methods of normalization; 50% MVC, isometric moment of force, the peak and the mean dynamic methods. They addressed how the inter-subject variability, subject-specific and situation specific conditions are affected by the method of normalization, demonstrating that normalization to the peak and mean value reduced the inter-subject variability by 12-73%. Further studies have examined different methods of normalization for different muscles and different tasks for non-pathological subjects (Bolgla and Uhl, 2007; Knutson L. M. et al., 1994; Kollmitzer et al., 1999), OA patients (French et al., 2015), and for subjects with ACL injury (Benoit et al., 2003). Burden et al. (Burden et al., 2003) investigated the intra- and the inter-subject variability, which is measured by variance ratio (VR) and coefficient of variation (CV), for the outcome measures for four techniques of normalization; PDM, MDM, MVC, and isokinetic MVC of the periarticular knee

muscles during gait. It was found that the intra-individual variability of the first three methods was identical to the un-normalized EMG and the isokinetic method produced higher intra-individual coefficients. The PDM and MDM gave lower inter-individual coefficients in comparison to isometric and isokinetic MVCs.

In an alternative study, Benoit et al. (Benoit et al., 2003) examined the sensitivity of MDM, PDM, and MVC normalisation methods for detecting neuromuscular alterations in ACL injured patients. They discussed how the method of normalization could affect the clinical interpretation of muscle activity for this patient group. Temporal and activation parameters were examined by adopting the three methods of normalization during walking. MVC and PDM were the most sensitive methods for detecting differences between injured and non-injured limbs, with a reduction in overall medial gastrocnemius activity; and increased peak activity of both rectus femoris and biceps Femoris for MVC and PDM respectively. Norcrossa et al. (Norcrossa et al., 2010) evaluated two methods of normalization: MVC and activity recorded during Single Leg Stance (SLS), and found that both methods have a good reliability. They recommended using the SLS approach for the gluteus maximus, gluteus medius, and adductors, as it provides a clear description of the relative contribution of muscles during this function task. However, it was not recommended for biceps Femoris, Vastus lateralis and rectus Femoris, due to a lack of precision and high intra-subject CVs for these muscle groups.

MVC is highly recommended by many reported studies as it reflects a true increase or decrease in the neural drive, if it is performed under isometric conditions, where muscle length does not change during contraction (Sousa and Tavares, 2012). However, EMGs normalized by MVC displayed poor reliability (Clarys, 2000; DeLuca, 1997; Yang and Winter, 1983). Both PDM and MDM during gait, are more

reliable and they have reduced inter-subject variability, however they only indicate the period at which the muscle is most active (Sousa and Tavares, 2012). On the other hand, Benoit et al. (Benoit et al., 2003) reported that PDM and MDM during dynamic activities give a better representation of coordinated muscle activity compared with isolated MVC.

Patients with compromised function due to disease or injury and in some cases, Non-pathologic (NP) subjects, are unable to maximally contract their muscles during MVC tasks (Yang and Winter, 1984). This limits the use of this approach across whole cohorts in studies involving patients with knee OA. Therefore, the current study examines if there is an alternative method that is comparable to the MVC in reflecting muscle activity for level gait, whilst having good repeatability.

2.1.2 Co-contraction

A frontal plane laxity and joint instability in patients with medial knee OA has been confirmed by (Sharma et al., 1999). Therefore muscles attempt to stabilize the knee joint by altering their activation patterns in a systematic manner, as shown in Figure 2.1, with increasing level of structural OA severity (Rutherford et al., 2013). Rudolph et al (2001) has shown that muscle activation patterns are different in subjects with knee OA which will alter individual muscle contributions to the total support moment. Selective activation of medial muscles has been observed by (Besier et al., 2003) as a means to resist the relatively high valgus moments applied to the knee joint during sidestepping tasks.

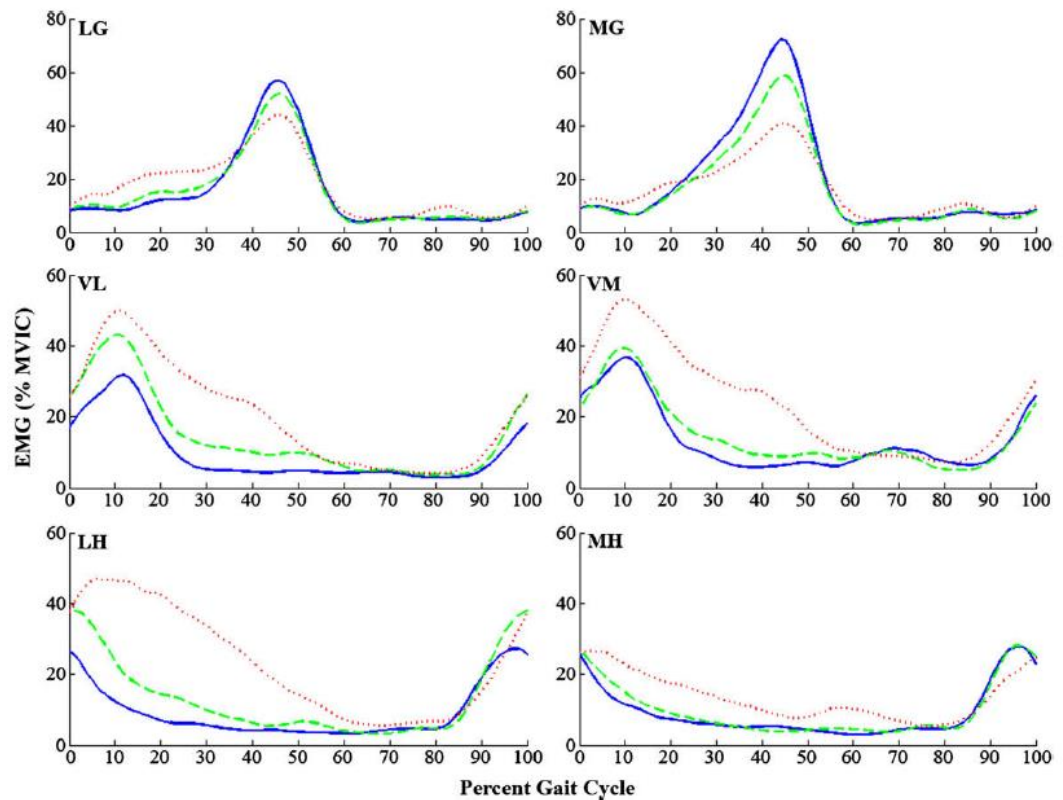


Figure 2. 1: Ensemble averaged electromyogram amplitude normalized to percent MVIC for each muscle included in the analysis. Asymptomatic (solid), Moderate knee OA (dashed) and Severe knee OA (dotted). LG = lateral gastrocnemius, MG= medial gastrocnemius, VL = vastus lateralis, VM = vastus medialis, LH = lateral hamstring and MH= medial hamstring.(Hubley-Kozey et al., 2009)

Overall, biasing of muscle activations, to lateral or medial muscles, plays an important role to influence the disease course (Hodges et al., 2016). Whether increased activation would be a positive or negative adaptation during walking, therefore, would rely on the outcome of the muscle activity. Activation of the lateral muscles (Hubley-Kozey et al., 2006; Heiden et al., 2009) could generate an internal abduction moment and reduce medial joint load. Conversely, bias towards medial muscles could increase medial joint load and promote medial cartilage loss (Lewek et al., 2005a; Hodges et al., 2016). Heiden et al (2009) has shown that laterally directed co-contraction of the knee muscles increases with increasing external knee

adduction moments in those with knee OA, suggesting that lateral muscle activation creates an internal abduction moment that balance the external adduction moment. However (Heiden et al., 2009) has developed their own equation to examine directed co-contraction ratio and determine levels of net muscle activation in knee OA patient.

Muscle co-contraction is defined as simultaneous activity of agonist and antagonist muscles crossing the same joint. When agonist/antagonist muscles work synergistically, the antagonist muscle acts as stabiliser during agonist muscle contraction (Busse et al., 2005). This synergy is important for providing optimal joint stability. Coordination of muscle activity is a determinant of knee loading (Shelburne et al., 2006; Winby et al., 2009). Increased co-contraction of knee muscles has been identified to compensate for joint laxity (Sharma et al., 1999). From a mechanical standpoint, co-contraction can function as a joint-protective mechanism by controlling the joint articulation and equalizing joint pressure distribution. This could potentially be a harmful strategy for long-term integrity, as it causes an increase in the net knee compressive contact load (Schipplein and Andriacchi, 1991; Lloyd and Buchanan, 2001) and may contribute to the progression of OA (Hodges et al., 2016). During gait, the ground reaction force passes medially to the knee joint centre, creating an external knee adduction moment throughout stance that causes medial tibial plateau compression. This moment is counterbalanced by an internal moment caused by muscles and contact forces, Figure 2. 2. 60-80% of total intrinsic knee load, which is primarily produced by muscle forces (Sasaki and Neptune, 2010), is distributed through the medial compartment of the tibiofemoral joint (Andriacchi, 1994). The pattern and magnitude of knee compressive forces are directly affected by the way that individuals activate their muscles.

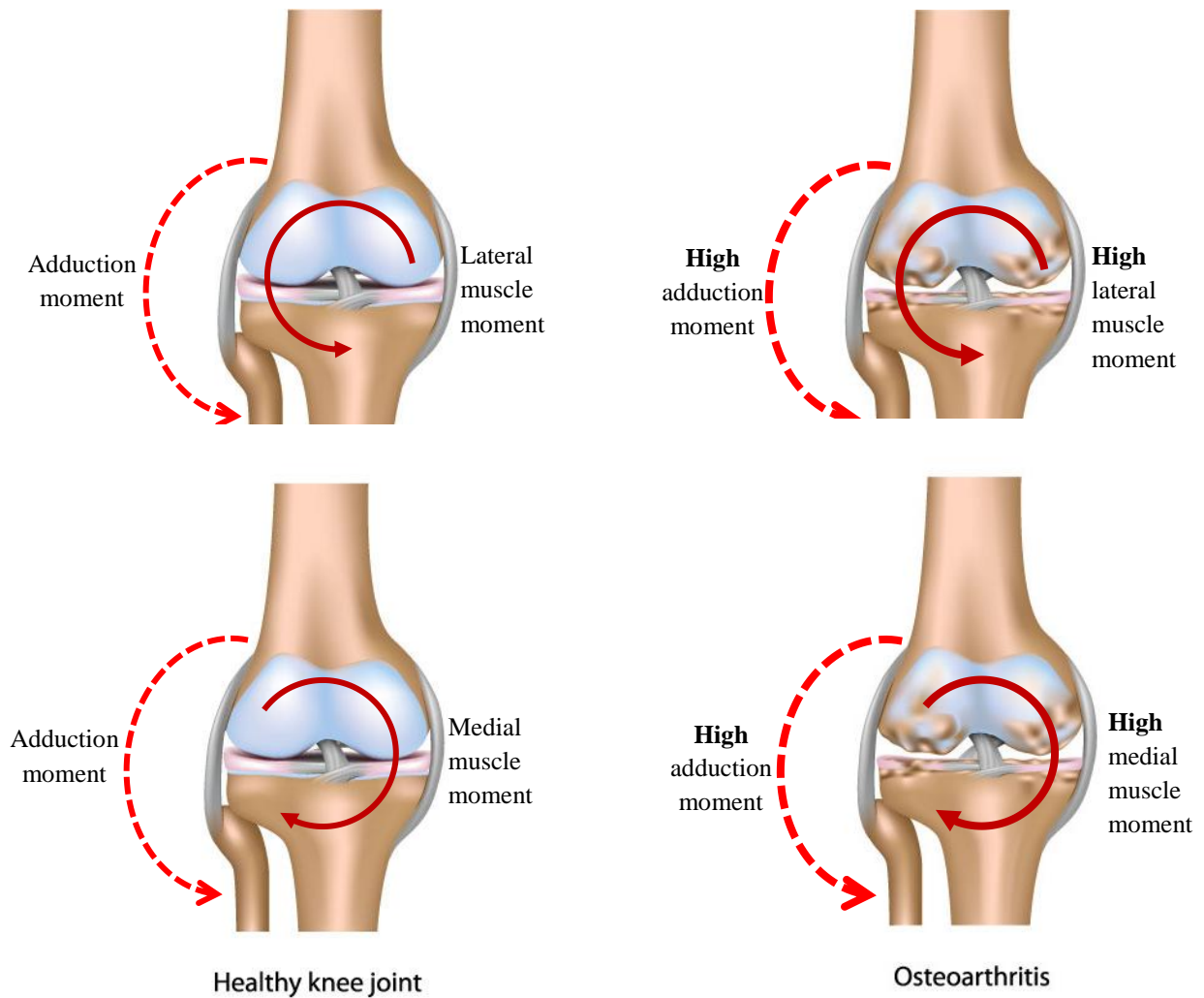


Figure 2. 2: Internal and external knee joint moments. Direction of internal moments (solid dark red line) generated by activation of lateral (top panel) and medial (bottom panel) knee muscle activation. External knee adduction moment is shown as dashed red line. The left panel represent Non-pathologic (NP) knee joint and the right panel represent knee joint with OA (where they have high adduction moment; represented here by a thick dashed red curved arrow).

Literatures have calculated co-contraction index (CCI) through different time intervals: the first group calculated CCI from 100 ms prior to initial contact (accounting for electromechanical delay (Vos et al., 1990)) to the early stance peak knee flexion angle, which represent the end of weight acceptance phase of gait cycle (Rudolph et al., 2001; Worthen-Chaudhari et al., 2014). The second group calculated the relative activation of muscle pairs over the phase of the gait cycle 100 ms prior to

initial contact to the peak knee adduction moment, i.e., the loading phase, (Lewek et al., 2004; Lewek et al., 2006; Ramsey et al., 2007; Hubley-Kozey et al., 2009). The third one calculated as the percentage of stride cycle (Fallah-Yakhdani et al., 2012). And the fourth group calculated CCI at each stage of stance (loading (Rudolph et al., 2007), early stance, mid-stance(Heiden et al., 2009), preparation and weight acceptance phase (Lewek et al., 2005a; Schmitt and Rudolph, 2007; Schmitt and Rudolph, 2008).

On the other hand, Lloyd and Buchanan (2001) studied quadriceps and hamstring muscle co-activations at each moment direction. They found that this muscle group co-contraction contributed to most of the muscular support of the varus and valgus moments. In addition, co-contraction supported 11–14% of the external moment in pure varus and pure valgus, respectively.

This co-contraction strategy manifests particularly among patients with substantial knee extensor weakness (Thoma et al., 2016). Hortobagyi et al. (2005) has found that alteration of muscle activity may interfere with normal load distribution in the knee and facilitate disease progression. They revealed that the source of the increased coactivity in OA patients was heightened hamstring muscle activity and reduced quadriceps activation, while executing activities of daily livings ADLs. Benedetti et al. (1999) state that co-contraction of knee flexors and extensors is a common strategy to reduce shear forces at the knee but increases compressive forces and joint loading. Authors reported a single case study carried out over two years on a patient that underwent total knee replacement. Two years after surgery, they found a prolonged co-contraction of knee agonist-antagonist muscles, which may compromise the durability of the prosthesis.

Temporal and amplitude parameters have been used to evaluate muscular co-contractions (Rosa et al., 2014b). Temporal parameter is defined as the time during which opposing muscles are simultaneously active and is usually classified using terms such as normal, longer or shorter muscle co-contraction duration. Temporal normalization involves defining a reference time period (e.g., whole gait cycle or weight acceptance phase) to enable comparison between individuals, across muscles or between trials. Magnitude of muscle co-activity is defined as the relative magnitude of simultaneous contraction between opposing muscles. Subjects with impaired mobility tend to increase the magnitude of their co-contraction (Rudolph et al., 2007; Schmitt and Rudolph, 2007; Hubley-Kozey et al., 2008) as well as co-contraction for longer, i.e. this is the case for stroke patients (Rosa et al., 2014a) and individuals with knee OA (Rudolph et al., 2001; Childs et al., 2004; Fallah-Yakhdani et al., 2012; Hodges et al., 2016); probably in an attempt to improve walking ability and to feel more stable.

2.1.2.1 Types of Co-contraction:

Generally, two types of muscle co-contraction have been introduced: directed co-contraction and generalised co-contraction. In directed co-contraction (Lloyd and Buchanan, 2001), medial agonists/antagonists muscles are activated to support abduction moments and lateral agonists/antagonists muscles are activated to support adduction moments, whereas in generalised co-contraction all agonists and antagonists of the knee co-activate equally. Directed co-contraction is believed to directly support the external knee adduction moment and reduce the concentration of articular loading in the medial knee compartment by distributing the load laterally. Generalised co-contraction can also have this effect but because of the non-

directionality it is less effective in preventing condylar lift-off, and may unduly increase all articular loading (medial and lateral compartment of the knee joint).

Reviewing the literature, researchers were divided into two groups:

The First group believed in directed co-contraction in patients with moderate and severe OA. A study performed by (Hubley-Kozey et al., 2009) suggested that patients with moderate OA have increased activations of their lateral site muscles, which reflects progression along the continuum from asymptomatic to severe OA. Ramsey et al. (2007) identified neuromuscular control patterns for vastus medialis-medial gastrocnemius (VMMG) muscle pairing between asymptomatic controls and OA subjects scheduled for a high tibial osteotomy. High muscle co-contraction in OA patients (Ramsey et al., 2007) or subjects with articular cartilage defects (Thoma et al., 2016) may be a response to weak quadriceps muscles. After surgery, VMMG muscle co-contractions were reduced, but their values remained higher than that of NP subjects. Therefore Ramsey et al. (2007) suggested that post-surgery, rehabilitation should focus on quadriceps strength and improving joint mobility to improve the long-term function of individuals with medial knee OA. Despite valgus knee realignment and reduced VMMG muscle co-contractions, VMMG muscle co-contraction remained higher than in NP subjects.

Hubley-Kozey et al. (2010) found an increase in muscle activations for both quadriceps and hamstrings and a decrease for gastrocnemius activations for pre-TKR subjects compared to controls. Post-TKR, changes moved toward the control patterns, supporting improved neuromuscular strategies during walking. Changes were consistent with a move towards more typical asymptomatic patterns, although post-TKA patterns remained outside the variance band for the asymptomatic controls

at specific phases, i.e. during mid to late stance for vastus lateralis, vastus medialis, rectus femoris and lateral hamstring muscles.

Schmitt and Rudolph (2008) investigated 20 patients with medial knee OA and found that higher muscle co-contraction was associated with greater self-report knee instability and the authors presumed that both joint instability and the co-contraction strategy may be detrimental to joint integrity and physical function. Rudolph et al. (2007) reported on knee laxity and muscle activation patterns in three age groups of subjects without symptomatic or radiographic knee OA (younger, middle-aged, and older adults) and compared it to OA patients to examine factors that are thought to contribute to the development of knee OA. They found differences in muscle co-contraction values between subjects with OA and young control subjects. Where, OA subjects used greater lateral gastrocnemius muscle activity during loading and greater quadriceps femoris-gastrocnemius muscle co-contraction on the medial and lateral sides compared with the young control subjects. No differences were observed between the subjects with OA and the middle-aged control subjects, suggesting aging is also an important factor to muscle control.

It has shown that greater lateral hamstring activation, relative to medial, during gait is adopted in moderate (Hubley-Kozey et al., 2006) and severe OA patients (Hubley-Kozey et al., 2008). This is possibly in an attempt to counteract the high knee adduction moment in these cohorts and control medial joint articular loading. However, these investigations either did not control for walking speed or age of the comparison group, or did not use a comparison group (Hubley-Kozey et al., 2008). On the other hand, Zeni et al. (2010) controlled gait velocity and found that when walking at a controlled speed of 1.0 m/s, subjects with moderate and severe

knee OA showed significantly higher co-contraction compared to NP group. While at freely chosen walking speeds only the moderate OA group had significantly higher co-contraction values. On the contrary to (Mundermann et al., 2004), who suggested that a reduction in walking speed is a mechanism to reduce joint load. Zeni et al (2010) has found that reduction in self-selected walking speed in subjects with OA does not effectively reduce antagonistic muscle activity to normal levels. Subjects with OA have higher antagonistic muscle activity during walking at control (1.0 m/s), self-selected and fast walking speeds. The fact that significant differences were seen when the effect of speed was removed suggests that coordination strategies resulting in higher CCI values are a result of the disease process and not due to differences in walking speed. One of the limitations in this study is that Zeni and his colleague has chosen vastus lateralis and semimembranosus as representative muscles of the knee extensors and flexors, respectively, regardless if it is medial or lateral muscles. This point is criticized because authors ignore the effect of muscle site. Childs et al. (2004) also selected this muscle pairing to calculate co-contraction index, i.e. vastus lateralis, medial hamstrings, tibialis anterior and medial gastrocnemius, and demonstrated that individuals with knee OA may utilize increased co-activation patterns and an increased duration of muscle activity during stance as well. In control subjects, a reduced walking velocity is linked to reduction in the amplitudes of muscle activation (Yang and Winter, 1985). However, for those with knee OA, despite reduced walking velocities, muscle activation amplitudes of the quadriceps and hamstrings were higher and more prolonged than faster walking controls (Hubley-Kozey et al., 2009; Rutherford et al., 2010).

The Second group believed there is a general co-activity for subjects with late stage of OA (Lewek et al., 2004; Hubley-Kozey et al., 2009; Fallah-Yakhdani et al.,

2012). Lewek et al. (2004) found a difference in VMMG between asymptomatic controls and severe OA patients. They reported that the greater VMMG co-contraction by the severe OA group may be a mechanism to increase stiffness in response to pain or laxity associated with decreased medial knee joint spacing and this strategy may increase loading on the medial side of the knee. This finding suggests that patients with severe OA use general co-contraction. It is consistent with this finding, (Hubley-Kozey et al., 2009; Fallah-Yakhdani et al., 2012) suggesting that late stages of knee OA induces more “general co-activity”.

After all, another key point that should be taken into consideration when using EMGs to calculate muscle co-contraction is normalization of the EMG. Ervilha et al (2012) tested the reliability of the estimated muscle co-activity by using EMG, and authors have found that normalization of the EMG is a crucial step to get reliable outcome of co-contraction index.

2.1.3 Knee contact force

Knee contact force during walking far exceeds body weight due to the propagation of the ground reaction force (GRF) up through the body, as the limb contacts the ground, and due to compression through muscle action. Theoretical modelling of knee joint loading including muscle force contributions has estimated that muscle forces during gait can contribute up to 60% of the total joint load (Taylor et al., 2004). Accordingly, assessment of muscle forces and joint contact loading is essential to fully understand mechanisms underlying incidence and progression of OA.

However, determination of tibio-femoral contact forces has been a challenging issue in biomechanics. Two different approaches have already been used to determine joint contact loads:

1. Measuring the contact loads in the knee joint by using a “**telemetric instrumented prosthesis**”. This generally consists of a tibial tray with a polyethylene articular surface and imbedded transducer strain gauges at the four corners, providing valuable in vivo joint contact forces obtained from instrumented implants (Fregly et al., 2012). Multiple studies used direct measurements of joint contact forces obtained from instrumented implants, eg. D’Lima et al. group (D’Lima et al., 2005; D’Lima et al., 2006; D’Lima et al., 2011; D’Lima et al., 2012), (Heinlein et al., 2009), (Kutzner et al., 2010), and (Bergmann et al., 2014). These studies have shown that peak knee contact force (KCF) ranges from 1.6 to 3.5 times body weight (BW). While instrumented prosthesis provide a detailed representation of joint loading, there are limitations that should be considered such as limited subject populations, data is illustrative just for particular post-operative situations, and inability to examine the contributions of muscle to joint loading. Therefore, another approach has been developed.
2. Calculating the contact loads in the knee joint by using a “**computational musculoskeletal model**” to estimate joint contact loads. This main practicable technique provides an important way to perform muscle and joint loading analyses. Researchers have adopted different approaches to estimating muscle forces and joint loading. “Static optimization (SO) and computed muscle control (CMC) (Thelen and Anderson, 2006)

approaches” track the desired kinematics to estimate muscle forces while “EMG-driven approach” tracks the kinetic input data as well to get better estimation of muscle forces. However, Richards et al. (2009) have shown that the CMC method estimates higher muscle forces than static optimization. This is due to the CMC method matching kinematics over the whole gait cycle, while static optimization produced joint moments at each time step, irrespective of the previous or forthcoming time step. Another model that was used to estimate muscle forces and joint loading is DeVita model, was created by DeVita and Hortobagyi (2001). The model simply consists of three muscles (quadriceps, hamstring, and gastrocnemius) inclined at angles (ϕ , β , and α) to the tibia, respectively; as shown in Figure 2.3.

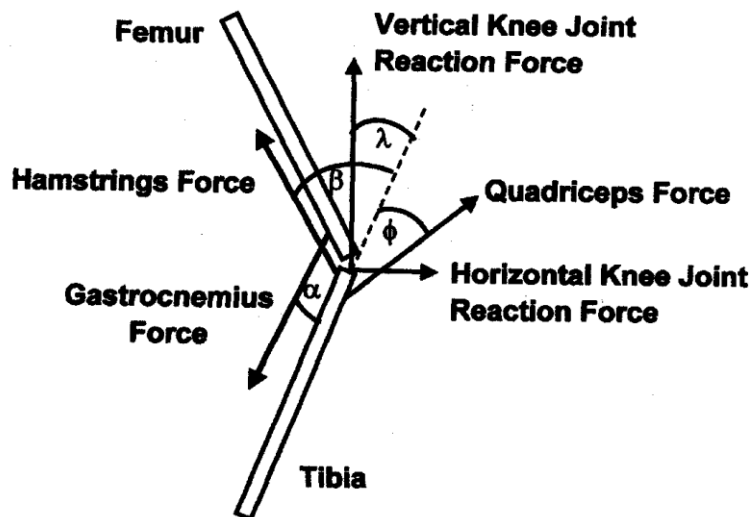


Figure 2. 3: Schematic representation of the DeVita model (DeVita and Hortobagyi, 2001).

In order to calculate the gastrocnemius force, it was assumed that all plantar/flexor torque originated from the gastrocnemius-soleus (GS) and there was no co-contraction of anterior muscles. The hamstring muscle

force was calculated by assuming that the force vector of the muscle is parallel with the femur and at an angle β to the tibia with no co-contraction of the hip flexors occurring during the initial part of stance. Then these forces were applied to the knee at angles α and β to the tibia to calculate their flexor torque. The quadriceps muscle force was calculated from the net torque and this flexor torque. The final step in this model was calculating the knee joint forces. All forces (including muscle forces and joint reaction) acting vertically were summed for the knee joint compressive force, while those acting horizontally were summed to find the knee joint shear force in the antero-posterior direction. A detailed description of model is well presented in (Wallace J., 2014).

An advantage to the musculoskeletal modelling is that large cohorts can be assessed, however there are obviously limits associated with simulations used to estimate muscle forces. Software programs have been developed to ease the process of simulation, example of software programme commonly used in research: SIMM, OpenSim, AnyBody, and CEINMS.

In the knee joint, the EMG-driven model was first used by White and Winter (White and Winter, 1993), where they used EMG based activations to estimate muscle forces. They validated the model by comparing the flexion/extension moment predicted from the model to that calculated using the inverse dynamics approach. They addressed the sources of error in their model, after identifying that the linear EMG-to-force relationship under isometric conditions may not be appropriate for all muscles modeled and needed to be reevaluated for movement situations involving different tasks and control strategies. It was also identified that the contribution of

the passive forces may improve the fit between the moment curves. Following from this, many studies have utilized this approach to estimate in vivo tissue loading.

In 2003 Lloyd and Besier (2003) presented their famous paper, where they used EMG based activations to calculate muscle forces and predict knee moments across a varied range of dynamic contractile conditions in a model that accounted for many factors that affect the EMG-force relationship. The model has an anatomical and physiological basis and is calibrated to an individual using appropriate physiological parameters across a selection of varied tasks, including passive and active flexion/extension in an isokinetic dynamometer, running, and cutting manoeuvres. They used a non-linear least squares algorithm to alter model parameters to predict flexion/extension moments; i.e., the closest estimation of joint moments compared to that measured using an inverse dynamics approach.

A year after, in 2004, Buchanan et al. (2004) used the same approach to estimate muscle forces. The model compares joint moments calculated from inverse dynamics to net flexion/extension muscle moments calculated from an EMG driven forward dynamics model that uses mathematical optimization to minimize the difference between the two calculated moments. The optimization process involves variables that characterize the EMG-force relationship based on the Hill-type muscle model. Basier et al. (2009) have adopted the same approach to estimate periarticular knee muscle forces during walking and running for patients with patello-femoral pain and compared these to pain-free controls. They found that the patello-femoral pain group had greater co-contraction of quadriceps and hamstrings and greater normalized muscle forces during walking as compared to controls, even though the net knee moment was similar between groups. Muscle forces during running were

similar between groups, but the net knee extension moment was less in the patello-femoral pain group compared to controls.

Kim et al. (2009) predicted contact forces at the tibiofemoral joint ranging from 1.9 to 3.5 BW and validated the results with instrumented prosthetics data. KCFs during walking at self-selected speeds averaged 3.9 BW for NP females and 3.4 BW for NP males (Kuster et al., 1997), and exceeded 4.0 BW when using EMG-driven models (Winby et al., 2009). Taylor et al. (2004) used a musculoskeletal model developed by (Heller et al., 2001) to calculate KCF during walking at self-selected speeds and showed forces averaging 3.1 BW.

There are three proposed explanations for the diversity of the predicted contact force among researchers: i) researchers adopted different musculoskeletal models, i.e. varied in their joints's degrees of freedom and number of muscles involved; no model contains all the muscles in the lower limb. Therefore, this requires some muscles in the model to be a combination of several anatomical muscles. ii) the accuracy of muscle parameters (maximum isometric force, muscle fiber length, tendon slag length, and pennation angle). The values for these have a significant influence on the predicted muscle force and joint loading. iii) different optimization methods resulted in a different estimation of muscle forces. Subject specific muscle activation patterns recorded using EMG can provide a higher level of accuracy when estimating muscle forces. However, the EMG-force relationship is time varying, non-linear, and influenced by many factors including the type of contraction, force length relationship, force-velocity relationship, pennation angles, and electromechanical delay. Herzog et al. (2003) indicated that muscle forces were the primary determinants of joint contact forces and that correctly predicted muscle

forces should result in sensible estimates of joint contact loads. However, to date, accurate measurement and prediction of individual muscle forces are still a major challenge.

Several studies have reported differences in KCF between NP subjects and patients with the OA. Henriksen et al. (2006) have found there is a significant difference for the KCF between OA and NP subjects. The average peak KCF calculated during early single limb support was 1.8 BW for OA subjects and 2.4 BW for NP, and 1.6 and 1.9 BW during late single limb support for OA and NP subjects, respectively. However, they found that pain relief in painful mild medial knee OA resulted in increased joint loads during the late single support phase of walking. Richards and Higginson (2010) confirm that there is an inverse relationship between joint loading and OA severity and report that the pattern of the KCF varies between groups. After an initial peak, subjects with severe OA continually unloaded the joint, whereas NP and moderate OA subjects reloaded the knee during late stance. Kumar et al. (2012) estimated different loading patterns during walking in an individual with medial knee OA and a control subject by using an EMG-driven forward dynamics model. The model showed that both subjects have a double-peak pattern of joint loading but the OA subject had greater medial loads, nearly 3 BWs which is about 50% greater than that of the control subject, and lower lateral loads. 75 to 80% of the total load was borne on the medial compartment in the control subject, compared to 90 to 95% in the OA subject. Bergmann et al. (2014) reports that up to 85% of the peak force were transferred on the medial side, depending on the valgus angle of the knee. The second interesting fact that Kumar and his colleague verified in their work, and confirmed in another literature, (Kumar et al., 2013), is the negative loading on the lateral compartment of the knee joint during the mid-stance phase in subject with

OA which implies that the joint surfaces were not in contact and the soft tissues on the lateral side were under tension. The model adopted by Kumar et al. (2013) showed that both flexion and adduction moments were positively associated with an increase in medial loading in the first half of stance phase. They explained that lateral compartment unloading, lateral compartment lift-off, occurs in people with medial knee OA as their muscles are unable to counter the higher knee adduction moment. Finally, they noted that the unloading occurred during mid to late stance, synchronized with the second peak of KAM, and not during the early weight acceptance phase where the first peak KAM occurs.

Contrary to this belief, the Winby et al. (2009) model predicted that there was no lateral unloading during stance phase in NP people owing to the contribution of the muscles, particularly the quadriceps and gastrocnemii and to a lesser extent the hamstring and tensor fascia lata (TFL), to stabilize the joint. They found that as the majority of load is transferred through the medial compartment of the knee joint during stance, the periarticular muscles react to oppose the lateral compartment unloading, which was stimulated by the knee adduction moment.

On the other hand, Steele et al. (2012) has demonstrated that walking in a moderate or severe crouch gait increases the compressive tibiofemoral force, which may contribute to knee pain and cartilage degeneration. Where as, Schlotman et al (2016) investigated 10 patients with medial knee OA and found that when using toe-in gait, all subjects uniformly decreased the relative medial knee contact load and adopting different muscle force modifications, the results being retained in all subjects after one month. This study showed the effectiveness of toe-in gait to improve overall knee function for individuals with knee OA. Likewise, Manal and Buchanan (2013)

studied the effects of using different gait patterns on joint loading. They implemented an EMG driven model to predict knee joint contact forces for two distinctly different gait patterns, normal walking and medial thrust gait. Their model correctly predicted that the medial compartment contact force for the medial thrust gait increased despite a decrease in the adduction moment. Although the model captured the general shape and timing of the contact force profiles with good predictions of medial contact for the medial thrust gait and lateral contact for normal walking, it underestimated the medial force during normal walking, 0.55 B.W, as well as overestimated the lateral force during medial thrust gait. Manal and Buchanan addressed the sources of error in their model, which labeled it as a blinded model, and modified it into a revised model. The modifications included using the accurate measure of tibial plateau and separate tunings for normal and medial thrust gait. The initial estimate of the tibial plateau width was too large and this had a direct effect on the location of the medial and lateral contact points. Under this circumstance, the muscle moment arms about the medial and lateral contact points were too large. The actual implant width of 74mm was obtained from the implant geometry and this was approximately 50% smaller than the width that was estimated from the motion capture data, where the estimation of the plateau width was based on markers positioned over the femoral condyles. The width of the distal femur is approximately 5%–10% greater than the width of the tibial plateau and this also contributed to using a value that was too large. As a result, the revised model estimated medial contact force during normal gait more closely to that measured by implant. In addition, the difference between peak lateral contact force for the medial thrust gait dropped from 0.59 to 0.13 B.W.

While information regarding knee joint loading is important, understanding the ways in which individual muscles contribute to the loading that occurs during

common daily activities is essential for early rehabilitation from surgical interventions in order to know the magnitudes of forces that the reconstructed joint must with-stand. Lloyd and Buchanan (2001) investigated the activation strategies used by individuals to support varus-valgus moments and the muscle loading patterns that result from these activation schemes during highly controlled isometric tasks. They found that the co-contraction of the hamstrings and quadriceps provided a positive support of valgus and varus loads at the knee. Whereas, Sartorius muscle appears to be activated to provide positive support of valgus loads and negative support of varus load at the knee. On the other hand, Wilson et al. (2012) associated EMG patterns of the knee periarticular musculature with post-operative tibial implant migration. They demonstrated that a prolonged muscle activation pattern for both the lateral gastrocnemius and vastus medialis muscles, during the stance phase, was related to increased posterior migration of the tibial component. Sartori et al. (2012) developed a comprehensive EMG-driven model of the lower extremity that introduced EMG signals from 16 muscle groups to 34 musculo-tendon units (MTUs) to predict muscle forces. Furthermore, they developed a calibration procedure that identifies a set of subject-specific parameters to address the physiological behaviour of the 34 MTUs. According to the experimental results, they found that multi-DOF model solutions give a better illustration of muscle behaviour than that of single-DOF models. Adouni and Shirazi-Adl (2014) developed a musculoskeletal model of the lower extremity to estimate muscle forces and knee joint stresses-strains during the stance phase of the walking cycle in a subject with knee OA and NP, the model was driven by gait data. They explored that muscle forces in patients with OA dropped through stance phase except for during mid-stance.

To date no studies have investigated how the periarticular knee muscles are changing their coordination in pre-HTO and pre-TKR patients, in line with changing the patterns and the magnitudes of the joint loading and muscle forces for these patient populations. It is not clear if the pattern of the joint loading are changed through the progression of OA and how this can be related to the changes that might be seen in joint kinematics, kinetics, and muscle forces. Accurate estimates of muscle forces and muscle co-contractions is based on the appropriate method of normalization used to normalized the EMGs. Traditionally neuromuscular studies have failed to provide a strong consensus in the literature for testing an appropriate method of normalization for OA patients. Therefore, the purpose of the present study was to examine different methods of normalization and used the method that is appropriate for OA patients to calculate muscle co-contraction and estimate muscle forces. Complete understanding of loading at the knee is of great interest, therefore, this study aims to provide information regarding the patterns and magnitude of the knee loading and the corresponding muscle forces.

Chapter 3

Can Activities of Daily Living Contribute to EMG Normalization for Gait Analysis?

3.1 Introduction

Surface electromyography (EMG) has been used for decades to evaluate neuromuscular responses during a range of activities, in Non-pathological subjects (Burden and Bartlett, 1999; Norcrossa et al., 2010) and to investigate alterations due to pathology (Benoit et al., 2003) and rehabilitation. The EMG signal amplitude and frequency components are affected by many factors: electrode placement and orientation (Jensen et al., 1993), subcutaneous fat thickness, muscle fiber type, and crosstalk from nearby muscles (McGill and Norman, 1986). Normalization of the EMG signal reduces the negative impact of the aforementioned variables and facilitates the comparison of EMG across muscles, between subjects, or between days for the same subject (DeLuca, 1997; Halaki and Gi, 2012; Kamen and Gabriel, 2010 ; Burnfield, 2010).

Different methods of normalization have been introduced and are in current practice, each with advantages and limitations related to inter-subject variability and the clinical interpretation of muscle activity. Maximum voluntary contraction (MVC) is considered as a gold standard for normalizing EMG data and it is highly recommended by many reported studies as it reflects a true increase or decrease in the neural drive, if it is performed under isometric conditions (Burden et al., 2003; DeLuca, 1997; Sousa and Tavares, 2012). For gait analysis studies, it is important to understand neuromuscular activation and how it contributes to external forces to stabilize joints and distribute joint loading. The ideal strategy to understand this scenario is to explore muscle activation patterns during activities of daily living (ADLs). During ADLs, subjects adopt individual strategies to muscle coordination. Two parameters should be taken into consideration when selecting the best method

of normalization: the reliability as well as the ability to mirror the changes seen in muscle activity.

Patients with compromised function due to disease or injury and in some cases, Non-pathological subjects (NP), are unable to maximally contract their muscles during MVC tasks (Yang and Winter, 1984). Consequently, the objective of this research is to examine if there is an alternative method that is comparable to the MVC in reflecting muscle activity for level gait, whilst having good repeatability. It is hypothesized that ADLs is a useful measure in EMG normalization. However, what is important is that these values are repeatable and give a representative measure of muscle activity during different ranges of motion. The work presented in this chapter is based on (Ghazwan et al., 2017).

3.2 Materials and methods

3.2.1 Experimental data

Following development of the protocol, three-dimensional kinematic and kinetic data of ten Non-pathological subjects (NP) were used; five collected by the investigator and five previously collected. The investigator have undergone training and assessment before being permitted to collect data. Further, the data collected by the investigator were observed by a senior who collected the previous five subjects. The mean and standard deviation of age, mass and height were 30.6(3.8) years, 78.04 (10.95) kg, and 1.74 (0.04) m respectively.

All subjects gave their informed written consent prior to data collection. The consent and data protocols were approved by the Research Ethics Committee for Wales and Cardiff and Vale University Health Board.

Experimental gait data was collected in the motion analysis laboratory at Cardiff School of Engineering. Gait analysis was performed using nine 120Hz infra-red motion capture units (Qualisys, Sweden). Qualisys Track Manager (QTM, Qualisys, Sweden) was used to capture full body motion using reflective markers placed on the trunk, pelvis, and both the upper and lower limbs (modified Cleveland clinic marker set)(Reinbolt et al., 2005). Four floor-embedded force platforms (Bertec Corporation) were used to capture the ground reaction force vectors with a sample rate of 1080 Hz.

Muscle electromyographic (EMG) data were collected bilaterally using Trigno™ Wireless EMG System (Delsys, Inc.) with a sampling frequency 1080Hz, for seven muscles: Rectus Femoris, Vastus Lateralis, Vastus Medialis, Biceps Femoris, Semitendinosus, Gastrocnemius Lateralis, and Gastrocnemius Medialis. The electrodes were placed longitudinally over the muscle bellies, as shown in Figure 3.1, after standard preparation of the skin, according to SENIAM recommendations (Hermens et al., 2000), involving shaving, exfoliation, cleaning of the skin and finally electrode gel was used to reduce the electrode–skin impedance (Doorenbosch and Harlaar, 2004).

MVC for all muscles were measured first. Three tests were performed to maximally activate knee muscles:

- Isometric MVC for Quadriceps: Each subject sat on a chair with their hips

flexed to 90° and their knee fully extended, they were asked to resist a force (from the investigator) being applied downwards on the extended leg at the level of the ankle joint. Testing was shown that doing MVC with knee fully extended resulted in higher quadriceps activity than when the knee is flexed.

- Isometric MVC for Hamstring: In a standing position, with one knee flexed to 90°, the subject was asked to resist a force applied (by the investigator) downwards on the flexed leg at the level of the ankle joint.
- Isometric MVC for Gastrocnemii: subjects were instructed to stand on toe-tips and maximally contract their shank muscles as much as possible.

Visual feedback of the EMG signal and strong verbal encouragement (Campenella et al., 2000) was provided for all tasks.

Then individuals were asked to perform different ADLs (i.e., walking at their comfortable speed, walking up and down stairs and finally sitting-to-standing). Meanwhile, information regarding muscle EMG, ground reaction force and three dimensional movements were collected using the synchronized movement analysis system. 6 trials of level gait, 6 trials of ascending/descending a four step staircase (Whatling et al., 2010), and 2 trials of sitting/standing were recorded for each subject.

The stance phase was determined by the ground reaction force measured by the force plate, at heel strike to toe-off.

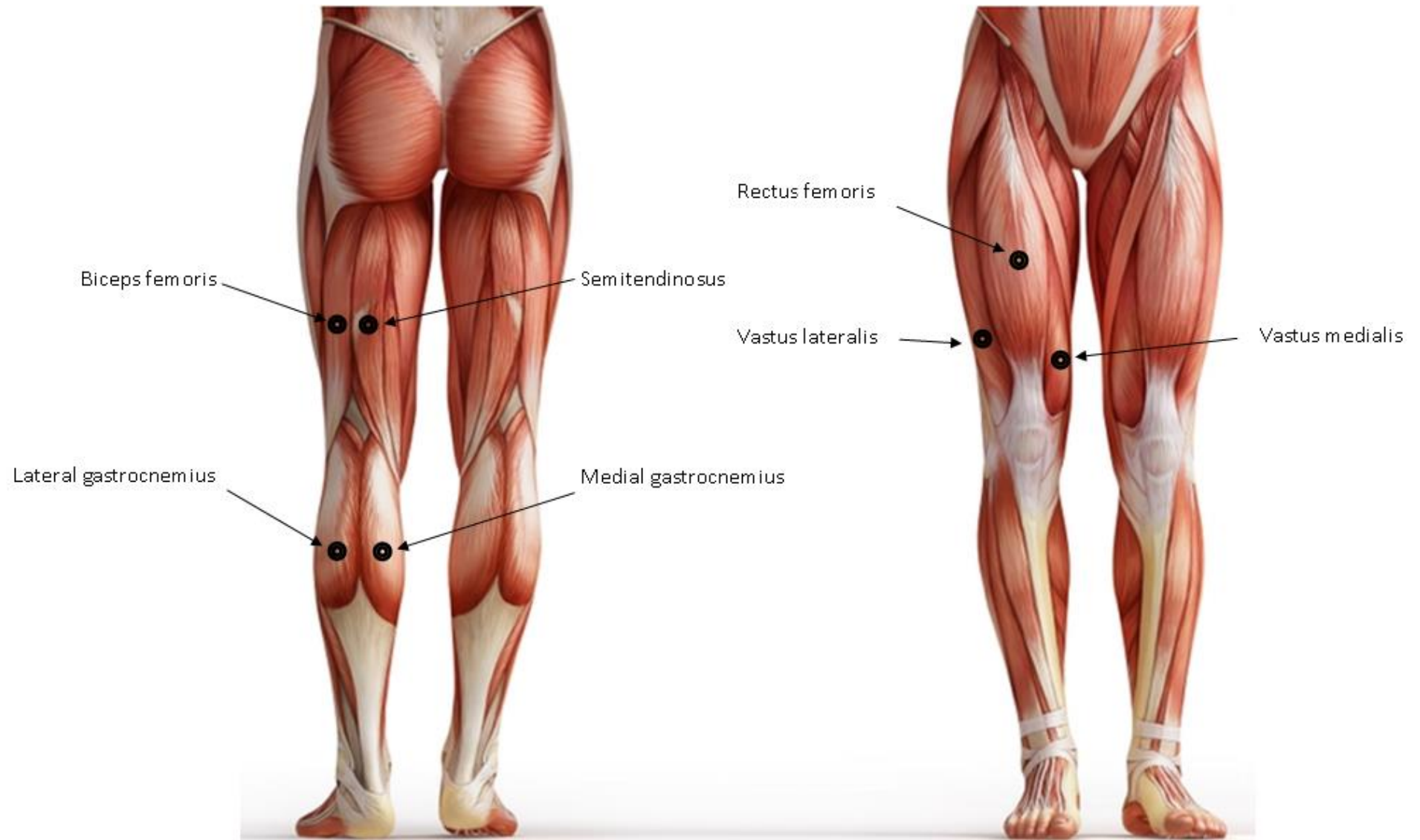


Figure 3. 1: EMG electrode placement.

3.2.2 Data Processing

EMG data, through stance phase, were analysed in custom Matlab (version R2013a, Mathworks Inc.) script. The raw EMG signals were band-pass filtered, to remove the movement artefacts, by a Butterworth 4th order filter at (10_450) Hz, rectified and finally low-pass-filtered with a 4th order Butterworth filter at 6 Hz to create a linear envelope for each muscle. Then linear envelopes for each muscle were normalized by using:

1. MVC, each data point during stance phase was divided by the peak value recorded from an isometric maximal voluntary contraction of the same muscle.

$$\text{Normalized EMG (unitless)} = \frac{\text{EMG}_i \text{ (mv)}}{\text{EMG}_{\text{Peak value of MVC}} \text{ (mv)}}$$

Where, EMG_i is the processed EMG value at the i th interval of the stance and $\text{EMG}_{\text{Peak value of MVC}}$ is the peak value of the processed EMG recorded through MVC.

2. PDM, each data point during stance phase was divided by the peak value for the muscle among six gait trials.

$$\text{Normalized EMG (unitless)} = \frac{\text{EMG}_i \text{ (mv)}}{\text{EMG}_{\text{Peak value through walking}} \text{ (mv)}}$$

Where, EMG_i is the processed EMG value at the i th interval of the stance and $\text{EMG}_{\text{Peak value through walking}}$ is the peak value of the processed EMG among six gait trials.

3. *PDM, each data point during stance phase was divided by the peak value for the muscle measured among six trials of level gait, six trials of ascending/descending stairs, and two trials of sitting/standing.

$$\text{Normalized EMG (unitless)} = \frac{\text{EMG}_i \text{ (mv)}}{\text{EMG}_{\text{Peak value through ADL}} \text{ (mv)}}$$

Where, EMG_i is the processed EMG value at the i th interval of the stance and $\text{EMG}_{\text{Peak value through ADL}}$ is the peak value of the processed EMG through ADLs.

4. **PDM, each point during stance phase was divided by the peak value for the muscle acquired from all trials of gait level, ascending/descending stairs, sitting/standing, and MVC.

$$\text{Normalized EMG (unitless)} = \frac{\text{EMG}_i \text{ (mv)}}{\text{EMG}_{\text{Peak value of MVC and ADL}} \text{ (mv)}}$$

Where, EMG_i is the processed EMG value at the i th interval of the stance and $\text{EMG}_{\text{Peak value of MVC and ADL}}$ is the peak value of the processed EMG through ADLs and MVC.

5. MDM, each data point during stance phase was divided by the mean value for the muscle from the six gait trials.

$$\text{Normalized EMG (unitless)} = \frac{\text{EMG}_i \text{ (mv)}}{\text{EMG}_{\text{Mean value through walking}} \text{ (mv)}}$$

Where, EMG_i is the processed EMG value at the i th interval of the stance and $\text{EMG}_{\text{Mean value through walking}}$ is the mean value of the processed EMG among six gait trials.

The EMG data were then normalized to 100 data points through the stance phase.

In order to determine which method of normalization provided the most repeatable data set, the variance ratio (VR) and coefficient of variation (CV) were calculated. Root Mean Square Difference (RMSD), Absolute Difference (ABSD), and Percentage Difference (%D) were measured to determine which normalization method more closely matched normalization by MVC.

An average of six trials for each muscle and for each participant were created to represent the mean muscle activity through stance.

3.2.3 Assessment of inter-individual variability

The Variance Ratio (VR)

Used to assess the inter-individual variability (i.e. reliability) of the non-normalized and normalized gait EMGs for each muscle (Hershler and Milner, 1978). Where, low levels of VR indicate low level of variability; i.e. more reliable.

$$VR = \frac{\sum_{i=1}^k \sum_{j=1}^n (X_{ij} - \bar{X}_i)^2 / k(n-1)}{\sum_{i=1}^k \sum_{j=1}^n (X_{ij} - \bar{X})^2 / (kn-1)} \quad (3.1)$$

where, k is the number of time intervals over the gait cycle, n is the number of trials (i.e. 6) for intra-individual variability, or the number of participants (i.e. 10) for inter-individual variability, X_{ij} is the EMG value at the ith interval for the jth trial (intra-individual variability) or participant (inter-individual variability), and \bar{X}_i is the mean of the EMG values at the ith time interval over j gait cycles (intra-individual variability) or participants (inter-individual variability), \bar{X} is the mean.

$$\bar{X} = \frac{1}{k} \sum_{i=1}^k \bar{X}_i \quad (3.2)$$

Coefficient of Variation (CV)

Useful for comparing the degree of variation from one data series to another, even if the means are drastically different from each other. The lower value of the coefficient of variation, the more precise.

$$CV = \frac{\sqrt{\frac{1}{k} \sum_{i=1}^k \sigma_i^2}}{\frac{1}{k} \sum_{i=1}^k |\bar{X}_i|} \quad (3.3)$$

where, k is the number of time intervals over the gait cycle, \bar{X}_i is the mean of the EMG values at the ith interval calculated over six trials for intra-individual variability or 10 participants for inter-individual variability, σ_i is the standard deviation of the EMG values about \bar{X}_i calculated over six trials for intra-individual variability or 10 participants for inter-individual variability.

The Root Mean Square Difference (RMSD), the Absolute Difference (ABSD), and the Percentage Difference (%D)

Useful for comparing the differences between the MVC and the other methods of normalization. A mean and SD was calculated for each of the three differences by including values from all gait cycles and for all participants.

$$RMSD = \sqrt{\frac{1}{k} \sum_{i=1}^k (X_{ia} - X_{ib})^2} \quad (3.4)$$

$$ABSD = \frac{1}{k} \sum_{i=1}^k |X_{ia} - X_{ib}| \quad (3.5)$$

$$\%D = \frac{1}{k} \sum_{i=1}^k \left(\frac{|X_{ia} - X_{ib}|}{X_{ia}} \right) 100 \quad (3.6)$$

where, k is the number of time intervals over the gait cycle, X_{ia} is the EMG value at the i th interval normalized using the isometric MVC method, and X_{ib} is the EMG value at the i th interval normalized using the other method of normalization.

3.3 Statistical Analysis

Muscle activations during each stance phase of gait were normalized to percentage stance phase and then the mean and standard deviation calculated for each subject. 95% confidence intervals were calculated to determine if statistically significant differences existed between the un-normalized and normalized EMGs. A Kruskal-Wallis test of nonparametric data was performed for each muscle in each subject using SPSS (version 20, Chicago, IL). Pairwise comparisons using the Dunn-Bonferroni approach are automatically produced for any dependent variables for which the Kruskal-Wallis test is significant. Group means and standard deviations were calculated among subjects and figures were created using Matlab 3013a.

3.4 Results

To enable comparisons with previous literature, EMG patterns for the quadriceps, hamstrings, and gastrocnemii were plotted through stance phase (Figure 3.3). In agreement with (Winby et al., 2009) and as shown in Figure 3.2, the hamstrings were predominantly activated in early stance followed by the quadriceps, to stabilize the knee joint during the load bearing period, whereas the gastrocnemii contributed to the tibiofemoral force in late stance.

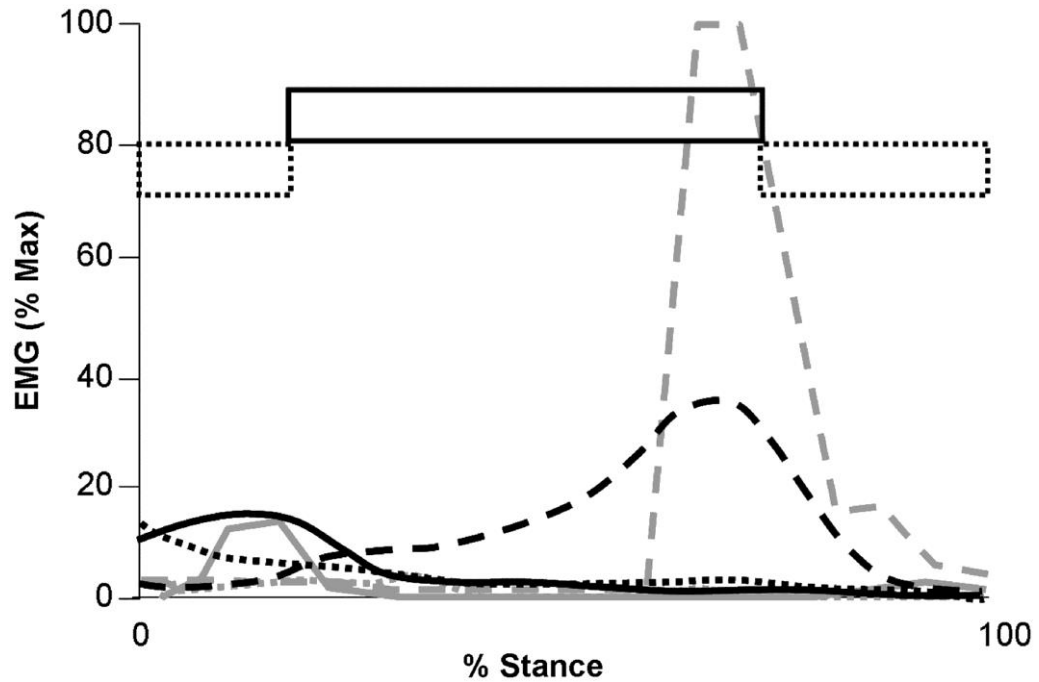


Figure 3. 2: Muscle EMG patterns for the quadriceps muscles (solid line), hamstrings (short dashed line), and gastrocnemii (long dashed line) (black lines) (Winby et al., 2009), the activation predictions of (Shelburne et al., 2006) (grey lines) and (Hurwitz et al., 1998) (dashed boxes—flexors; solid box—quadriceps).

Data across participants were consistent and one data set was illustrated as a representative example; i.e. Figure 3.3(A, B, C, D, E, and F) shows the un-normalized EMG signals and those normalized by MDM, PDM, MVC, *PDM and **PDM, respectively for the individual during the stance phase (mean of 6 gait trials). While there were similarities between the activation patterns for the methods of normalization, in which hamstring is highly activated in early stance followed by quadriceps and finally by gastrocnemius, there were also profound differences in terms of relative amplitude. Results showed that the amplitude of the normalized muscle were significantly greater ($p < 0.05$) than the un-normalized for all methods of normalization.

During ADLs, subjects adopt different strategies to muscle coordination. There is no clear trend regarding which activity gives the peak value for each muscle across subjects, with the exception for vastii during ascending stairs; where the vastus lateralis reached maximum values in 7 from 10 subjects and Vastus medialis reached maximum values in 6 from 10 subjects. The other muscles reached their maximum values through ascending stairs, in just 4 from 10 subjects.

Figure 3. 4 (A, B, C, D, E, and F) shows the un-normalized EMG signals and those normalized by MDM, PDM, MVC, *PDM and **PDM, respectively for 10 NP subjects during stance phase.

Figure 3. 4 -D illustrates a high standard deviation for the quads when using the MVC method of normalization, which demonstrates the potential negative impact of this method.

Figure 3. 5 presents the outputs of the different methods of normalization i.e., MDM, MVC, PDM, *PDM, and **PDM, to illustrate which method is closest to MVC.

For comparison, the different methods of normalization are expressed as a ratio of the MVC, i.e (MDM,PDM,MVC,*PDM,**PDM)are divided by the peak value of MVC.

Table 3.2 and Table 3.3 summarize the reliability indices across trials and subjects; i.e., CV and VR, respectively. No significant differences were found for the inter-individual variability, VR and CV, of the un-normalized and normalized EMG. Table 3. 4 and Table 3. 5 summarize descriptive statistics for RMSD, ABSD, and %D measured between the MVC and the other methods of normalization for knee flexor and knee extensor muscles, respectively.

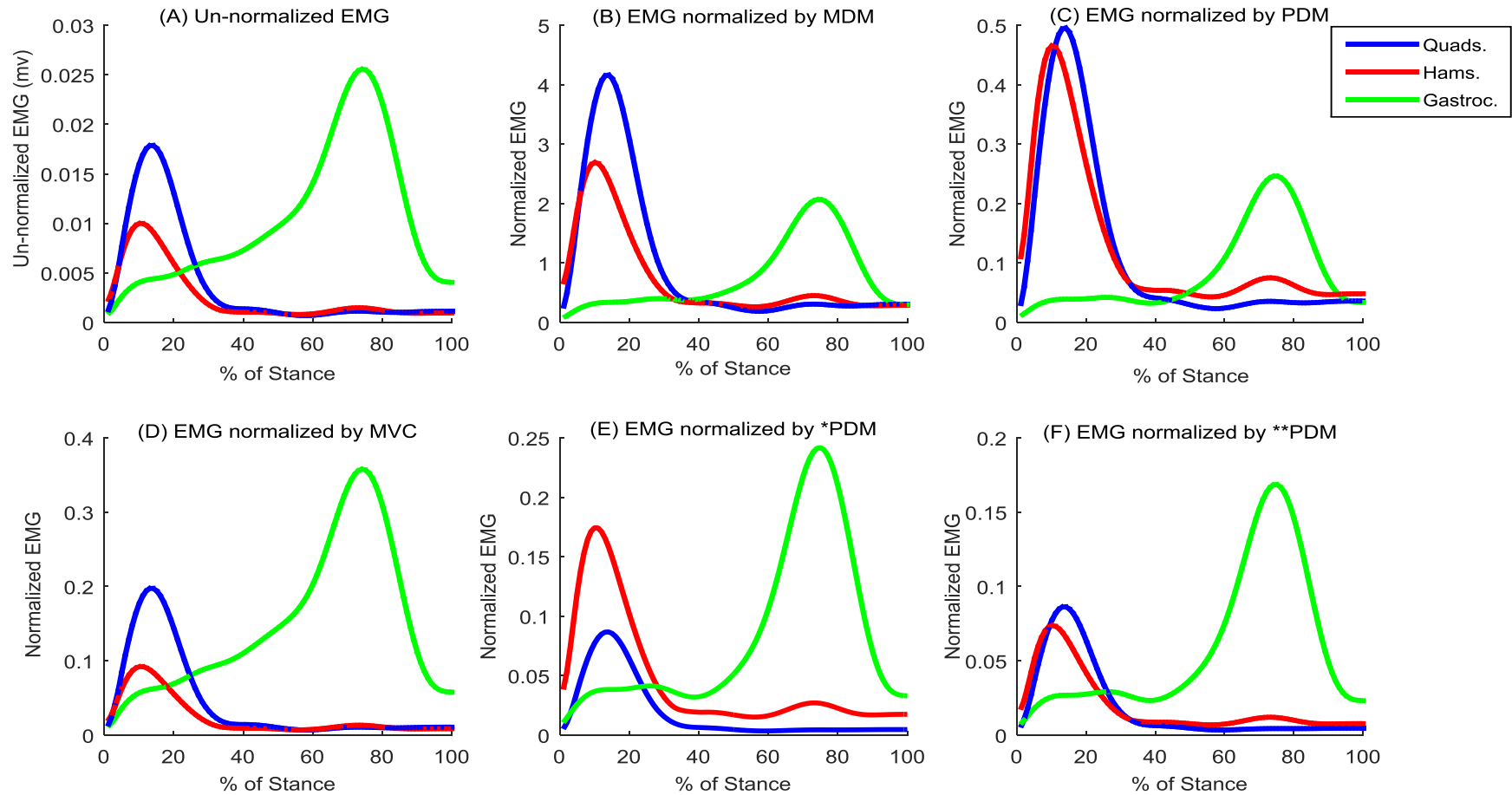


Figure 3. 3: Muscle activity, for a NP subject (mean for 6 trials) expressed in percent Stance Phase for un-normalized EMG; (A), EMG normalized by MDM; (B), EMG normalized by PDM; (C), EMG normalized by MVC ; (D), EMG normalized by *PDM;(E), and EMG normalized by **PDM; (F). Quads. =quadriceps muscles, Hams. =hamstring muscles, Gastroc. =gastrocnemii muscles.

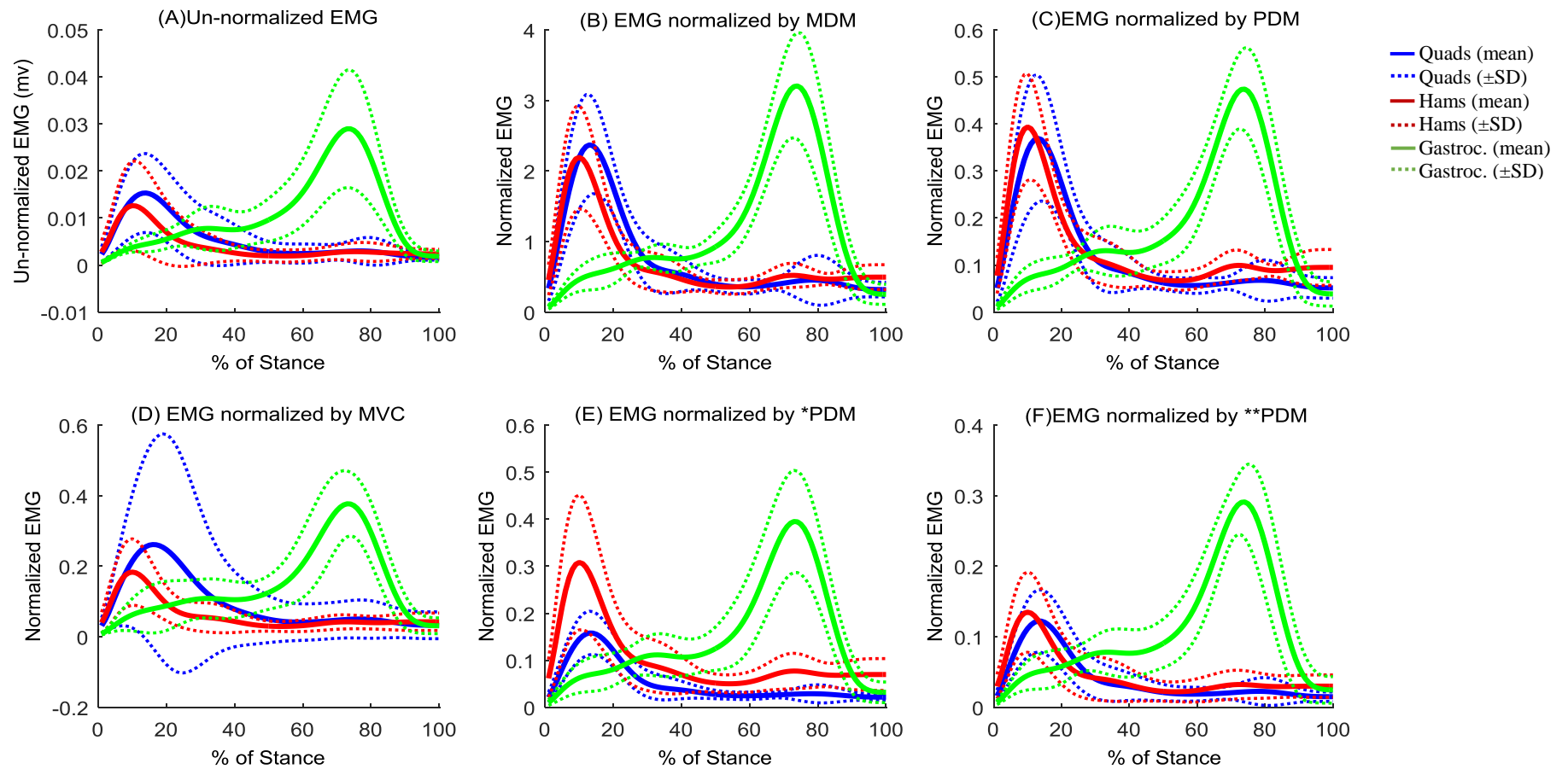


Figure 3. 4: Muscle activity, for 10 NP subjects (mean \pm SD) expressed in percent Stance Phase for un-normalized EMG; (A), EMG normalized by MDM; (B), EMG normalized by PDM; (C), EMG normalized by MVC; (D), EMG normalized by *PDM;(E), and EMG normalized by **PDM; (F). Quads=quadriceps muscles, Hams=hamstring muscles, Gastroc=gastrocnemii muscles, n=10.

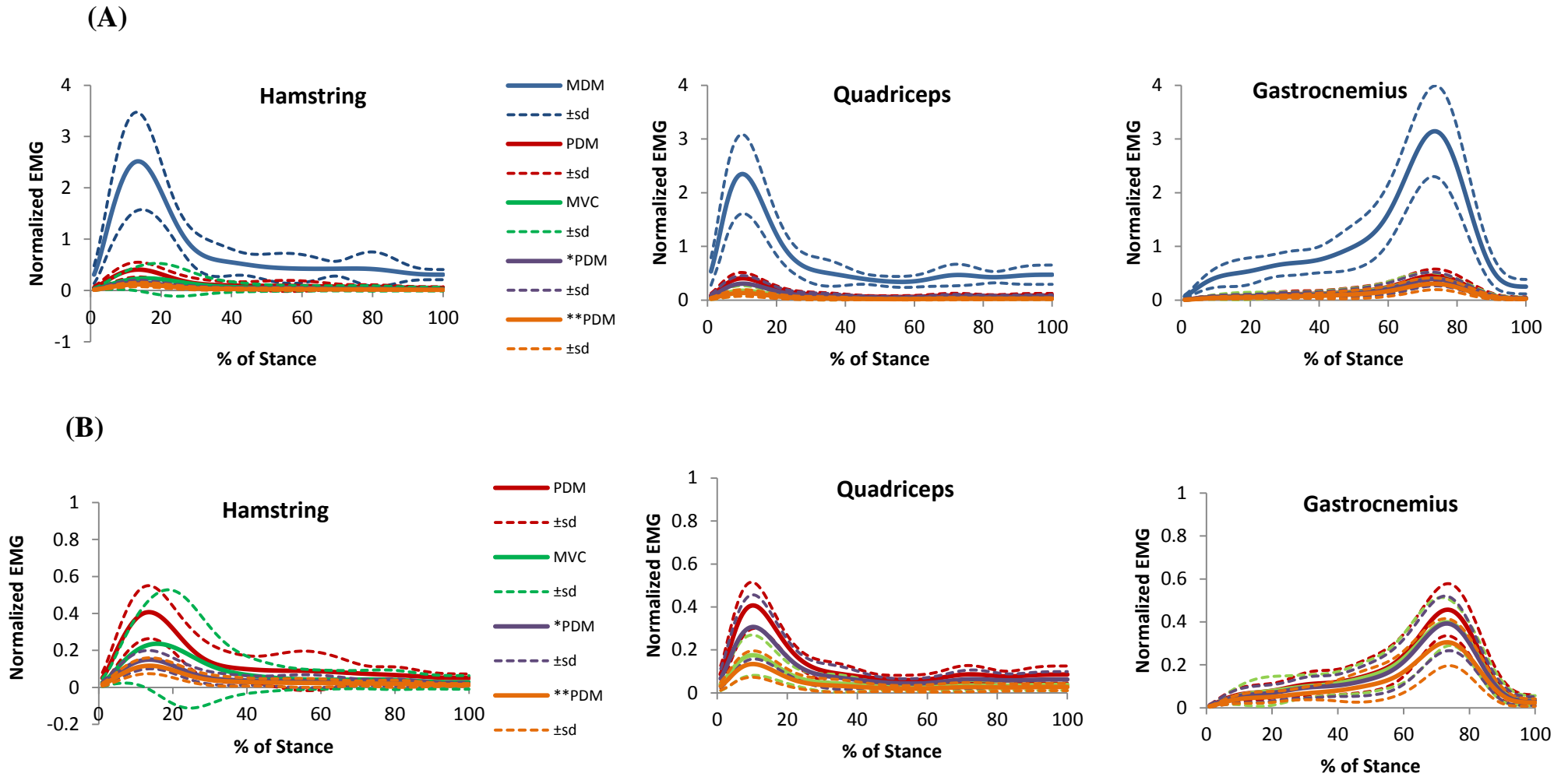


Figure 3. 5: The y-axis is the magnitude of the normalized EMGs for 10 NP subjects (mean \pm SD) and the x-axis is percent stance phase. The upper panel (A) EMG normalized by (MDM, PDM, MVC, *PDM, and **PDM) and the lower panel (B) EMG normalized by (PDM, MVC, *PDM, and **PDM).

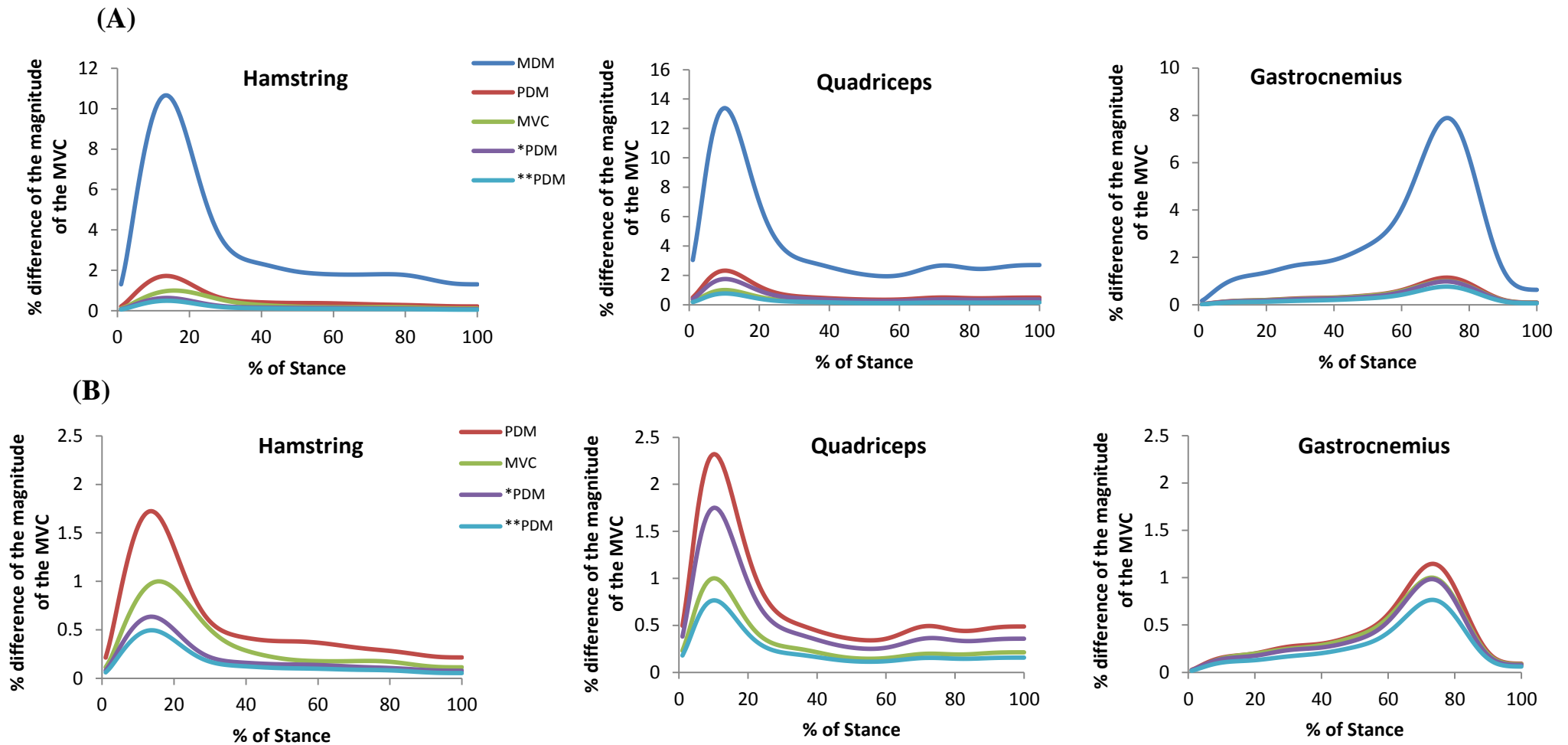


Figure 3. 6: The y-axis is the percentage difference of the magnitude of the normalized EMGs relative to the MVC for 10 NP subjects and the x-axis is percent stance phase. The upper panel (A) EMG normalized by (MDM, PDM, MVC, *PDM, and **PDM) and the lower panel (B) EMG normalized by (PDM, MVC, *PDM, and **PDM). For example by using PDM, the peak hamstring is 1.75*MVC, the peak quadriceps is 2.3*MVC, and the peak gastrocnemius is 1.1*MVC.

Table 3. 1: Intra-individual variability (CV =Coefficient of Variation; VR=Variance Ratio) for un-normalized EMGs* during stance phase of gait cycle, n=10.

		RF	VL	VM	BF	ST	LG	MG
CV	mean	0.53	0.43	0.42	0.48	0.43	0.40	0.31
	SD	0.52	0.16	0.17	0.16	0.12	0.11	0.06
VR	mean	0.34	0.18	0.22	0.30	0.29	0.23	0.17
	SD	0.28	0.12	0.14	0.18	0.09	0.15	0.07

RF, Rectus Femoris; VL, Vastus Lateralis; VM, Vastus Medialis; BF, Biceps Femoris; ST, Semitendinosus; LG, Lateral Gastrocnemius; ML, Medial Gastrocnemius.

*intra-individual variability were the same for the un-normalized EMGs and those normalized by the methods employed.

Table 3. 2: Inter-individual variability (Coefficient of Variation; CV) for un-normalized EMGs and EMGs normalized by MDM, PDM, *PDM, and **PDM during stance phase of gait cycle, n=10.

	RF	VL	VM	BF	ST	LG	MG
Un-normalized	1.13	1.68	0.84	0.84	1.02	0.53	0.67
MVC	1.97	3.54	1.16	3.64	3.92	3.43	3.87
MDM	0.63	0.57	0.56	0.48	0.53	0.48	0.59
PDM	0.77	0.57	0.65	0.51	0.54	0.51	0.61
*PDM	0.97	0.70	0.78	0.59	0.79	0.48	0.65
**PDM	1.60	0.93	0.94	0.89	1.25	0.60	0.71

RF, Rectus Femoris; VL, Vastus Lateralis; VM, Vastus Medialis; BF, Biceps Femoris; ST, Semitendinosus; LG, Lateral Gastrocnemius; ML, Medial Gastrocnemius.

Table 3. 3: Inter-individual variability (Variance Ratio; VR) for un-normalized EMGs and EMGs normalized by MDM, PDM, *PDM, and **PDM during stance phase of gait cycle, n=10.

	RF	VL	VM	BF	ST	LG	MG
Un-normalized	0.91	0.86	0.61	0.58	0.74	0.37	0.57
MVC	1.03	1.02	0.79	1.06	1.06	1.08	1.06
MDM	0.62	0.29	0.34	0.31	0.39	0.31	0.48
PDM	0.70	0.29	0.44	0.37	0.40	0.34	0.51
*PDM	0.83	0.39	0.56	0.43	0.63	0.32	0.55
**PDM	0.99	0.50	0.62	0.65	0.84	0.43	0.60

RF, Rectus Femoris; VL, Vastus Lateralis; VM, Vastus Medialis; BF, Biceps Femoris; ST, Semitendinosus; LG, Lateral Gastrocnemius; ML, Medial Gastrocnemius.

Table 3. 4: Root mean square (RMSD), absolute difference (ABSD), and percentage difference (%D) between the amplitude of knee flexors EMGs normalized using the isometric MVC method and MDM, PDM, *PDM, and **PDM methods.

		Knee Flexors											
		BF			ST			LG			MG		
		RMSD	ABSD	%D	RMSD	ABSD	%D	RMSD	ABSD	%D	RMSD	ABSD	%D
MVC : MDM	Mean	1.51	1.18	2372.06	2.91	2.30	1537.82	5.23	4.44	939.38	5.72	4.52	889.68
	SD	1.58	1.26	2483.34	5.85	4.56	835.27	10.73	9.59	542.97	13.09	10.28	739.26
MVC : PDM	Mean	0.79	0.63	313.96	2.28	1.78	231.89	4.06	3.60	80.68	4.81	3.79	111.04
	SD	2.07	1.65	343.71	6.42	5.02	158.89	11.90	10.57	100.14	14.03	11.02	94.80
MVC : *PDM	Mean	0.74	0.59	158.65	2.23	1.74	110.33	4.05	3.58	59.49	4.79	3.77	94.83
	SD	2.09	1.67	237.10	6.44	5.03	78.27	11.90	10.57	49.30	14.03	11.03	84.56
MVC : **PDM	Mean	0.71	0.57	58.22	2.16	1.69	34.19	4.02	3.56	29.24	4.74	3.73	40.17
	SD	2.10	1.67	97.65	6.46	5.05	32.30	11.91	10.58	30.72	14.05	11.04	38.27

RF, Rectus Femoris; VL, Vastus Lateralis; VM, Vastus Medialis; BF, Biceps Femoris; ST, Semitendinosus; LG, Lateral Gastrocnemius; ML, Medial Gastrocnemius.

Table 3. 5: Root mean square (RMSD), absolute difference (ABSD), and percentage difference (%D) between the amplitude of knee extensors EMGs normalized using the isometric MVC method and MDM, PDM, *PDM, and **PDM methods.

		RF			VL			VM		
		RMSD	ABSD	%D	RMSD	ABSD	%D	RMSD	ABSD	%D
MVC : MDM	Mean	0.97	0.81	2142.97	2.76	1.94	1826.84	1.43	1.05	2421.68
	SD	0.29	0.25	1885.32	3.77	2.64	2184.82	0.37	0.18	2655.96
MVC : PDM	Mean	0.26	0.21	585.63	1.90	1.35	260.08	0.14	0.10	241.95
	SD	0.25	0.21	770.35	4.52	3.17	340.95	0.07	0.05	314.31
MVC : *PDM	Mean	0.12	0.10	103.64	1.86	1.32	83.39	0.08	0.07	67.22
	SD	0.17	0.14	61.40	4.60	3.23	86.81	0.09	0.07	67.19
MVC : **PDM	Mean	0.10	0.09	45.03	1.87	1.33	84.33	0.09	0.07	51.21
	SD	0.18	0.15	35.59	4.60	3.23	88.32	0.09	0.08	40.76

RF, Rectus Femoris; VL, Vastus Lateralis; VM, Vastus Medialis; BF, Biceps Femoris; ST, Semitendinosus; LG, Lateral Gastrocnemius; ML, Medial Gastrocnemius.

3.5 Discussion

Patients with a neurological disorder are not always able to perform a maximal effort contraction during MVC recordings. Results of this study indicate that normalization by adopting the peak value measured during different daily activities in addition to MVCs (**PDM) can mimic the relative amplitude expressed when using MVCs alone and therefore overcome this problem. In addition, measuring peak EMG during ADLs is useful to determine the maximum capacity of each muscle required to perform these daily activities during their functional range of motion. In situations where MVC are not feasible, normalization by *PDM has been shown to be superior to normalization using MDM and PDM methods.

All normalization methods yielded the same pattern of gait EMGs as they all divided the un-normalized EMGs by a single reference value. As shown in Figure 3.3, muscle activation patterns did not change across the different methods of normalization. Whereas the relative amplitude, which gives an indication on the strategies that subjects used to activate their muscles during a specific task, are changed among the normalization methods (Burden et al., 2003). Moreover, these muscle activations play a role in predicting muscle forces, so it's important to adopt the method of normalization that reflects the subject's ability to contract the muscle.

As illustrated in Figure 3.3 and Figure 3.4, the EMG of gastrocnemius peaked at approximately 70% of stance phase, after heel off when the knee moves into peak flexion. This muscle acts as an important knee and ankle joint flexor whilst providing joint stability. Whereas, quadriceps activated in early stance, acts with the hamstring muscle to stabilize the knee joint at the weight acceptance phase of the gait cycle (Winby et al., 2009).

Figure 3. 3-B and C, shows normalisation by MDM and PDM, respectively and illustrates that these methods cannot be used to calculate muscle co-contraction or estimate muscle forces, as the magnitude of the muscle activation does not reflect the true muscle activity. Benoit et al. (2003) demonstrated that EMG normalized by the peak value through gait cycle “does not indicate the muscle’s ability to activate. Accordingly, the amount of activation cannot be related to any physiological measure and patients’ inability to contract the muscle due to pain inhibition, and altered neuromuscular performance, may not be observed” (Sousa and Tavares, 2012). As illustrated in Figure 3.3-F, the muscle activity curves resulting from **PDM more closely matches MVC, Figure 3. 3-D, in terms of relative amplitude between the three groups of muscles. Figure 3. 3-E also shows acceptable matching of *PDM and MVC for the quadriceps and gastrocnemii. However since the hamstrings are activated more highly than the quadriceps, this muscle does not fully mirror the outputs from MVC.

As previously stated, the normalization methods used in this study yield an output that is simply the ratio of the task EMG to the EMG used as the denominator in the normalization equation. As such, depending on the nature of the denominator, outputs from different normalization methods can differ in magnitude. The results show a higher magnitude of output from the MDM, Figure.3. 5 -A, which occurs by virtue of the smaller denominator used in the normalization equation. Therefore, this method is not recommended as it does not give an indication of what this activity level means with respect to the muscle’s ability to activate. As a consequence of this and because the MDM scale is very high, Figure.3. 5 -B presented the outputs of the different methods of normalization without MDM, i.e., MVC, PDM, *PDM, and **PDM, to illustrate which method is closest to MVC.

The PDM resulting in hyper estimation of the hamstring, quadriceps and gastrocnemius muscles as compared to MVC. It has been shown that profiles of the gastrocnemius muscle obtained from different methods of normalization are close to each other (PDM=0.46±0.12, MVC=0.39±0.11, *PDM=0.39±0.13, **PDM=0.31±0.11), and this may indicate that the range of the maximum capacity of the gastrocnemius muscle during walking and ADL is near to that seen during the MVC protocol. Therefore, if not MVC nor ADL data are available to normalize the gastrocnemius muscle, normalization by using the peak value of the walking trials (PDM) can be used alternatively. For the quadriceps muscle, a hyper estimation of the *PDM, as compared to MVC, suggesting that this method, although desirable for cohorts where MVCs cannot be obtained, should be interpreted with caution, or other additional activities considered for inclusion to this method.

For more explanation, the outputs of the different methods of normalization were plotted as a ratio of the peak value of the MVC method, Figure 3.6. Where, the different approaches of normalization can be presented as a multiplication or fraction from the MVC. As illustrated in Figure 3.6-A, by using the MDM, the MVC maximal value was underestimated nearly by 10%, 12%, 8% for the hamstring, quadriceps, and gastrocnemius, respectively. Therefore, Figure 3.6-B presented the other approaches of the normalization without MDM, to easily visualize which approach is closest to MVC. For example, for the hamstring, the PDM is 1.75 times the MVC, while for the *PDM and **PDM are 0.6 and 0.5 times the MVC, respectively. Gastrocnemius has shown a low percentage of variation for the PDM compared to MVC; i.e., PDM is 1.1 times the MVC and this reveal the suggestion that was addressed in the previous paragraph, i.e., PDM could be used as a method of normalization for studies focusing on evaluating the activity of the gastrocnemius

muscle during gait. Among the different muscles, quadriceps has shown the highest hyper estimation by using the PDM method, where the PDM has a peak that is 2.3 times that of the normalization by using MVC (Figure 3. 6). Therefore, attention should be taken when using the method (PDM) to calculate muscle co-contraction or estimate muscle forces, as the normalized EMG does not accurately represent muscle activity.

Different approaches, such as RMSD, ABSD and %D, were used to compare the amplitude as well as the pattern of the EMG normalized by MVC with the MDM, PDM, *PDM, and **PDM (Table 3.4 and Table 3.5). These are presented in terms of mean and SD for all participants, six stances for each one. By comparing MVC with the other four methods of normalization, **PDM and *PDM show minor differences in the level of activation, especially for rectus femoris, the mean RMSD and ABSD for the aforementioned muscle were 0.10, 0.09 0.12, 0.10 respectively. Moreover %D also gives a clear overview of the similarities between MVC and the other methods, and range between (29.24-84.33) in **PDM to (889.68-2421.68) in MDM. This indicates that both *PDM and **PDM would be the closest results compared to the MVC, as illustrated in Table 3.3.

To enable comparisons with previous literatures (Burden et al., 2003), CV, VR, RMSD, ABSD, %D were considered. However, a number of studies (Norcrossa et al., 2010; Winter and Yack, 1987; Yang and Winter, 1984) have just measured CV to demonstrate the intra and inter-individual variability. Burden (2010) revealed the limitation of this coefficient to investigate the variability across subjects, and (Burden et al., 2003; Knutson L. M. et al., 1994) measured VR as well as CV to investigate the variability between subjects that have different means.

Table 3.1 presents the variability between trials (averaged for 10 subjects). CVs ranged from 0.31, in medial gastrocnemius, to 0.53, in Rectus femoris. There is a good agreement between the CV and VR presented here and those calculated in (Burden et al., 2003; Winter and Yack, 1987) for Vastus lateralis, Vastus medialis, Biceps femoris and Semitendinosus, with the exception of lower CV for Biceps femoris (0.48 calculated in this study, compared to 0.62 in (Winter and Yack, 1987)). A similar trend was seen with VR, which ranged from 0.17 in Medial gastrocnemius to 0.34 in Rectus femoris. In agreement with (Burden et al., 2003), the intra-individual variability of the un-normalized EMGs was identical to that normalized by different methods of normalization.

In terms of inter-subject variability, the CV and VR values listed in Table 3.2 and Table 3.3 are similar to the values presented in (Burden et al., 2003; Yang and Winter, 1984), with the exception of higher inter-individual variability for the MVC method. Other studies (Hershler and Milner, 1978; Shiavi et al., 1998) have reported that both CV and VR are sensitive to the processing parameters of the EMG signal, such as the cut off frequency of the linear envelope. Therefore smoothing the signal may remove meaningful aspects of the original data and will consequently produce a lower CV and VR.

Regarding the CV values, MVC methods have greater variability between subjects especially for Semitendinosus, 3.92. For the **PDM method, both Rectus femoris and Semitendinosus show a greater variability compared to the other muscles. Across the different methods of normalization the ranking of inter-individual variability between muscles are different. However, this variability arises from those muscles combining efforts in different ways for different individuals to perform level gait.

Therefore, the peak values through gait would differ depending on how the subject's muscles are coordinated and correlated.

Also in agreement with (Burden et al., 2003; Nishijima et al., 2010) inter-individual VR from the different normalization methods for each muscle showed a similar trend to CV. However, both PDM and MDM through walking reduced inter-individual variability the most, in comparison to the MVC; these methods do not have the potential to provide any information on the degree of muscle activation that occurs during gait. Instead, MVC reflects the true activity in neural drive. Both MVC and **PDM are very similar, in terms of their relative amplitude of quadriceps, hamstrings, and gastrocnemii, however **PDM has lower inter-individual variability.

Figure 3. 4 illustrates the normalization across 10 NP subjects, presenting their mean and standard deviation. Overall, the relative amplitude illustrated in Figure 3. 4 has almost a similar scenario that seen in Figure 3. 3. The high standard deviation across subjects that can be seen in Figure 3. 4-D, MVC method, was due to two participants having lower MVC EMG peak signals for specific muscles compared to their EMG peaks during gait. It can be interpreted that the subjects are able to reach their maximal activity during their functional range of motion, however, when they attempt to maximally contract their muscles outside this range, they fail to reach the maximum value capacity. Additionally, the high standard deviation resulting from the MVC method highlights the negative impact of this method of normalization. If control subjects are unable to elicit maximal isometric contractions; comparisons of activity levels between muscles in different individuals are not valid. This in turn

may have bigger negative impact in patient cohorts where they cannot maximally contract.

This work illustrates the higher reliability of **PDM and *PDM than MVC in EMG normalization. The findings from this study have important applications to examiners who apply EMG methodology in diagnosis and evaluation of disease and treatment. Moreover, this study provides alternative approaches to normalization that overcomes the difficulty which may be encountered in securing a maximal contraction from patients with neurological dysfunction; i.e., patients with Osteoarthritis (OA).

Further study is needed to determine if the findings from this study can be applied to other cohorts, i.e., to detect differences in muscle activity between OA and control subjects, to test the sensitivity of the methods recommended.

3.6 Limitations

The study was conducted on a small number of participants to generate important information that can be applied to a large cohort. The methods of normalization recommended from this study (*PDM and **PDM) have a high coefficient of variation and variance ratio, however, they are still lower than the commonly used MVC.

3.7 Summary

EMG is a valuable tool for understanding concomitant changes in neuromuscular response in patients with knee OA. Results of this study demonstrated that normalization by adopting the peak value from ADLs and MVC combined, i.e.,

**PDM, shows good repeatability and can be used as a reliable alternative to using MVC alone in studies that are quantifying muscle activity for level gait. However, for patients at the end stage of knee OA (pre-TKR), who are unable to perform MVC tasks, this approach may not be appropriate. As an alternative for this group of patients, using ADLs alone was demonstrated to provide a useful method for EMG normalization.

These two approaches to normalizing EMG will be used in chapter four to calculate muscle co-contraction and in Chapter five to estimate muscle forces for NP, pre-HTO, and pre-TKR groups.

Chapter 4

The Importance of Knee Muscle Coordination in patients with OA

4.1 Introduction

Since tibio-femoral loading are primarily produced by muscle forces (Sasaki et al., 2010), muscle coordination plays a pivotal role in determining tibio-femoral loads. Therefore identifying muscle coordination patterns that alter tibio-femoral loads may assist in the design of rehabilitation programs to restore and maintain the health of the knee.

Literature has shown that people with knee OA tend to walk with greater muscle co-contraction (Andriacchi, 1994; Childs et al., 2004; Hubley-Kozey et al., 2006; Heiden et al., 2009; Zeni et al., 2010; Mills et al., 2013) to compensate for joint instability. Simultaneous activation of antagonist muscles increases joint stability by controlling the joint articulation and equalizes joint pressure distribution. This could potentially be a harmful strategy for long-term joint integrity, as it causes an increase in the net knee compressive contact load and may contribute to the progression of OA. Where the pattern and magnitude of knee compressive force have found to be directly affected by the way that individuals used to activate their muscles. In other words, bias of muscle activations, to lateral or medial muscles, play an important role to influence the disease course (Hodges et al., 2016). Activation of the lateral muscles (Heiden et al., 2009; Hubley-Kozey et al., 2006) could generate an internal abduction moment and reduce the medial joint load. Conversely, bias towards medial muscles could increase medial joint load and promote medial cartilage loss.

This co-contraction strategy manifests particularly among patients with substantial knee extensor weakness (Thoma et al., 2016). Hortobagyi et al. (2005) have found that alteration of muscle activity may interfere with normal load distribution in the knee and facilitate disease progression. They revealed that the source of the increased

coactivity in OA patients was heightened hamstring muscle activity and reduced quadriceps activation, while executing ADLs. Benedetti et al. (1999) state that co-contraction of knee flexors and extensors is a common strategy to reduce shear forces at the knee but increases compressive forces and joint loading. Authors reported a single case study carried out over two years on a patient that underwent total knee replacement. Two years after surgery, they found a prolonged co-contraction of knee agonist-antagonist muscles, which may compromise the durability of the prosthesis.

Different methods of quantifying co-activation in OA subjects were reported in section 2.1.2. Childs et al. (2004) reported increased in amplitude and onset times. Heiden et al. (2009) have shown that laterally directed co-contraction ratio increased in people with knee OA. However, the method used by (Heiden et al., 2009) provides a good estimate of the directed co-contraction. It gives a measure of the directed co-contraction ratio for the whole lateral and medial muscles rather than individual muscle pairing. Further, this approach did not evaluate the amplitude and temporal characteristics of the muscle activation waveforms. Lewek et al. (2004) calculated a co-activation index from waveform data over the initial 10–15% of the gait cycle. This approach provides a good estimate of co-activity if the time interval is short and minimal variation is expected during that time period, but co-activation indices do not have unique solutions and are unable to capture the shape and amplitude characteristics of the entire waveform.

The approach proposed in this study attempted to capture waveform characteristics and determine if a general pattern of co-activation among the major muscles surrounding the knee joint exists in individuals with OA progression or not. Establishing such a pattern could serve to distinguish disease progression, assisting

clinicians in establishing disease severity. As well as, a better understanding of the neuromuscular alterations associated with OA progression could provide a framework for prescribing appropriate interventions aimed to improve the mechanical environment of the joint and perhaps prolong the need for an invasive intervention. The ideal strategy to understand this scenario is to explore how the coordination between quadriceps, hamstrings, and gastrocnemii are affected through the progression of knee OA.

This study had four objectives. The first was to compare co-contraction indices of four separate muscle pairs among NP, pre-HTO, and pre-TKR groups in order to determine whether a strategy of generalized increased co-contraction was present in OA groups. It was hypothesized that co-contraction would be significantly higher for OA groups compared to NP and for pre-TKR compared to pre-HTO.

Co-contraction can be calculated during different phases or time intervals during gait. The time interval selected could play an important role when differentiating between different stages of OA progression. The second objective was to test which time interval should be used for calculating co-contraction index for OA subjects: stance phase or gait cycle. It was hypothesized that both intervals give the same significant differences between groups.

The method of normalization that is used to normalize EMG and then to calculate CCI, is critical for the accurate comparison of CCI among the different groups. Therefore, the third objective was to test the impact of using different methods of normalization for calculating co-contraction index. It was hypothesized that both methods (*PDM and **PDM) can be used to differentiate between the three cohorts.

The final objective was to determine whether a positive relationship exists between OA progression and muscular co-contraction. We hypothesized that CCI is positively correlated with OA severity. To test the last hypothesis, a correlation analysis between CCI and OA progression was tested using Pearson's correlation.

4.2 Methods

Data used in this study was collected by the investigator and supplemented by pre-collected data at Cardiff University. All subjects gave their informed written consent prior to data collection. The consent and data protocols were approved by the Research Ethics Committee for Wales and Cardiff and Vale University Health Board. The inclusion/exclusion criteria for the participants have been described in details previously, section 1.3. Data was used from twenty-six fully consented subjects: ten Non-pathological subjects (NP), ten with medial knee OA listed for high tibial osteotomy surgery (pre-HTO), and six with late-stage OA listed for total knee replacement (pre-TKR). The mean and SD of mass, height, and age for NP, pre-HTO and pre-TKR cohorts were (78.04±10.96 kg, 84.9±15.58 kg, 89.75±15.75 kg), (174.31±4.23 cm, 171.26±8.96 cm, 168.16±10.21 cm), (31.6±4.90 years, 50.2±6.71 years, 64.6±10.67 years), respectively. The affected leg for the two OA groups and a randomly selected leg for the NP group were studied.

Details regarding experimental procedures and data reduction analysis have been described in details previously, sections 3.2.1 and 3.2.2, and will be briefly presented below.

EMGs were recorded from vastus lateralis, vastus medialis, biceps femoris, semitendinosus, gastrocnemius lateralis, and gastrocnemius medialis. Two time

intervals were defined, the stance phase and the whole gait cycle. The stance phase was determined using the ground reaction force measurements and foot marker positions at heel strike and toe-off. EMGs were processed to create normalized EMGs, of which the values ranged between 0 and 1; details regarding EMG processing have been described in section 3.2.2.

Two approaches have been used in this chapter:

- The initial approach is calculating CCI for the NP and pre-HTO cohorts by using EMGs normalized by **PDM while for pre-TKR cohort EMGs normalized by *PDM.
- The revised approach is calculating CCI for the NP, pre-HTO, and pre-TKR cohorts by using EMGs normalized by *PDM.

The time interval of the EMG data was normalized to 100 data points. Finally, the co-contraction index (CCI) was calculated for each muscle pair using (eq.4. 1), which was developed by (Rudolph et al., 2000),

$$CCI = \sum_{i=1}^{100} \left[\frac{\text{low EMG}_i}{\text{high EMG}_i} \times (\text{high EMG}_i + \text{low EMG}_i) \right] / 100 \quad (4. 1)$$

This equation was calculated for the following muscle sets: Vastus Lateralis-Lateral Gastrocnemius (VLLG), Vastus Lateralis-Lateral Hamstring (VLLH), Vastus Medialis- Medial Gastrocnemius (VMMG), and Vastus Medialis -Medial Hamstring (VMMH). The resulting values were averaged to arrive at a single value representing the magnitude of co-contraction between the two muscles, and then the mean for the 6 trials was calculated. This resulted in CCI for each subject during stance phase and gait cycle.

The reason of using different approaches is that the results from the previous chapter demonstrated that normalization by adopting the peak value through ADLs, in addition to MVCs, ***PDM*, provided a good ability to reflect the relative magnitude of muscle activity, in a similar way to that seen in MVC alone and with excellent reliability across subjects. Therefore this method of normalization was adopted for NP and pre-HTO groups to get an accurate estimate of CCI for these groups. However, pre-TKR group was unable to perform MVC tasks, therefore, ***PDM* cannot be used. Alternatively, normalization by adopting the peak value through ADLs (**PDM*) was used for TKR group to calculate CCI. The limitation of using (**PDM*) is the hyper estimation of the hamstring. The initial approach compared CCI between groups adopted different methods of normalization. While the revised approach compared CCI between groups by using EMG normalized by **PDM* for all groups (NP, Pre-HTO, Pre-TKR). Therefore it is interesting to find how the CCI will be changed if the method of normalization is changed.

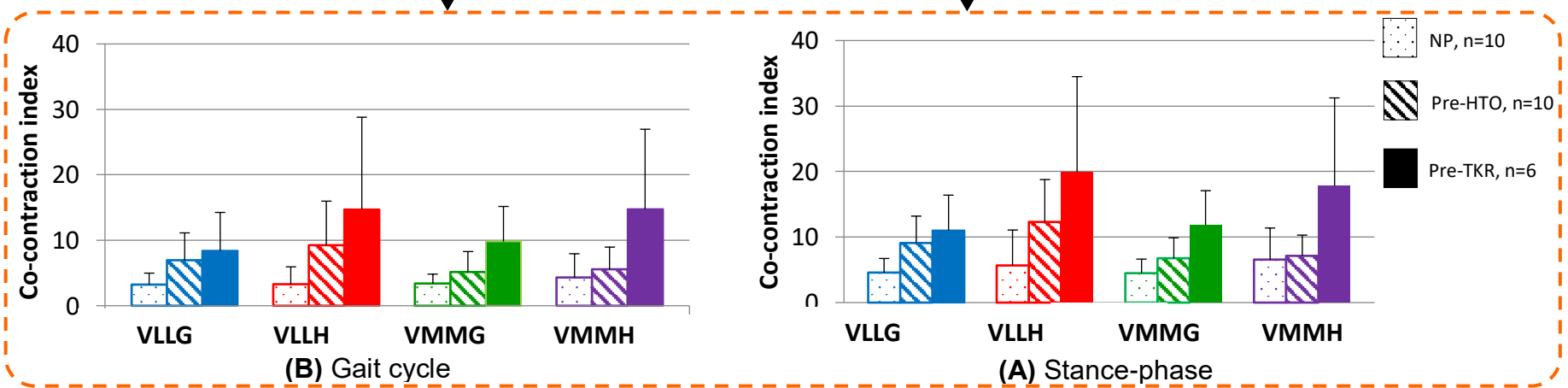
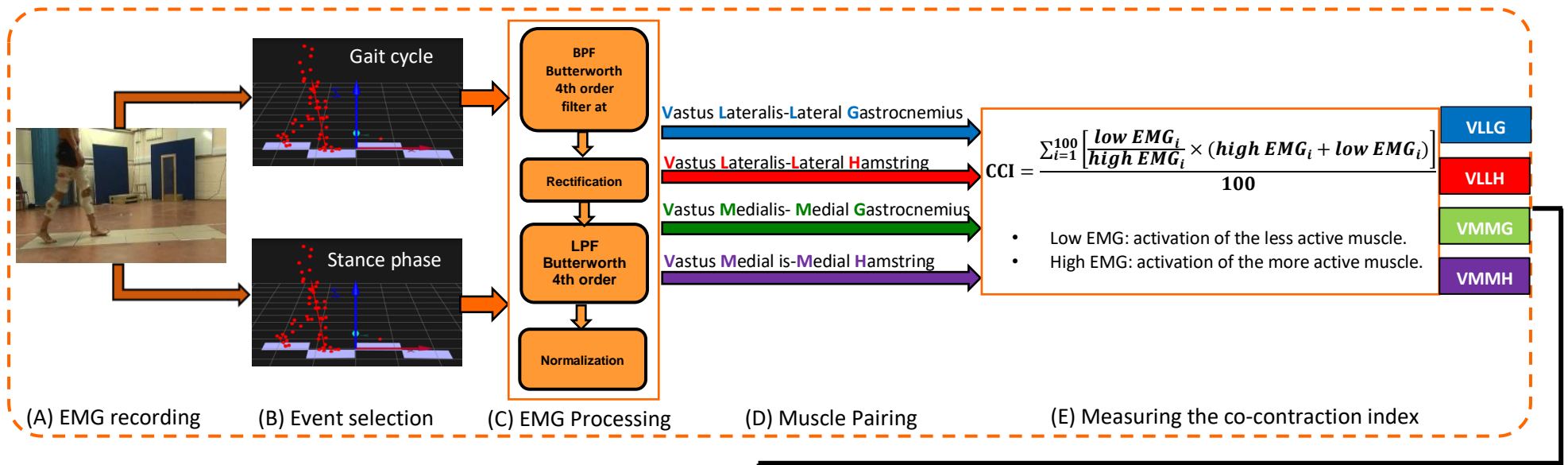


Figure 4. 1: Methodological flow-chart for calculating co-contraction index.

4.3 Statistical analysis

Statistical analysis was undertaken with SPSS (version 20, Chicago, IL). Significance was set at $P < 0.05$. To investigate the differences between disease progression (dependent variable) and co-contraction measures (independent variable), a Kruskal Wallis test of nonparametric data was performed to compare the four co-contraction indices among groups. All pairwise tests were used to determine significant interactions when main effects were present. Pairwise comparisons using the Dunn-Bonferroni approach are automatically produced for any dependent variables for which the Kruskal-Wallis test is significant. A Pearson correlation was performed in order to determine the association between co-contraction values and the progression of OA during stance. If correlations were found to be significant, linear regressions would be performed to determine the strength of the relationship.

4.4 Results

Co-contraction (CCI) index provides a measure of the relative activation of muscle pairs over a specific time interval. Figure 4.2 and Figure 4.3 show the CCI for NP, pre-HTO, and pre-TKR subjects during stance phase and gait cycle, respectively, by using the initial approach. Data were tabulated in Table 4.1, which demonstrated the mean values of CCI among NP, pre-HTO, and pre-TKR.

As expected, patients with OA have a higher CCI compared to NP subjects. The CCI for subjects with advanced knee OA (pre-TKR subjects) is higher than pre-HTO subjects, with medial knee OA. Significant differences in the CCI between groups were identified. On the lateral side of the knee joint, the OA subjects had a significantly greater VLLH co-contraction index (19.9 ± 14.5) and (12.3 ± 6.5) for

pre-TKR and pre-HTO, respectively compared to NP subjects, which was 5.7 ± 5 . No significant difference was observed between OA groups for the VLLH. On the medial side, a pre-TKR had a significant higher VMMH (17.8 ± 13.4) compared to Pre-HTO (7.1 ± 3.2), where the latter also had significantly increased levels of co-contraction compared to NP subjects (6.6 ± 4.8). Further, we examined the muscle co-contraction levels during gait, Figure 3.3. A similar trend was seen for the indices calculated during gait to that calculated during stance and the same significant differences were detected.

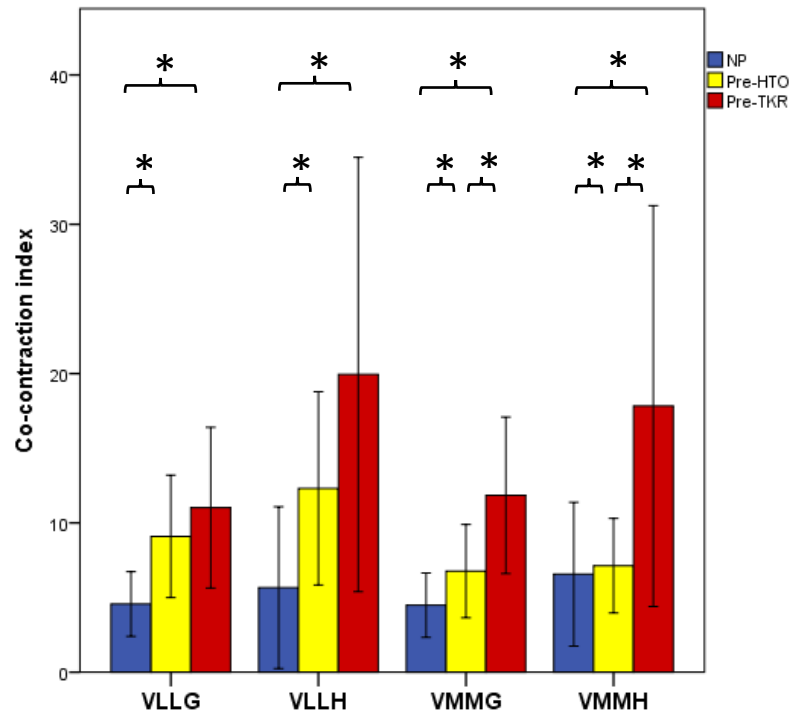


Figure 4. 2: Co-contraction index during stance-phase for NP, pre-HTO, and pre-TKR subjects by using the initial approach (EMGs from NP and pre-HTO normalized by **PDM while for pre-TKR normalized by *PDM). Values represent mean and standard deviation, (*) means the difference is significant ($p < 0.05$).

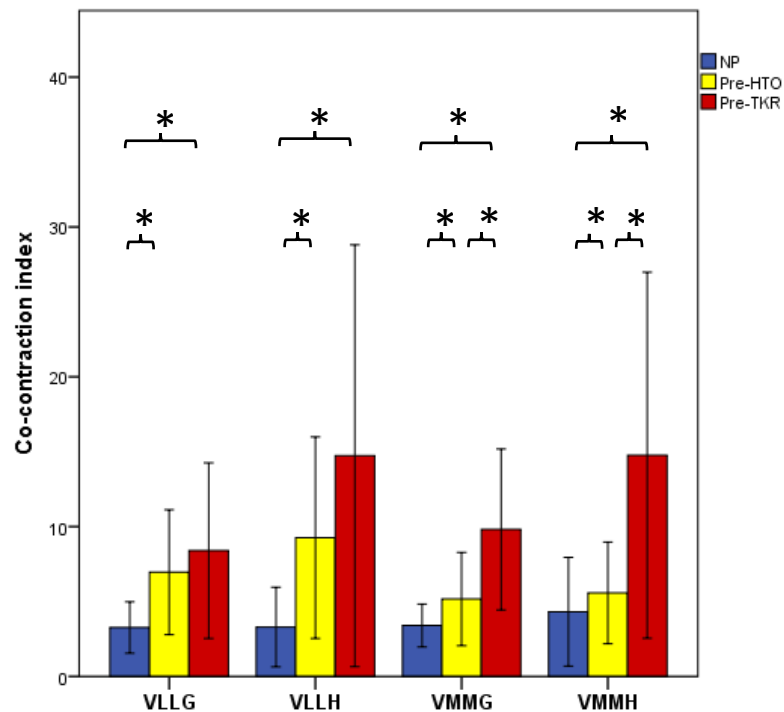


Figure 4. 3: Co-contraction index during gait cycle for NP, pre-HTO, and pre-TKR subjects by using the initial approach (EMGs from NP and pre-HTO normalized by **PDM while for pre-TKR normalized by *PDM). Values represent mean and standard deviation, (*) means the difference is significant ($p < 0.05$).

Table 4. 1: Co-contraction index by using the initial approach for NP, pre-HTO, pre-TKR. NP, pre-HTO groups during stance and gait.

CCI	NP	Pre-HTO	Pre-TKR	P	P	P	
	n=20	n=30	n=30	NP vs. HTO	NP vs. TKR	HTO vs. TKR	
Stance	VLLG	4.57±2.17	9.10±4.10	11.02±5.38	<0.001†	<0.001†	0.064
	VLLH	5.66±5.42	12.31±6.47	19.94±14.55	<0.001†	<0.001†	0.54
	VMMG	4.49±2.15	6.77±3.12	11.85±5.24	<0.001†	<0.001†	<0.001†
	VMMH	6.56±4.82	7.14±3.17	17.82±13.42	0.016†	<0.001†	<0.001†
Gait	VLLG	3.27±1.72	6.96±4.18	8.40±5.86	<0.001†	<0.001†	1.000
	VLLH	3.29±2.66	9.26±6.73	14.73±14.08	<0.001†	<0.001†	1.000
	VMMG	3.40±1.43	5.16±3.11	9.81±5.37	<0.001†	<0.001†	<0.001†
	VMMH	4.32±3.63	5.57±3.40	14.76±12.22	0.006†	<0.001†	<0.001†

† Significant differences between groups (p<0.05).

For consistency, CCI was calculated for all groups (NP, pre-HTH and pre-TKR) by using EMGs normalized by using ADLs; i.e. *PDM. Figure 4.4 shows the results of the calculated indices during stance phase by using the revised approach. Table 4.2 reported the indices for the initial and revised approach during stance to illustrate the impact of changing the method of normalization on the findings of the initial approach.

An overall significant correlation was found between CCI (calculated by using revised approach) and OA severity, as reported in Table 4. 3.

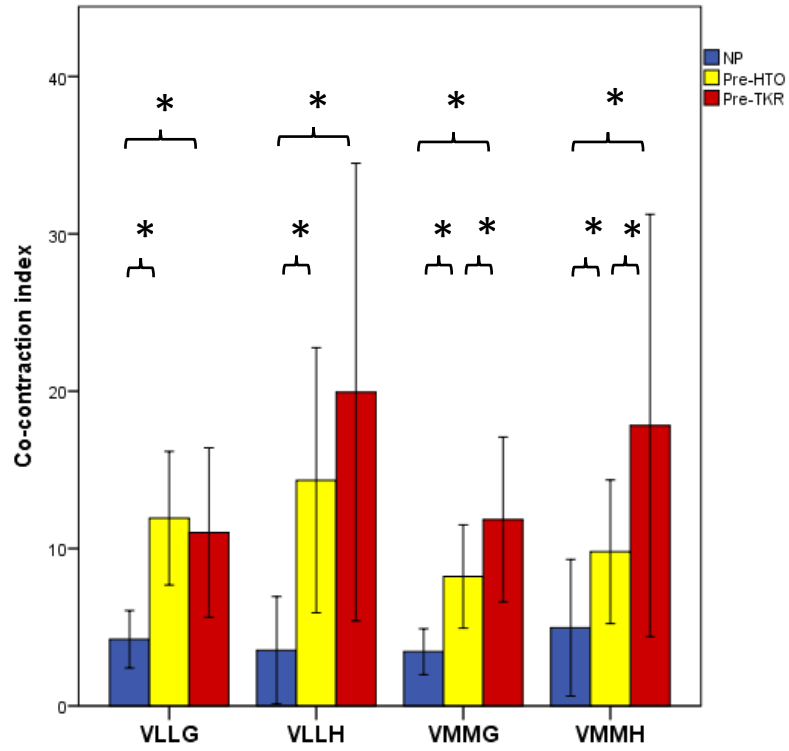


Figure 4. 4: Co-contraction index during stance-phase for NP, pre-HTO, and pre-TKR subjects by using the revised approach (EMGs from NP, pre-HTO and pre-TKR normalized by *PDM). Values represent mean and standard deviation, (*) means the difference is significant ($p < 0.05$).

Table 4. 2: Co-contraction index during stance-phase for NP, pre-HTO, pre-TKR. NP, pre-HTO groups for the initial and revised approaches.

CCI	NP	Pre-HTO	Pre-TKR	P	P	P	
	n=20	n=30	n=30	NP vs. HTO	NP vs. TKR	HTO vs. TKR	
Initial approach	VLLG	4.57±2.17	9.10±4.10	11.02±5.38	<0.001†	<0.001†	0.064
	VLLH	5.66±5.42	12.31±6.47	19.94±14.55	<0.001†	<0.001†	0.54
	VMMG	4.49±2.15	6.77±3.12	11.85±5.24	<0.001†	<0.001†	<0.001†
	VMMH	6.56±4.82	7.14±3.17	17.82±13.42	0.016†	<0.001†	<0.001†
Revised approach	VLLG	4.20±1.84	11.83±4.32	11.02±5.38	<0.001†	<0.001†	0.48
	VLLH	3.51±3.41	14.22±8.46	19.94±14.55	<0.001†	<0.001†	1.00
	VMMG	3.42±1.47	8.16±3.32	11.85±5.24	<0.001†	<0.001†	<0.001†
	VMMH	4.93±4.34	9.72±4.59	17.82±13.42	<0.001†	<0.001†	0.002†

† Significant differences between groups (p<0.05).

Table 4. 3: The relationship between CCI and OA progression during stance.

Co-contraction index	r	p
VLLG	0.516	0.009*
VLLH	0.653	0.001*
VMMG	0.671	0.000*
VMMH	0.595	0.002*

*P <0.05 = significant relationship.

4.5 Discussion

In answer to the first hypothesis, it appears that there is a trend in co-contraction index and OA progression. In agreement with literature (Andriacchi TP, 1994; Hubley-Kozey et al., 2009), our results suggest that people with medial knee OA and varus deformity, listed for high tibial osteotomy surgery (pre-HTO), have increased lateral CCIs which may help to unload the medial compartment; i.e. redistribute the load laterally. This finding suggests an important compensatory mechanism for reducing load on the painful side. While people with severe knee OA, i.e., listed for total knee replacement surgery (pre-TKR), uses “general co-activity”, which was confirmed by (Fallah-Yakhdani et al., 2012; Heiden et al., 2009; Hubley-Kozey et al., 2009). Where (Lewek et al., 2004) have found that patients with severe OA use high medial muscle co-contraction, which may increase loading on the medial compartment of the knee joint. In fact, according to the results presented in Figure 3.3 it can be seen that during gait, pre-TKR subjects induced higher medial co-contraction than the lateral and a similar pattern has been found during stance (Figure 3. 2), except for VMMH where it is lower than its lateral component. Examining the differences between groups revealed that pre-TKR subjects do not have a significant main affected side (medial vs lateral); i.e., OA can affect the three knee compartments to same degree. Generally pre-TKR had a higher co-activation muscle activity on both sides; i.e. medial and lateral. It is possible that people with pathologic conditions in the knee may limit knee motion through different muscle co-contraction strategies.

In answer to the second hypothesis, it appears that both stance phase and gait cycle can be used to differentiate OA progression. The CCIs for NP group presented in

Figure 3.2 are similar to the literature (Hubley-Kozey et al., 2009) however the time interval that was selected to calculate the indices are different. Interestingly, the significant differences of CCI between groups were not affected by the definition of the time interval for CCI calculation. This study shows that lateral indices are increased ($p < 0.05$) almost two-fold for the pre-HTO group compared to NP group. Whereas, no significant differences were found for the lateral indices between the pre-HTO group and pre-TKR group. Lewek et al. (2005b) has found that the greater lateral/medial co-contraction ratios are strongly related to larger knee adduction moments in NP individuals but not in the OA group. They demonstrated that individuals with medial knee OA do not increase their lateral co-contraction to any great extent when large adduction moments are present. The most important parameter that Lewek et al. (2005b) didn't mention in their work is the disease severity; i.e. if the patients are in a moderate stage or in a severe stage of OA. In fact, the individuals with severe knee OA could be using increased medial and lateral co-contraction, to reduce knee instability. This scenario was not the case for pre-HTO subjects, where higher co-contraction of the lateral muscle could help to unload the medial compartment of the knee joint.

The progression of OA plays a significant role in the strategy that the muscles used to coordinate themselves, unload the medial component of the knee and stabilize the joint. According to the data presented in Figure 3.2 and Figure 3.3, knee with medial OA (pre-HTO patients) have higher lateral indices in an attempt to create a high internal moment to counteract the high external knee adduction moment (Figure 5.16); details for the knee kinematics and kinetics will be addressed in the next chapter. For the current analysis, both the medial and lateral indices have significantly

increased for pre-TKR group compared to pre-HTO and NP, to counteract the net joint moment with different muscle activation patterns.

Gastrocnemii indices are doubled in the pre-HTO group as compared to NP subjects. For the pre-TKR group, in addition to the gastrocnemii role that is associated with a two-fold increase in the CCI, hamstring muscles also have a potential to provide stability for the knee joint. Hamstring indices increased almost 250% on the lateral side and 170% on the medial side, as compared to NP individuals. There was also a significant increase ($p < 0.05$) in VLLH for the pre-TKR group, which may contribute to a reduction in the medial contact force. Significant differences ($p < 0.05$) were identified for the medial side indices between the two OA groups, **Error! Reference source not found.** and **Error! Reference source not found.**. During the stance phase of walking, the pre-HTO cohort has significantly increased lateral CCIs, and in agreement with (Hubley-Kozey et al., 2009) this may help to unload the medial compartment. This increase is also evident for late-stage knee OA (pre-TKR). We can speculate that the significant increase of the medial muscle co-contractions in severe OA may lead to a greater risk of increase loading on the medial compartment of the knee joint, this was also revealed by (Lewek et al., 2004).

Weaker quadriceps in OA subjects might result in higher levels of muscle co-contraction. Where pre-TKR group had a higher muscle co-contraction compared to pre-HTO, i.e. indicating an increase in CCI with disease progression, which is consistent with previous literature. A similar trend is evident for the indices measured during stance phase and during the whole gait cycle. The CCIs are higher when calculated during stance.

In answer to the third hypothesis, both approaches gave the same significant differences between cohorts. However, pre-HTO group has shown the highest VLLG among NP and pre-TKR for the revised approach. The interesting thing to find, as shown in Table 4. 2, is that all the indices in the revised approach are lower than that in the initial approach for NP group and vice versa for the pre-HTO group. This can be explained by taking two scenarios:

The first scenario is for NP subjects, in reference to the illustrative example presented in Chapter Three; Figure 3. 3. For example, the CCI for the muscle pair (hamstring:quadriceps) normalized by *PDM and **PDM at t=15% of stance can be calculated by:

$$\text{*PDM: Hamstring}=0.18, \text{ Quadriceps}=0.09. \therefore \text{CCI} = \frac{0.09}{0.18} \times (0.18 + 0.09) = 0.14$$

$$\text{**PDM :Hamstring}=0.08, \text{ Quadriceps}=0.09. \therefore \text{CCI} = \frac{0.08}{0.09} \times (0.09 + 0.08) = 0.15$$

This simply explains why CCI for NP subjects in the initial approach (i.e, EMGs normalized by **PDH) is higher than that in the revised approach (i.e, EMGs normalized by *PDH). It is obvious from the equation that what is important is the relative amplitude between muscle pair as well as which one is higher and which one is lower. As this value will affect the ratio $(\frac{\text{low EMG}_i}{\text{high EMG}_i})$. Therefore, hyper estimation or underestimation of each muscle will have a critical effect on the first part of CCI equation.

The second scenario is for pre-HTO subjects, where they experience higher indices when their EMGs normalized by ADL (i.e., *PDM) as compared to **PDM. This may result from that pre-HTO subjects due to a limited range of motion, their

ADLs is much lower than that of MVC. Therefore, the normalized EMGs by using ADL (i.e., *PDM) is higher than that EMGs normalized by using the peak values through ADL and MVC (i.e., **PDM). However of these differences, both *PDM and **PDM methods of normalization can be used to calculate CCI, where both initial and revised approaches showed significant differences of CCI with the progression of OA.

In answer to the fourth hypothesis, results from linear regression revealed that increases in CCI were significantly associated with an increase in OA progression. we conclude that dynamic muscle co-contraction can be used as a surrogate for OA progression.

4.6 Limitation

Three limitations of this study should be considered before generalizing the whole picture on how the peri-articular knee muscles co-ordinated themselves through different stages of OA. One limitation is the moderate sample size of the cohorts. However, the results presented in this study showed consistency with previous literature; i.e regarding muscle co-activation among the asymptomatic group and those with OA. The second limitation is the large standard deviation in VLLH and VMMH of the pre-TKR group. After further investigation, this variability arises from the muscles, i.e. hamstrings, combining efforts in different ways for different individuals to perform level gait. Therefore, agonist-antagonist contraction differs depending on how the subject's muscles are coordinated and correlated. One factor that could have influenced the results is that the changes in walking speed were not considered in this study. Some previous studies reported that high muscle activity

(Franz and Kram, 2012) are related to increases in walking speed, where they are likely associated with increased muscle and joint contact forces.

4.1 Summary

Quadriceps and hamstring muscles alter their coordination in an attempt to stabilize the knee. Lateral versus medial site differences were demonstrated in pre-HTO subjects as a complementary strategy to unload the medial compartment of the knee. For pre-TKR subjects, alterations most likely occur in both lateral and medial sites. Results of this study supported the hypothesis that there is a trend in co-contraction index and OA progression and both stance phase and gait cycle can be used to differentiate between groups. Further, the impact of using different methods of normalization for calculating co-contraction index have been studied and results have shown that both methods (*PDM and **PDM) can be used to differentiate between the three cohorts. Finally, results have shown that increases in CCI were significantly associated with an increase in OA progression.

Muscle activation from normalized electromyography does not reflect the actual mechanical action of the muscles. For example the lateral muscle co-contraction (VLLH and VLLG) does not reveal the extent of the lateral muscle contribution to support the external knee adduction moment (KAM). This moment is affected by many factors; e.g. muscle physiological cross section area, muscle fibre force-length and force-velocity relationships, and muscle moment arm (Lloyd and Buchanan, 2001; Lloyd et al., 2005), in addition to muscle activation. The effectiveness of muscle stabilization and the effect on articular loading requires studies that employ neuromuscular skeletal modelling (Lloyd et al., 2005).

Therefore, the next chapters will adapt musculoskeletal modelling, to the three cohorts studied in this chapter, to investigate individual muscle forces developed in relation to applied external moments at the knee joint as well as provide information on corresponding joint forces. Nevertheless, the characteristics of co-contraction patterns still provide information about the motor patterns used by the knee OA patients.

Chapter 5

Muscles Strategies in Patients with OA

5.1 Introduction

Biomechanical evaluations of people with OA are frequently performed to identify impairments in gait. While many studies have calculated net joint moments to evaluate biomechanical load, such measures do not provide quantitative information about the function of individual muscles. Information about the timing and level of activation of particular muscle during movement is crucial to understand how and why these typical responses are altered with pathology, in particular with knee OA.

During walking, subjects adopt individual strategies to coordinate their muscles and loading the joint. Muscle coordination is achieved by muscle excitation governed by the central nervous system (CNS) to enable body motion. This causes the generation of individual muscle forces that, through tendon insertions into bones, are transmitted to the skeletal system and moving joints. Therefore, estimation of muscle forces based on EMG activations is fundamental to understanding joint function, injury, and disease and important for developing better rehabilitation programs. Where this approach, i.e. EMG-driven model, tracks the desired kinetic and kinematics to get better estimation of muscle forces.

Based on cross-sectional studies, specific muscle activation differences have been related to degree of OA severity (Hubble-Kozey et al., 2009; Zeni et al., 2010); however, further studies are needed to establish relationships between OA progression and neuromuscular responses during walking. These findings provide the foundation for evaluating the effect of interventions on muscle activation characteristics during gait and alterations have been reported for both surgical and non-surgical treatments (Hubble-Kozey et al., 2010; Ramsey et al., 2007). Of interest

to the present study is to understand how and why these typical responses are altered with pathology, in particular with knee OA, in an attempted to capture a more complete neuromuscular and biomechanical description of lower extremity changes during gait that characterize different levels of disease severity. This would greatly enhance our understanding of the underlying neuromuscular mechanisms and provide us insight into the changes associated with disease progression.

The approach proposed in this study attempted to determine if changes can be captured on a general pattern of muscle forces among the major muscles surrounding the knee joint exists in those with OA progression or not. Establishing such a pattern in severe OA could serve to distinguish disease progression assisting clinicians in establishing disease severity. As well, a better understanding of the neuromuscular alterations associated with severe knee OA could provide a framework for prescribing appropriate interventions aimed to improve the mechanical environment of the joint and perhaps prolong the need for an invasive intervention.

Two different questions were posed. First, does the neuromuscular system modify their activation patterns to stabilize the knee joint, in line with the biomechanical changes associated with OA severity? We hypothesized that altered gait function at the hip and ankle joints would be present in OA patients to compensate for the impaired knee function. Second, do the patterns of muscle forces change in pathological gait? We hypothesized that knee muscle forces are lower in people with OA compared to NP.

5.2 Methods

5.2.1 Subjects

At Cardiff University, there is a large amount of pre-collected historical data available. Ethical approval was obtained from the Research Ethics Committee for Wales and Cardiff and Vale University Health Board. Data was used from thirty participants, each gave their informed written consent prior to data collection, divided into three groups: eleven Non-pathological subjects (NP), ten with medial knee OA awaiting high tibial osteotomy (pre-HTO), and nine with late stage knee OA awaiting total knee replacement (pre-TKR). The mean and SD of mass, height and age for NP, pre-HTO and pre_TKR cohorts were (79.5±12.6 kg, 87.8±14.9kg, 88.7±20.3 kg), (175.5±3.7cm, 173.4±8.8cm, 169.8±7.8cm), (32.9±5.2 years, 50.3±6.9 years, 66.6±9.8 years) respectively.

NP participants had no knee pain in the past during daily activities and have not been diagnosed with lower extremity joint OA. All OA patients participated in this study were selected by orthopaedic consultants from the University Hospital of Wales, Cardiff. The inclusion/exclusion criteria for the participants have been described in details previously, section 1.3.

5.2.2 Data Acquisition

Experimental gait data was collected in the motion analysis laboratory at Cardiff School of Engineering. Gait analysis was performed using nine 120Hz infra-red motion capture units (Qualisys, Sweden) for HTO and 60Hz for TKR cohorts. Qualisys Track Manager (QTM, Qualisys, Sweden) was used to capture full body motion using reflective markers placed on the trunk, pelvis, and both the upper and

lower limbs (modified Cleveland clinic marker set)(Reinbolt et al., 2005) for pre-HTO cohort and eight NP subjects. The CAST protocol marker set was used for the pre-TKR cohort and three NP subjects. The configuration of the markers is shown in the Figure 5.1, for pre-HTO cohort, and Figure 5.2 for pre-TKR cohort. Four floor-embedded force platforms (Bertec Corporation) were used to capture the ground reaction force vectors with a sample rate of 1080 Hz. Prior to data collection, the laboratory is calibrated to define the global coordinate system (GCS).

Muscle electromyographic (EMG) data were collected bilaterally, using Trigno™ Wireless EMG System (Delsys, Inc.) with sampling frequency of 1080 Hz, for seven muscles: rectus femoris, vastus lateralis, vastus medialis, biceps femoris, semitendinosus, gastrocnemius lateralis, and gastrocnemius medialis. The electrodes were placed longitudinally over the muscle bellies after standard preparation of the skin, according to SENIAM recommendations (Hermens et al., 2000), involving shaving, exfoliation, cleaning of the skin and finally electrode gel was used to reduce the electrode–skin impedance (Doorenbosch and Harlaar, 2004).

Participants were asked to perform different ADLs (i.e., walking at their self-selected walking speed, walking up and down stairs and finally sitting-to-standing). Meanwhile, information regarding muscle EMG, ground reaction force and three dimensional movements of the markers were collected using the synchronized movement analysis system. Six trials of level gait, six trials of ascending/descending a four step staircase, and two trials of standing/sitting were recorded for each subject. The stance phase was determined by the ground reaction force measured by the force plate, at heel strike to toe-off.

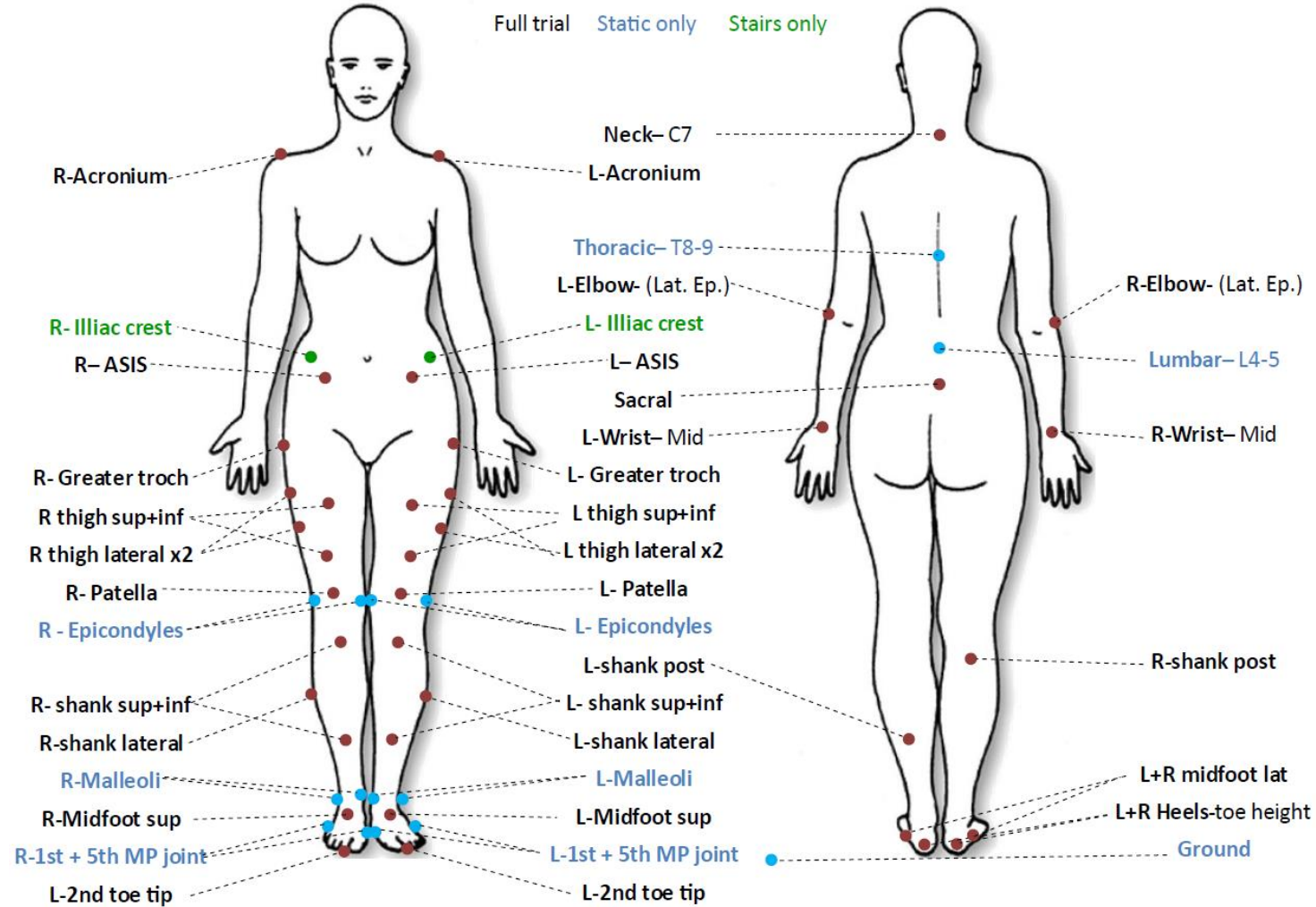


Figure 5. 1: A modified Cleveland clinic marker set used for pre-HTO cohort, illustrating tracking (red), anatomical (blue), and joint anatomical and tracking (blue with red circle).

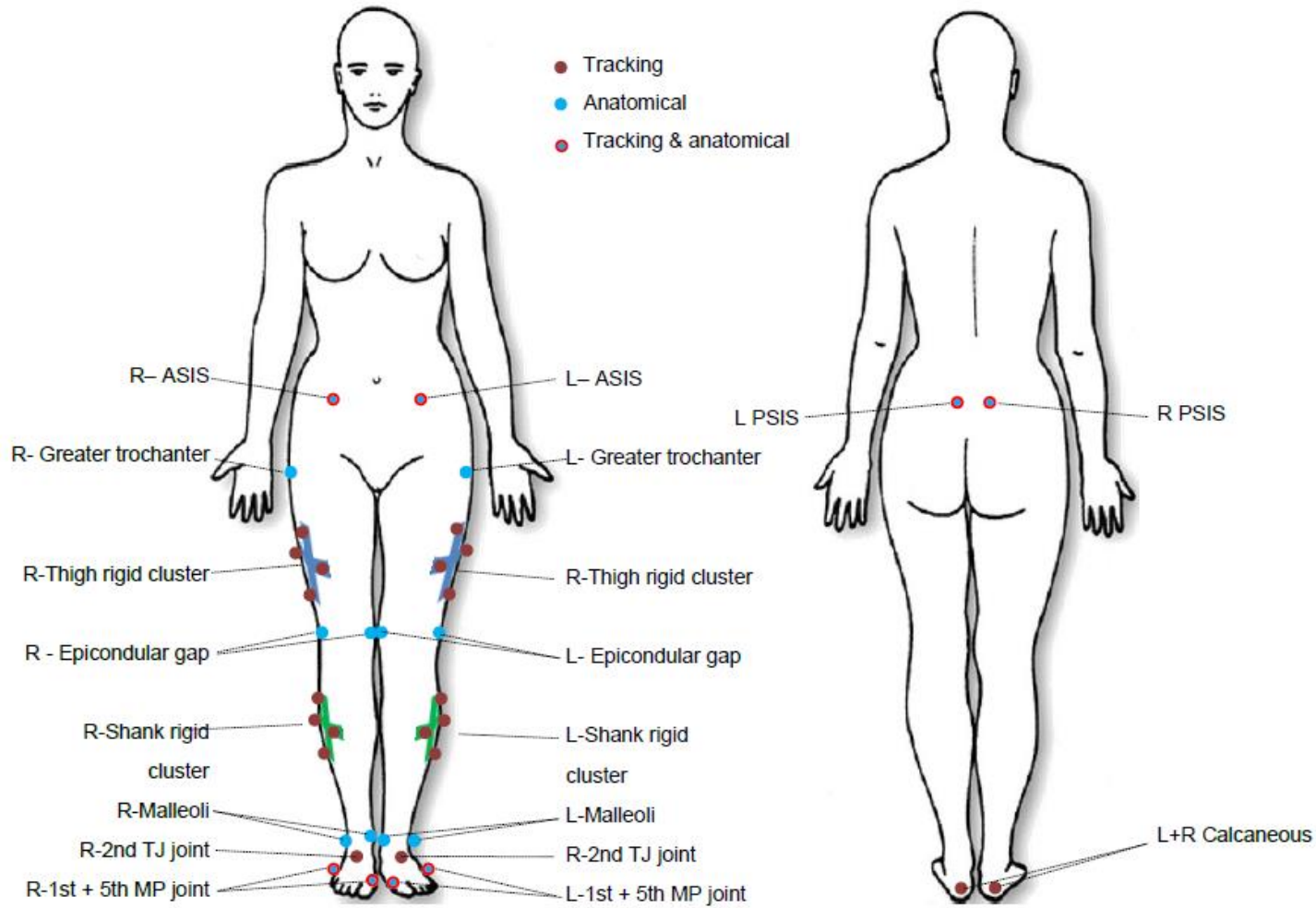


Figure 5. 2: CAST protocol marker set used for pre-TKR cohort, illustrating tracking (red), anatomical (blue), and joint anatomical and tracking (blue with red circle).

5.2.3 Data Reduction and Analysis

The experimental data for each participant was saved in *.c3d format. A MATLAB toolbox to process motion data for neuromusculoskeletal modeling and simulation (MOtoNMS) (Mantoan et al., 2015b) was used to extract marker trajectories, ground reaction forces, and EMG signals as a *.trc format (Track Row Column) for marker trajectories and as *.mot format (Motion) for ground reaction forces and EMG signals. These formats are compatible to both: OpenSim and CEINMS (**Error! Reference source not found.**).

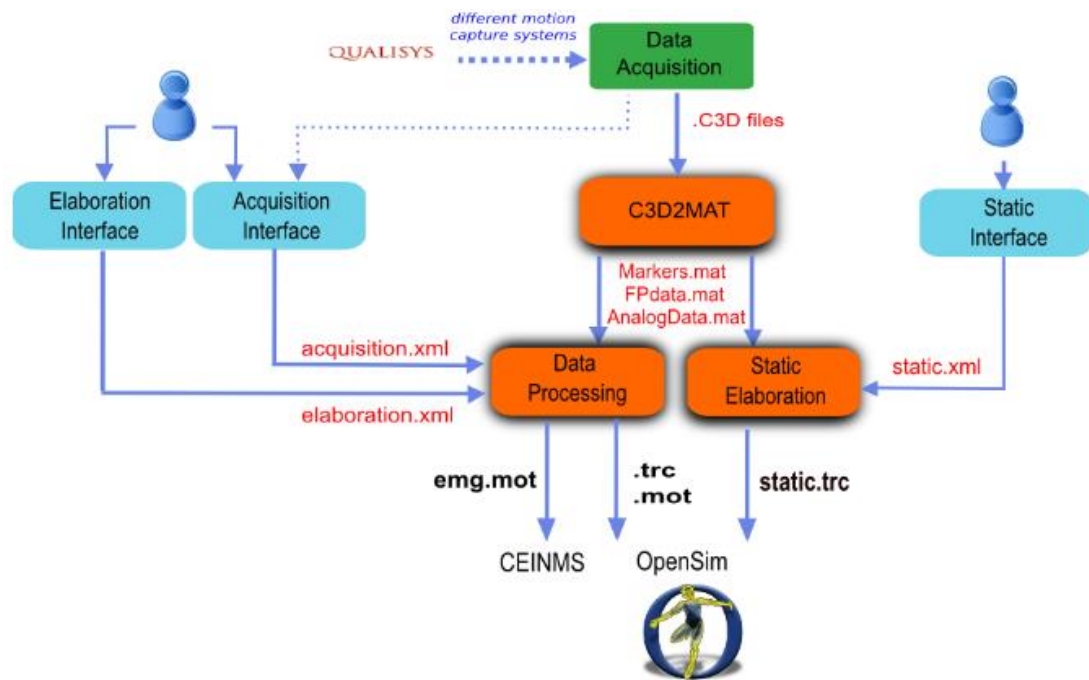


Figure 5. 3: Sequence of steps taken to obtain the OpenSim input files containing the kinematic and kinetic data (*.trc and *.mot files, respectively) (Mantoan and Reggiani, 2015).

After this, the data was defined in the OpenSim coordinate system. Then, gait biomechanics were determined using OpenSim v3.3 (Delp et al., 2007). For each participant, the customized generic anatomic model was scaled to the participant's

anthropometry, by using a static trial. The final anatomic model was then used to calculate joint angles, moments and musculo-tendon unit (MTU) kinematics (lengths and moment arms) for walking trials using OpenSim inverse kinematics (IK), inverse dynamics (ID) and muscle analysis tools, respectively. Gait biomechanics and processed EMGs were then used to calibrate and execute an EMG-driven model, to each subject, to estimate muscle forces by using CEINMS (Pizzolato et al., 2015). This pipeline is summarized in **Error! Reference source not found.** and will be described in detail in the following sub-sections.

The model consists of four basic components, as summarised below and it is described in further details in (Buchanan et al., 2004; Buchanan et al., 2005; Kumar et al., 2012; Lloyd and Besier, 2003; Manal and Buchanan, 2013):

1. An anatomical model to estimate muscle-tendon lengths and moment arms.
2. An EMG to activation model to represent muscle activation dynamics.
3. A Hill type muscle model to characterize muscle tendon contraction dynamics and estimate the forces in the muscle-tendon complex.
4. Model calibration.

5.2.3.1 The Anatomical Model:

A generic anatomic model was created using OpenSim v3.3(Delp et al., 2007). The customized generic anatomic model, (previously adapted in collaboration with Leuven), was used as a template for each participant, Figure 5.4. This model is composed by the head, torso and lower limbs, having 92 musculo-tendon actuators and 23-degrees-of-freedom (DOFs). The DOFs included in the model include: pelvis position (3 DOFs), pelvis orientation (3degrees of DOFs), lumbar joint (3 DOFs),

and for each leg, hip flexion–extension, abduction–adduction, and internal–external rotation, knee flexion–extension, ankle plantar flexion–dorsiflexion, inversion–eversion and toes flexion–extension. The tibio-femoral joint was customized to permit flexion/extension and internal/external rotations while knee adduction/abduction rotations were locked, because these rotations cannot be accurately measured with skin-surface markers (Benoit et al., 2006). Moreover, allowing knee adduction/abduction rotations would have resulted in condylar lift-off, a feature not observed in instrumented prosthetic knee implants (Fregly et al., 2012). Overall, the customized anatomic model enabled the calculation of three external knee moments, while preventing non-physiological knee rotations.

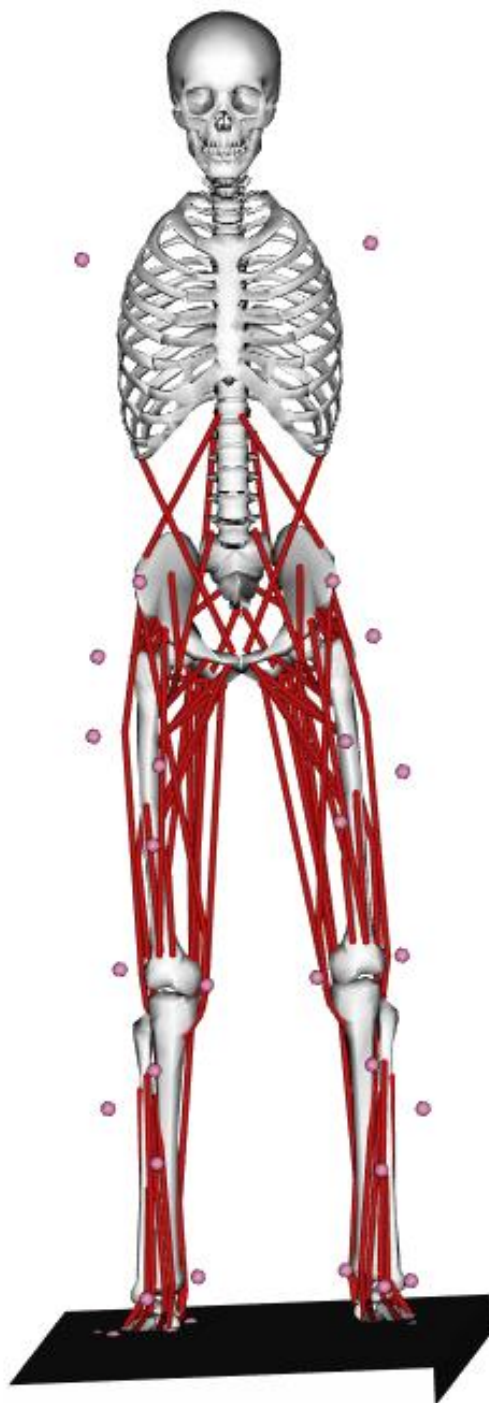


Figure 5. 4: The OpenSim generic 3D knee anatomic model used as a template for each participant. The tibio-femoral mechanism was customized to permit flexion/extension and internal/external rotations while locking adduction/abduction rotations (Benoit et al., 2006; Saxby et al., 2016).

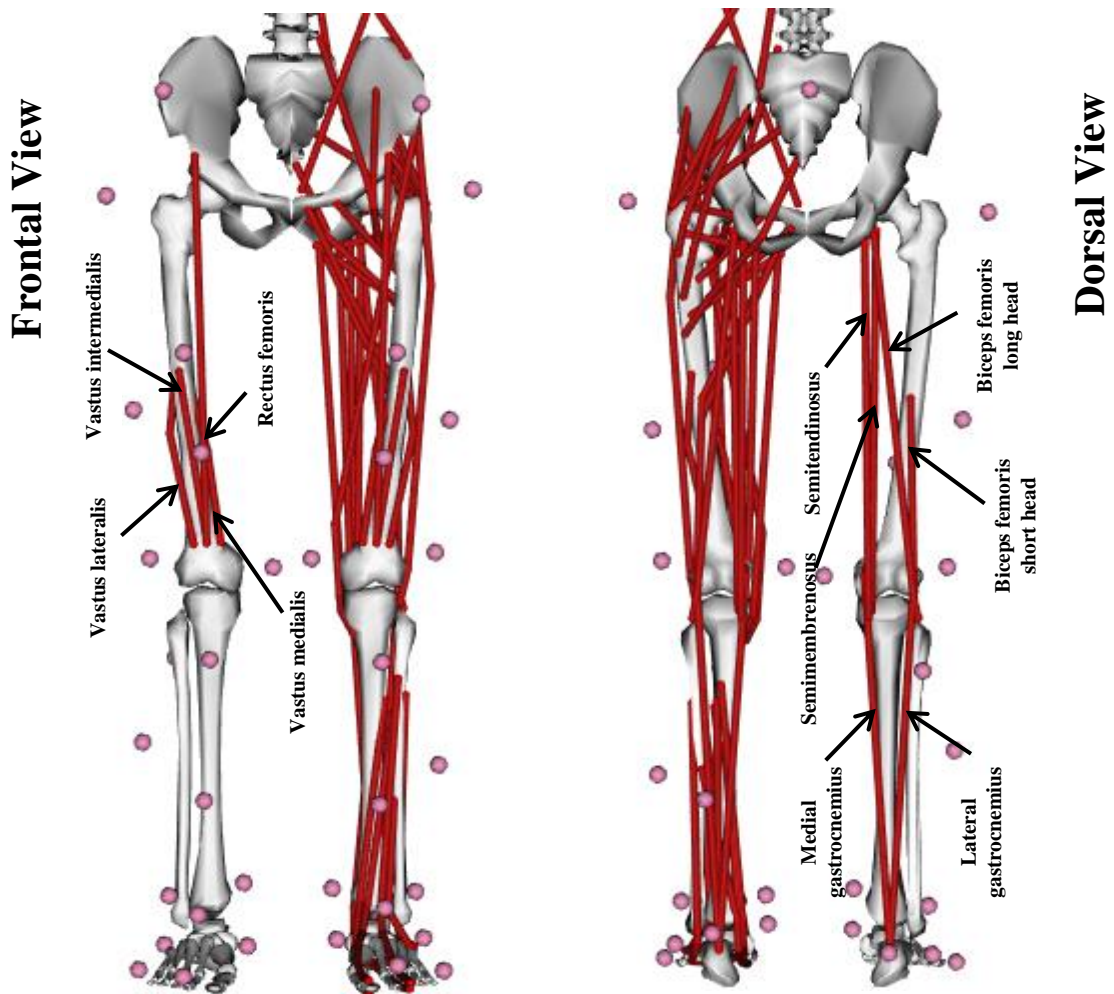


Figure 5. 5: Muscles examined in the EMG-driven model to estimate their forces, where the Quadriceps muscles are shown in the frontal plane, while the Hamstrings and Gastrocnemius muscles are shown in the dorsal view.

5.2.3.1.1 Scaling the model:

Marker location data from anatomical landmarks during a standing reference trial were used to scale the model in OpenSim, adapting it to the dimensions and mass of the subject, by scaling with the Scale Tool. In doing this step, the bones and muscle attachment points of the model were scaled to match the anthropometrics of the subject.

Cardiff marker configuration was used, which are different from the default used in OpenSim. Hence, some model markers were excluded and others were created, for example: HTO and TKR protocols have their own marker set and their marker configuration are shown in Figure 4.1 and Figure 4.2, respectively.

The scaling tool allows manual changes to the dimensions of each body. However, the scaling based in the measurements was used. Using this option, as shown in Figure 4.6, the distance (m_1) between each pair of virtual markers (the markers placed in the model Gait_2392) and the corresponding marker pair used in the experimental trial (e_1) is calculated. Considering these two distances, the scale factor ($s_1 = e_1/m_1$) is determined and used to change the dimensions of the body associated with the markers pair.

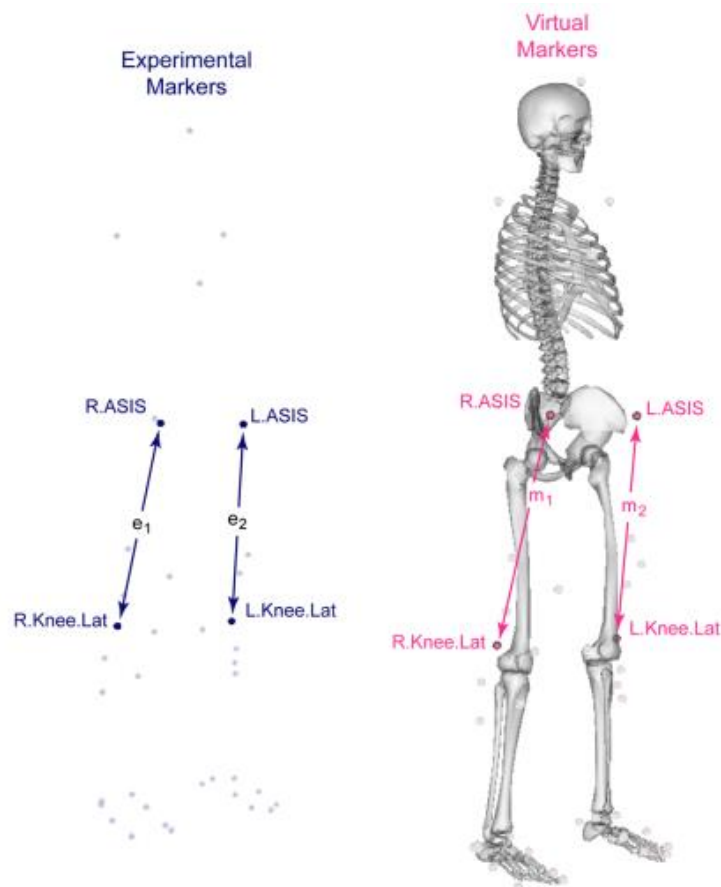


Figure 5. 6: A simplified illustration of how the scaling factor is calculated (Anderson et al., 2010).

It was necessary to associate each body one or more marker pairs, so that the corresponding scale factor was applied to that body. In the case of using more than one marker pair, the scale factor is computed as the average between the factors computed for each one. Figure 4.7 shows each body and the corresponding marker pairs associated. It is recommended that the pelvis is scaled non-uniformly (Anderson et al., 2010), this is, with different scale factors in the three directions. For that reason, markers over the anterior superior iliac spines (ASIS) were used to adjust the width of the pelvis while xy direction of the pelvis was associated with the marker pairs L.Asis/Sacral and R.Asis/Sacral. The greater trochanter marker was used for femur scaling. C7, ASIS markers and ASIS and sacral markers were used as scaling pairs for the torso.

Markers were weighted while those representing bony landmarks and functional joint centres (hip, knee and ankle joint) were given larger weights compared to other markers, i.e. these markers are tracked more tightly and the tracking errors are more penalized.

As recommended in the OpenSim guide (Anderson et al., 2010), the coordinates representing the subtalar and metatarsophalangeal joints were locked, as the model does not possess enough muscles to control these joints.

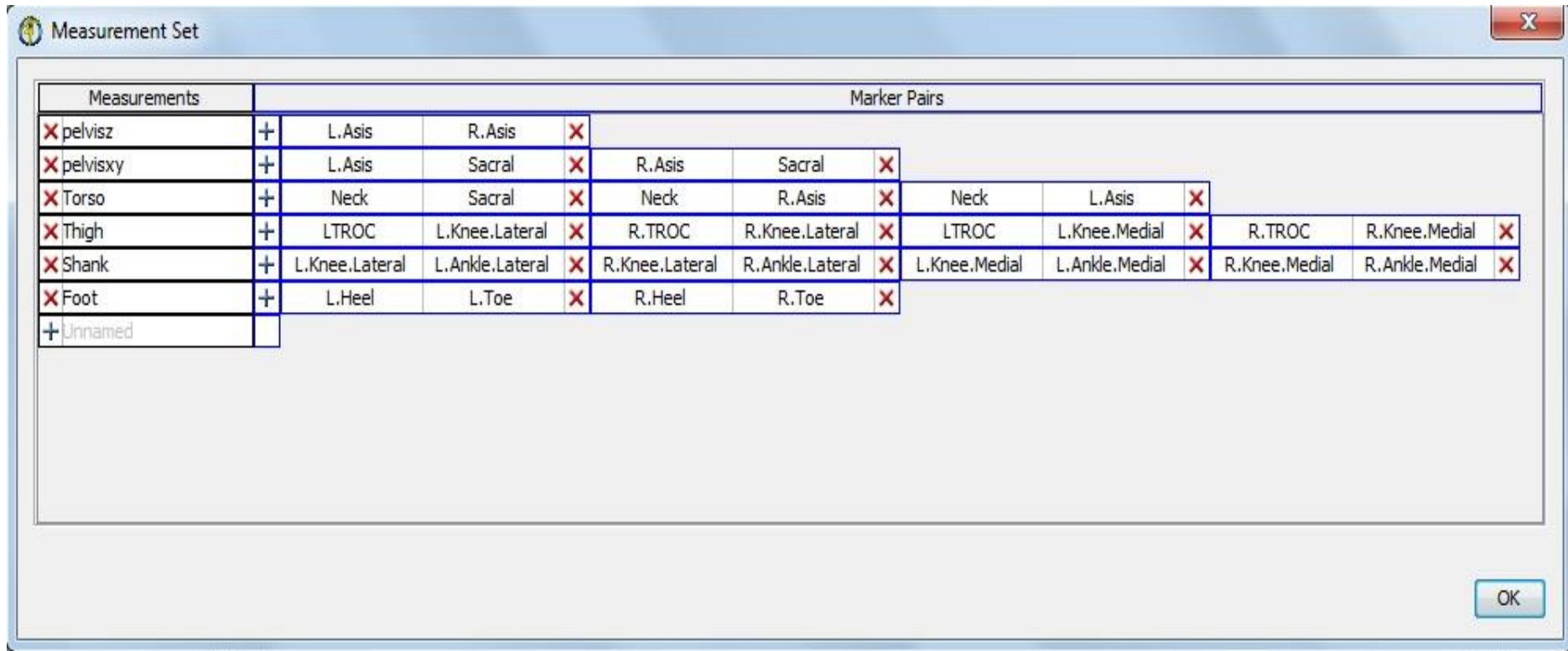


Figure 5. 7: Display of the Measurement Set of the Scaling Tool. At the left is presented a list of the measurements, associated with the scale factors are computed using the marker pairs shown at the right.

5.2.3.1.2 Estimation of joint angles and joint moments in gait:

The OpenSim inverse kinematics tool was used to estimate joint angles through each step of motion. This step can be expressed as a weighted least squares problem, which minimizes the errors between experimentally measured marker trajectories and trajectories of the corresponding virtual markers.

$$\text{Squared Error} = \sum_{i=1}^{\text{markers}} w_i (\vec{x}_i^{\text{subject}} - \vec{x}_i^{\text{model}})^2 + \sum_{j=1}^{\text{joint angle}} w_j (\vec{\theta}_j^{\text{subject}} - \vec{\theta}_j^{\text{model}})^2 \quad (5.1)$$

$\vec{x}_i^{\text{subject}}$ and \vec{x}_i^{model} are the three-dimensional positions of the i^{th} marker, for the subject and the model; $\vec{\theta}_i^{\text{subject}}$ and $\vec{\theta}_i^{\text{model}}$ are the angles of the j^{th} joint, for the subject and the model; w_i and w_j are weighting factors to allow marker and joint angle data to be weighted separately (Delp et al., 2007).

In the inverse kinematics solution only flexion/extension and internal/external rotation were permitted at the knee whereas adduction/abduction was fixed (Benoit et al., 2006; Gerus et al., 2013; Saxby et al., 2016). However, this configuration enabled flexion/extension, internal/external rotation and adduction/abduction moments at the knee joint to be determined via inverse dynamics. The inverse dynamics tool was used to estimate moments at each joint responsible for a given movement by taking into consideration the measured kinematic information and ground reaction forces, according to the basic equations of motion.

5.2.3.1.3 Muscle analysis:

The analyze tool was used to estimate muscle-tendon lengths and moment arms of the muscle-tendon units relative to the degree of freedom, during the stance phase of the gait cycle.

5.2.3.2 EMG Activation Model (muscle activation dynamics):

The transformation from normalized EMG to muscle activation was obtained by including second-order dynamics, electromechanical delay and a non-linear relationship between EMG and muscle activation. This step was achieved by using the Matlab toolbox, MOtoNMS, that converts raw EMG data, marker trajectories, and ground reaction forces (GRF) from C3D file to .mot, .trc and .mot files, respectively.

This step involves transformation of an EMG signal to a parameter called muscle activation, e_i , as shown in Figure 5. 1. EMG data were processed and normalized according to both maximal isometric contraction and ADLs, as recommended in chapter 2 (**PDM). Muscle activation, e_i , represented mathematically as a time varying value with a magnitude between 0 & 1. The muscle activation of semimembranosus was assumed to be equal to that of Semitendinosus; biceps femoris-long head and biceps femoris-short head were assumed to be identical and the muscle activation of vastus intermedius was the average of that from vastus lateralis and vastus medialis.

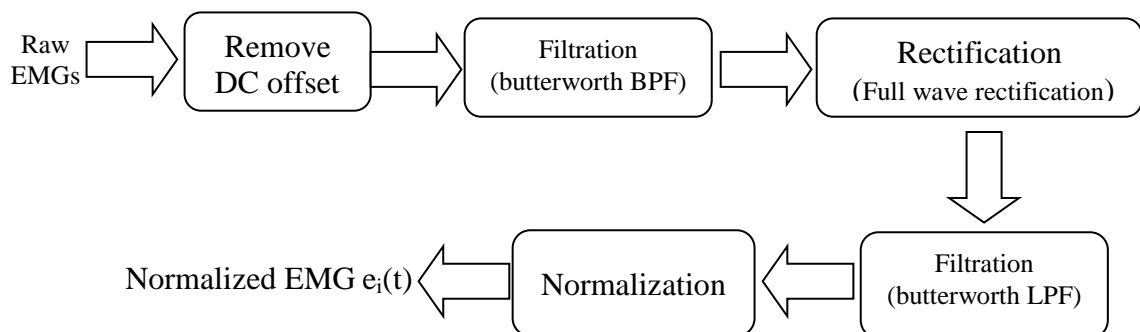


Figure 5. 8: Transformation of raw EMG to muscle activation (Buchanan et al., 2004; Manal and Buchanan, 2013).

$e(t)$ for each muscle can then be converted to $u(t)$ by equation,

$$\mathbf{u}(t) = \alpha \mathbf{e}(t - d) - \beta_1 \mathbf{u}(t - 1) - \beta_2 \mathbf{u}(t - 2) \quad (5.2)$$

$$\beta_1 = \gamma_1 + \gamma_2, \quad \beta_2 = \gamma_1 \times \gamma_2, \quad \alpha - \beta_1 - \beta_2 = 1$$

initial guesses for ($\gamma_1=0.5$, $\gamma_2=0.5$, $d=200$ ms, and $A=0.1$) and they will be refined later.

then $u(t)$, neural activation, be converted to $a(t)$, muscle activation, by equation,

$$\mathbf{a}(t) = \frac{e^{A\mathbf{u}(t)} - 1}{e^A - 1} \quad (5.3)$$

5.2.3.3 A Hill-type muscle model (muscle contraction dynamics).

The general arrangement for the muscle-tendon unit is represented by one non-linear spring (the tendon) in series with an active contractile element (muscle fibers), which is in parallel with a passive elastic element (representing passive properties of surrounding tissues). The pennation angle of the muscle is also taken into account as described by Zajac (Zajac, 1989) and shown in Figure 4. 9.

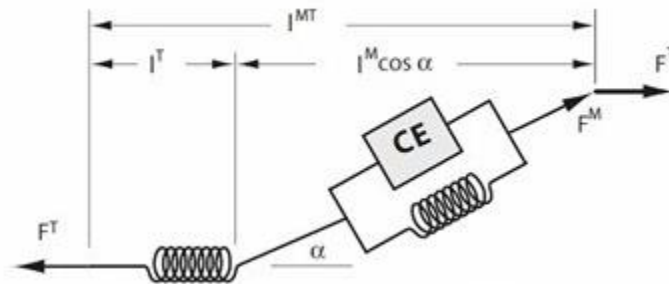


Figure 5. 9: Mechanical representation of Hill Model as described by Zajac in 1989 (Zajac, 1989). LMT is the length of the muscle-tendon unit, IT is the length of the tendon unit, IM is the length of the muscle, F^T is the force transmitted by the tendon,

F^M is the force produced by both the contractile element (CE) and passive element of the muscle, and α is the pennation angle.

The Hill-type muscle model is used to estimate the force that can be generated by the contractile element of the muscle fibre, with the general form of the function given by:

$$\mathbf{F}^m(\mathbf{t}) = \mathbf{f}(\mathbf{v}) \mathbf{f}(\mathbf{l}) \mathbf{a}(\mathbf{t}) \mathbf{F}_0^m \quad (5.4)$$

Where,

$F^m(t)$ = time varying muscle fiber force.

$f(v)$ = normalized velocity dependent fiber force.

$f(l)$ = normalized length dependent fiber force.

$a(t)$ = time varying muscle activation.

F_0m = maximum isometric muscle fiber force.

A three component Hill model is often used to describe the mechanical components of the muscle-tendon unit in motion. This model is based on several known mechanical properties of skeletal muscles and connective tissue, such as the force-velocity and the force-length characteristics, as will be described next, and allows musculoskeletal researchers to account for the viscoelasticity in the system. This representation of the muscle tendon unit is very common within musculoskeletal models, such as those described by (Arnold et al., 2010; Delp et al., 1990).

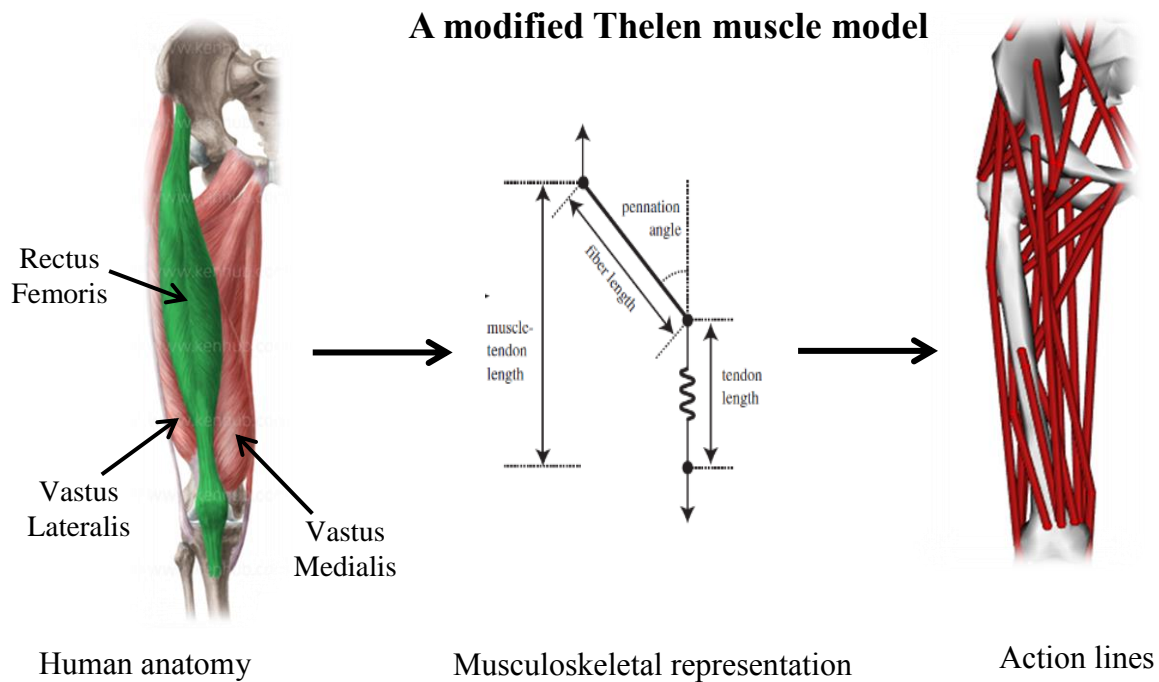


Figure 5. 10: Representation of the muscle within musculoskeletal models.

Thelen (2003) modified the muscle model that was frequently used in order to allow for more subject-specific adjustments of parameters affecting muscle function. To do this, Thelen simplified the Force-length model into two portions, a Gaussian (active) portion and an exponential (passive) portion and presented a parametric equation to model the force generated due to tendon strain. Thelen modified parameters of the musculo-tendon model (deactivation time constant, maximum muscle contraction velocity, and passive muscle strain due to maximum isometric force) to more accurately represent muscle function data reported in older adults. Thelen's representation of the Hill-type muscle-tendon unit is commonly used and is the default muscle-tendon representation used in OpenSim models (Arnold et al., 2010; Delp et al., 2007).

Then the Musculo-tendon force is calculated by equation,

$$\begin{aligned}
 F^{mt}(\theta, t) &= F^t \\
 &= [F_A m + F_P m] \cos \phi \\
 &= [f_A(l) f(v) a(t) F_0 m + f_P(l) F_0 m] \cos \phi
 \end{aligned} \tag{5.5}$$

5.2.3.3.1 Force-Velocity Relationship:

Hill (Hill and Sec, 1938) mathematically described the contractile relationship between F (the tension/load in the muscle) and v (the velocity of the contraction) in terms of thermodynamics. He found experimentally that when a muscle was shortened a distance x, it gave off a “shortening heat” (H) such that:

$$\mathbf{H} = \mathbf{a} \mathbf{x} \tag{5.6}$$

Where

a = is a thermal constant related to the cross-sectional area of the muscle.

Hill also proposed that the muscle force decreases while the muscle is shortening and increases while the muscle is lengthening. He found that $\frac{a}{F_0^m} \sim 0.25$, where F_0^m is the maximum muscle force generated when the muscle fibres are at optimal length, l_0^m .

The total energy of the system is the sum of the energy associated with the shortening heat and that due to work (force \times distance). Thus,

$$\mathbf{total\ energy} = \mathbf{F^m x} + \mathbf{H} = (\mathbf{F^m} + \mathbf{a})\mathbf{x} \tag{5.7}$$

by differentiating eq.(5. 7), the rate of energy liberation is

$$(F^m + a) \frac{dx}{dt} = (F^m + a)v^m \quad (5.8)$$

This rate of energy liberated must be proportional to the change in force. Since muscle forces started at maximal values, F_0^m , this can be written as

$$(F^m + a)v^m = b(F_0^m - F^m) \quad (5.9)$$

Where the constant b defines absolute rate of energy liberated.

The Hill equation can be rewritten as

$$F^m = \frac{F_0^m b - av^m}{b + v^m} \quad (5.80)$$

Where v^m is the muscle fiber contraction velocity, which in this equation is muscle shortening velocity only (i.e., concentric contractions).

5.2.3.3.2 Force-Length Relationship:

The Musculo-tendon unit is composed of two parts: an active part which generates force when activated, like a motor, and a passive part that applies a resistive force when stretched beyond a resting length, like a rubber band.

The active part of a muscle is caused by the contractile elements. These yield a peak force when the sarcomeres are at an optimal length, i.e., when there is optimal overlap of the actin and myosin myofilaments. When the muscle is at a length above that optimal length, it cannot generate as much force because there is less actin-myosin overlap which reduces the force-generating potential of the muscle. Likewise, if it is below that length, its maximal potential force will drop off. Human muscles reach their peak force values when the sarcomeres are at a length of $2.8 \mu\text{m}$

(Walker and Schrodt, 1974). When the sarcomeres within a muscle fibre are at this length, we say that the fibre is at optimal fibre length, l_0^m .

This active muscle force function is given by:

$$\mathbf{F}_{Am} = \mathbf{f}_A(l) \mathbf{F}_0^m \mathbf{a}(t) \quad (5.9)$$

where F_{Am} is the muscle force represented by the active part of the force-length curve.

Whereas the passive muscle force function is given by:

$$\mathbf{f}_p(l) = \frac{e^{10(l^m-1)}}{e^5} \quad (5.10)$$

where l^m is normalized passive muscle force and \tilde{l}^m is normalized muscle length.

The actual passive muscle force is a function of maximum isometric force (Zajac, 1989), given by

$$\mathbf{F}_{Pm} = \mathbf{f}_p(l) \mathbf{F}_0^m \quad (5.11)$$

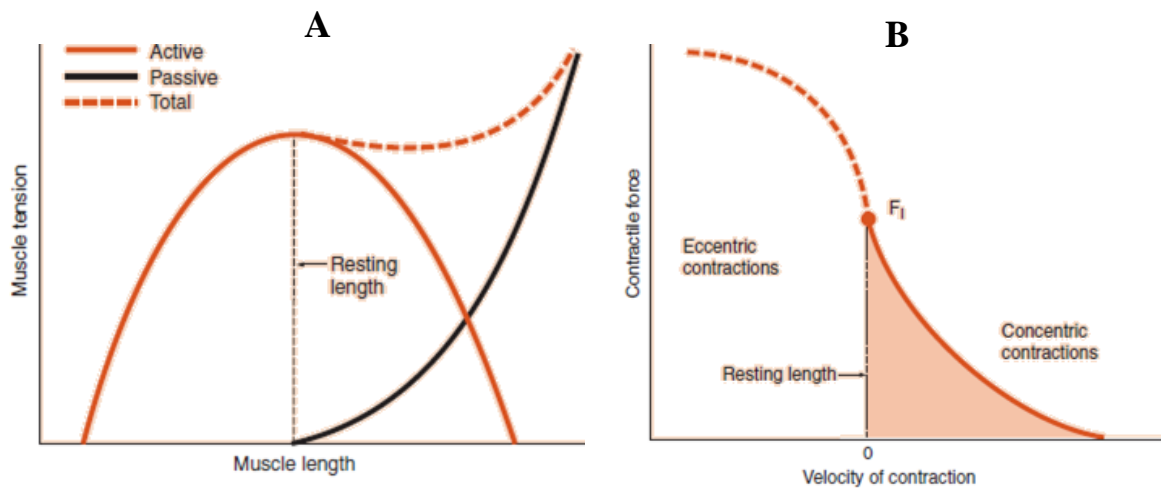


Figure 5. 11: A.) Tension-length and B.) Force-velocity characteristics of skeletal muscle (Shiva, 2007).

5.2.3.3.3 Pennation Angle:

The pennation angle is the angle between the tendon and the muscle fibres and it has a significant effect on the force (Figure 5.9). Since the tendon is in series with the muscle fibres, the force in the tendon, F^t , is given by

$$F^t = F^m \cos(\phi) \quad (5.12)$$

Is the pennation angle constant? This question was addressed by (Buchanan et al., 2004), who reported that although the pennation angle changes with joint angle and muscle activation, very little work has been done to verify this with in-vivo imaging studies.

A typical equation to calculate pennation angle, $\phi(t)$, at time t is:

$$\phi(t) = \sin^{-1} \left(\frac{l_0^m \sin \phi_0}{l^m(t)} \right) \quad (5.13)$$

where $l^m(t)$ is the muscle fiber length at time t, and ϕ_0 is the pennation angle at muscle optimal fibre length, l_0^m .

Hill-type models take into account the force-length and force-velocity relationships.

So, the musculo-tendon force is calculated by equation,

$$\begin{aligned} F^{mt}(\theta, t) &= F^t \\ &= [F_A m + F_P m] \cos \phi \\ &= [f_A(l) f(v) a(t) F_0 m + f_P(l) F_0 m] \cos \phi \end{aligned} \quad (5.14)$$

Where,

F_{Am} is the muscle force represented by the active part of the force-length curve.

$$F_{Am} = f_A(l) F_{Om} a(t)$$

F_{Pm} , is the passive muscle force which is given by,

$$F_{Pm} = f_P(l) F_{Om}$$

This step requires input from the musculoskeletal geometry model.

The final MTU force depends on:

1. MTU's maximum active isometric muscle force and contraction velocity.
2. Optimal fiber length(L_m^o).
3. Instantaneous pennation angle.
4. Instantaneous muscle fibre length.

The force for each muscle is then multiplied by its moment according to the musculoskeletal geometry.

5.2.3.4 Model Calibration:

For each participant in this study, a calibration step was performed using four walking trials, which were not the walking trials used for estimating muscle forces. During calibration, each of the MTU parameters were constrained to change within predefined boundaries to ensure that the muscle operated in their physiological range. For example: L_m^o and L_t^s change within $\pm 5\%$ from their initial values, while the shape factor A was bounded between -3 and 0 and the coefficients γ_1 and γ_2 between -1 and 1. A strength coefficient bounded between 0.5 and 2.5. These coefficients were used to scale peak isometric force of the different muscle groups.

This step is important to tune the model parameters to minimize the difference between the EMG-driven model joint moment and the moment computed using inverse dynamics.

EMG for muscle, m , at time, t , was transformed into muscle activation (a) to activate a Hill-type muscle model (muscle contraction dynamics). The force, F , for each muscle was then multiplied by its sagittal plane moment arm according to the musculoskeletal geometry obtained using OpenSim. Individual muscle moments were then summed at each point in time to obtain the model estimated sagittal plane knee moment, $M_{\text{model}}(t)$. The knee moment was also calculated using inverse dynamics from 3D video-based motion capture data, $M_{\text{Expt}}(t)$. EMG-driven model parameters including activation coefficients, optimal fibre length (OFL), resting tendon length (RTL), and the maximum isometric force (Max Force) for each muscle were iteratively adjusted to minimize the sum-squared difference between the model estimated moment and the moment computed from inverse dynamics (represented by the crossed circle). The process of optimally adjusting model parameters is depicted by the light blue dotted arrows, Figure 5. 12.

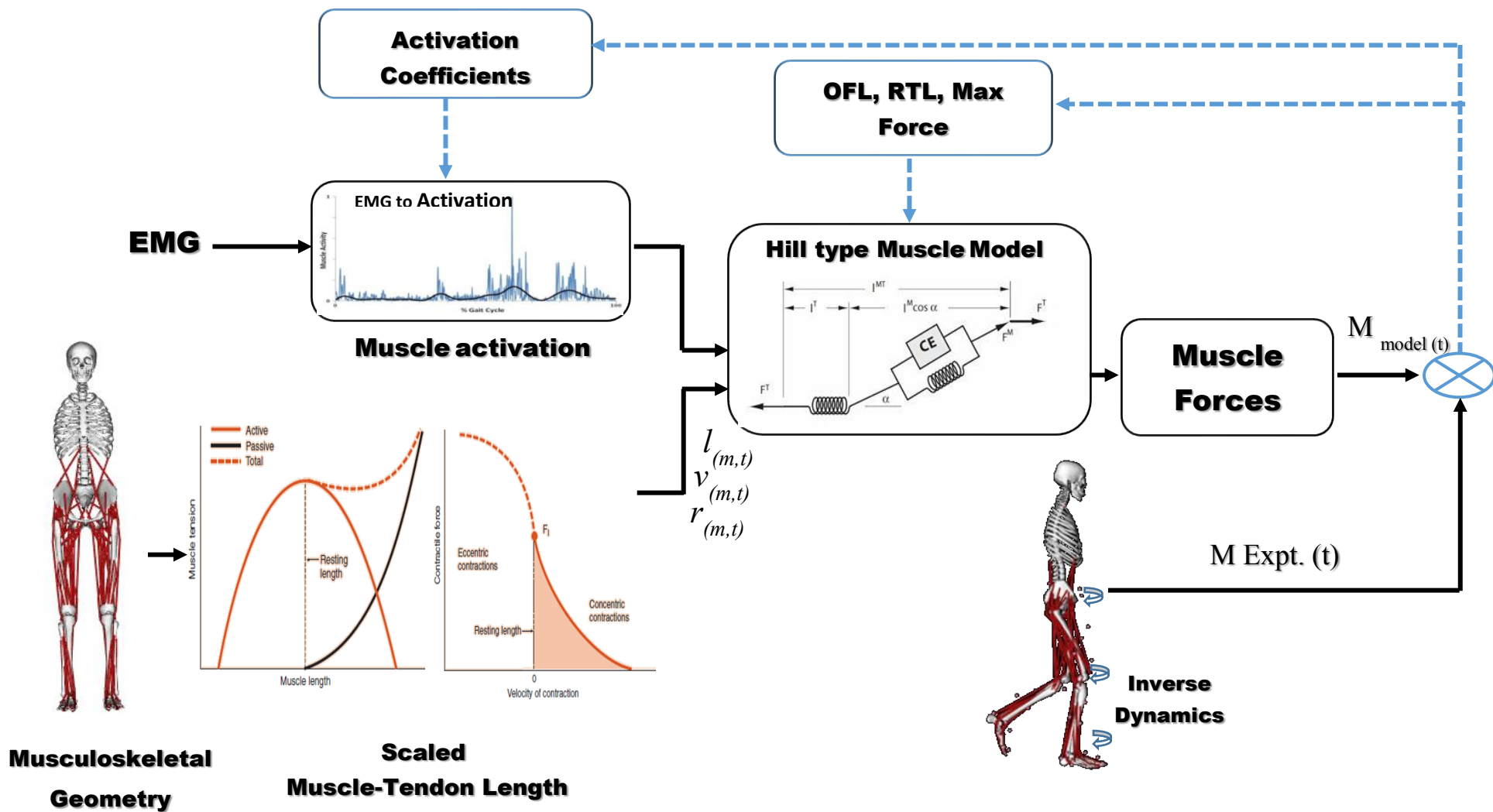


Figure 5. 12: Flowchart of the EMG- Driven musculoskeletal model to estimate muscle forces.

5.2.4 Initial and revised approach

As shown in Figure 5.1 and Figure 5.2, marker set used in pre-HTO differs from that used in pre-TKR. Where the former, has a full body marker set and the latter has markers just on the lower limb. Therefore, the estimated muscle forces will be compared across the three groups by using an initial approach and a revised approach.

Where

The Initial approach:

- NP and pre-HTO cohorts used a full body model driven by EMGs normalized by **PDM.
- Pre-TKR cohort used a lower limb model driven by EMGs normalized by *PDM.

The Revised approach:

- NP, pre-HTO, and pre-TKR cohorts used a lower limb model driven by EMGs normalized by *PDM.

5.2.5 The gait cycle

The typical walk consists of a repeated gait cycle. The cycle itself contains two phases:

- Stance phase (weight bearing) - accounts for 60% of the gait cycle.
- Swing phase (non-weight bearing) - accounts for 40% of the cycle.

For obvious reasons the stance phase is of importance, particularly given that the foot has several unique functions to fulfill during the time it is in contact with the ground. As it must absorb shock at heel strike, adapt to the ground surface, and provide a stable platform for the body

Stance phase begins with heel strike the ground and ends with toe off of same foot and it is broken up into five sub-phases:

- Initial contact (heel strike): occurs when the heel contact to the ground; i.e, 0% of stance.
- Loading response (foot flat): is defined as the first 10% of the gait cycle, which is about 16.7% of the stance phase.
- Mid-stance (single leg stance): is defined as the first 10-30% of the gait cycle, which is about 16.7-50% of the stance phase.
- Terminal-stance (heel off): is defined from 30-50% of the gait cycle, which is about 50-83% of the stance phase.
- Pre-swing (Push off): is the final stage of the stance phase. It begins immediately as the heel lifts off the ground. Defined from 50-60% of the gait cycle, which is about 83-100% of the stance phase.

5.2.6 Knee Pain, Function and Stiffness

Physical function, pain and stiffness were assessed using the Oxford Knee Score (OKS), Knee Outcome Survey (KOS), Western Ontario and McMaster University Osteoarthritis Index (WOMAC), Pain Audit Collection System (PACS), and Knee injury and Osteoarthritis Outcome Score (KOOS). Each patient completed these questionnaires at their assessments to provide a subjective measure of how they perceive their knee function.

- The Oxford Knee Score (OKS) (Dawson et al., 1998) is intended specifically for use with knee surgery and asks the patients to assess their knee function by looking back over the last 4 weeks. It consists of 12 questions. There are

5 categories of response, each scored from 1 to 5, from least to most difficulty or severity. The scores are combined to produce a single score with a range from 12 for least difficulties to 60 for most difficulties. The final score is represented as a percentage.

- Knee Outcome Survey (KOS) (Irrgang et al., 1998) consists of 17 questions; seven relating to symptoms and ten relating to functional disability. The subject must select one from a number of associated statements which best describes their recent experience. A scoring system is used to rate knee function and display it as a percentage. A high final score is associated with a high level of knee function and vice-versa. Participants also rated their global knee function on a scale from 0% to 100% where 100% indicates no disability.
- The Western Ontario and McMaster University Osteoarthritis Index (WOMAC) (Bellamy, 1989) consists of 24 items divided into 3 subscales: pain (5 items), stiffness (2 items) and physical function (17 items) subscales. The WOMAC was designed as a 5-point Likert scale for each item, with high scores indicating high degree of impairment. The total score was normalised to a 0–100 score.
- Pain Audit Collection System (PACS) (Griffiths et al., 2003) uses 0-10 numerical rating scales, from least to most difficulty or severity, to assess the interference of pain with mood, walking, general activity, work, relations with other, sleep and enjoyment of life.
- The Knee injury and Osteoarthritis Outcome Score (KOOS) (Roos et al., 1998) holds five separately scored subscales: Pain, other Symptoms, Function in daily living (ADL), Function in Sport and Recreation (Sport/Rec), and

knee-related Quality of Life (QOL). The previous week is the time period considered when answering the questions. Standardized answer options are given (5 Likert boxes) and each question is assigned a score from 0 to 4. Scores are then transformed to a 0-100 scale, with zero representing extreme knee problems and 100 representing no knee problems.

5.3 Statistical Analysis

Mean and standard deviation were calculated from the measured parameters. The Kolmogorov–Smirnov and Levene tests were used to assess the normality of distribution ($p > 0.05$) and the equality of variances, respectively. Not all data were normally distributed nor homogeneous. Accordingly, a Kruskal Wallis test of nonparametric data was performed. All statistical analyses were performed using SPSS (version 20, Chicago, IL). Pairwise comparisons using the Dunn-Bonferroni approach are automatically produced for any dependent variables for which the Kruskal-Wallis test is significant.

The stance of gait was divided into early stance, the first 50% of stance, (loading) and late stance, the second 50% of stance, (propulsion) phases. The following variables were calculated for statistical analysis: hip, knee, and ankle joint moments and knee muscle forces during early and late stance. These variables were compared between the two OA groups and NP. All pairwise tests was used to determine significant interactions when main effects were present.

5.4 Results

Knee outcome measures are different among the OA groups. These are summarized in Table 5.1. The oxford knee score, knee outcome measures, western ontario and mcmaster universities osteoarthritis index (WOMAC), pain audit collection system (PACS) were found to be higher for the pre_TKR group , compared the pre_HTO group, indicating more severe self-reported pain and stiffness, and reduced function. This is also approved in knee injury and osteoarthritis outcome score (KOOS), were pre-TKR patients have lower scores than pre-HTO. A low score is associated with extreme knee problems and vice-versa.

Table 5. 1: Study population knee outcome measures (mean \pm SD) for OA subjects (n= 9 for Pre-TKR subjects, n=10 for Pre-HTO subjects).

Dependent Variable	Covariates	mean \pm sd
Pre-TKR	Oxford	29.2 \pm 9.5
	KOSOADL	49.1 \pm 13.9
	WOMAC	49.8 \pm 21.5
	PACS	47.6 \pm 24.1
	KOOS Pain	54.0 \pm 22.9
	KOOS Symptom	53.6 \pm 22.2
	KOOS ADL	59.6 \pm 21.5
	KOOS Sport/Rec	18.8 \pm 23.4
	KOOS QOL	32.8 \pm 22.1
Pre-HTO	Oxford	25.8 \pm 10.0
	KOSOADL	48.8 \pm 15.8
	WOMAC	38.9 \pm 23.2
	PACS	39.3 \pm 25.0
	KOOS Pain	63.1 \pm 24.7
	KOOS Symptom	65.0 \pm 19.5
	KOOS ADL	69.4 \pm 24.4
	KOOS Sport/Rec	41.1 \pm 32.7
	KOOS QOL	43.1 \pm 21.7

Group ensemble-averaged waveforms for gastrocnemii, quadriceps and hamstrings muscle forces illustrate that specific changes were systematic with increased structural severity (Figure 5.13). A less range of sagittal plane knee joint angle was observed for OA cohorts as compared to NP, Figure 5.14. Hip, knee and ankle moment curves (normalized to body weight and height (%BW.H)) for NP, pre-HTO and pre-TKR patients are provided in Figure 5.15. In agreement with (Asthephen et al., 2008), less range of sagittal plane joint moments were seen at the knee, hip, and ankle joints. Both OA groups had increased their hip abduction moment. However, pre_TKR group exhibited different pattern than pre-HTO and NP subjects. A similar trend can be seen on the knee adduction moment. Where pre-TKR subjects do not have a clearly defined double peak and there is a trend of having a higher mid to terminal stance knee adduction moment, related with OA severity. This pattern was consistent with previous literatures (Asthephen et al., 2008; Rutherford et al., 2008).

The sequence and timing of muscle activity predicted by the model was consistent with previous literature (Winby et al., 2009), where vasti and gastrocnemius generated the largest forces about the knee, for NP subjects. Whereas, individuals with OA had elevated quadriceps and lateral hamstring activity compared to NP (Rutherford et al., 2011).

A summary of the individual muscle forces estimated by using revised approach is reported during early and late stance, Table 5. 2 and Table 5 .3, respectively.

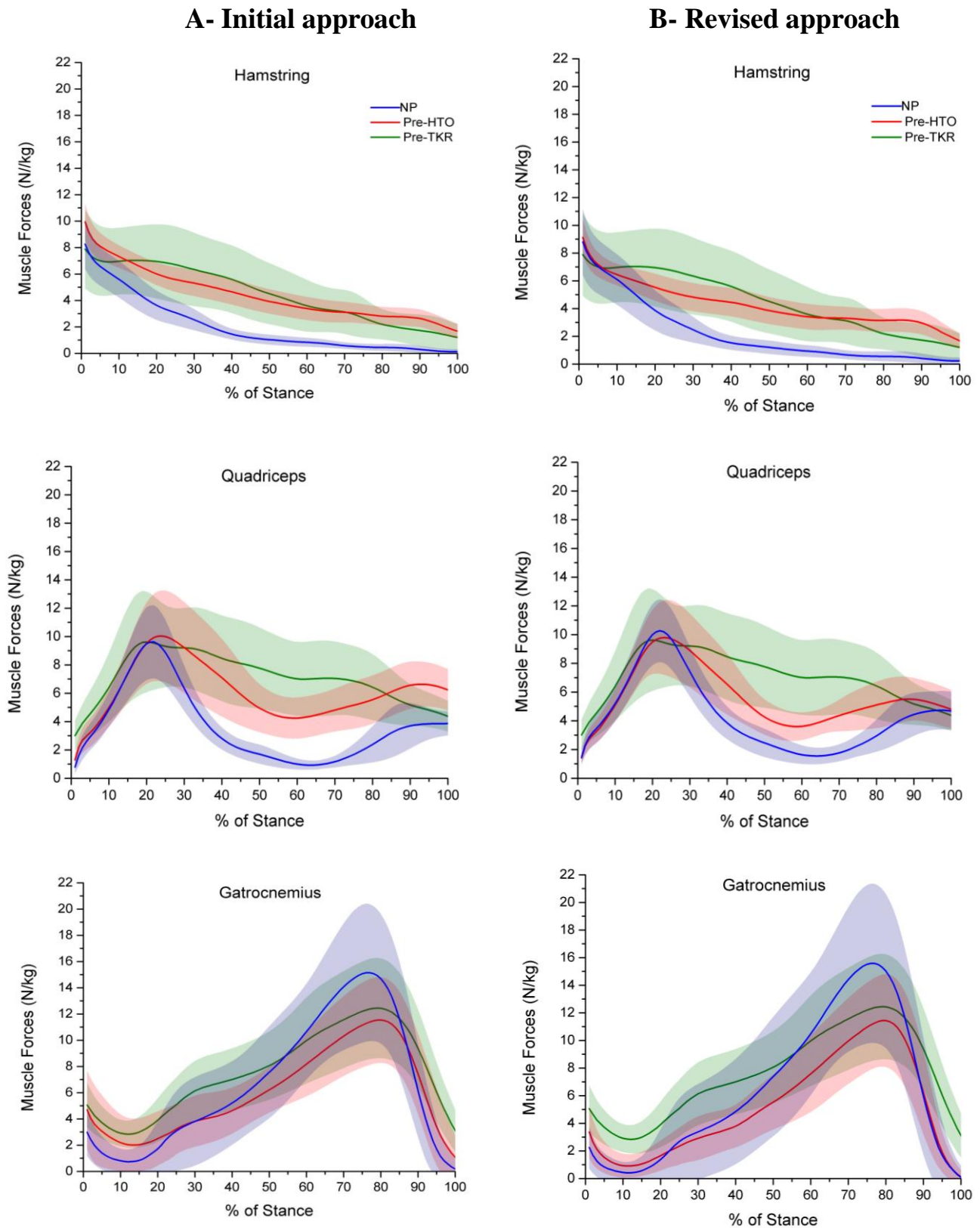


Figure 5. 13: Muscle Forces estimated by using full-body model driven by EMG normalized by **PDM for (NP & pre-HTO) and lower limb model driven by EMG normalized by *PDM for pre-TKR –**Initial approach (A)** and by using lower limb model driven by EMG normalized by *PDM for all cohorts –**Revised approach (B)**.

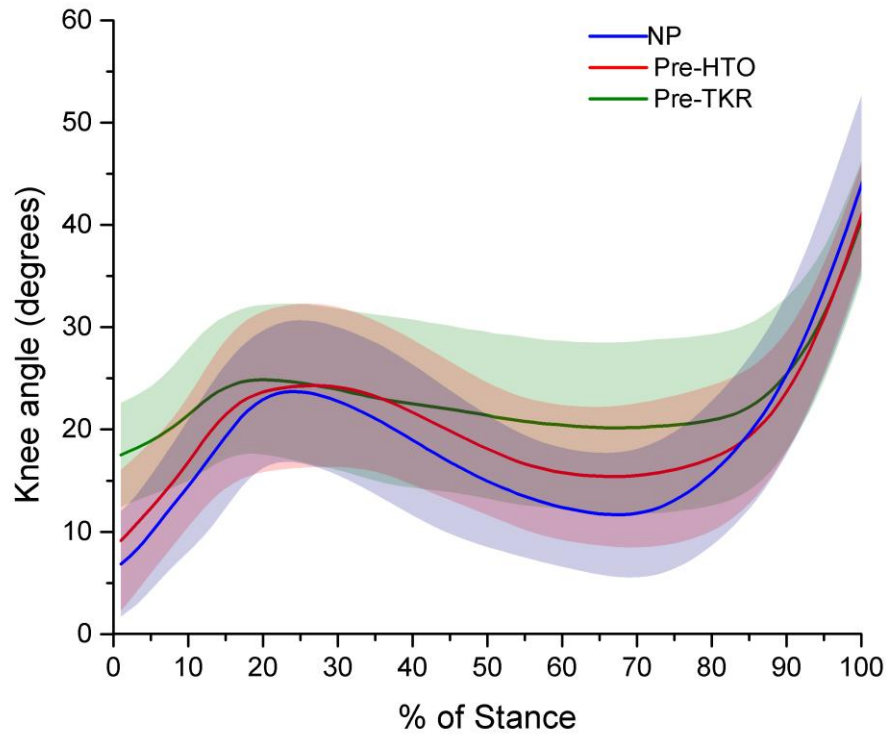


Figure 5. 14: Mean knee kinematic waveforms during stance-phase for NP, Pre-HTO and pre-TKR subjects calculated by using lower limb model for all cohorts – Revised approach.

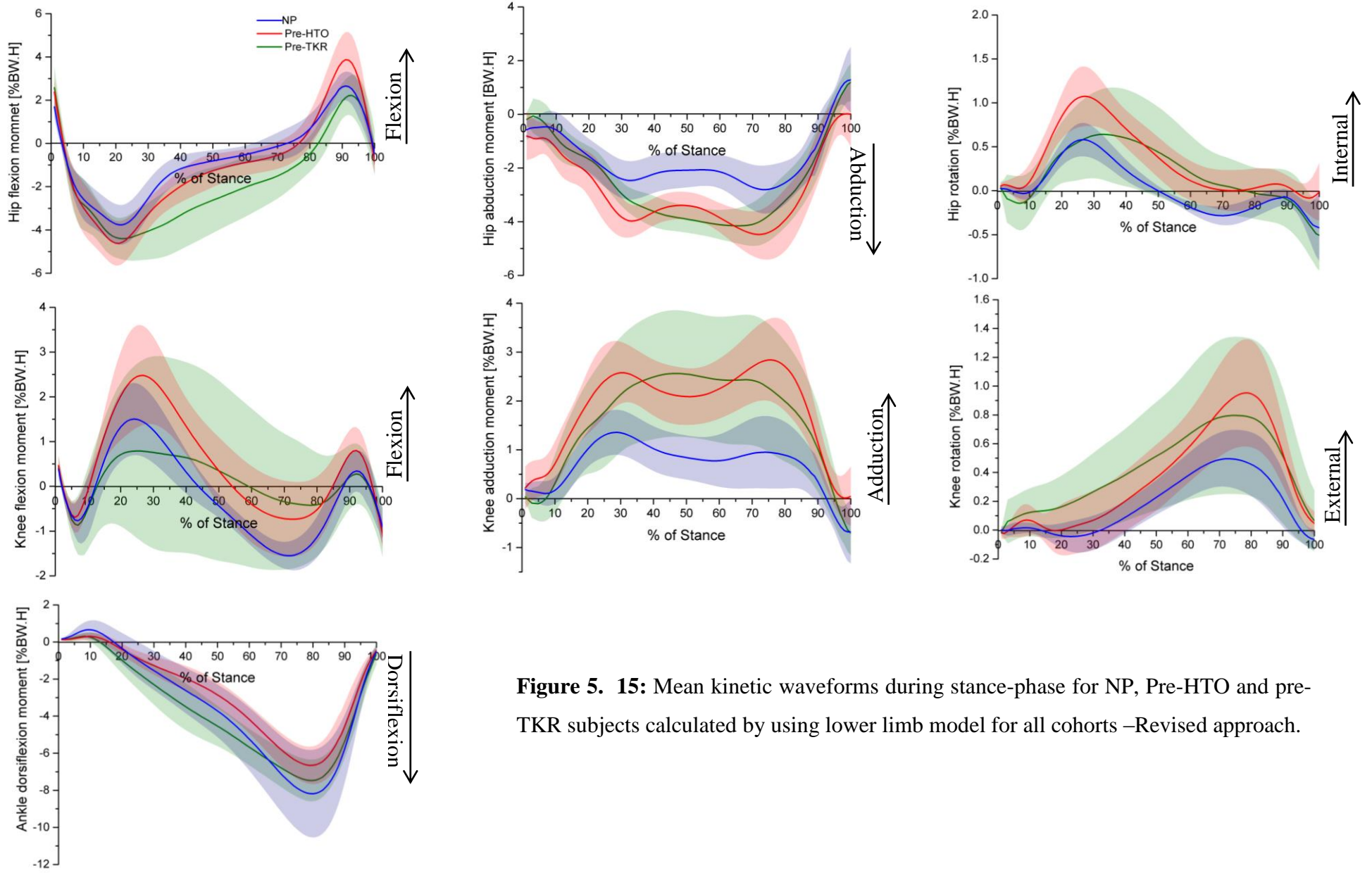


Figure 5. 15: Mean kinetic waveforms during stance-phase for NP, Pre-HTO and pre-TKR subjects calculated by using lower limb model for all cohorts –Revised approach.

Table 5. 2: Early stance peak knee extensor and flexor muscle forces for NP subjects, pre-HTO and pre-TKR patients, estimated by using lower limb model driven by EMG normalized by *PDM for all cohorts (Revised approach).

Muscle Group	Muscle	Force (N/kg)			P NP vs. HTO	P NP vs. TKR	P HTO vs. TKR
		NP n=11	Pre-HTO n=10	Pre-TKR n=9			
Knee Extensors	Rectus Femoris	1.43±1.55	2.98±1.72	3.03±1.91			
	Vastus Medialis	2.12±1.55	2.35±1.43	3.22±2.35			
	Vastus Intermedius	2.30±1.77	3.37±1.60	3.54±1.71			
	Vastus Lateralis	3.02±2.41	3.74±1.68	3.58±1.56			
	Sum(Quadriceps)	9.74±5.32	10.27±4.25	13.12±5.03			
Knee Flexors	Semimembranosus	3.81±3.07	3.68±2.03	4.36±1.86			
	Semitendinosus	1.09±0.84	1.03±0.64	1.09±0.37			
	Bicep Femoris Long Head	2.14±1.60	2.75±1.30	2.30±0.61			
	Bicep Femoris Short Head	1.12±0.88	2.57±1.53	2.80±1.67			
	Sum (Hamstrings)	8.10±5.02	9.25±4.27	9.56±3.31			
	Medial Gastrocnemius	5.68±4.48	2.36±0.96	5.27±4.43	0.013†		
	Sum (Gastrocnemius)	6.77±4.84	6.17±1.64	8.98±5.40			

† Significant differences between groups (p<0.05).

Table 5. 3: Late stance peak knee extensor and flexor muscle forces for NP subjects, pre-HTO and pre-TKR patients, estimated by using lower limb model driven by EMG normalized by *PDM for all cohorts (Revised approach).

Muscle Group	Muscle	Force (N/kg)			P NP vs. HTO	P NP vs. TKR	P HTO vs. TKR
		NP n=11	Pre-HTO n=10	Pre-TKR n=9			
Knee Extensors	Rectus Femoris	1.16±1.50	2.48±0.92	2.98±1.75			
	Vastus Medialis	0.88±0.59	1.50±0.74	1.92±0.68			
	Vastus Intermedius	0.94±0.83	1.88±0.83	2.52±1.64		0.006†	
	Vastus Lateralis	1.20±0.93	2.23±0.87	2.38±1.12			
	Sum(Quadriceps)	4.88±3.77	6.55±2.51	9.40±3.70			
Knee Flexors	Semimembranosus	0.34±0.33	0.68±0.57	1.57±1.24			
	Semitendinosus	0.19±0.21	0.58±0.55	0.64±0.34			
	Bicep Femoris Long Head	0.24±0.37	1.37±1.27	1.46±0.65		0.003†	
	Bicep Femoris Short Head	0.38±0.34	1.98±1.54	2.42±1.08	0.038†	0.002†	
	Sum (Hamstrings)	1.09±0.94	4.37±2.94	5.87±2.46	0.024†	<0.001†	
	Medial Gastrocnemius	11.28±6.05	5.03±2.99	9.35±6.49	0.001†		
	Lateral Gastrocnemius	3.51±1.91	3.08±1.50	5.55±5.13			
Sum (Gastrocnemius)	14.71±7.42	11.76±3.51	14.79±8.22				

† Significant differences between groups (p<0.05).

Table 5. 4: Early and late stance peak hip, knee, and ankle kinetics for NP, pre-HTO and pre-TKR subjects, calculated by using lower limb model for all cohorts (Revised approach).

Gait event	Joint Kinetics	Moment [%BW.H]			P NP vs. HTO	P NP vs. TKR	P HTO vs. TKR
		NP n=11	Pre-HTO n=10	Pre-TKR n=9			
Early Stance	Hip flexion(+)/extension (-)	-3.82±0.91	-4.66±1.01	-4.82±1.20			
	Hip adduction/abduction	-2.54±0.74	-4.06±0.65	-3.94±0.58	0.001†	0.004†	
	Hip internal/external rotation	0.60±0.19	1.11±0.32	0.76±0.45	0.004†		
	Knee flexion(+)/extension (-)	1.53±0.80	2.55±1.09	1.38±1.58			
	Knee adduction/abduction	1.39±0.44	2.66±0.64	2.51±1.18	0.007†	0.029†	
	Hip internal(+)/external rotation(-)	-0.08±0.08	-0.09±0.12	-0.04±0.06			
	Ankle plantar-flexion(+)/dorsiflexion(-)	0.35±0.19	0.69±0.48	0.32±0.25			
Late Stance	Hip flexion(+)/extension (-)	2.74±0.70	3.95±1.27	2.42±0.90	0.038†		0.02†
	Hip adduction/abduction	-2.91±0.85	-4.61±0.87	-4.32±0.63	0.002†	0.014†	
	Hip internal/external rotation	-0.30±0.11	-0.05±0.20	-0.17±0.37	0.031†		
	Knee flexion(+)/extension (-)	-1.59±0.31	-0.85±0.79	-0.76±1.60			
	Knee adduction/abduction	1.02±0.70	2.88±0.79	2.60±1.33	0.004†	0.033†	
	Hip internal(+)/external rotation(-)	0.51±0.20	0.96±0.37	0.87±0.50	0.034†		
	Ankle plantar-flexion(+)/dorsiflexion(-)	-8.23±2.37	-6.73±1.00	-7.50±1.12	0.007†		

† Significant differences between groups (p<0.05).

5.5 Discussion

Results showed that knee OA is a multifactorial disease process, involves many interrelated factors that interact to produce biomechanical and neuromuscular changes throughout the disease process.

The key finding for the gastrocnemius muscles was that subjects with OA had reduced muscle forces compared to NP individuals during the second half of the stance (Figure 5.13). This could be happening as a consequence of a reduction in knee extension moment (Figure 5.15) for OA groups; i.e, the role of a plantar flexor–knee extension couple.

A plantar flexor–knee extension couple, which was addressed by (Gage., 2004; Zajac and Gordon, 1989), plays a key role in knee control during gait. According to this phenomenon, under load, the plantar flexors (i.e gastrocnemius) are capable of holding the tibia back and this extends the knee; Figure 5.16. Brunner and Rutz (2013) found that knee extensors (quadriceps) can control only the first phase of knee extension, during the response to loading. The second phase, resulting in maximal knee extension in NP individual, is contributed by the plantar flexors. In line with this finding, results of this study have shown that patients with OA had reduced their knee extension moment during late stance. Therefore, less gastrocnemius muscle force were developed in OA groups compared to NP, to control knee extension moment during late stance.



Figure 5. 16: Schematic drawing of the plantar flexion–knee extension couple (working only under load) (Brunner and Rutz, 2013).

On the other hand, OA patients in the current study employed greater levels of quadriceps and hamstring forces during 30-80 % of stance, which is synchronized with high adduction moment at the knee. This finding is supported by an earlier research (Lloyd et al., 2005), where it was found that these muscle groups appear capable of supporting up to 100% of the applied adduction/abduction moment because of their abduction and /or adduction moment arm. Quadriceps muscle plays a major role in knee joint stability. Shortly after heel strike, it acts to prevent excessive or rapid knee flexion. OA subjects used substantially higher quadriceps and hamstring muscle force than NP subjects in an attempt to support the joint against an excessive knee adduction moment and a reduced knee flexion moment, Figure 5.15.

Previous research (Adouni and Shirazi-Adl, 2014) demonstrated that muscle forces in patients with OA dropped through stance phase except for mid stance. On the other hand, (Kumar et al., 2009) have reported that patients with OA used higher

hamstring and gastrocnemius muscle forces at both loading response and mid-stance phases of the gait cycle, than NP subjects.

Three explanations of why there is a variability of the predicted muscle forces between different studies. **First**, researchers adopted different musculoskeletal models to estimate muscle forces, where these models vary in terms of their joints' degrees of freedom and number of muscles involved, and no model contains all the muscles in the lower body. This requires some muscles in the model to be a combination of several anatomical muscles. **Second**, different methods were used to estimate muscle forces; “static optimization and computed muscle control (CMC) (Thelen and Anderson, 2006) methods” track the desired kinematics to estimate muscle forces while “EMG-driven approach” tracks the kinetic as well to get better estimation of muscle forces. However, Richards et al. (2009) has shown that the CMC method estimates higher muscle forces than static optimization. Where, the CMC method matches kinematics over the whole gait cycle, while static optimization produces joint moments at each time step, irrespective of the previous or forthcoming time step. Xiao and Higginson (2007) demonstrated that the cost function in CMC may not be perfect for OA subjects. **Third**, the method of normalization that is used to normalize muscle activity is critical for the accuracy of model predictions. Mantoan et al. (2015a) tested the impact of using different methods of normalization on model results. They normalized the data by using: the peak value obtained from different walking trials (WTN) and comparing the estimated muscle force with that predicted by normalizing the processed EMG by using Maximum voluntary contraction (MVC). They found that WTN can lead to unreliable results. A part of this was confirmed in chapter two, in which different methods of normalizations were tested and an illustrative example was presented, to

illustrate how different methods of normalization lead to a different estimate of muscle force for level gait.

However studies (Adouni and Shirazi-Adl, 2014; Kumar et al., 2009) have reported changes in muscle forces in patients with OA. These studies do not capture the shape and amplitude characteristics of the entire waveform. The approach proposed in this study attempted to determine waveform characteristics and the pattern of muscle forces in individuals with various severity of OA. Results showed an increase in quadriceps and hamstring activations in subjects with knee OA during 30-80 % of the stance phase of gait. An increase in muscle activation levels may indicate a weak muscle, resulting from a compensatory increase in neural drive to achieve the required muscle force to complete the given task (Ling et al., 2007; Sims et al., 2002).

The current findings are also consistent with other studies (Astleith et al., 2008; Levinger et al., 2013); a less range of sagittal plane knee joint angle was observed for OA subjects as compared to NP, Figure 5.14, which is commonly reported as a response to the pain and dysfunction associated with degenerative joint disease (Kaufman et al., 2001; Childs et al., 2004).

In principle, muscle control and external moments are the key to stance stability. Throughout stance, muscles contract when body alignment creates a moment antagonistic to weight bearing stability of the limb and trunk, and the amount of contraction is proportional to the magnitude of the demand torque that must be restrained. The next section will explain in details how hip, knee, and ankle joints have changed their kinetics through the disease progression.

5.5.1 Gait Kinetic changes with knee OA:

In the stance phase of the gait cycle, there are at least four crucial sub-phases where each one has a different role.

First, the initial heel contact (HS), at this moment the line of action of ground reaction force (GRF) passes posterior to the ankle centre, producing a plantar-flexion moment at the ankle. This moment is countered by the activation of ankle dorsiflexor muscles; this was the case for all groups. At the knee joint, the ground reaction force passes anterior to the knee axis creating an extension moment which is eccentrically controlled by hamstring muscles to avoid hyper-extension of the knee and slow the forward movement of the leg down by eccentrically contracting force. A higher knee flexion at HS was found in OA groups compared to NP, (18 ± 5 , 9 ± 6 , 7 ± 5 degrees for pre-TKR, pre-HTO, and NP, respectively), Figure 5.14. This may result to an increase in quadriceps and hamstring forces at heel strike for OA subjects where they are co-contracted to complete the given task and stabilize the joint. At the hip joint, the GRF passes anterior to the hip centre creating a flexion moment. Hip flexion moment is high in OA patients compared to NP, (2.6 ± 1.0 , 2.4 ± 0.6 , 1.7 ± 0.5 degrees for pre-TKR, pre-HTO, and NP, respectively), Figure 5.15. This changes might be a compensation mechanism to avoid using the quadriceps, and thereby reduce articular loads.

Second is the loading response phase. During this phase the ankle dorsiflexors eccentrically contract as the foot reaches the ground. The knee extensors contract to correct the position of the knee before it accepts weight. When the GRF vector is behind the joint axis, a knee flexion moment is created. As the vector moves forward of the knee axis, an extension moment is created at the knee which is mainly controlled by quadriceps muscle.

Third is the mid-stance phase, where by midstance the knee is extended & ankle is neutral again. Higher muscle forces appeared during this phase when the KAM is high and also as the knee extends in single limb support; i.e. peak quadriceps action occurs during this phase. OA patients exhibited greater peak knee flexion during early stance and less knee extension during late stance (Table 5.4). In the frontal plane, hip abduction moment is significantly high in OA patients compared to NP. However, the pre-TKR cohort exhibited a different adduction pattern than NP and pre-HTO cohorts. In both NP and pre-HTO subjects, the frontal plane moment are characterized by two distinct peaks, where the first peak was higher for the pre-HTO compared to the control group. This is attributed to the shift in the alignment of the femur laterally. A same trend was seen in the knee adduction moment, where a significant increase was identified for the pre-HTO and pre-TKR (2.66 ± 0.64 %BW.H, 2.51 ± 1.18 %BW.H), respectively, compared to NP (1.39 ± 0.44 %BW.H). Our results have shown that the pattern of KAM is a more important parameter than the peak value for distinguishing between NP and severe OA; i.e. mid- and terminal-stance knee adduction moment is a speed-independent measure, unlike the peak knee adduction moment.

Fourth, terminal stance and push-off phase, where the leg is accelerated forward by gastrocnemius pushing off against the ground and hip flexor activity, i.e., rectus femoris. During this phase there is a maximal knee extension moment, second peak knee adduction moment, and peak dorsiflexion moment. Nonetheless, the OA groups have reduced their dorsiflexion moment (Figure 5.15 and Table 5.4) and less gastrocnemius force was used (Figure 5.13 and Table 5.3), which may imply that people with knee OA inadvertently used greater hip flexors muscle force, rectus femoris, to propel the body forward, (2.98 ± 1.75 N/kg, 2.48 ± 0.92 N/kg, and

1.16±1.50 N/kg) for pre-TKR, pre-HTO and NP subjects, respectively. When comparing quadriceps muscle forces between groups, vastus inter-medialis significantly produced higher forces in pre-TKR subjects than NP. This may contribute to the reduced knee ROM both in stance and in swing. Mazzoli et al (2017) have pointed out that hyper activity of vastus inter-medialis can keep the knee extended and brake the knee flexion velocity at toe-off. The clinical relevance of this finding can be appreciated by considering that the vastus inter-medialis cross-sectional area, and consequently its force, is about four times that of the rectus femoris (Trappe et al, 2001). Where the latter responsible to propel the body forward during terminal stance.

Both OA groups had reduced late stance knee extension moment. This was happened as a compensation strategy, where they lean their trunk forward in order to shift the GRF close to the knee joint center of rotation, reducing knee extension moment. This position is controlled by the hip extensors (hamstring) as the hip is passively flexed. A significant increase was found for hip flexion in pre-TKR as compared to NP and pre-HTO groups. The consequence concerns of this is a reduced ankle dorsiflexion moment during late stance for OA groups (significantly for pre-HTO) compared to NP, allowing them to maintain forward motion despite limitations in hip extension.

In the transverse plane, the hip is significantly more internally rotated in pre-HTO than NP in the first half of stance, while less external rotation was seen for OA groups in the second half of stance.

A remarkable increase in the first peak of KAM for NP, in comparison to the second peak, was mainly contributed to the increase in the quadriceps force resisting the external knee flexion moment at this time interval. In contrast, the moderate increase of the second peak in the pre-HTO cohort, in comparison to the first peak, was due to

the increase in both quadriceps and hamstring muscle forces in this time interval as compared to NP. The double peak could not be identified in severe OA.

Symmetrically higher quadriceps and hamstring forces suggest that their co-contraction with gastrocnemius muscles could lead to higher joint contact forces that, combined with the excessive loading due to high KAM, would exacerbate joint destruction. Nonetheless, the OA group used greater vastus lateralis muscle force than control subjects, which may imply that people with knee OA inadvertently increase the activity of vastus lateralis as a compensatory strategy to reduce medial joint compression and subsequent pain. For OA, a reduced dorsiflexion moment and less gastrocnemius co-contraction suggest that gastrocnemius overload may not be the primary cause of joint degeneration. If this is the case, then an attention should be addressed on the counterbalancing role of the quadriceps and hamstrings during dynamic movements to stabilize the knee.

5.6 Limitations

There are some potential limitations with this study. One limitation is that the smaller sample size in the present study resulted in a low statistical power. However, joint angles, joint moments, and muscle activity from these simulations were compared to the results from previous studies with larger populations to ensure our subject had a typical gait pattern. Possible future research may be to increase the sample size to re-evaluate the conclusions of this study. Second, changes in walking speed were not considered in this study. Some previous studies have reported that differences in gait parameters (Zeni and Higginson, 2009) and high muscle activity (Franz and Kram, 2012) are related to increasing walking speed, where they are likely associated with increased muscle and joint contact forces. However, D’Lima et al. (2008) reported no

significant changes in contact forces during “normal” walking speeds, ranging from (0.47 m/s) to (1.34 m/s). Furthermore, an analysis at both a self-selected and controlled (1.0 m/s) walking speed, (Zeni and Higginson, 2009) revealed that subjects with knee OA had lower hip, knee and ankle joint moments when walking at freely chosen speeds.

Another limitation is that EMGs were recorded from just seven muscles bilaterally and used in this model to represent 10 muscles crossing the knee joint in the human body. This means that some muscles in the model represented the combination of multiple muscles in the human body that had similar functions. This may affect the evaluation of magnitude for knee muscle forces in this study.

5.7 Summary

This study provides meaningful information on gait adaptations used by patients with knee OA. Pre-TKR subjects adopt a gait pattern that differs from pre-HTO and NP subjects. Potential mechanisms identified to unload the affected structures, possibly by changing muscle coordination's (as explained in the previous chapter) as well as moments at the adjacent ankle and/or hip. Further, a reduction in gastrocnemius muscle force is linked to OA severity. Whereas, higher employment of both quadriceps and hamstring muscles during mid to terminal stance.

Because of limited number of EMG data, the study was conducted on a small number of participants in each cohort to generate important information that can be applied to a large cohort. The next chapter, large number of participants will be used to estimate muscle forces by using static optimization, i.e, no need for EMGs, to approve the differences seen in this chapter. However providing information of adaptation strategies for knee muscles in NP, pre-HTO, and pre-TKR subjects is

important, but it only tells one part of the story. Understanding the changes of the loading patterns and the corresponding changes in muscle forces are highly valuable to provide a clear image of how NP, pre-HTO, and pre-TKR subjects adopted different neuromuscular mechanisms and loading the knee. This information will be addressed in the next chapter.

Chapter 6

Alterations in Knee Loading and Neuromuscular Activity in Patients with OA

6.1 Introduction

A combination of biochemical, biomechanical, and neuromuscular factors are thought to lead to the development and progression of OA (Felson et al., 2000). The progression of OA is often accompanied by pain and may result in changes in gait and neuromuscular function, which may in turn lead to increased wear on the joint and further progression of the disease (Aststephen et al., 2008). However traditional gait analysis, using inverse dynamics, has provided significant information about biomechanical changes in OA (Aststephen et al., 2008; Sharma et al., 1998; Thorp et al., 2006; Zeni and Higginson, 2009). It is limited by its ability to create an integrated understanding of muscle activities and joint movements (Pandy and Andriacchi, 2010).

Advances in musculoskeletal modelling (MSK) has enabled researchers to generate gait simulations in efforts to estimate joint moments, muscle forces, and joint loading (e.g., (Kim et al., 2009; Lloyd and Besier, 2003; Winby et al., 2009)). Where joint contact forces are exerted between articulating surfaces of two adjacent bone segments, representing the sum of joint inter-segmental forces (or joint resultant forces) and joint compressive forces. Inter-segmental forces are due to body inertial forces and external forces applied, compressive forces are due to muscle forces and forces in other soft tissues (e.g., ligaments) crossing the joint. Muscle and joint contact forces, assuming ligament forces negligible, constitute the physiological loading condition of a bone segment. They anatomically represent the internal loads balancing the external loads in the instantaneous equilibrium of a bone segment.

Accurate knowledge of muscle forces is essential for planning and evaluating therapeutic approaches that aim to specifically alter the mechanics of tibio-femoral articulation. Therefore knowledge of muscle and joint contact forces during normal and pathological gait is valuable for researchers to provide insight into loading mechanisms associated with the progression of OA and would assist clinicians in diagnosing musculoskeletal disorders and developing new or improved treatments. However providing information of joint loading for NP, pre-HTO, and pre-TKR subjects is important, but it only tells one part of the story. Understanding the changes of the loading patterns and the corresponding changes in muscle forces are highly valuable to provide a clear image of how NP, pre-HTO, and pre-TKR subjects adopted different neuromuscular mechanisms and loading the knee.

The purpose of this study is to estimate knee contact force (KCF) in OA patients. It is hypothesized that loading patterns in OA subjects can be used to characterize the progression of OA. The second hypothesis is that muscle strategies would be different across NP and those pre-HTO and pre-TKR subjects, and have a significant effect on the magnitude of the knee joint loading.

6.2 Methods

6.2.1 Subjects

Data from eighty participants were used in this analysis, a mixture of data collected both prior to and during this PhD. Ethical approval was obtained from the Research Ethics Committee for Wales and Cardiff and Vale University Health Board. All

participants gave their informed written consent prior to data collection, and were divided into three groups: twenty NP subjects, thirty with medial OA awaiting high tibial osteotomy (pre-HTO), and thirty with late stage OA awaiting total knee replacement (pre-TKR). The mean and SD of mass, height and age for NP, pre-HTO and pre-TKR cohorts were (73.0±14.3, 88.2±21.7, 87.4±20.5) kg, (170.8±6.8, 173.5±10.5, 166.2±10.0) cm, (36.0±9.8, 50.6±7.7, 69.1±9.3) years, respectively; Table 6.1.

NP participants had no knee pain in the past during daily activities and not been diagnosed of lower extremity joint OA. All OA patients participated in this study were selected by orthopaedic consultants from the University Hospital of Wales. The inclusion/exclusion criteria for the participants have been described in details previously, section 1.3.

Table 6. 1: Demographics for NP, pre-HTO and pre-TKR subject (mean±sd).

Characteristics	NP	Pre-HTO	Pre-TKR
	n=20	n=30	n=30
Age, years	36.0±9.8	50.6±7.7	69.1±9.3
Mass, kg	73.0±14.3	88.2±21.7	87.4±20.5
Height, m	1.71±0.68	1.74 ±1.1	1.66±1.0
BMI, kg/m ²	24.96	29.13	31.71

OA=osteoarthritis; BMI = Body mass index.

6.2.2 Data Acquisition

A detailed methodology of experimental procedures and data reduction analysis were explained in details in Chapter Five, i.e., subsections 5.2.2 and 5.2.3, respectively. Below is a brief summary about the musculoskeletal workflow that was used to obtain measure of joint loading.

6.2.3 Data Reduction and analysis

Gait biomechanics for six trials from each subject were determined using OpenSim v3.3. Figure 6.1 shows the sequence of steps taken to estimate loading on the knee joint. The customized generic lower limb model was scaled to each participant's anthropometry, Figure 6.2. Joint angles and moments were then calculated using OpenSim inverse kinematics (IK) and inverse dynamics (ID) tools, respectively. Individual muscle forces were calculated via static optimization and tibiofemoral knee contact forces (KCF) were computed using the Joint Reaction Force (JRF) Tool in OpenSim. These forces represent the resultant forces and moments that the tibiofemoral joint structure carries due to all muscle forces, external loads, and inertial loads of the model. The compressive tibiofemoral force was computed as the component of the resultant force acting on the tibia and parallel to the long axis of the tibia, while the anterior-posterior and medio-lateral shear components of the contact force were orthogonal to the axial component. KCFs were normalized to BW of each subject, while muscle forces were normalized to body mass. All data were collected from six stances, normalized to each stance, averaged across six stances for each subject, and then averaged across subjects to obtain group means.

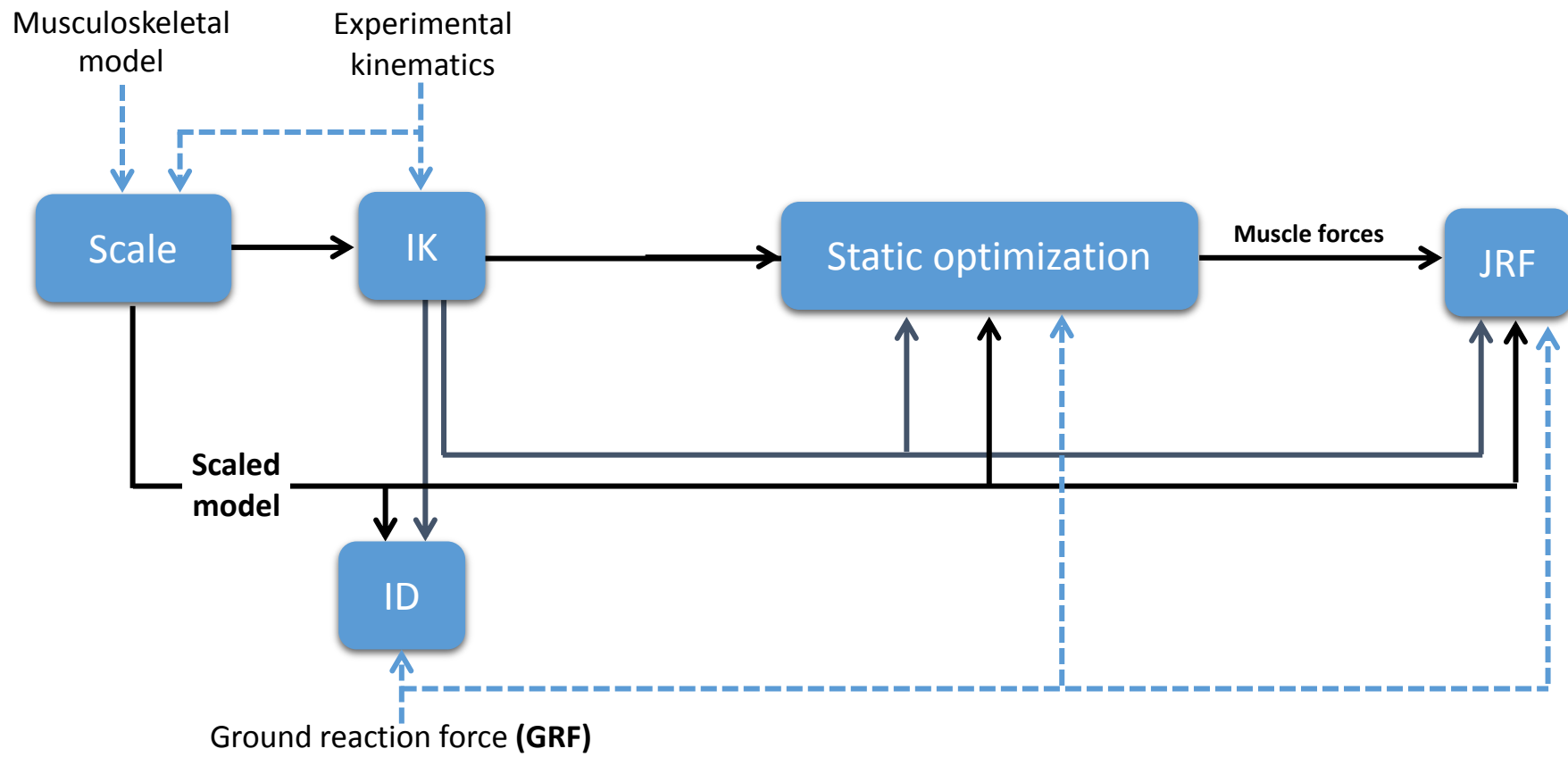


Figure 6. 1: Flowchart of the Musculoskeletal Simulation to Estimate Muscle Forces.

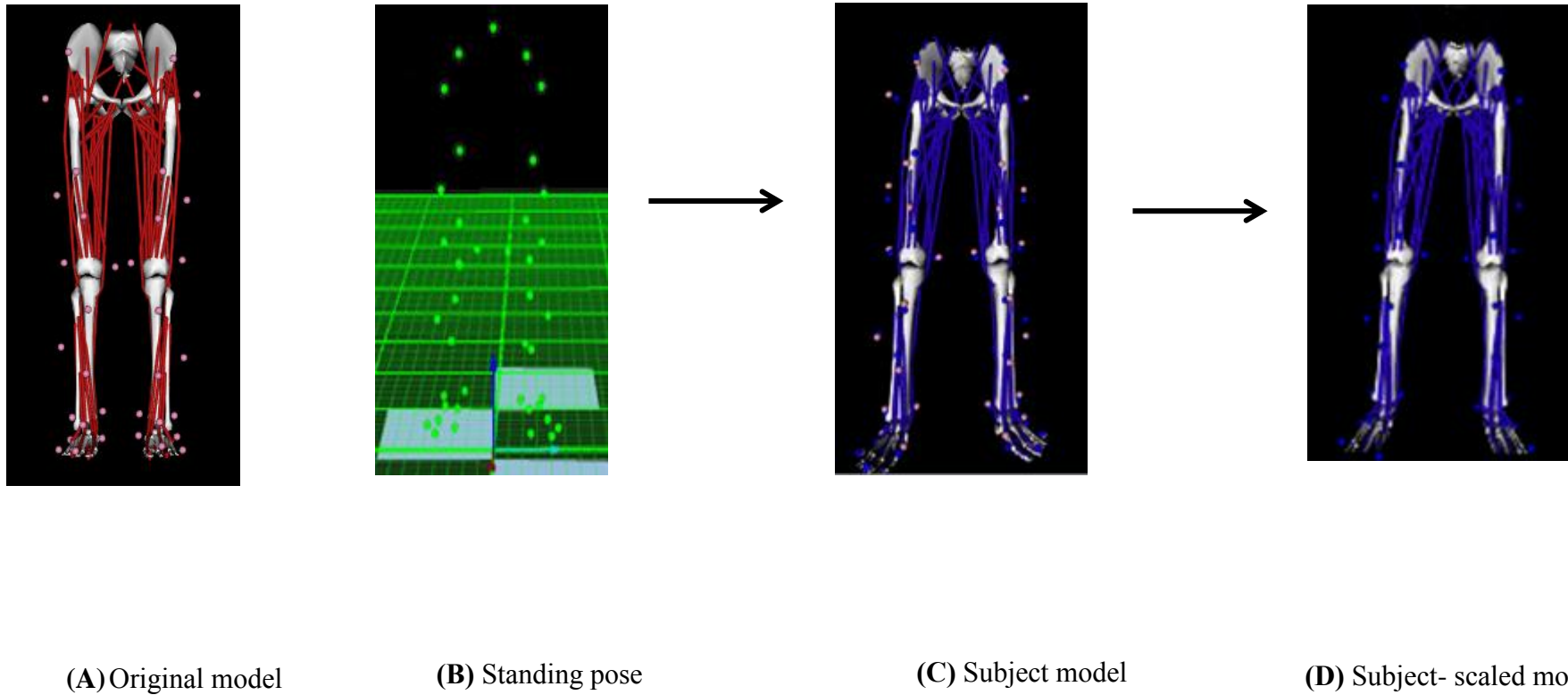


Figure 6. 2: Scaling of the model, the model virtual markers (pink) are placed on the model. During scaling the model's markers (pink) were optimized to match experimental marker (blue) locations in static pose.

6.3 Statistical Analysis

The stance of gait was divided into early stance, the first 50% of stance, (loading) and late stance, the second 50% of stance, (propulsion) phases. The dependent variables included: 1st and 2nd peak anterior-posterior shear force, 1st and 2nd peak knee compressive force, peak medial-lateral shear force, 1st and 2nd peak knee extensor and flexor muscle forces. The average of each variable for six stances of each subject was used in statistical analysis. In order to compare differences between NP , pre-HTO, and pre-TKR subjects, a Kruskal Wallis test of nonparametric data was performed using SPSS (version 20, Chicago, IL) with an alpha level set at 0.05 a priori. Pairwise comparisons using the Dunn-Bonferroni approach are automatically produced for any dependent variables for which the Kruskal-Wallis test is significant.

6.4 Results

A total of 480 predictions of KCF were generated for 80 subjects, with 6 simulations for each participant. The KCF curves demonstrate a well-defined double peak for both NP and pre-HTO cohorts in terms of the shear (Figure 6. 3), and compressive (Figure 6. 4) components, while pre-TKR subjects exhibited a different pattern; i.e, without a distinct double peak.

Peak anterior-posterior (A-P) shear force at the knee occurred during early stance, at about 25% of stance as shown in (Figure 6. 3). OA patients have reduced their first peak, compared to NP, where pre-TKR have the lowest peak. No significant differences were found due to high standard deviation of the three cohorts as shown

in (Table 6. 2). Pre-TKR group exhibit a different pattern than NP and pre-HTO subjects.

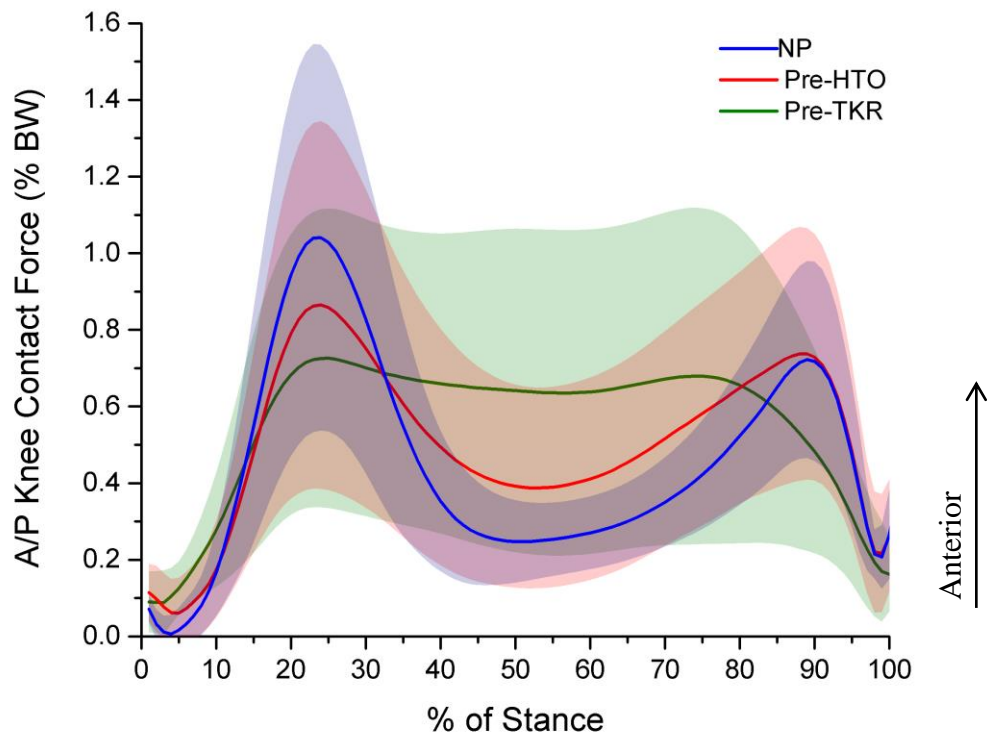


Figure 6. 3: Anterior-Posterior shear Knee Contact Force during stance phase for the three cohorts. Values represent mean±sd.

Peak compressive knee contact force occurred during late stance and reduced significantly from NP and pre-HTO to pre-TKR group. Figure 6. 4 shows the changes seen in compressive KCF for the three cohorts.

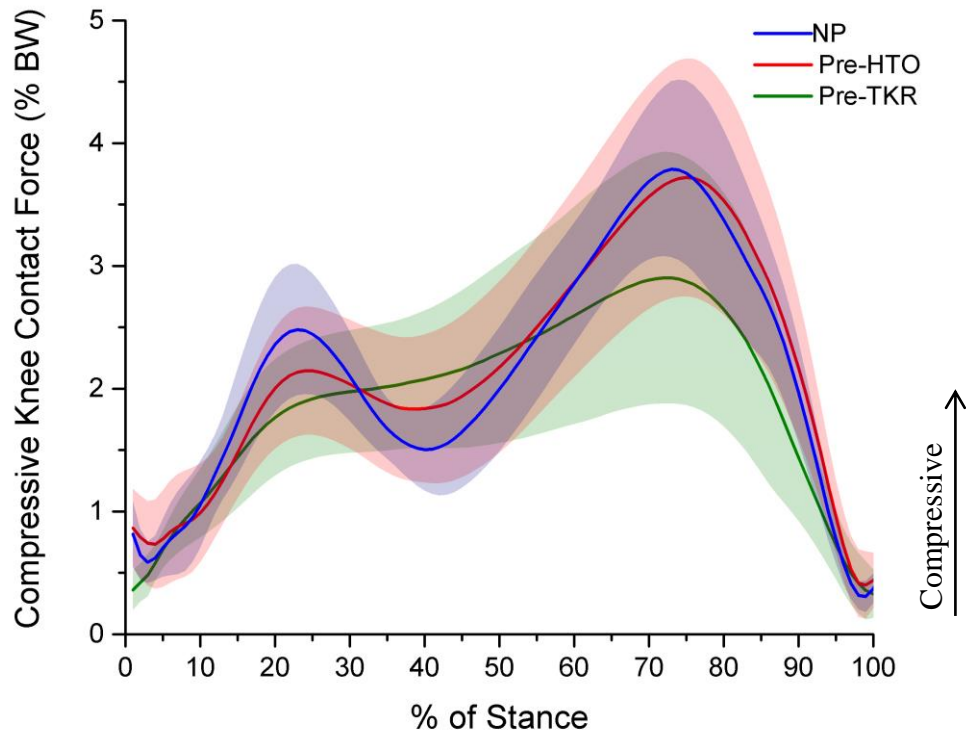


Figure 6. 4: Compressive Knee Contact Force during stance phase across the three cohorts. Values represent mean \pm sd.

Figure 6. 5 shows the changes in medial-lateral (M-L) shear forces at the knee for the three cohorts (NP, pre-HTO and pre-TKR subjects).

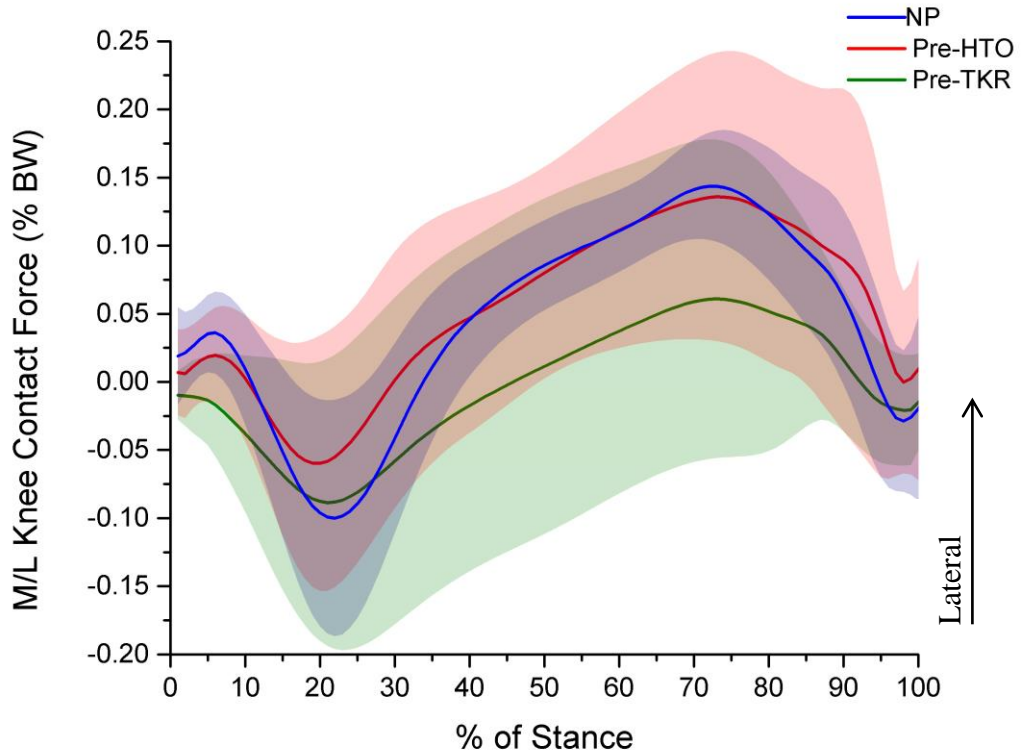


Figure 6. 5: Medial-Lateral shear Knee Contact Force during stance phase across the three cohorts. Values represent mean±sd.

A summary of the predicted joint loads during early and late stance is given in Table 6. 2.

Table 6. 2: KCF peaks for NP controls, HTO and TKR patients during walking (Mean \pm SD).

Variable	Force (x BW)			P NP vs. HTO	P NP vs. TKR	P HTO vs. TKR
	NP	Pre-HTO	Pre-TKR			
	n=20	n=30	n=30			
Peak A-P shear KCF	1.05 \pm 0.49	0.90 \pm 0.48	0.71 \pm 0.40			
Early Stance Peak compressive KCF	2.50 \pm 0.52	2.28 \pm 0.58	2.06 \pm 0.49		0.006 \dagger	
Peak M-L shear KCF	-0.11 \pm 0.08	-0.07 \pm 0.08	-0.08 \pm 0.21			
Peak A-P shear KCF	0.73 \pm 0.26	0.79 \pm 0.30	0.66 \pm 0.44			
Late Stance Peak compressive KCF	3.83 \pm 0.71	3.76 \pm 0.98	2.98 \pm 1.01		0.003 \dagger	0.002 \dagger
Peak M-L shear KCF	0.15 \pm 0.04	0.16 \pm 0.11	0.07 \pm 0.23			

\dagger Significant differences between groups ($p < 0.05$).

Three muscle groups were studied: quadriceps, hamstrings and gastrocnemius. Figure 6. 6 shows the sum of forces produced by the muscles crossing the knee joint and the corresponding resultant KCF for the three cohorts.

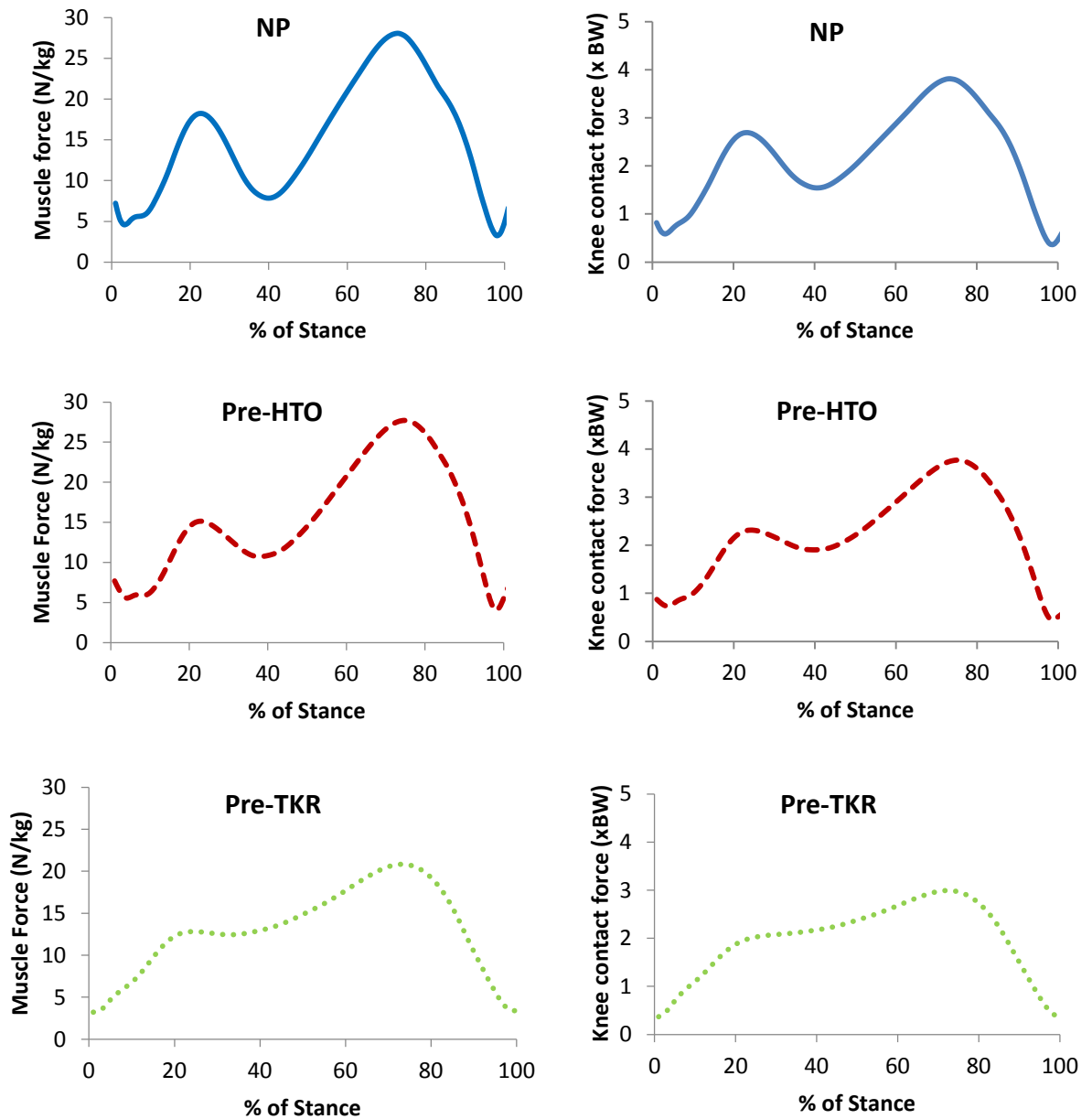


Figure 6. 6: On the left is the total muscle force and on the right is the corresponding resultant knee contact force during stance-phase for control subjects, pre-HTO subjects , and pre-TKR subjects . Values represent mean.

Figure 6. 7 shows individual muscle forces in subjects with varying degrees of knee OA. The long head of the biceps femoris, Figure 6. 7, showed peaks at the beginning and the end of stance phase for NP and pre-HTO subjects, where the latter had higher peak on late stance than NP subjects. Pre-TKR subjects had relatively higher muscle force through mid-stance and pre-swing phase; i.e., higher than NP and pre-HTO. The short head biceps femoris, as shown in (Figure 6. 7), allows knee rotation laterally and to flex the knee. Pre-TKR had significantly reduced muscle forces at late stance, and that resulted in a reduction in their peak shear knee contact load (Figure 6. 5). Semimembranosus and semitendinosus had a high early stance peak, were both OA groups reduced their peak to a similar level as compared to NP subjects; i.e. both OA groups had significantly reduced their semitendinosus peak force compared to NP individuals. During late stance, pre-TKR patients showed higher muscle forces compared to NP and pre-HTO individuals, with a significant increase in the semitendinosus force when compared to NP subjects (Table 6. 4).

The rectus femoris muscle force showed a smaller early stance peak and a larger late stance peak, were the pre-TKR had different patterns to NP and pre-HTO. The Vastus medialis muscle had one large peak at the beginning of stance phase for all groups, with OA patients exhibiting a significantly reduced peak compared to NP controls (Figure 6. 7). In addition, the Pre-TKR group had increased force during late stance compared to the other groups. Vastus inter-medialis had the same trend of vastus medialis. The vastus lateralis muscle force had a large late stance peak (Figure 6. 7) and the sum of knee extensor muscle forces had a large early stance peak and smaller late stance peak for NP and pre-HTO subjects, while Pre-TKR subjects do

not have a clearly defined double peak with a trend of having a higher forces during 35-60% of stance (Figure 6. 8). The early stance peak muscle forces of the rectus femoris ($p=0.005$), vastus medialis ($p < 0.001$), vastus inter-medialis ($p =0.019$) and sum of knee extensor forces ($p = 0.014$) were reduced in pre-TKR patients compared to NP individuals (Table 6. 3, Figure 6. 7). The late stance peak muscle force of rectus femoris was significantly reduced in pre-TKR patients compared to their NP and pre-HTO counterparts (Table 6. 4, Figure 6. 7). However, the late stance peak vastus medialis and inter-medialis force were significantly greater in pre-TKR patients compared to NP and pre-HTO subjects.

The medial and lateral gastrocnemius muscle force showed a large peak during late stance, were it significantly reduced with increased OA progression.

Results from linear regression are presented in Figures 6. 9-18, which show the correlation between each component of the knee contact force and muscle force. As shown, the correlations are plotted in a unit scale across the different cohorts, to facilitate easily visualization of the differences between cohorts and to see the distribution of data within each cohort.

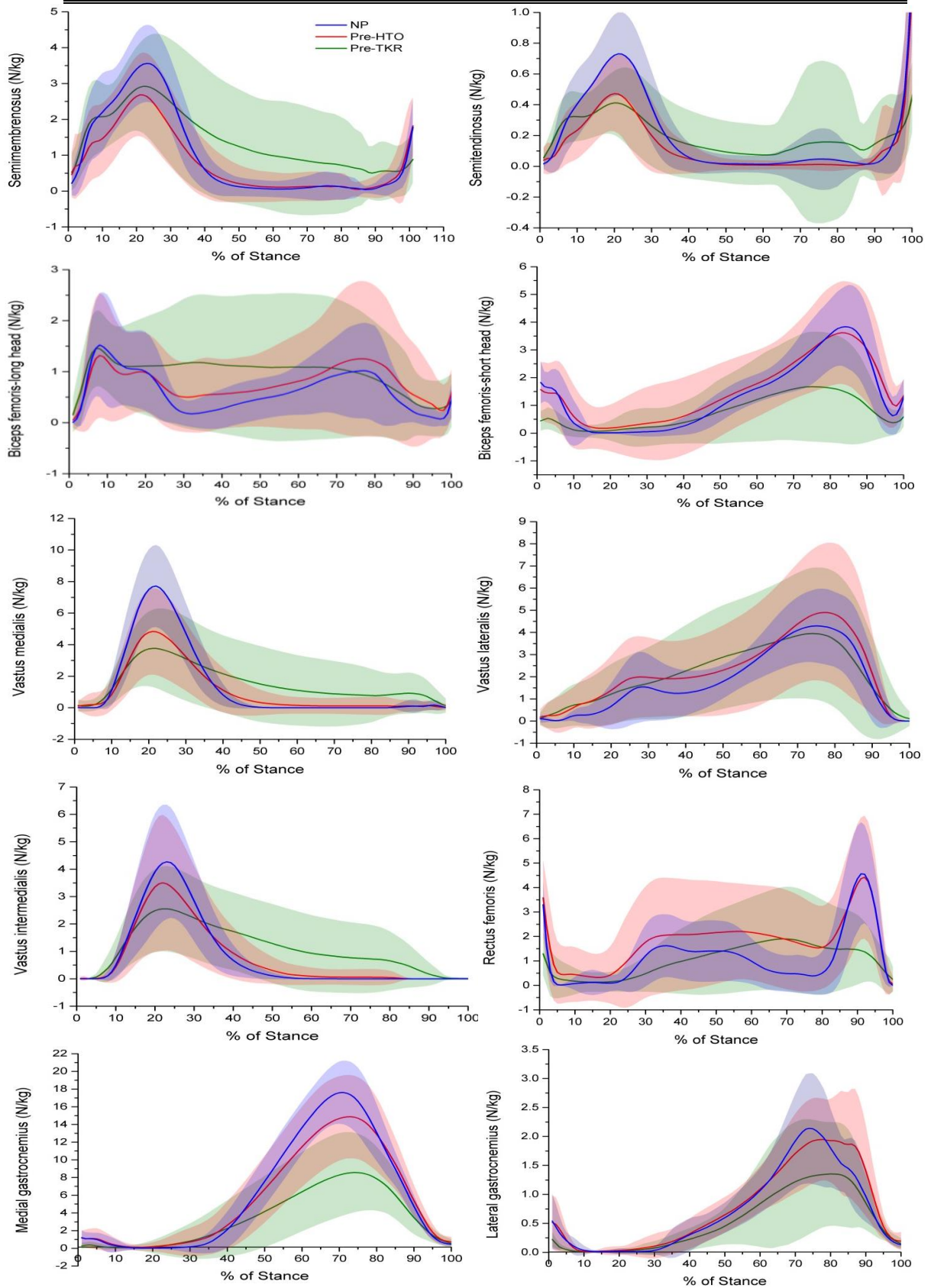


Figure 6. 7: Mean estimated forces of muscles crossing the knee joint during stance-phase for NP, pre-HTO, pre-TKR subjects. Values represent mean \pm sd.

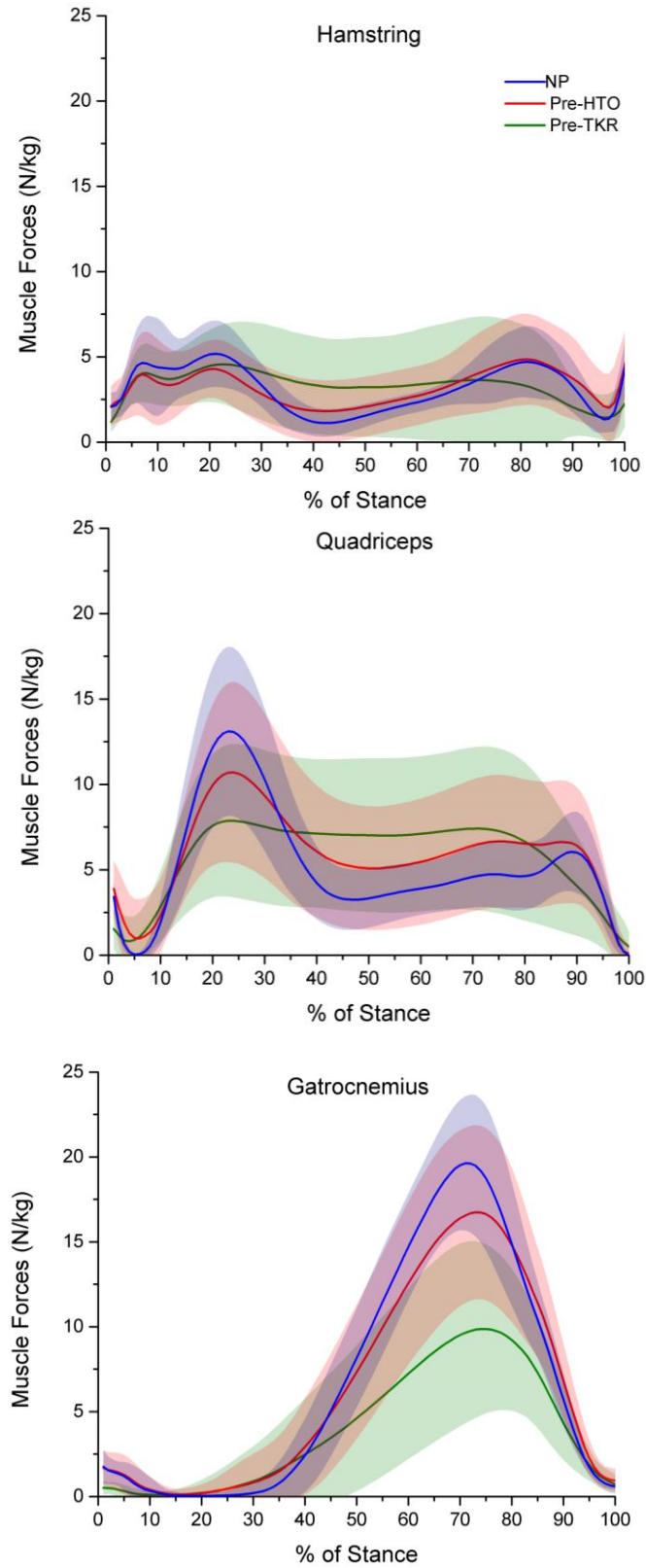


Figure 6. 8: Hamstring, quadriceps, and gastrocnemius muscle forces during stance phase for NP subjects, pre-HTO, and pre-TKR subjects. Values represent mean \pm sd.

Table 6. 3: Early stance peak knee extensor and flexor muscle forces for NP subjects, pre-HTO and pre-TKR patients during walking (Mean ± SD).

Muscle Group	Muscle	Force (N/kg)			P NP vs. HTO	P NP vs. TKR	P HTO vs. TKR
		NP	Pre-HTO	Pre-TKR			
		n=20	n=30	n=30			
Knee Extensors	Rectus Femoris	3.44±0.88	4.33±2.10	2.05±1.60		0.005†	<0.001†
	Vastus Medialis	7.84±2.58	5.18±2.72	4.21±2.55	0.010†	<0.001†	
	Vastus Intermedius	4.41±2.00	3.74±2.39	2.84±1.61		0.019†	
	Vastus Lateralis	2.28±1.26	2.66±1.97	2.98±2.35			
	Sum(Quadriceps)	13.25±4.93	11.42±5.04	9.17±4.54		0.014†	
Knee Flexors	Semimembranosus	3.73±1.03	2.82±1.12	3.32±1.37	0.027†		
	Semitendinosus	0.77±0.25	0.52±0.26	0.48±0.21	0.005†	0.001†	
	Bicep Femoris Long Head	1.74±1.06	1.67±1.16	1.90±1.28			
	Bicep Femoris Short Head	2.19±0.81	2.34±1.29	1.10±1.03		<0.001†	<0.001†
	Sum (Hamstrings)	6.16±2.61	5.21±2.10	5.46±2.60			
	Medial Gastrocnemius	7.57±2.78	6.76±3.68	4.22±4.04		0.001†	0.012†
	Lateral Gastrocnemius	0.81±0.36	0.84±0.39	0.49±0.29		0.016†	0.001†
Sum (Gastrocnemius)	8.16±2.92	7.40±3.87	4.69±4.29		0.002†	0.010†	

† Significant differences between groups (p<0.05).

Table 6. 4: Late stance peak knee extensor and flexor muscle forces for NP subjects, pre-HTO and pre-TKR patients during walking (Mean \pm sd).

Muscle Group	Muscle	Force (N/kg)			P NP vs. HTO	P NP vs. TKR	P HTO vs. TKR
		NP n=20	Pre-HTO n=30	Pre-TKR n=30			
Knee Extensors	Rectus Femoris	4.93 \pm 1.85	4.95 \pm 2.23	2.48 \pm 2.02		<0.001 \dagger	<0.001 \dagger
	Vastus Medialis	0.28 \pm 0.52	0.38 \pm 0.81	1.79 \pm 2.52		0.018 \dagger	<0.001 \dagger
	Vastus Intermedius	0.09 \pm 0.10	0.26 \pm 0.47	1.27 \pm 1.47		0.003 \dagger	0.006 \dagger
	Vastus Lateralis	4.63 \pm 1.60	5.17 \pm 3.09	4.17 \pm 3.01			
	Sum(Quadriceps)	6.51 \pm 2.22	7.95 \pm 3.61	8.26 \pm 4.83			
Knee Flexors	Semimembranosus	1.80 \pm 0.79	1.96 \pm 0.99	1.93 \pm 1.64			
	Semitendinosus	1.77 \pm 0.54	1.51 \pm 0.77	0.72 \pm 0.49		<0.001 \dagger	<0.001 \dagger
	Bicep Femoris Long Head	1.42 \pm 0.81	1.84 \pm 1.45	1.44 \pm 1.42			
	Bicep Femoris Short Head	4.04 \pm 1.44	4.00 \pm 1.63	2.03 \pm 1.84		<0.001 \dagger	<0.001 \dagger
	Sum (Hamstrings)	6.64 \pm 2.01	6.76 \pm 2.21	5.07 \pm 3.63		0.005 \dagger	0.001 \dagger
	Medial Gastrocnemius	17.94 \pm 3.64	15.32 \pm 4.83	9.23 \pm 4.40		<0.001 \dagger	<0.001 \dagger
	Lateral Gastrocnemius	2.28 \pm 0.96	2.43 \pm 1.06	1.56 \pm 1.10		0.002 \dagger	<0.001 \dagger
Sum (Gastrocnemius)	19.87 \pm 3.99	17.19 \pm 5.18	10.67 \pm 4.96		<0.001 \dagger	<0.001 \dagger	

\dagger Significant differences between groups ($p < 0.05$).

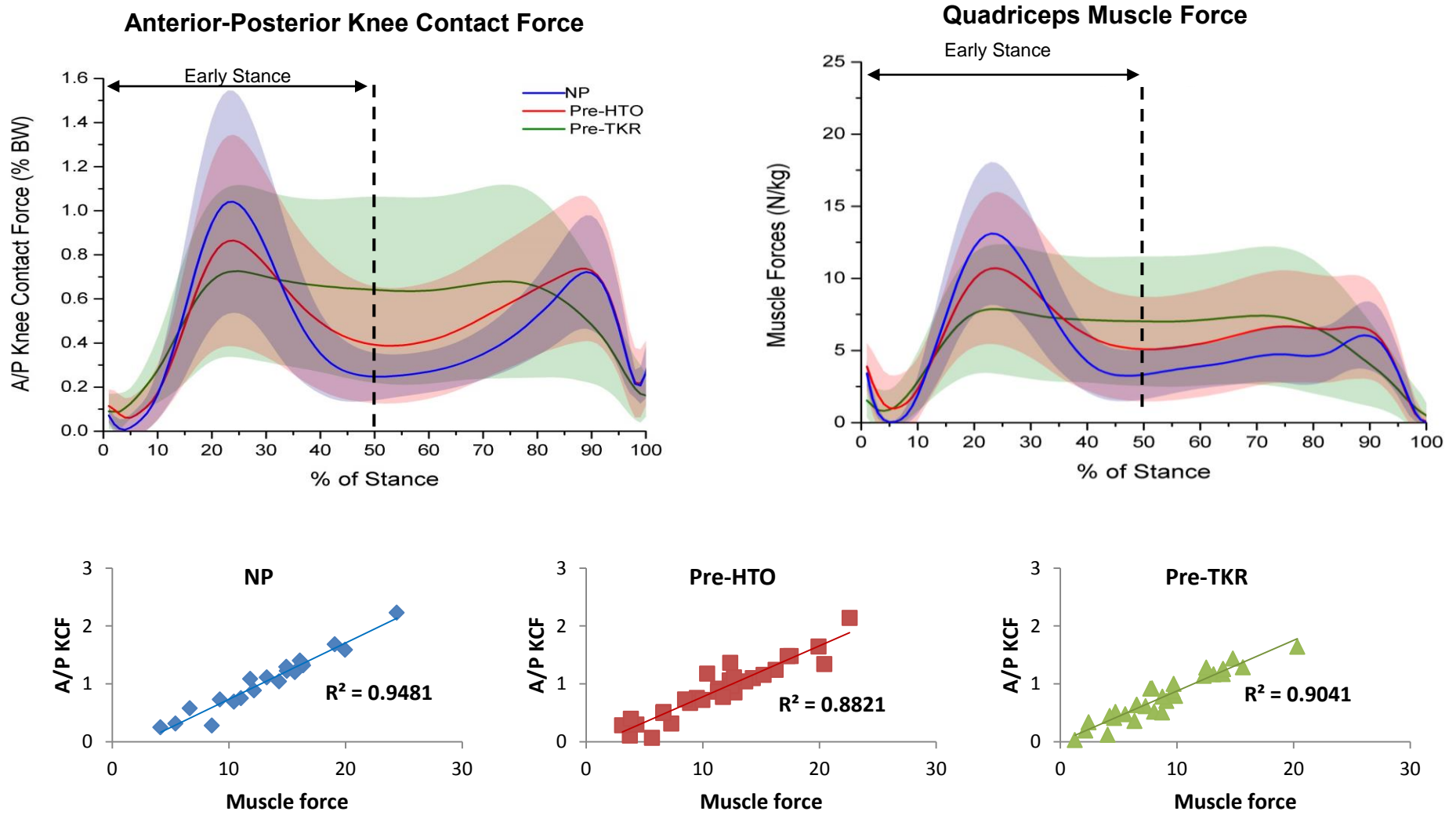


Figure 6. 9: Relationship between A/P KCF and quadriceps force during early-stance.

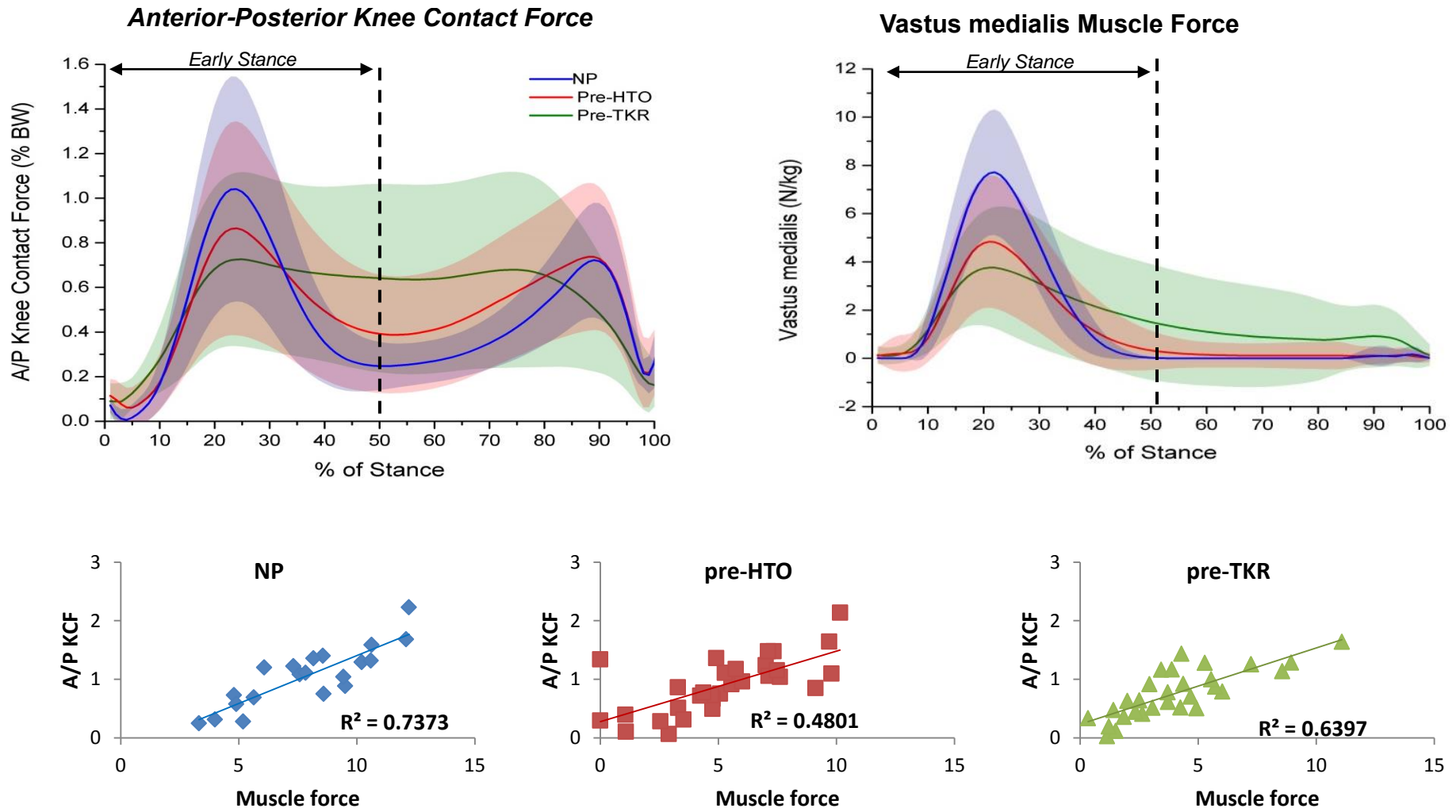


Figure 6. 10: Relationship between A/P KCF and vastus inter-medialis force during early-stance.

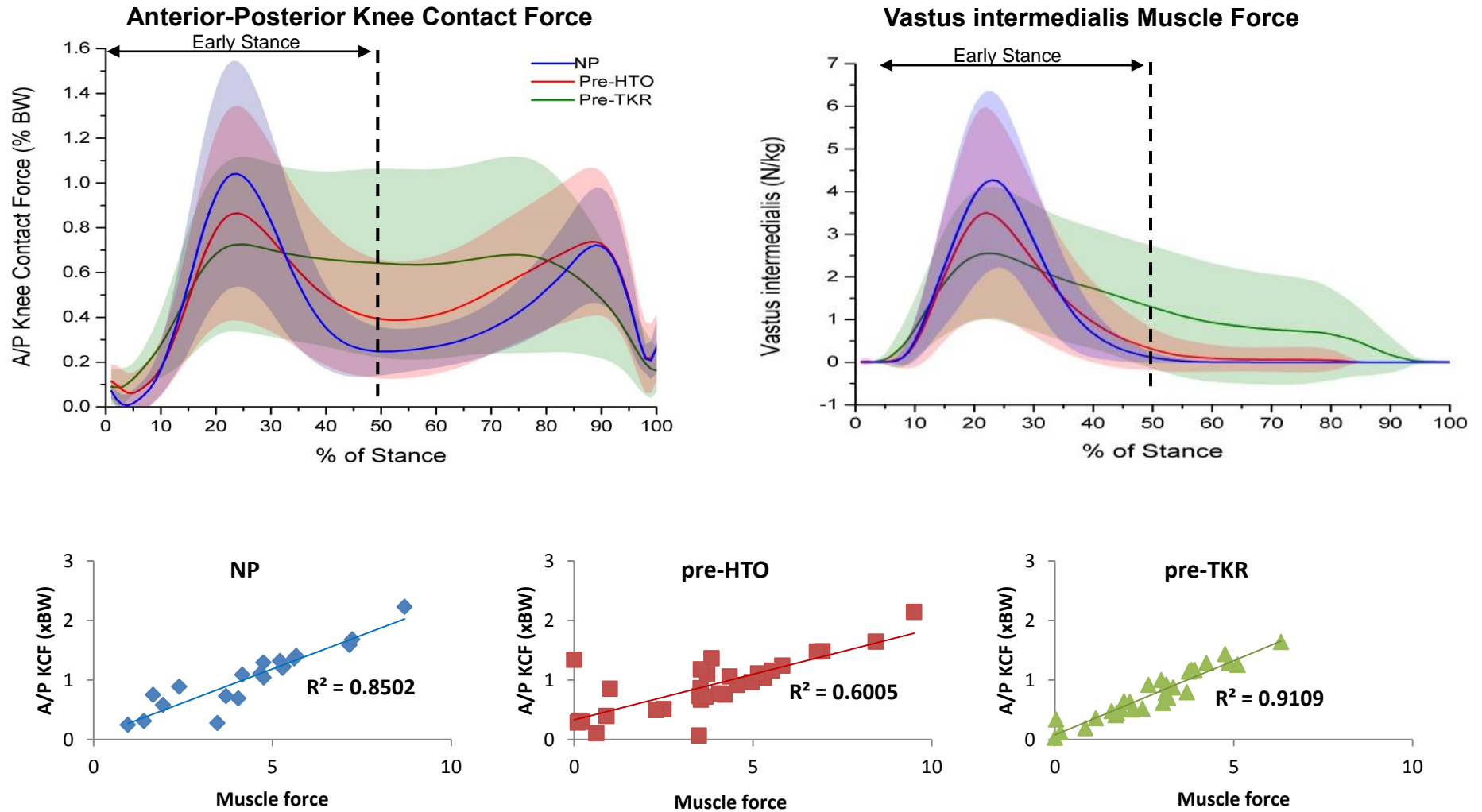


Figure 6. 11: Relationship between A/P KCF and quadriceps force during mid-stance.

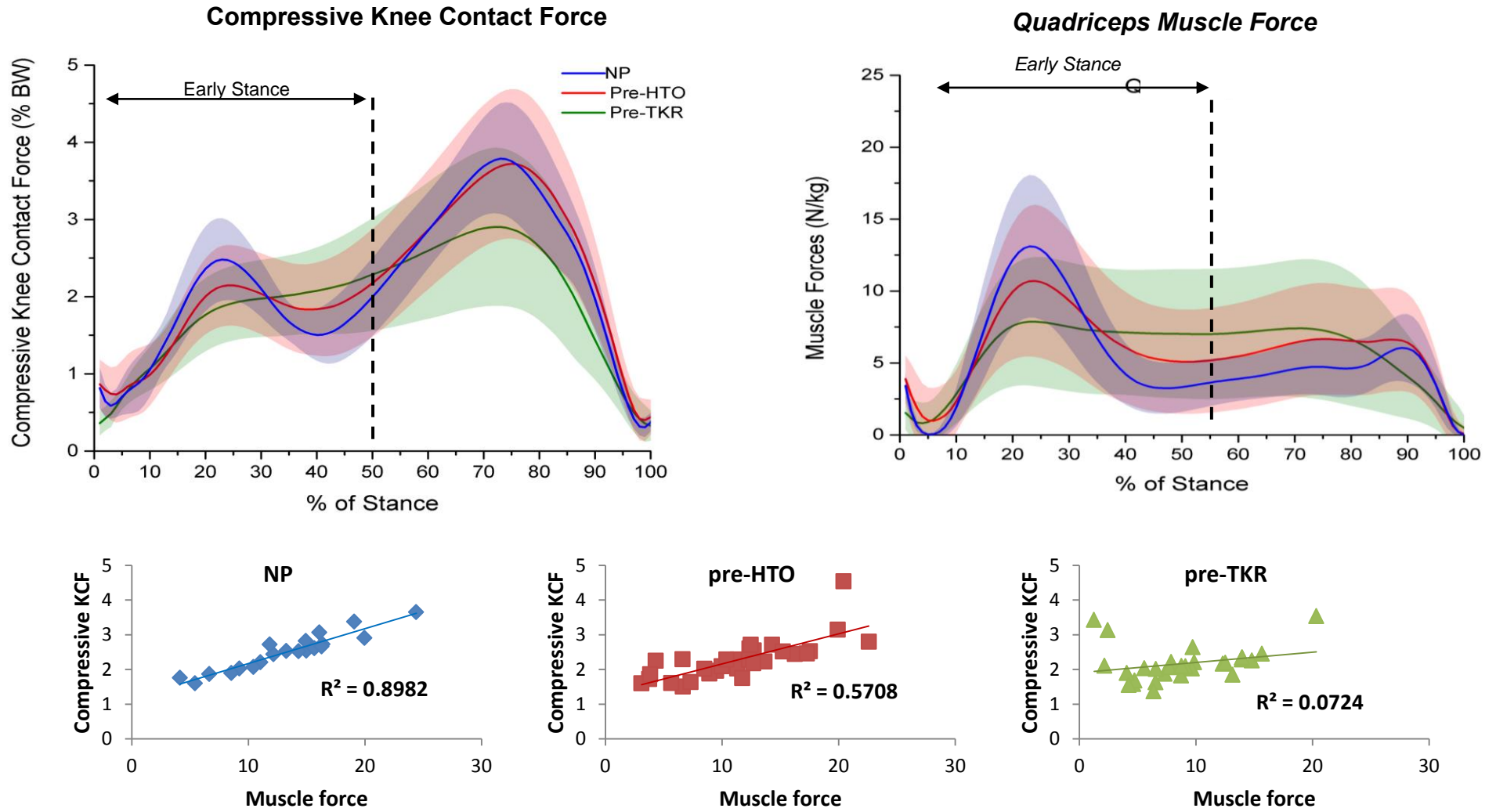


Figure 6. 12: Relationship between compressive KCF and quadriceps force during early-stance.

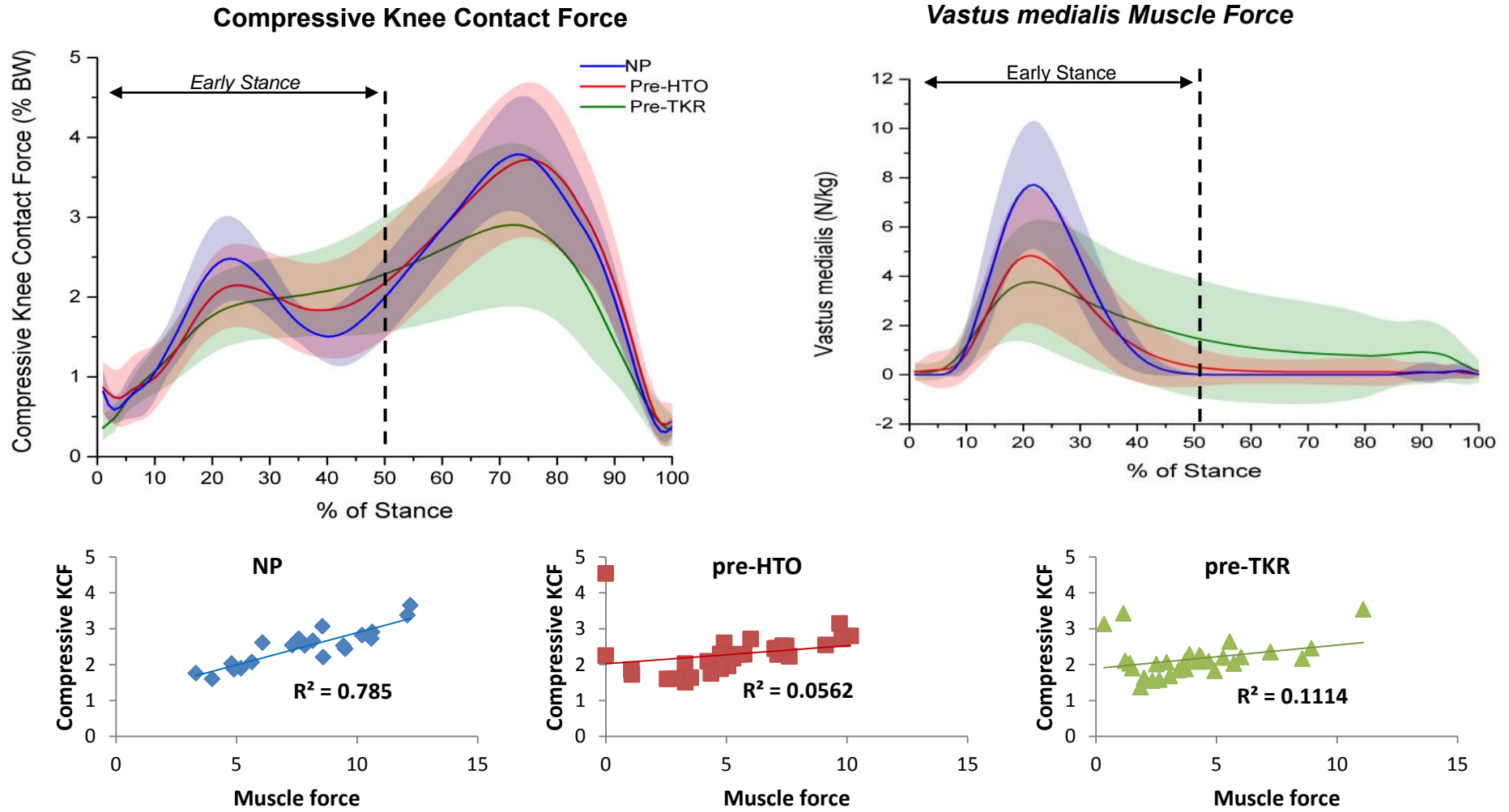


Figure 6. 13: Relationship between compressive KCF and vastus medialis force during early-stance.

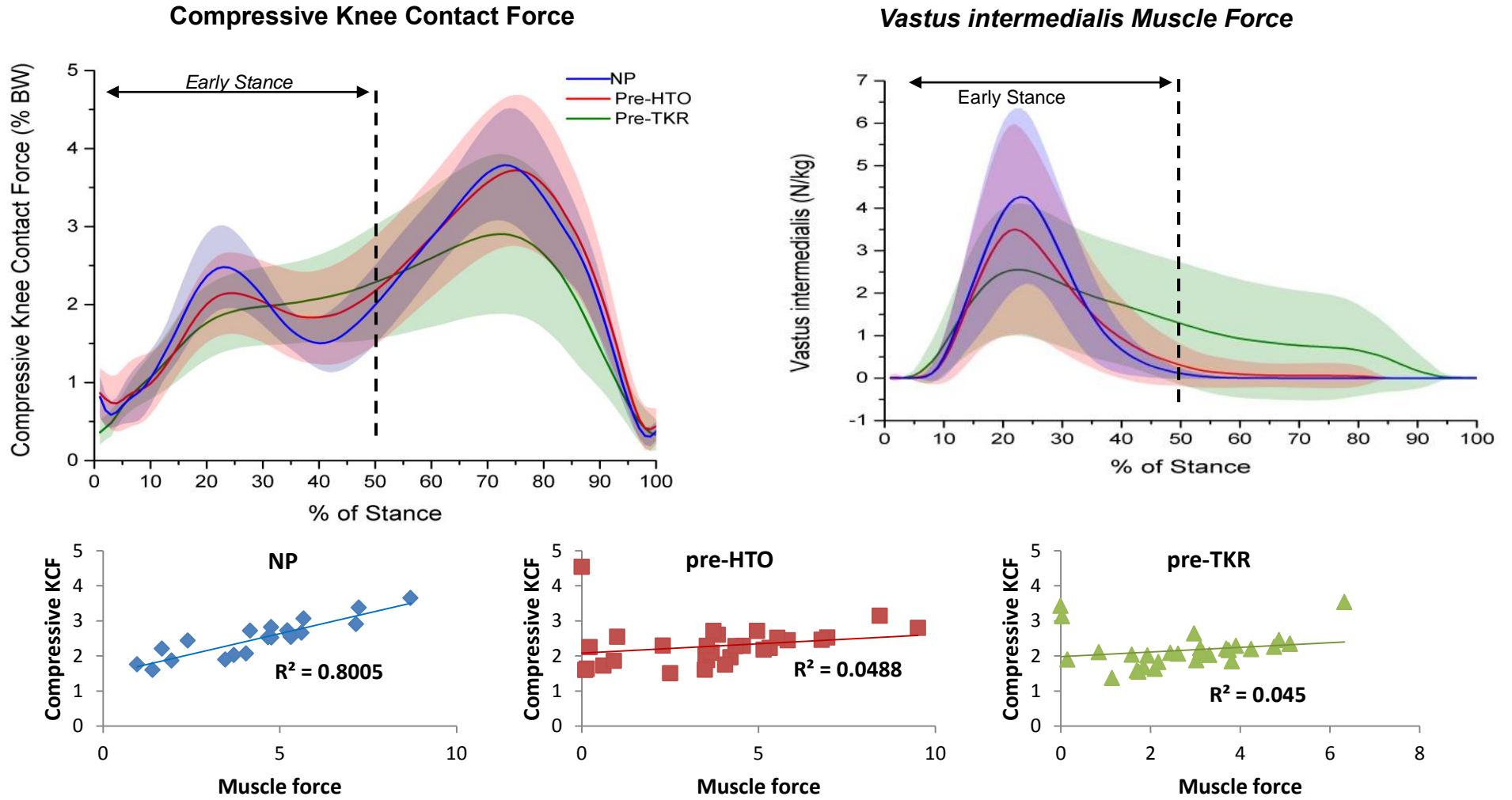


Figure 6. 14: Relationship between compressive KCF and vastus intermedius force during early-stance.

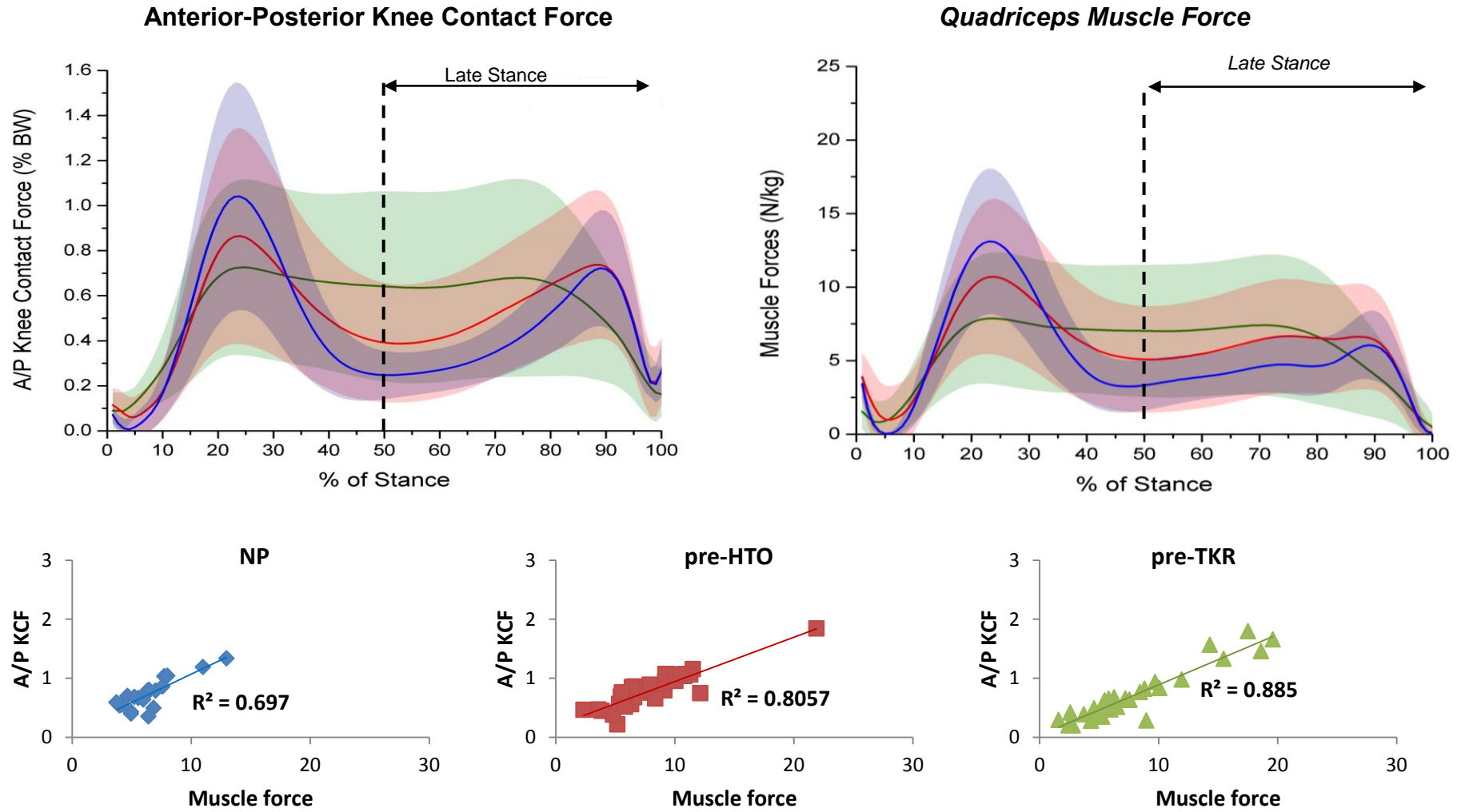


Figure 6. 15: Relationship between A/P KCF and quadriceps force during late-stance.

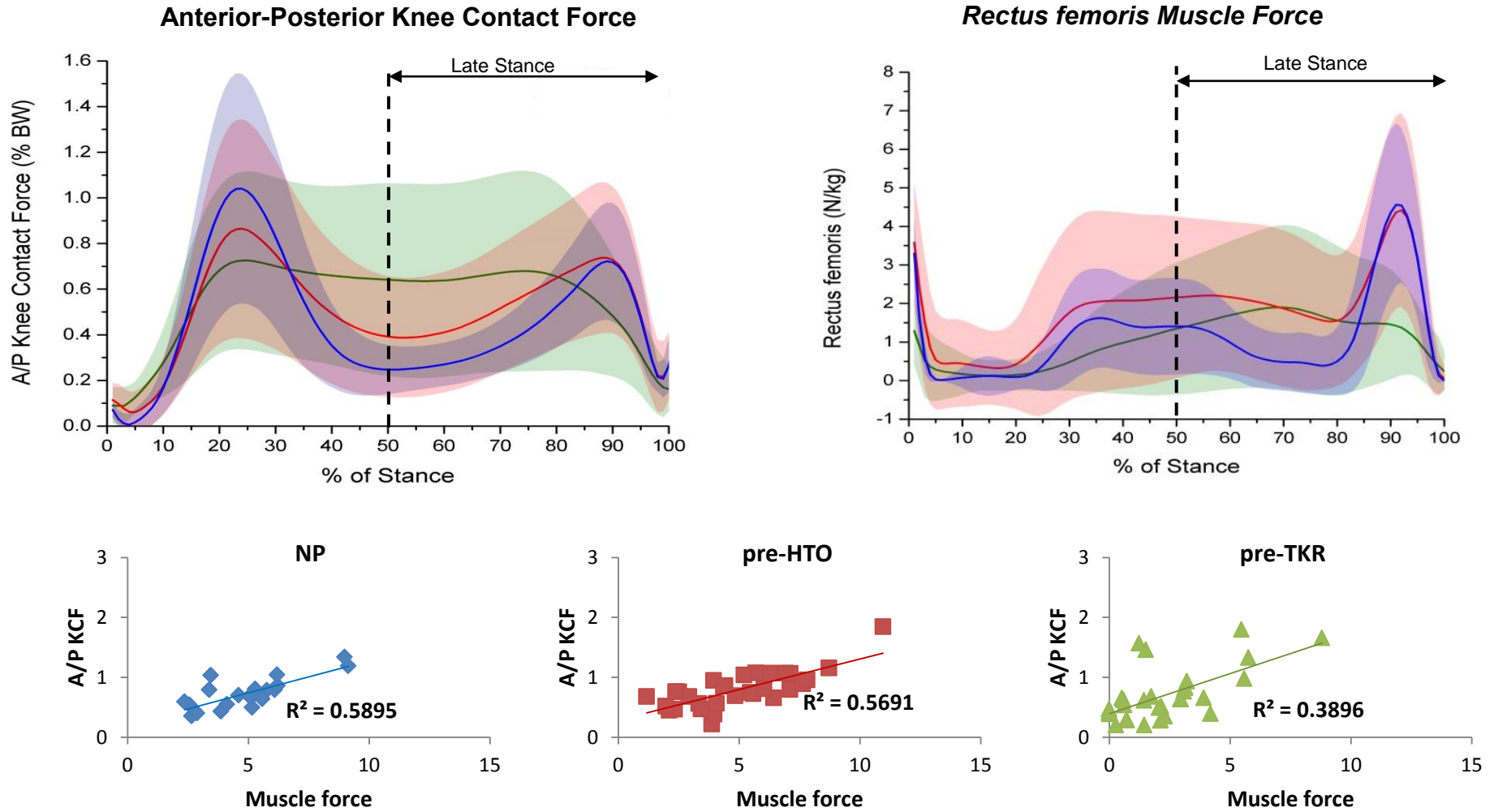


Figure 6. 16: Relationship between A/P KCF and Biceps femoris_short head force during late-stance.

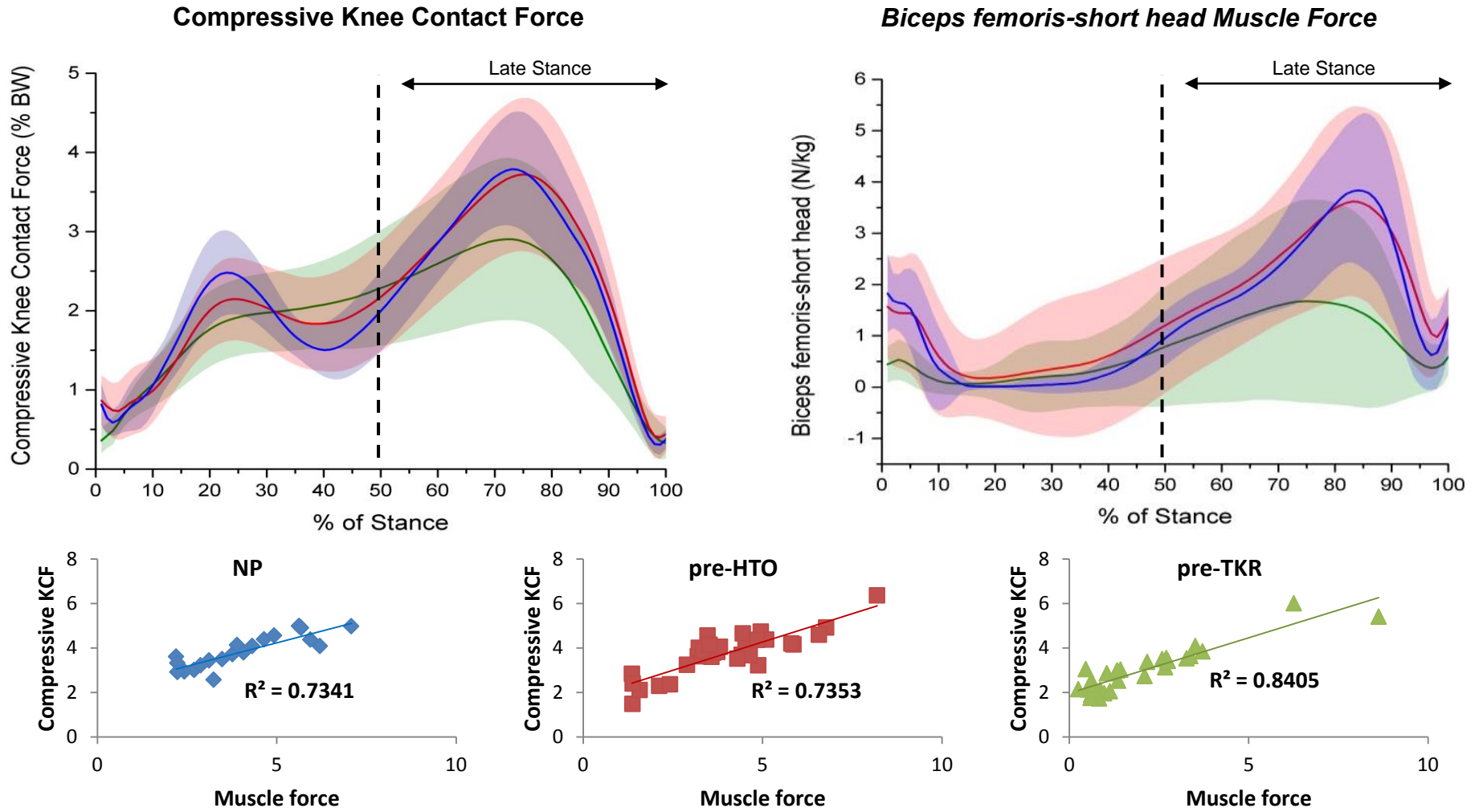


Figure 6. 17: Relationship between compressive KCF and Biceps femoris_short head force during late-stance.

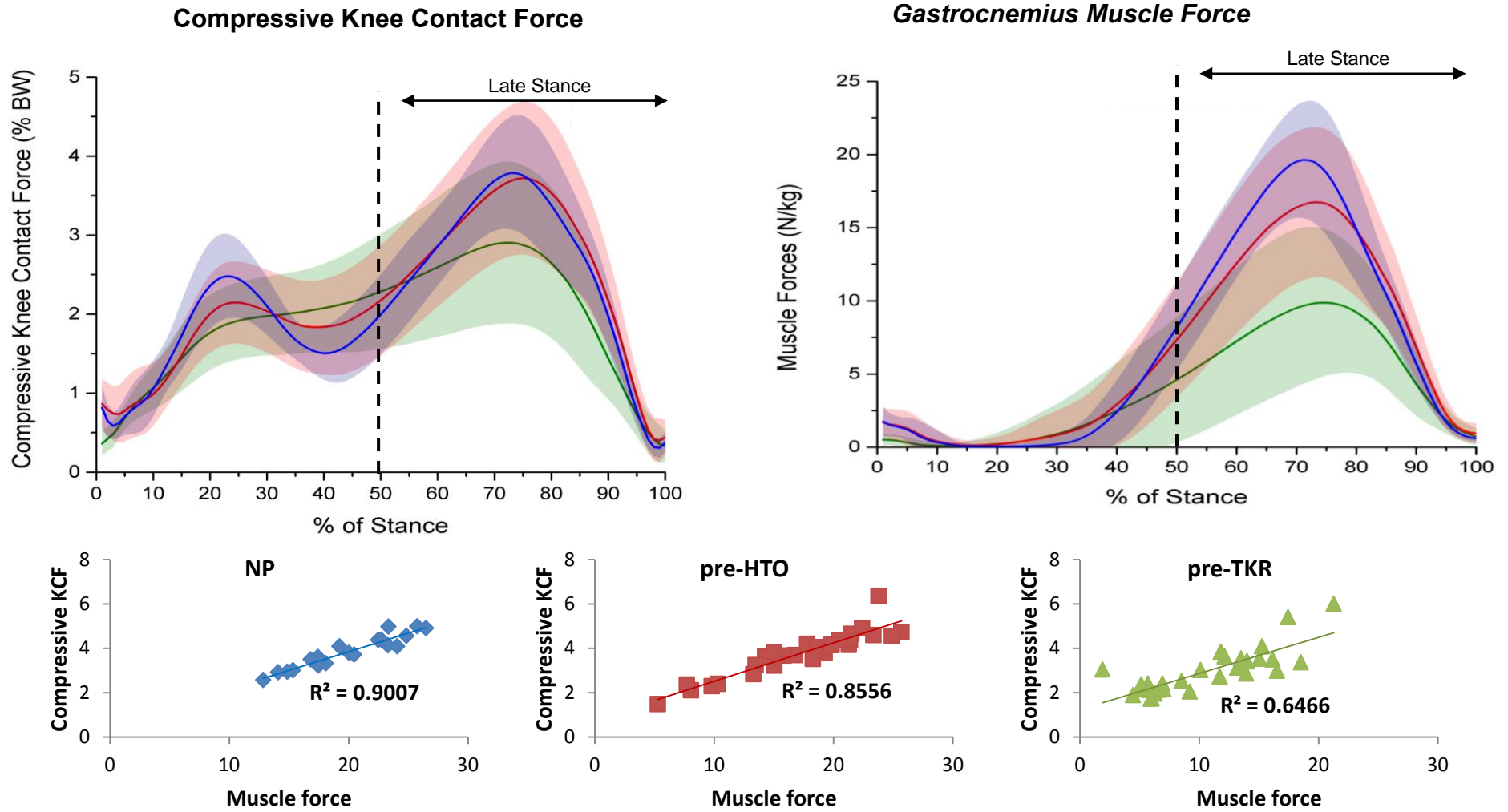


Figure 6. 18: Relationship between compressive KCF and gastrocnemius force during late-stance.

6.5 Discussion

The objective of this study was to compare muscle forces, A-P shear, compressive, and M-L shear KCFs between NP, pre-HTO and pre-TKR patients. The results from Figure 6. 3-5 support the hypothesis that the loading patterns in OA subjects can be used to characterize the progression of OA. It is speculated that differences in muscle forces would be found between groups during walking, and the way that the muscles activate themselves will affect the magnitude and the pattern of joint loading. Changes in loading patterns were identified for both OA cohorts with more substantial changes for pre-TKR patients.

The A-P KCF pattern, for the NP and pre-HTO subjects, during stance had two major peak forces, with the first peak occurring in early stance and the second occurring in late stance, (Figure 6. 3). OA patients reduced their first peak, compared to NP, where pre-TKR reduced their first peak by about 32.4% (1.05 BW to 0.71 BW) as compared to NP. This is due to a significant reduction of the force developed by quadriceps for pre-TKR cohort, Table 6. 3. Figure 6. 9 shows a strong relationship between the first peak of anterior KCF and the peak quadriceps force during early stance. Figure 6. 11 shows a strong correlation between anterior KCF and vastus inter-medialis during early stance for pre-TKR cohort. The moderate relationship for pre-HTO subjects suggests that these individuals have increased their joint loading to an extent that is not corresponding with an increase in muscle force. However, the strategy that was adopted by pre-HTO during early stance by significantly reducing the force developed by vastus medialis, as compared to NP (Table 6. 3), may be assisting with the distribution of forces off the medial compartment of the knee joint, i.e. reducing medial joint loading.

A reduction in anterior KCF during early stance is strongly related to reduction of quadriceps force during this time interval, Figure 6. 9. As shown in Figure 6. 15, there is a moderate correlation between anterior KCF and quadriceps force during late stance for OA cohorts. Peak A-P shear forces for NP subjects were found to range between 0.73 to 1.05 BWs, which is within the range that was addressed by (Lerner et al., 2014). Taylor et al. (2004) has addressed that A-P shear loading during periods of knee flexion above approximately 15° rapidly increased. Figure 5. 15, in the previous Chapter has shown that OA patients were flexed more during mid to terminal stance, as compared to NP. As a corresponding of that, higher shear forces can be seen in OA patients during the these intervals.

For NP and pre-HTO subjects, the compressive KCF had two distinct peaks; a smaller early stance peak, at 23% of stance, and a larger late stance peak, at 75% of stance for NP and at 77% of stance for pre-HTO (Figure 6. 4). This pattern was consistent with previous studies (D'Lima et al., 2006; Heinlein et al., 2009; Lerner et al., 2014; Richards and Higginson, 2010; Sasaki and Neptune, 2010; Taylor et al., 2004). Over-ground walking, the peak knee compressive force ranged between 2.0 to 4.45 BWs (Lerner et al., 2014; Richards and Higginson, 2010; Sasaki and Neptune, 2010); our data lay within the ranges.

The first peak did not differ significantly between NP controls (2.50 ± 0.52 BW) and pre-HTO patients (2.28 ± 0.58 BW) in the present study. However, pre-HTO patients exhibited a slight increase in the second half of mid-stance and the first half of terminal stance. Consistent with previous literature, pre-TKR patients showed a

significant reduction in the compressive KCF; 17.6% and 22.2% as compared to NP subjects for the first and second peaks, respectively. In addition, in Pre-TKR subjects there is a trend of having a higher KCF in the second half of mid-stance and the first half of terminal stance; i.e. 35 - 60% of stance. This may result from a higher knee adduction moment (Figure 5. 1) as well as both quadriceps and hamstring producing high muscle forces during this time interval, as shown in Figure 6. 8. Both OA cohorts have a reduction in their second peak of the compressive KCF which is attributed to decreased gastrocnemius force (for both OA cohorts), as shown in Figure 6. 8 and rectus femoris force (for pre-TKR cohort), as shown in Figure 6. 7. Where, the gastrocnemius muscle group and rectus femoris are the most significant contributors to the peak KCF occurring during late stance as reported by (Sasaki and Neptune, 2010; Steele et al., 2012). Demers et al. (2014) postulated that decreasing activations of the bi-articular knee muscles (gastrocnemius and rectus femoris) may decrease tibiofemoral loading; our results support this idea. The presence of a limited flexion of the knee joint at heel strike, associated with premature activity of the lateral gastrocnemius for pre-HTO subjects at the loading response, is considered as a mechanism adopted by pre-HTO subjects to preserve weight bearing stability, possibly by co-contracting vastus lateralis-lateral gastrocnemius as shown in (Figure 4. 1), and avoiding further knee flexion in this phase.

The magnitudes for compressive loading seen in this study were consistent with those seen in the literature (Kutzner et al., 2010; Richards and Higginson, 2010; Saxby et al., 2016). Pre-TKR patients were found to have an early stance peak

compressive loading of 2.06 ± 0.49 BW and late stance peak of 2.98 ± 1.01 BW compared to instrumented implant literature which ranged from 2.5 to 3.06 BW (D'Lima et al., 2005; D'Lima et al., 2006; Heinlein et al., 2009). The high standard deviation that were reported for the first and second peak compressive KCF in pre-HTO cohort might have resulted from four pre-HTO patients having a KL grade =4. Therefore their muscle strategies might be close to that seen in pre-TKR, rather than their cohort.

It was interesting to note that unloading occurred for NP and pre-HTO, while pre-TKR exhibits different patterns. Due to quadriceps weakness at the loading response phase, both quadriceps and hamstrings utilized high levels of muscle forces at 35 - 60% of stance to stabilize the knee which in turn results in high compressive KCF. This suggests that subjects with OA, the higher KCF is attributed to increased counterbalancing role of the quadriceps and hamstrings during dynamic movements to stabilize the knee, where muscle forces are represented as the main contributor of KCF.

The findings of the present study suggest that OA patients and NP produce similar M/L shear loading patterns, (Figure 6. 5). However, pre-TKR patients had a lower KCF compared to NP in late stance, i.e reduced by 53.3% (0.15 BW to 0.07 BW). In agreement with Benedetti et al. (1999), co-contraction of knee flexors and extensors is a common strategy to reduce shear forces at the knee but increases joint compressive forces and joint loading.

Muscle strength has long been an important part of the management of people with knee OA (Sharma et al., 2003a). Sharma et al (2003b) reported that strong quadriceps muscles are associated with a greater likelihood of progression of knee OA in patients with knee mal-alignment or excessive frontal plane laxity.

The support on the first half of stance is generated by the actions of the knee extensors, which explain the appearance of the first peak of the resultant KCF in early stance, whereas the ankle plantar-flexors are responsible for the appearance of the second peak in late stance, Figure 6. 6. The actions of these muscles also explain the shape of the KCF calculated in the anterior-posterior direction: The vasti decelerates the centre of mass in early stance, whereas the gastrocnemius accelerates it in late stance.

Instrumented prosthesis has been used to validate joint loading estimated from musculoskeletal modelling. Multiple groups have reported knee joint loading by using instrumented knee implants, generally consisting of a tibial tray with a polyethylene articular surface and imbedded transducer strain gauges at the four corners. The D'Lima et al. group conducted multiple studies by implementing different generations of devices and found that peak resultant tibial contact forces increased steadily during the first 12 months post-operative period. They reported axial tibial tray loading remained near 2.5 BW during self-selected speed walking (D'Lima et al., 2012; D'Lima et al., 2011; D'Lima et al., 2005; D'Lima et al., 2006). The group of Heinlen et al. (Heinlein et al., 2009) has reported similar loadings as that reported by D'Lima. The level walking data from each group showed an average

profile with two distinct peaks, and in agreement with our results Kutzner et al. (Kutzner et al., 2010) showed that the second peak was higher than the first one, while D'Lima et al. showed the first one being slightly higher.

As seen, the changes in muscle forces with OA progression can be reported with increase or decrease in magnitude, (ex: vastus medialis, vastus inter-medialis during early stance and biceps femoris-short head and medial and lateral gastroc during late-stance), or change in pattern, (ex: biceps femoris-long head, lateral gastroc and rectus femoris during mid to late-stance).

During early stance, vastus medialis and vastus inter-medialis represent the main contributor to muscle force, and to less extent semimembranosus, semitendinosus and biceps femoris muscles contribute to develop muscle forces. As shown in (Table 6.3), a significant reduction was reported in vastus medialis, vastus inter-medialis, and semitendinosus for pre-TKR patients compared to NP subjects. While during late stance, medial gastrocnemius, lateral gastrocnemius, biceps femoris-short head and rectus femoris represent the main contributor to develop forces during late stance. As shown in Table 6.4, pre-TKR patients have significantly reduced the forces developed by medial gastrocnemius, lateral gastrocnemius, biceps femoris-short head and rectus femoris compared to NP subjects.

Group ensemble-averaged waveforms for gastrocnemii, quadriceps and hamstrings muscle forces illustrate that specific changes were systematic with increased structural severity, as shown in Figure 6. 8. Consistent with previous literature

(Richards and Higginson, 2010), the impact of muscle forces on knee joint loading is demonstrated in Figure 6. 6.

Muscles made the largest contribution to the pattern of the resultant force acting between the femur and tibia (Figure 6. 6) and the strategies that the muscles used to develop their forces will reflect on overloading of the knee during 35-60% of stance. In support of the hypothesis, these results suggest that combined knee extensor muscle forces during the loading response phase were reduced in pre-TKR and pre-HTO patients compared to NP (Figure 6. 8) and (Table 6. 3). This finding suggests that while quadriceps reduced their forces, this may cause deficiencies in knee extensor moment production. A concomitant increase in co-contraction from the knee flexors will occur in an attempt to stabilize the knee.

It can be seen that the majority of muscle force during the loading response phase is from the vastus medialis in NP individuals (Figure 6. 7). However, OA patients utilized less vastus medialis, vastus inter-medialis, semitendinosus, and semimembranosus than NP. During 35-60% of stance, the results showed that pre-TKR patients utilized high levels of muscle forces compared to HTO and NP controls. They employed the medial and lateral hamstrings, vastus medialis, and vastus inter-medialis more than that seen in other cohorts.

On the other hand, it can be seen that the majority of muscle force during the push-off phase is from medial gastrocnemius and rectus femoris in NP individuals (Figure 6. 7). However, pre-TKR patients utilized the vastus medialis, vastus inter-

medialis, semitendinosus, and semimembranosus more during push-off than NP and pre-HTOs. Pre-HTO patients primarily used biceps femoris more.

OA patients may be utilizing the muscles differently as a compensatory strategy for the reduced knee extensor strength. In support to the hypothesis, combined knee extensor muscle forces during the loading response phase were reduced in pre-TKR and pre-HTO patients compared to NP controls (Table 6. 3). The peak vastus lateralis and vastus inter-medialis forces were reduced in OA patients resulting in a reduced sum of knee extensor muscles in loading response while increased during 35-60% of stance. These results suggest that the differences between pre-TKR patients and NP subjects during the loading response phase are influenced by the differences in muscle forces.

6.6 Limitations

This study encountered a number of limitations that need to be considered. First, the possibility of some of NP controls could have had undiagnosed knee OA, as knee radiographs were not obtained for the normal subjects. However, NP participants reported that they had no knee pain in the past during daily activities and have not been diagnosed with lower extremity joint OA to ensure they were appropriate to include in the study. Further, this study does not take into account gender differences. Debi et al. (2009) identified that there are differences in gait patterns and muscle strength between male and female. Another limitation is the amount of adipose tissue on the participants, particularly TKR patients; some patients had

substantial adipose around the anterior-superior iliac spine and iliac crest. We are limited by the placement of reflective markers and marker motion artefact. Finally, knee ligaments were not included in the musculoskeletal model that was used to estimate joint loading, which may be important for reducing residual loads in anterior–posterior tibial force. However, a previous study has shown that the ligaments influence is much lower than the quadriceps (Shelburne et al., 2006).

6.7 Summary

In agreement with the previous chapter, muscle forces estimated in this study (by using SO) reported a reduction in gastrocnemius muscle force in OA groups while quadriceps and hamstring muscles developed higher forces during mid to terminal stance for OA groups.

Loading curves show a high A-P and compressive knee contact force during mid to terminal stance for OA groups compared to the NP, due to counterbalancing role of quadriceps and hamstring during this interval.

The second peak of the compressive KCF is lower in subjects with OA, suggesting that less muscle force is being produced in late stance and subjects are not driving themselves forward with the same strategy as the control group.

Finally, This study introduced the importance of considering the interrelationships between gait and neuromuscular adaptation in the study of knee OA disease progression.

Chapter 7

Conclusions and Future Work

7.1 Summary and Conclusions

The overall aim of this thesis was to investigate the changes in knee loading with the progression of knee OA and correlate these changes to the underlying neuromuscular mechanisms adopted during gait for NP, pre-HTO, and pre-TKR subjects. This was undertaken in 4 distinct steps.

Chapter 2: Can Activities of Daily Living Contribute to EMG Normalization for Gait Analysis?

The overall aim of this study was to examine alternative methods of normalization that effectively reflect muscle activity as compared to Maximal Voluntary Contraction (MVC). Results demonstrated that normalization by adopting the peak value through ADLs, in addition to MVCs, **PDM, provided a good ability to reflect the relative magnitude of muscle activity, in a similar way to that seen in MVC alone and with excellent reliability across subjects. It is also useful for determining on-off timings of muscle activity. Therefore, this method of normalization could be used alternatively when the subject has difficulties with performing MVCs, i.e. patients with OA, or even if their MVCs were less than their muscle activation through walking. If the activities required for **PDM are not available then *PDM is the second preferred option, where the peak value through ADLs are used.

Chapter 3: The Importance of Knee Muscle Coordination through Different Stages of Osteoarthritis

This study aimed to determine the changes in co-contraction indices for muscles controlling the knee joint in patients with varying degrees of OA severity. In addition, it identified whether the selected time interval for calculating CCI could play an important role when differentiating between different stages of knee OA severity

Results showed that both hamstring and gastrocnemii muscles play a significant role in stabilizing the knee joint and their coordination changes with the progression of OA. An increase in the lateral muscle co-contraction reflects the progression from NP to pre-HTO. For pre-TKR subjects, alterations most likely occur in both lateral and medial sites.

Further, CCI calculated during both the stance phase and the gait cycle can be used to differentiate between different the progression of OA. Both intervals can be used to differentiate between the three studied cohorts (NP, pre-HTO, and pre-TKR).

Finally, two methods of normalization (*PDM and **PDM) have been used to calculate CCI. Both methods have shown that CCI were significantly associated with an increase in OA progression.

Chapter 4: Estimate Muscle Strategies during Different Stages of OA

The purpose of this study was to estimate quadriceps, hamstrings and gastrocnemius forces in patients with varying degrees of OA severity by using an EMG-driven model. In conclusion, a reduction in gastrocnemius muscle force is linked to OA severity. Quadriceps and hamstring muscles play a significant role in stabilizing the knee joint during mid-stance with altered coordination and increased forces through different stages of OA.

Moreover, patients with severe knee OA adopt a gait pattern that differs from that of patients with moderate OA and control subjects, in an attempt to unload the affected structures during walking, possibly by changing muscle coordination's as well as moments at the adjacent ankle and/or hip.

Chapter 5: Alterations in Knee Loading and Neuromuscular Activity are Associated with OA Severity

The purpose of this study was to estimate KCF in patients with varying degrees of OA severity and correlate the changes that might be seen in joint loading with muscle forces. Results showed that differences in the patterns and magnitudes of the KCF waveforms provide information on gait changes associated with knee OA severity. The findings of the present study suggest that pre-HTO patients and NP controls produce similar loading patterns, while pre-TKR exhibited a different pattern. The highest KCF was found for the control cohort, followed by moderate stage OA (pre-HTO) and then late stage OA (pre-TKR). Also, loading curves show a high A-P and compressive knee contact force during mid-stance for OA groups

compared to the control group, due to counterbalancing role of quadriceps and hamstring during mid-stance. Further, the second KCF peaks are lower in subjects with OA. This suggests that less muscle force is being produced in late stance and therefore the subjects are not driving themselves forward with the same strategy as the control group.

As far as we know, this is the first study provides pertinent information about the approaches of EMG normalization, knee kinematic and kinetic, muscle coordination strategies, muscle forces, and joint loading for NP, pre-HTO, and pre-TKR subjects. This section will briefly summarise the primary novel contributions to knowledge made by this research. The key findings have been summarised:

- Despite receiving little focus in the literature, normalization of EMG for OA subjects is very important to be able to explore and compare muscle activation patterns and co-contractions through the disease progression. Activities of daily living (ADLs) is demonstrated in this work as a useful measure in EMG normalization.
- Co-contraction index (CCI) can be considered as a useful marker for OA progression, where results have shown that increases in CCI were significantly associated with an increase in OA progression.
- Differences in the patterns and magnitudes of the knee contact force (KCF) waveforms provide information on gait changes associated with knee OA progression.

- The second peak of the compressive KCF is lower in subjects with OA. This suggests that less muscle force is being produced in late stance and therefore the subjects are not driving themselves forward with the same strategy as the NP.

7.2 Future Work

- While this thesis provides pertinent information about kinematic, kinetic, muscle coordination strategies, muscle forces, and joint loading alterations for subjects with varying degrees of knee OA progression, this information are not able to ascertain whether some variables are related to the cause or the effect of the disease process. Further work is required investigating the neuromuscular adaptations associated with early OA. The rationale for studying patients with early OA is to determine the alterations that might be expected before severe pain, to improve our understanding of the causative factors in OA development and to inform early rehabilitation strategies.
- Future research utilizing musculoskeletal modelling can be adopted to investigate alterations in muscle forces and coordination strategies depending on rehabilitation approaches and examines if the knee loading, kinetics, and kinematics are recovered to the level of healthy individuals following the rehabilitation.
- Comparisons of pre- and post-surgery data would also provide a more clear insight into how well the HTO and TKR aid in correcting moderate and end-

stage of OA , respectively. Further, this kind of comparison helps to see how the mechanical loadings on the knee joint are changed before and after surgery, and if they are within the range of controls or not. Further, to demonstrate if the post-surgery patients will activate their muscles in the same strategies that were used before the surgery.

- This thesis looked at the muscle strategies for OA subjects, such information can be used clinically to re-establish gastrocnemius muscle force for example, by using gait training. This will lead to potential interventions that may decrease the rate of knee joint degeneration, i.e., can aid in restoring OA patients to normal loading and movement patterns.
- The total loading on the knee joint show significant differences in magnitude and patterns through OA progression. This study can be extended to calculate loading on the medial and lateral compartment of the knee. Patient populations including individuals with medial knee OA and varus deformity (pre-HTO) and those with end stage of knee OA (pre-TKR) often have more medial knee contact load. Therefore, it is interesting to examine the muscular contributions to medial and lateral compartment loads.

Chapter 8

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