USING COMPUTATIONAL MODELING TO ESTIMATE CHANGES IN JOINT REACTION FORCES IN THE KNEE OF SYMPTOMATIC OSTEOARTHRITIS PARTICIPANTS USING A GAIT RETRAINING INTERVENTION WITH REAL-TIME BIOFEEDBACK

by

Matthew Prebble
A Dissertation
Submitted to the
Graduate Faculty
of
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The Requirements for the Degree
of
Doctor of Philosophy
Education

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Dedication

This is dedicated to my mom who has always been my biggest supporter and believer and always challenged me to pursue my dreams. Her dedication and hard work have always been an inspiration and given me a wonderful guiding light to follow throughout my life.

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I would like to thank the many friends, relatives, classmates, faculty, and professors past and present who have made this possible. I could not have completed this journey without the support and friendship of my classmates in the Kinesiology program at George Mason University. Amanda (Cary) Estep, Ph.D., Oladipo Eddo, Ph.D., Bryndan Lindsey, Ph.D., Trish Kelshaw, Ph.D., Jen Fields, Ph.D., Justin Merrigan, Ph.D., Ana Morais Azevedo, Ph.D., Jessica Pope, Ph.D., Stuart McCrory, Richard Shaw, Kate Romm, and many more were a constant source of support, inspiration, and friendship throughout the long and difficult process. Their kindness, intelligence, and dedication to the field were an inspiration and I could not have completed this journey without them. I also owe a special thanks to Dr. Robert Ruhling, my advisor in my GMU master's program, who was a key inspiration that led me to the decision to pursue this journey and I will always be grateful for his advice. I would also like to acknowledge the contributions and mentorship of Dr. Amanda Caswell, Dr. Shane Caswell, Dr. Jatin Ambegaonkar, Dr. Joel Martin, Dr. Qi Wei, and Dr. Angela Miller from GMU and Dr. B.J. Fregly from the University of Florida and Dr. Wendi Weimar from Auburn University. Whether through classes or research projects each of those faculty members had a huge impact on my growth and development as a student and scholar and their dedication to teaching and mentoring was a source of motivation and encouragement. Finally I need to provide a special acknowledgement to Dr. Nelson Cortes who was my primary advisor and mentor throughout my doctoral journey. His advice, encouragement, teaching, and mentorship were the key driving forces behind my success in the program and I will always be thankful for his insightful advice and opportunities he provided. Special thanks also goes to Elsevier for permission to reuse the figure "Atlas of individual radiographic features in osteoarthritis, revised." Lastly I also need to thank my dog Jack, who was there to remind me of the importance of not forgetting about the little things in life, like taking a break to go for a walk, playing a bit of fetch, or to just lay on the couch to cuddle when the stress and anxiety of trying to complete a dissertation during a global pandemic were overwhelming.

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List of Abbreviations

Analysis of covariance	ANCOVA
Analysis of variance	ANOVA
Anterior cruciate ligament	ACL
Body mass index	BMI
Body weight	BW
Computed muscle control	CMC
Control	CO
Electromyography	EMG
Female	F
Foot progression	FP
Gastrocnemius	GAS
Ground reaction force	GRF
Hierarchical linear modeling	HLM
Joint reaction force	JRF
Kilogram	kg
Knee adduction moment	KAM
Knee flexion moment	KFM
Lateral trunk lean	LTL
Left	L
Male	M
Maryland	MD
Maximum voluntary isometric contraction	MVIC
Medial knee thrust	MKT
Meter	m
Multivariate analysis of variance	MANOVA
Neuromusculoskeletal tracking	NMT
Newton	N
Normal gait	NG
Number	n
Numeric rating scale	NRS
Osteoarthritis	OA
Randomized controlled trial	RCT
Real-time biofeedback	RTB
Rectus femoris	RF
Repeated measures analysis of variance	RM ANOVA
Right	R

Root mean squared error .... RMSE
Standard deviation .... SD
Static optimization .... SO
Toe-in gait .... TIG
Trunk lean .... TL
Vastus intermedius VI
Vastus lateralis VL
Vastus medialis .... VM
Vertical ground reaction force .... vGRF
Western Ontario and McMaster Universities Osteoarthritis Index .... WOMAC
Years .... yrs

Abstract

USING COMPUTATIONAL MODELING TO ESTIMATE CHANGES IN JOINT REACTION FORCES IN THE KNEE OF SYMPTOMATIC OSTEOARTHRITIS PARTICIPANTS USING A GAIT RETRAINING INTERVENTION WITH REAL-TIME BIOFEEDBACK

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This dissertation evaluates the effect of gait modifications on the joint reaction forces (JRF) estimated via computer simulation using the OpenSim software tool. Osteoarthritis (OA) of the knee is a common and progressive condition that can lead to the need for a full or partial joint replacement. Identifying interventions that can slow the progression of the disease can help improve the quality of life and reduce impairments to activities of daily living in those diagnosed with knee OA. Modified gait interventions are a common approach that seek to reduce the loading in the knee joint, and significant research has demonstrated gait modifications' effect on the knee adduction moment (KAM) and knee flexion moment (KFM). The KAM and KFM are common surrogate measures of joint loading and many gait interventions have been shown to reduce KAM and/or KFM. Recent advances in computer technology have enabled more efficient and practical use of simulation for estimating the joint reaction forces in the knee during a variety of tasks, such as walking and running. These approaches are often validated using data from subjects with instrumented knee implants and their accuracy and use have been growing. This dissertation covers 3 independent studies that sought to estimate the effect of gait interventions on the JRF in the knee. The first study used existing data published in the biomechanics community, via the Grand Challenge Competition to Predict in Vivo Knee Loads, to validate the use of the Lerner knee model in participants implementing 2 common gait interventions: the medial knee thrust (MKT) and the lateral trunk lean (LTL). The second study built on the first and implemented the simulation approach in 20 healthy participants who performed 3 gait modifications: the toe-in gait (TIG), the MKT, and the LTL. The final project of this dissertation research was a 10-week randomized controlled trial (RCT) that used real-time biofeedback (RTB) to implement the LTL in participants diagnosed with medial compartment knee OA. The results of this work validated the use of the Lerner knee model in modified gait, such as MKT and LTL. They also provided evidence to suggest that the LTL may not be as effective as previously thought at lowering the JRF in the medial compartment of the knee. Further work is needed to validate these findings and directions of future research are also discussed.

Chapter 1. Introduction

Degenerative joint disease, commonly referred to as osteoarthritis (OA), is a serious medical condition and the most frequent cause of disability in the United States.[1] OA is characterized by the progressive inflammation, breakdown, and eventual loss of cartilage in the joints. The most often diagnosed sites are the hands, hips, and knees with knee OA affecting over 30 million adults in the United States.[2,3] Globally, knee OA was ranked as the 11th highest contributor to disability with an age-standardized prevalence of 3.8%.[4] Common risk factors for OA include previous joint injury, age, gender, obesity, and genetics.[2]

Epidemiology of Osteoarthritis

Epidemiological research, and studies conducted with twins, have suggested that about 50% of the variation in susceptibility to OA in the knee, hip, and hands is accounted for by genetic factors.[5-8] The knee is the most common joint diagnosed with OA[9] and a number of risk factors have been identified related to both extrinsic and intrinsic variables.

Extrinsic risk factors for knee OA include previous injury, frequent squatting, and frequent kneeling.[10,11] A menisci injury that requires surgery increases the risk of future knee OA by 2.6 times when compared to individuals with normal menisci.[12,13] Similarly, research has shown that that occupations that involve squatting or kneeling for over 2 hours per day are associated with a two-fold increase in the risk of moderate to severe knee OA.[10]

Intrinsic factors that have been linked to an increased risk for developing knee OA include age, gender, obesity, genetics, muscle weakness, and joint dynamics.[8,10] About 10% of men and 13% of women 60 years and older have symptomatic knee OA.[10] In general, women tend to have higher rates of knee OA than men, and of particular concern are women over 55 who have been shown to have more severe OA in the knee compared to men of a comparable age.[10] Obesity has been associated with an increased risk of OA in the knee, hip, and hands. While excess weight may be partially responsible for the increased risk of OA in the knee and hips, excess adipose tissue has been linked to humoral factors which may alter the metabolism of articular cartilage and also increase the risk of OA.[10] There is conflicting evidence in the literature with regards to the effect of thigh muscle weakness on knee OA. Some studies indicated that muscle weakness was a factor in the progression of knee OA while other studies suggested that this relationship was more relevant in women.[14-16] A recent systematic review found that the evidence of an increased risk of joint deterioration in individuals with knee muscle strength deficits was inconclusive.[17]

Osteoarthritis of the Knee

Osteoarthritis is the result of the cartilage that protects the articulating surfaces of joints wearing down over time. In the early stages abnormal joint motion leads to spatial shifts in the contact locations and load-bearing regions in the joint. This abnormal motion leads to damage in the collagen network located on the articulating surfaces. Damaged tissue leads to increased friction in the joint and reduces the compressive stiffness. As the disease progresses the increased friction can lead to shearing on the joint surface, and higher shear stress in the cartilage, which causes further breakdown of the tissue. Figure 1 shows a visual depiction of the progression of the disease. Due to the damage, the joint is less able to accommodate typical compressive loads and the rate of progression becomes dependent on the magnitude of compressive forces.[18] A number of biomechanical changes are thought to contribute to the initiation and progression of knee OA with increased tibiofemoral rotation and peak knee adduction moment (KAM) being 2 commonly identified factors.[19-21]

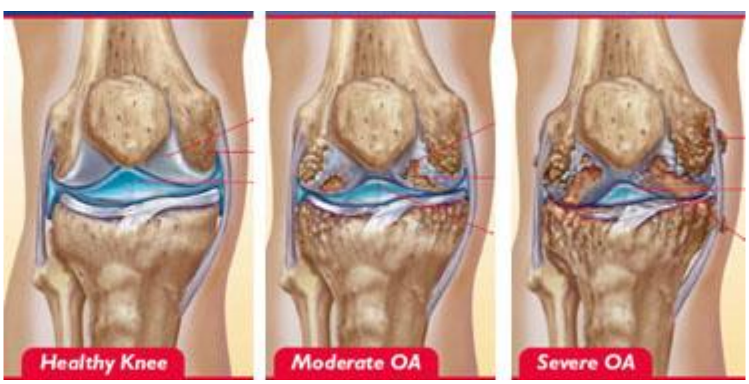

Figure 1. Progression from a Healthy Knee Joint to Severe Knee Osteoarthritis (OA)[22]

The combination of a growing population of older adults and high levels of obesity may lead to an increased incidence and prevalence of knee OA in the United States and globally.[4] Unfortunately, there is currently no cure for the condition and the disease can progress to a point where it requires a total joint replacement. Research from the Mayo Clinic indicates that about 1 million hip and knee replacements are performed in the U.S. each year. In 2010 the prevalence of knee replacements was 2.2%, which translates to about 6.7 million people living with knee replacements.[23] Understanding the factors that lead to the progression of knee OA may help identify interventions that could reduce the burden of the disease and delay or prevent the need for a total joint replacement.

A recent review article has identified opportunities to intervene at multiple stages of the disease progression, which could reduce the initiation or progression of knee OA.[24-26] The first opportunity identified is increased prevention of modifiable risk factors such as obesity or knee injury. Proper diet and exercise can reduce weight gain and there is robust research looking at reducing the risk of various types of knee injuries, such as anterior cruciate ligament (ACL) tears, which are a major risk factor for the development of knee OA.[27,28] An increased focus on these issues could reduce knee OA from developing, or delay its initiation until later in life. A second opportunity identified is earlier recognition of the disease in individuals, including those who may be presymptomatic. Early identification allows a wider array of options for interventions and could delay the seriousness and progression of the disease, or may be able to reverse the course of the disease. However, early diagnosis is challenging and further work is needed to accurately identify the condition in its early stages.[11] A final opportunity identified is improvement in the currently poor implementation of clinical guidelines. The article argues that there is a well-documented stepwise approach to the management of OA that has not consistently been implemented at the clinical level.[26] One type of clinical intervention that is currently a focus of research is gait modification strategies, which are intended to slow the progression of OA.

Gait Modifications

One approach to slow the progression of knee OA is to use a gait modification to attempt to reduce the joint reaction forces in the knee during gait. A number of modifications have been studied, including: reducing gait speed, foot orthotics, altering foot progression angle (e.g. toe-out gait or toe-in gait), medial knee thrust, and lateral trunk lean.[29-45] Altering the foot progression angle and the lateral trunk lean are 2 relatively simple and well-tolerated interventions that are of interest. The foot progression angle modification is where the subject walks with either a toe-in or toe-out gait which is thought to reduce the contact forces in the knee during foot contact and the stance phase of gait.[29,32,34,36-38,42,46] The lateral trunk lean (LTL) modification shifts the center of mass of the body over the support limb during the stance phase of gait as a way to reduce the joint moments and, hopefully, the joint reaction forces.[35,40,43,44]

Estimation of Joint Reaction Forces in the Knee

Due to the decreased function of the cartilage in a knee diagnosed with OA, to handle typical joint loading it is important to understand the joint reaction forces between the femur and tibia. This information can increase understanding about how activities of daily living, such as stair climbing, can increase the risk of OA progression and can also help inform the design and implementation of interventions that can reduce the joint loading and hopefully slow the progression of the disease. While it is not practical to directly measure these forces, 2 common approaches are used to estimate these values.

The first method is to use a surrogate measure for the forces and the second approach is to estimate the forces using computer modeling and simulation.

Knee adduction moment and knee flexion moment. The 2 most common surrogate measures for joint loading are the knee adduction moment (KAM), which is the joint moment in the frontal plane (Figure 2), and the knee flexion moment (KFM), which is the joint moment in the sagittal planes. KAM is one of the most commonly studied surrogate measures and research has identified a relationship between the magnitude of KAM and joint reaction forces.[18,20,21,34,47-49] The KFM is another important surrogate measure of interest and research has found that both KAM and KFM need to be considered when investigating how interventions alter the moments at the knee.[50-53] It is possible for a reduction in KAM to occur while an increase in the KFM occurs.[50] Both KAM and KFM are proxy measures for joint reaction forces and are not direct estimates of the contact forces acting between the tibia and femur. In contrast to joint moments, computer simulation can be used to directly estimate contact forces acting on the knee joint.

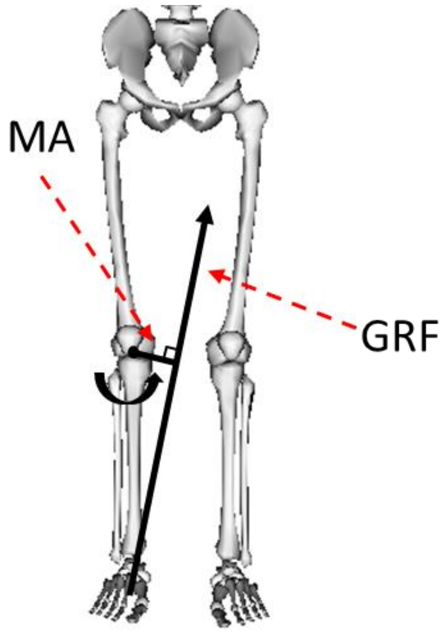

Figure 2. Diagram of Elements to Calculate Knee Adduction Moment, which is Equal to the Magnitude of the Ground Reaction Force (GRF) Multiplied by the Length of the Knee Joint Moment Arm (MA)

Estimation of joint reaction forces via computer simulation. A second approach to estimated joint loads is to use computer simulation of human movement to estimate forces and loads. While there were early attempts at this approach in the 1970s, as technology and computational power have increased over the past several decades the sophistication and complexity of the models have improved significantly. Two common techniques used to solve the equations of motion in these models are forward and inverse dynamics.[54] Forward dynamics uses estimates of the muscle forces and moments which would be needed to generate the subsequent position, velocity, and acceleration of the body segments. In contrast, inverse dynamics takes the position, velocity, and acceleration of the segments as inputs and calculates the forces and moments that would have been required to create those positions, velocities, and accelerations.

OpenSim software is an open source tool commonly used in the biomechanics field to simulate musculoskeletal motion of humans and animals.[55] It is possible to extend the functionality of the software by creating custom software add-ons; recent work has provided an update to the default OpenSim human model with an enhanced knee joint model which enables estimating the joint reaction forces in both the medial and lateral compartments of the knee.[56] Prior to this work OpenSim could only provide an estimate for the total force through the knee joint center. A key aspect of the enhanced knee joint is the ability to customize it to individual subject's anatomical knee alignment and joint contact geometry. This is done by inputting the angles of the alignment of the knee between the femur and tibia as well as being able to specify the specific contact locations between the femur and tibia with in the knee joint.

Research Problem and Approach

Identifying effective interventions that reduce the loading in the knee joint is important to help slow the progression of knee OA and reduce the burden of the disease. The main purpose of this project was to assess the effect of gait interventions using real-time biofeedback (RTB) on the joint reaction forces estimated via computer simulations. To accomplish this goal 3 independent projects were completed including an initial validation study (Study 1, in Chapter 3), a within-subjects repeated measures design on healthy control subjects (Study 2, in Chapter 4), and a 10-week randomized controlled trial (RCT) using RTB (Study 3, in Chapter 5).

Study 1. The goal of this project was to ensure that the Lerner knee model, which was previously validated in normal walking gait, can accurately estimate joint loads in subjects using modified gait strategies such as the medial knee thrust and lateral trunk lean gait. In order to validate the model, data from an individual with an instrumented knee implant was used to compare measured in vivo joint reaction forces with the estimated forces from the simulation model.

Study 2. The goal of this project was to analyze the effect of 3 common gait interventions—lateral trunk lean, medial knee thrust, and toe-in gait—on estimated joint reaction forces. A within-subjects repeated measures design was conducted on healthy subjects to determine the effects of the 3 interventions on the joint reaction forces estimated via computer simulation.

Study 3. The goal of the final project was to determine the effect of a 10-week gait intervention, using RTB, on the simulated joint reaction forces. A preliminary RCT was conducted on participants with symptomatic medial compartment knee OA. Participants were randomized into either a control or intervention group and the effect of a lateral trunk lean gait intervention using RTB on the joint reaction forces was analyzed. Baseline biomechanical gait data were collected, followed by a 10-week intervention, and included 3 postintervention biomechanical gait assessments.

***Hypothesis 1*.** It is hypothesized that the accuracy of the Lerner knee model estimates for knee joint reaction forces in participants implementing modified gait strategies, such as medial knee thrust and lateral trunk lean, will be similar to the values found for normal walking gait.

***Hypothesis 2*.** It is hypothesized that the medial compartment joint reaction forces will decrease for participants implementing the 3 identified gait modification strategies when compared to their baseline values.

***Hypothesis 3*.** It is hypothesized that the medial compartment joint reaction forces will decrease for participants implementing a selected gait modification, using real-time biofeedback, when compared to a control group in a randomized controlled study design.

Chapter 2. Literature Review

Osteoarthritis

Osteoarthritis (OA), sometimes referred to as degenerative joint disease, is a leading cause of disability in the United States and affects about 32 million people.[2,3] The hip, knee, and hands are the most common sites for OA.[3] A study that used radiocarbon dating on cartilage in humans suggested that articular cartilage is a permanent structure that undergoes no significant turnover in adults and therefore has a minimal capacity for repair.[57] The development and progression of the disease is a dynamic process where the loads applied to the articular cartilage of the joint produce damage that cannot be repaired by the biological repair mechanisms.[58] Figure 3 shows the radiographic progression of knee OA from grade 0 (no OA) to grade 3 (moderate OA).

Figure 3. Radiographic Progression of Knee Osteoarthritis (OA): (A) Grade 0 Normal, (B) Grade 1 Medial Femoral Osteophyte, (C) Grade 2 Medial Femoral Osteophyte, and (D) Grade 3 Medial Femoral Osteophyte [Copyright (2007) Elsevier][59]

The knee joint is the most common site for OA[9] and risk factors include both extrinsic and intrinsic variables. The most common extrinsic knee OA risk factors include previous injury, frequent squatting, and frequent kneeling.[10] A large longitudinal cohort study conducted in Sweden calculated a 6-fold increase in OA risk in young adults who experience knee injury as compared to uninjured individuals.[60] The types of injuries identified in the study that lead to the increased risk were cruciate ligament injuries, meniscal tears, and tibial fractures. A meat-analysis that focused on the risk of OA after ACL injury found a near 7-fold increase after ACL injury and almost an 8-fold increase in OA risk after ACL reconstruction surgery.[27] Surgery to the menisci increased the risk of future knee OA by 2.6 times when compared to individuals with normal menisci.[12,13] In addition to acute injuries, occupations that involved squatting or kneeling for over 2 hours per day are associated with a 2-fold increase in the risk of moderate to severe knee OA.[10]

Intrinsic factors that increase the risk for developing OA include age, gender, obesity, genetics, muscle weakness, and joint dynamics.[10] In individuals 60 years and older about 10% of men and 13% of women have symptomatic knee OA.[10] Research has indicated that women tend to have higher rates of knee OA than men, and women over 55 had more severe OA in the knee compared to men of a similar age.[10] Obesity has been implicated with an increased risk of OA in the knee, hip, and hands. Studies that have looked at cartilage loss in individuals with OA found that the loss progressed faster in participants with an average BMI of 30 kg/m^2 and higher and was slower in individuals whose BMI was less than 30 kg/m^2.[61,62] Research has also suggested that excess adipose tissue produces humoral factors that may alter the metabolism of articular cartilage and some researchers hypothesize that the leptin system is a link between metabolic abnormalities and increased risk of OA.[10] Epidemiological research in families and studies in twins have provided evidence that about 50% of the variation in susceptibility to OA in the knee, hip, and hands is accounted for by genetic factors.[5-7] There is conflicting evidence in the literature with regards to the effect of thigh muscle weakness on knee OA. Some studies indicated that muscle weakness was a factor in the progression of knee OA while other studies suggested that this relationship was more relevant in women.[14-16] However, a recent systematic review found that the evidence of an increased risk of joint deterioration in individuals with knee muscle strength deficits was inconclusive.[17]

Biological factors in the osteoarthritis process. Osteoarthritis occurs when the cartilage that protects the articulating surfaces of joints wears down over time. Cartilage is a firm and flexible connective tissue that covers the articulating surfaces of bones in synovial joints.[63,64] It is about 70 to 85% water with the remainder being composed of proteoglycans, collagen, and a small amount of lipids.[64,65] There are 2 main types of collagen fibers: Type I and II. Type I collagen is the most common form and is present in tendons, ligaments bone, the dermis, and in scar tissue. Type II collagen is the foundation of articular cartilage and hyaline cartilage. The collagen fibers provide strength, the proteoglycans provide shock absorption, and the movement of water into and out of the extracellular matrix allows the cartilage to compress and expand to absorb repeated loads in the joint.[63-65]

Swelling in the extracellular matrix is the first stage of cartilage breakdown leading to OA. This leads to the tissue becoming more porous, allowing water to escape more easily, and reduces the stiffness of the cartilage which in turn allows it to deform faster when loads are applied to the joint.[66] Typically the cartilage is not uniformly affected and adjacent areas of softness and stiffness are created. Neighboring regions with different tissue properties are implicated in a cascade of events leading to the necrosis of some Type II collagen fibers and a loss of proteoglycan.[63,66] Healthy chondrocytes adjacent to degenerating ones attempt to repair the damage by producing additional cartilage which contains Type I collagen.[67] Type I collagen is mechanically inferior to Type II and is less capable of dissipating loads. This alteration in the mechanical properties of the tissue reduces the shock-absorbing capabilities, leading to a cyclic degeneration of cartilage tissue.[67]

Subchondral bone is a layer of bone just beneath the cartilage in a joint and has many blood vessels that supply it with nutrients and oxygen.[68-70] Cartilage does not have its own blood supply and relies on the subchondral bone for its nourishment.[70] Subchondral bone also helps attenuate forces and loads in the joint and helps protect articular cartilage from damage due to excessive loading.[68] Some research has indicated that stiffening of the subchondral bone and/or systemic inflammation may be a factor in the initiation or progression of OA.[68-72] The stiffening reduces the ability of the subchondral bone to absorb forces, which could increase the stress placed on the articular cartilage, leading to degeneration of the cartilage. Changes to the subchondral bone may precede changes to articular cartilage and any imbalance between the 2 tissues could alter the physiological balance, contributing to knee OA.[70] Another possibility is that local production of inflammatory mediators, which are known to contribute to cartilage degradation, that result from systemic inflammation could initiate or aggravate OA.[72]

Mechanical factors in the osteoarthritis process. It is generally believed that the biological changes associated with the initiation and progression of knee OA are influenced by mechanical factors.[73-75] Some have suggested that abnormal mechanical factors, such as previous injury, abnormal joint shape, or excessive loading, are the primary cause of most, if not all, incidences of OA.[74,75] Research in elderly subjects indicated that greater moments at the knee contributed to the development of future knee pain at follow up.[76] Another study showed a correlation between knee moments and lateral to medial shear forces which suggested the possibility that abnormal gait could increase the risk for developing knee OA.[75] Additional support for this hypothesis was a study that found participants in certain sports, such as soccer, long distance running, competitive weight lifting, and wrestling, had higher prevalence of knee OA.[77] However, the authors of the study could not determine if the contribution of other factors, such as previous joint injury, impacted the occurrence of OA in their study population. A study that looked at sport participation in healthy young adults found a decrease in knee cartilage volume after 12 weeks of running or cycling.[78] Similarly, a study in beginner marathon runners also found a statistically significant loss of cartilage during training; however, the loss was considered not clinically relevant and it may be possible that the previous 12-week study was showing a transient loss of cartilage that would have been reversed had the researchers continued to follow the subjects for a longer period of time.[78,79]

While some studies have suggested a relationship between abnormal or excessive joint forces and the development of knee OA, other research has provided evidence that during development knee cartilage shows positive adaptations to excessive cyclic loading of walking and running.[80-82] Detailed analysis of the variation in thickness of knee cartilage across the joint found that areas exposed to higher contact forces tended to have increased thickness.[80] It is believed that knee cartilage can adapt to excessive external loads, such as running, and repeated exposure to running does not lead to knee OA in the absence of preexisting damage (e.g. ACL injury) in the knee joint.[81,82] A short-term study in marathon runners found that some areas of the knee showed improvements after training while others showed increased damage; however, the authors suggested that some of the areas that worsened in the study may have resolved themselves with a longer term follow up.[83] A 10-year longitudinal study in marathon runners found no long-term damage to the internal structures of the knee, in the absence of preexisting damage, despite high training volumes.[84] Another study that investigated the in vivo tibiofemoral cartilage deformation during gait found that during the stance phase deformation due to contact ranged between 7% and 23% of resting cartilage thickness and the larger deformations occurred in the regions that had thicker cartilage.[85] These results support the previous research about the development of cartilage thickness in areas of higher joint loads. It is theorized that cartilage adaptation can occur up to a certain age, after which a maximum cartilage thickness is reached, and no further positive adaptation can occur past that age. Lastly, a large longitudinal study found running does not increase the risk of OA and may actually reduce the risk due to lower BMI values.[86]

A framework for the biomechanical initiation and progression of OA includes an initiation phase and a progression phase.[18] In the initiation phase abnormal joint kinematics leads to spatial shifts in the contact locations and load-bearing regions of the joint. This causes damage to the collagen network located on the articulating surfaces. This damage increases the friction in the joint and reduces the compressive stiffness. In the progression phase the increased friction can lead to shearing on the joint surface and higher shear stress in the cartilage, leading to further matrix breakdown. Due to the damage the joint becomes less able to handle typical compressive loads and the rate of progression becomes dependent on the magnitude of compressive forces.[18]

The knee is commonly considered to behave like a hinge joint with 1 degree of motion rotating in the sagittal plane. In reality the joint is more complex and includes both rotation and translation between the femur and tibia in multiple planes. In the sagittal plane the knee can rotate up to 160 degrees during flexion-extension, in the frontal plane the knee can rotate between 6 to 8 degrees varus/valgus, and in the transverse plane it can internally/externally rotate 25 to 30 degrees while in flexion.[87] In healthy knees cartilage is thickest in the lateral compartments of the knee and thinnest in the medial compartment;[88] however, alterations in the biomechanical function of the knee may alter the loading patterns and create increased forces in areas not normally exposed to high contact loads. Interestingly, research has suggested that gait changes due to age, obesity, or joint trauma converge on a similar set of kinematic changes and often occur before the onset of OA.[73] Therefore, there may be opportunities to intervene prior to the onset of knee OA, for example with preventative gait modification strategies. Experimental studies using knee cartilage have found that after a certain magnitude of deformation the tissue may experience permanent damage which would lead to degradation.[89] Therefore, the best strategies to prevent OA would include interventions that occur prior to the initiation of degradation of the tissue.

Tibiofemoral rotation. The lack of normal rotational dynamics in surgically repaired knees and the higher rates of OA in individuals post-ACL surgery have led to the suggestion that rotational dynamics in the knee are a possible contributor to knee OA. In contrast to individuals with healthy knees, those with knee OA display greater femoral internal rotation, decreased tibia posterior translation, and dysfunction in the "screw home mechanism" during extension.[90] Possible mechanisms for altered knee rotation and translation are injury to the ACL or osteophyte formation.[90] The ACL provides stability in the anteroposterior and rotational movements of the knee. Loss of this stability can lead to increased loading in the medial compartment, which is thought to contribute to higher rates of OA in individuals who have a history of ACL injuries.[18,80,88]

While reconstructive surgery of the ACL has been shown to restore anteroposterior stability, it does not consistently restore normal rotational alignment and motion.[18,88] One possible problem with this shift to increased contact forces in the medial compartment of the knee is the differences in shape between the lateral and medial sides of the tibia. The medial tibia plateau is concave and with increased internal rotation the femur will have a larger contact surface area over a region with less thick cartilage.[88] Therefore, abnormal tibiofemoral rotation can contribute to increased risk of OA and is related to the degree of internal rotation, the location of the rotation, and the amount of contact in the medial compartment of the knee.[19]

Knee Joint Loading

The load placed on the knee joint and the contact forces between the tibia and femur are important factors in understanding the initiation and progression of knee OA. However, these variables cannot typically be directly measured in vivo and as a result a number of surrogate measures are used to estimate the magnitude of, and changes in, the knee joint loading and contact forces. A number of factors impact the contact forces in the knee and their surrogate measures, including the anatomical alignment of the knee, the activity of muscles that cross the knee, and the gait speed. The knee adduction moment (KAM) is a widely used surrogate measure for the medial contact forces in the knee. Significant research has been done to estimate the KAM and the effect of interventions on reducing KAM. Research has indicated a good correlation between KAM and the forces in the medial plateau of the knee during early stance phase.[91] The KAM impulse is another surrogate measure that estimates both the magnitude and duration of loading; some research has suggested it provides a better estimate of the joint load on the knee during dynamic activities.[92] Recent research has indicated that KAM alone is not sufficient to predict the medial contact forces in the knee and that the knee flexion moment (KFM) and the KFM impulse are also important surrogate measures.[50,52,53]

Anatomical alignment of the knee. The alignment of the knee with respect to the ankle and hip influences how joint loads are distributed at the knee. A varus alignment increases the load on the medial compartment of the knee and a valgus alignment increases the load on the lateral compartment.[21,93-95] Figure 4 shows a visual depiction of normal, varus, and valgus knee alignments.

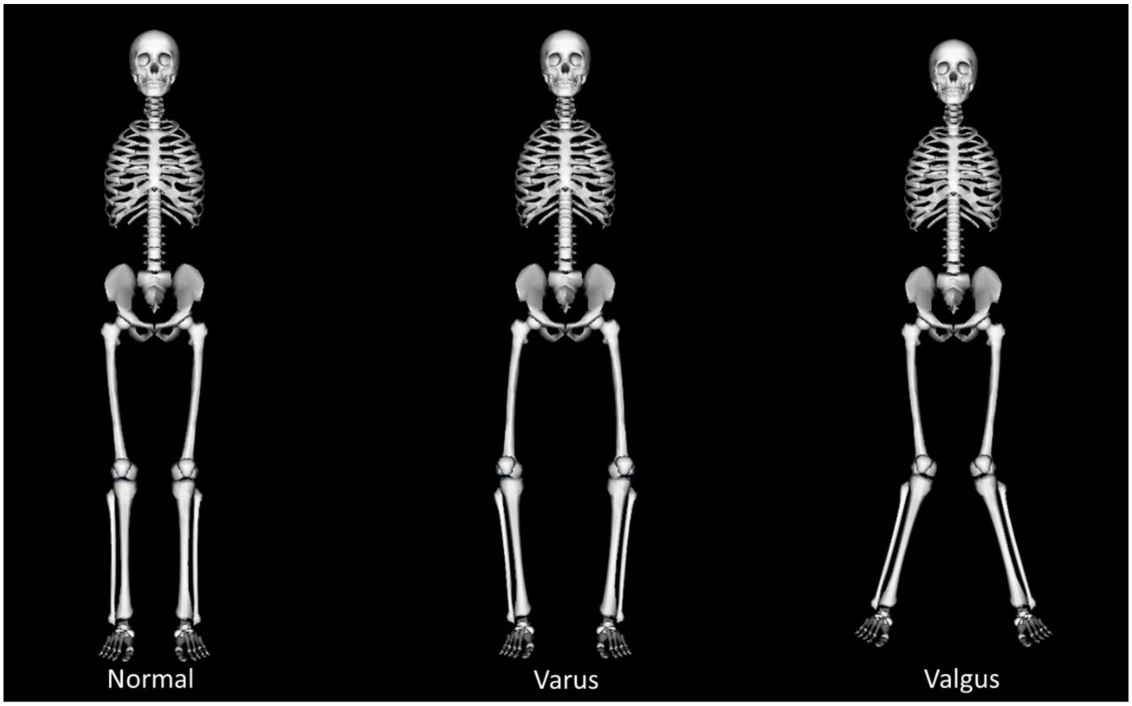

Figure 4. Normal, Varus, and Valgus Knee Alignment

Varus alignment influences the magnitude of KAM, may increase the risk of developing medial compartment OA, and may also be related to the progression of OA.[21,61,93,94,96,97] Sharma[93] found that a varus alignment at baseline was associated with an increased risk in the progression of medial OA by a factor of 4. Another study found higher varus thrust in both early and established knee OA, indicating the potential for varus alignment to identify individuals at higher risk for knee OA early in the disease state.[97] Research has also found that the alignment of the knee can change as a result of the progression of OA in the knee.[98] In a large longitudinal study a progressor group that lost knee cartilage faster was found to have a trend towards increasing varus alignment while a nonprogressor group maintained their alignment.[61] Gait analysis in the study found that those who progressed to higher varus alignment had a 13% higher KAM than the nonprogressors. In addition to frontal plane knee alignment, research has also found that rotational malalignments, in the transverse plane, can also increase the contact pressures of the medial knee compartment and may be another risk factor for the development of medial knee OA.[99]

Another factor that may alter the alignment of the knee is surgery, such as ACL reconstruction.[100,101] Since previous injury and surgery are risk factors for the future development of knee OA, the possibility of malalignment from surgery may be a cause of the increased risk or may lead to a greater increase in the risk of developing knee OA. While there may be great differences in alignment between individual subjects, research has found that there may also be differences based on race. A study that compared the knee alignment between Chinese and Caucasians found that Chinese had a more valgus alignment, which increases the load on the lateral compartment of the knee, and may partially explain the greater prevalence of lateral knee OA in that population.[102]

Muscle activity and joint loading. To understand the function of both healthy and pathological knee joints it is necessary to understand how the lower extremity muscles affect the knee during gait and other activities. As discussed earlier, varus alignment has implications for the initiation and progression of knee OA; one possible mechanism for increased varus thrust is reduced strength in knee extensor and flexor muscles, which is related to increased magnitudes of varus thrust in individuals with knee OA.[95,96] One study found that the endurance of the quadriceps muscle, but not the strength, was correlated with KAM during gait, while neither the strength nor endurance of the hamstrings showed any relationship to KAM in patients diagnosed with medial knee OA.[103] Other research has shown that the activity of antagonist muscles during knee flexion/extension can increase the joint compressive forces experienced at the knee.[104] Simulation studies that looked at ways to reduce loading in the knee during walking found that models could reduce peak forces in the knee by reducing the use of the gastrocnemius as well as walking with a shorter stride.[105-107] Recent research by Uhlrich et al.[107] found that with real-time biofeedback, healthy subjects could alter the relative contributions between their gastrocnemius and soleus muscle activations, and this gastrocnemius avoidance gait reduced peak JRF in the knee during late stance phase.

Gait speed and joint loading. It has long been established that walking speed can be a useful indicator of gait abnormalities associated with pathological knee conditions.[95,108] Previous research has demonstrated that gait speed influences many of the parameters of gait in both healthy subjects and those with knee OA.[95,109,110] In general, increases in gait speed lead to increased ground reaction forces, joint forces, and joint moments.[19,95,111] In healthy subjects increasing gait speed influenced the cadence, step length, walking base, knee joint motion, hip joint motion, and rotation of the pelvis. Increasing gait speed also impacted these parameters in patients with either hip or knee OA.[110] A study that investigated the effect of gait speed on biomechanical variables associated with joint loading found that subjects with moderate to severe knee OA had lower knee joint moments, ground reaction forces, knee reaction forces, and knee excursion when walking at a self-selected speed. When the authors controlled for the walking speed only knee joint excursion was shown to be lower. This suggests that the differences in joint kinetics and kinematics, other than knee excursion, were a result of a slower self-selected walking speed.[112] It may be possible that patients with less severe knee OA could reduce the maximum knee adduction moment by walking at a slower speed, which would hopefully reduce the progression of the disease.[30] However, in many studies the peak KAM value is not completely explained by the gait speed and other adaptations are occurring that are attempting to reduce the load on the medial compartment of the knee.[19] When assessing the effect of interventions on the initiation and progression of knee OA it is thus important to control for gait speed during the design and analysis of the study.

There is conflicting evidence in the literature about the relative contribution of the quadriceps' muscles during different stages of the gait cycle while walking at various speeds.[113-129] The quadriceps serve multiple purposes during gait with the bi-articulate rectus femoris muscle contributing to both hip flexion and knee extension while the vasti muscles are mainly involved in knee extension.[130,131] Early studies that looked at the effect of speed on neuromechanical variables of gait identified decreased EMG activity in lower extremity muscles at slower gait speed,[113,114,117] suggesting that slower speed would requires less force output from the muscles involved in propulsion.[124] Work by Shiavi et al.[116] identified greater variations in individual EMG muscle patterns at slower speeds, while faster speeds elucidated patterns with much less variance. This suggests that there is greater uniformity in neuromuscular strategies for propulsion at faster speeds but that at slower speeds there is more variation in how individuals accomplish the task of walking slower than a preferred gait speed. Previous research using both human subjects and computer simulation has suggested that faster speeds require more input from muscles for propulsion, support, and leg swing, while slower speeds require greater muscular effort for balance, control, and to make up for the loss of elastic energy.[113,115,117,125,126] Studies that have examined the effect of speed on vertical ground reaction force (vGRF) have provided evidence that the vGRF is an important measurement variable when investigating gait at varying speeds.[132-136]

Knee adduction moment. The knee adduction moment (KAM) is a common variable of interest in individuals with OA and describes how the joint contact load is distributed across the medial and lateral tibia plateaus.[19,137,138] KAM is produced when the foot contacts the ground and creates a force vector that passes to the medial side of the knee joint. The greater the distance between the force vector and the center of the knee joint, the larger the value of KAM and the greater the load that is placed on the medial plateau of the tibia.[19,34] KAM has been associated with increased levels of pain and higher levels of baseline KAM are associated with the progression of knee OA.[75,76,137,139] Research has supported the relationship between KAM and joint reaction forces, but the relationship was strongest during early stance phase; there was greater variability and only moderate correlations in late stance.[34,91,137,138,140] There have been several interactions found between joint moments and specific regions of the knee. For example, some research has found that KAM may have a larger influence on changes to femoral cartilage changes, as opposed to changes in cartilage on the tibia.[141,142] Varus alignment of the knee increases the joint load on the medial side of the joint and static alignment may also be associated with the initiation and progression of OA.[21,97,137,143,144]

Increased varus alignment can cause the joint to move laterally relative to the foot and increases KAM, which may lead to larger forces acting on the medial plateau of the tibia. Zeighami et al. identified KAM as a strong predictor of JRF in the medial compartment for both healthy and OA subjects.[140] However, for the lateral compartment they found that KAM was less predictive than the knee flexion moment.[140] Another factor in KAM is the change in lever arm post knee surgery. Research found that in subjects post partial meniscectomy, there was an increase in the lever arm and an increase in frontal plane vGRF that contributed to an increase in KAM.[145] Some research suggests the relationship between KAM and JRF may not be as strong, and work is continuing to further evaluate the exact relationship between KAM and the JRF in the knee.[146]

Peak KAM is the maximum value of KAM during the gait cycle and there are often 2 distinct peaks, 1 in early stance and 1 in late stance.[138] Often the first peak KAM is considered to be more predictive of knee OA.[48,147] Overall, peak KAM has been identified as a surrogate measure for medial joint reaction forces,[34,138] is considered a clinically significant factor in medial compartment knee OA,[95] and larger values of peak KAM have been implicated in disease severity and progression.[18-21,47,49,52,75,80,147-151] Higher levels of peak KAM were linked to 3-year joint space narrowing in the medial compartment.[147] Additionally, higher levels of peak KAM also interact with body mass and research has found that large values of peak KAM in subjects with high BMIs may exacerbate the loss of cartilage volume in symptomatic individuals.[152,153] Research suggested that for each pound lost there was a 4 times reduction in the load at the knee per step.[153] While higher magnitudes of KAM are typically implicated in OA progression, some research has found subjects post ACL surgery who developed OA had lower values of KAM and estimated joint contact forces.[154] It is also interesting to note that in healthy individuals higher values of KAM have been associated with higher ratios of medial/lateral cartilage thickness, whereas in those with knee OA higher values of KAM are associated with thinner cartilage values.[19,155] A summary of study results that investigated peak KAM and knee OA initiation and/or progression is shown in Figure 5. While a number of studies support the relationship between KAM and JRF, some studies find only a weak relationship between KAM and knee JRF.[156] Additionally, 1 study suggested that patients with early stages of OA did not demonstrate increased joint loading, and the authors suggested that increased KAM may be a factor, or outcome, in later stages of the disease.[157]

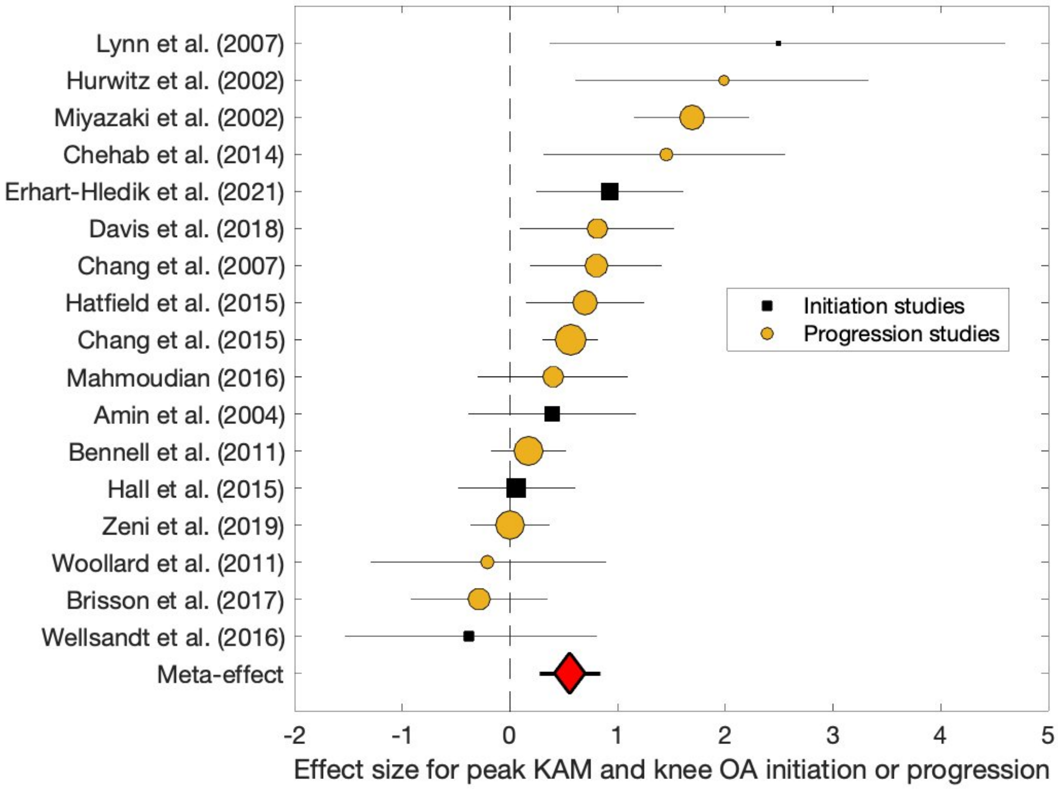

Figure 5. Meta-effect of Peak Knee Adduction Moment (KAM) on the Initiation and/or Progression of Knee Osteoarthritis (OA)[158]
Used with permission.

Knee adduction moment impulse. While peak KAM and its relationship to knee OA has been extensively studied, another related surrogate measure that has been predictive of knee OA is the KAM impulse.[150,159-163] Impulse is the integral of force over the time that the force is acting. Therefore, KAM impulse not only takes into account the magnitude of the force being applied but how long the force is applied to the knee joint. An early study that looked at KAM impulse identified a relationship between the measure and the amount of pain experienced during walking.[160] Later research determined that KAM impulse, but not peak KAM, was associated with greater loss of cartilage in the medial tibia plateau over a 12-month period.[161] Research that compared the peak KAM to the KAM impulse suggested that while both were predictive for knee OA, the KAM impulse was a more sensitive measure when trying to distinguish between severity of knee OA.[150,159] A more recent study found that higher KAM impulse was associated with greater pain, as determined by Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), in moderate disease diagnoses, but with less WOMAC pain in severe disease.[163] However, later research that compared the amount of variability in knee cartilage thickness using both peak KAM and KAM impulse found that regression models using each measure produced similar explanations of variance in knee cartilage thickness.[162]

Knee flexion moment. While the KAM has been frequently used as a surrogate measure of joint reaction forces in the knee, recent findings indicate it may be an incomplete metric with regard to the knee joint reaction forces. The knee flexion moment (KFM) acts in the sagittal plane and an increase in KFM may lead to an increased activity in the quadriceps to produce an internal knee extension moment to counteract the external KFM.[50] This increased muscle activity could lead to increased compressive forces and thus increase the knee joint reaction forces. A study that investigated the use of alternative walking patterns to reduce KAM found that while KAM was reduced in subjects, there was also an increase in KFM.[33,50] Therefore, the expected reduction in joint reaction forces due to reduced KAM may have been less than anticipated due to the increase in the magnitude of the KFM.[50] Manal et al.[52] investigated the relationship between KAM and KFM on joint reaction forces and found that peak KAM accounted for

63% of the variance in the peak medial loading while both KAM and KFM together accounted for 85% of the variance. Research has also found that KAM may have a larger relationship with femoral cartilage while KFM may be more related to changes in tibial cartilage.[141] The authors concluded that when investigating approaches to reduce joint reaction forces the combined use of both the knee flexion and adduction moments provides a more accurate estimate of joint loading.[52,138] However, a study by Chang et al.[150] that investigated OA progression found a relationship between KAM and KAM impulse to OA progression but failed to find a strong relationship between peak KFM and the progression of the disease. As discussed in the section on KAM, recent work by Zeighami et al. and others has found that KFM was a strong predictor of joint load in the lateral compartment of the knee, but has not found a strong relationship between KFM and the medial compartment.[138,140]

Knee flexion moment impulse. Similarly to the KAM impulse, the KFM impulse is the integral over time of the KFM. It is important to understand not only the magnitude of the moments acting at the knee but the duration of time over which they are acting. Research conducted by Teng et al.[53] found that higher peak KFM and KFM impulse was associated with worse cartilage health in the knee. They also found that peak KFM and KFM impulse during the second half of the stance phase of gait was related to the progression of patella-femoral joint OA. While not yet as frequently cited in the research literature as KAM impulse, the findings of the KFM's impact on the joint reaction forces indicates that the KFM impulse should also be of interest to researchers investigating the initiation and progression of knee OA.

Modifying Knee Joint Loading with Gait Modifications

Gait modifications provide a noninvasive and inexpensive approach that may slow the progression of knee OA. A number of modifications have been tested; the most commonly studied include altered foot progression angle (e.g. toe-out gait or toe-in gait), altered gait speed, medial knee thrust, lateral trunk lean, and foot orthotics.[29-45,164] While there is varying evidence to support the different gait strategies' effects on reducing the contact forces in the knee and the progression of knee OA, 3 of are particular interest: altered foot progression angle, medial knee thrust, and lateral trunk lean. These modifications are easy to implement and well tolerated by subjects.

Altered foot progression angle. Research suggests that in addition to the anatomical alignment of the knee the peak KAM during the stance phase of gait is also related to the foot progression angle during stance.[29,165] Specifically, it has been suggested that a toe-in gait reduces the peak KAM when compared to normal gait and toe-out gait.[29,46,166] However, other research identified a deceased risk for the progression of knee OA and a decreased KAM with a toe-out gait.[32,34,36,167] One study suggested that the decrease in KAM during toe-out gait led to an increase in KFM,[36] while a different study that found a decrease in KAM with toe-in gait did not lead to an increase in KFM.[46] While there is a lack of agreement regarding the effect of toe-in versus toe-out gait on KAM, one confounding factor in this research may be the gait speed during the trials. One study that looked at different magnitudes of foot progression angle identified that a slower walking speed was adopted by the subjects when walking with an altered foot progression angle.[37] As discussed earlier, a slower gait speed generally leads to a lower magnitude of joint moments, so it is possible that in the previous research, if walking speed was not controlled for, the reduction in KAM and/or KFM may have partially been a result of a change in gait speed.[30,37,168,169] A study that looked at toe-in gait while controlling for speed indicated that the modification did provide small reduction in KAM, but mostly in the first half of stance.[164]

Medial knee thrust. The medial knee thrust (MKT) gait modification was developed with the aid of computer modeling with the goal of reducing both the first and second adduction peaks during gait. The modification involves medializing the knee by bringing it closer to the center of the body while also shifting the center of pressure under the foot laterally during the stance phase of gait. The goal of the modification is to offload the medial compartment of the knee, thus reducing the joint reaction forces.[33] A study that implemented the MKT in a subject with an instrumented knee implant determined that the modification reduced the joint reaction forces by 16% during the stance phase[39] while another study reported a reduction in both first (4.7% to 15.4%) and second peak (9.5% to 11.7%) KAM.[41] Studies that compared reductions in KAM across multiple gait modifications found that MKT decreased peak KAM more than a toe-in gait and a lateral trunk lean gait, and that there was dose response relationship between the reduction and magnitude of the modification.[164,170] More recent research has found a link between the foot center of pressure and the modification in relation to its effect on reducing KAM.[171]

Lateral trunk lean. The goal of the lateral trunk lean gait modification is to shift the center of mass over the support leg during walking in order to decrease the knee adduction moment and reduce the joint reaction forces in the medial compartment of the knee. This reduction would hopefully reduce the level of pain and slow the progression of knee OA. Research by Hunt et al.[35] determined that about 25% of the variation in the first peak KAM was a result of the axis angle; they also found that patients with greater levels of pain had naturally increased their trunk lean, possibly as a way to reduce the pain during walking. Further studies have found that a lateral trunk lean is effective in reducing the joint moments in the frontal plane, or estimated JRF, and there may be a dose-response relationship between the amount of lean and the joint moments.[40,43,164,172] However, some subjects did experience discomfort in the lower spine and/or the ipsilateral hip or knee as a result of the modification.[40] Walking with an increased lateral trunk lean increases the energy cost of walking, which may make the intervention challenging for some subjects, such as elderly individuals.[44]

Real-time biofeedback. An important element that is often paired with gait modification studies is providing real-time biofeedback (RTB) to participants to improve their implementation of the modified gait strategies.[45,107,166,172] A variety of types of RTB can be provided including visual, auditory, haptic, or any combination of the 3.[45,107,166,172] RTB has several advantages including the ability to implement gait modifications with specific parameters, for example the degree of trunk lean, as well as improving the ability to measure and analyze a dose response relationship to gait modifications.[43,45,107,164,166,170,172] Studies using RTB have also provided evidence that subjects may be able to alter muscle activation patterns and use 1 synergistic muscle preferentially over another, for example increasing the use of the soleus over the gastrocnemius.[107]

Modeling and Simulation of Human Movement

One of the earliest documented biomechanical analyses was the book *De Motu Animalium* (*On the Movement of Animals*), written during the Middle Ages by the Italian mathematician Giovanni Alfonso Borelli.[173] The book was published in 1680 and includes tables and figures of animals and humans as well as human mechanical models. The first part of the book describes mechanical motions actuated by the muscles while part 2 describes the contraction of muscles.[173-175] In 1836 another seminal work, *Mechanik der Menschlichen Gehwerkzeuge* (*Mechanics of the Human Walking Apparatus*), was published by 2 German brothers.[176] The book describes an interdisciplinary approach to the science of human walking and running. The authors divided the body into 2 parts—carrying and supporting—and the legs are modeled by pendula swinging at the trunk. The book presents detailed anthropometric measurements as well as graphical analyses of motion.[175-177] An important contribution to the theoretical foundations of the mechanics of human motion was provided by German physicist and mathematician Otto Fischer.[178] In his book *Theoretische Grundlagen fur eine Mechanik der Lebenden Korper* (*Theoretical Foundations for a Mechanics of Living Bodies*) Fischer used a planar three-link system to model human walking and applied inverse dynamics to calculate the moments generated by the muscles.[175,178] Prior to the availability of advanced computer hardware and software, an early attempt at modeling the reaction forces in the knee joint was done in 1970. The researcher formulated a simplified model of the knee using mechanical principles from physics and engineering; the joint forces transmitted to the knee were calculated using experimental measurements collected from male and female participants walking at a normal pace.[179] As technology and computational power have advanced, a number of approaches have been used to simulate the motion of human movement, with multibody mechanical modeling being a key approach.

Multibody mechanical models are formulated using laws from physics and engineering and often fall into 2 categories: forward (or predictive) simulation and inverse simulation models.[55,56,180-183] Predictive simulation models attempt to calculate muscle control, forces, and/or energetics to predict the kinematics of motion. In contrast, inverse models are informed by data gathered from human subjects performing complex movement tasks, such as walking, and estimate muscle forces and activations needed to drive the model to match the experimentally collected kinematics. In this approach the main data collection methods of interest include motion capture, ground reaction forces, electromyography (EMG) of the muscles, as well as subject height and weight. The motion capture data provide the position, velocity, and acceleration of the segments of interest and this data can be used to estimate joint angles during motion. The ground reaction forces are important for estimating the loads placed on the body during the movement tasks and are used in inverse dynamics to estimate joint loads in the lower extremities. EMG data measure the muscle activity during movement and are useful for informing forward dynamics calculations or to validate the results from inverse dynamic analysis. The height and weight of the subjects as well as the motion capture data are used to scale models to individual subject anthropometrics.

Kinematics, kinetics, and dynamics. Kinematics is the study of the position, velocity, and acceleration of bodies during motion. Kinetics is the study of the motions of bodies and the forces and moments that cause the motion. Dynamics is the branch of science that studies kinematics and kinetics, and the relationship between the motion of bodies and the causes of that motion. Multibody mechanical systems is a subfield in dynamics, studying a collection of bodies where some, or all, of the bodies interconnected by joints are studied. Often computer models of the interlinked system are created in order to simulate and analyze motion.

Motion capture. The earliest study using motion capture was conducted by Eadweard Muybridge with a horse as a subject. Muybridge was enlisted by the Governor of California, Leland Stanford, to answer a hotly debated question of the time. The goal of the study was to determine if, at any time, during the animal's trot, all 4 legs were off the ground. In 1878 he arranged 12 cameras in series to capture the movement of the animal and was able to provide evidence that indeed, there is a point in the horse's gait cycle that all 4 legs are airborne (Figure 6). Motion capture evolved quickly during the 1900s and has become a widely used technique in a variety of disciplines including biomechanics, robotics, computer animation, video games, and cinema.

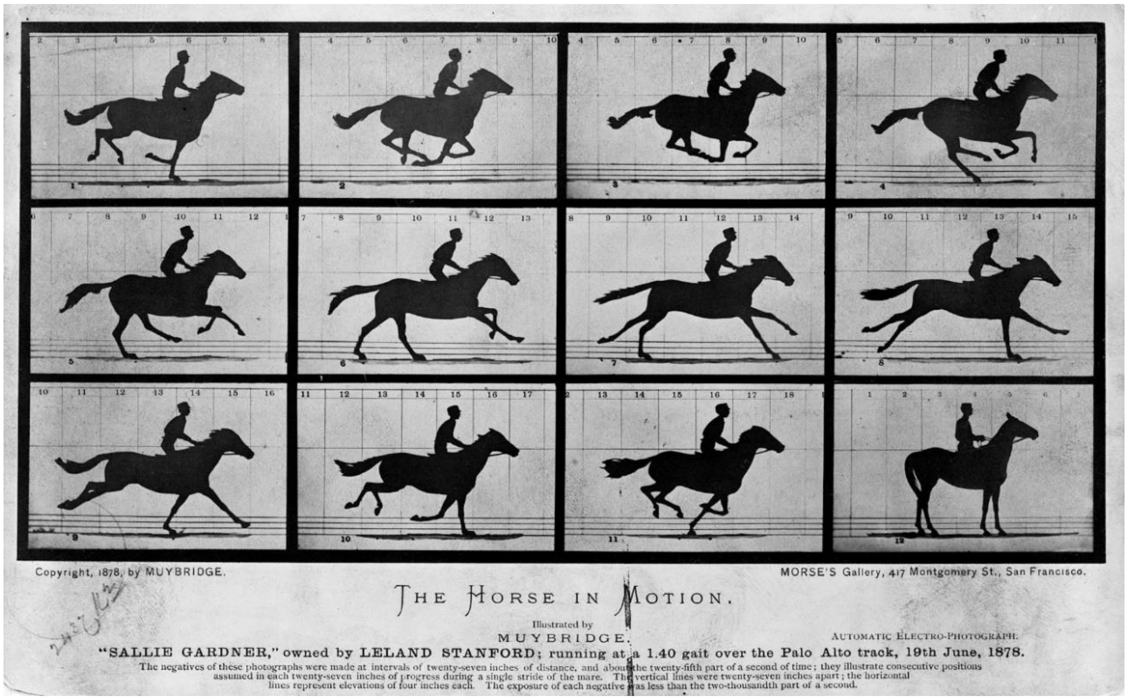

Figure 6. Muybridge's *The Horse in Motion*.[184]
Note. In the public domain.

There are currently a number of different motion capture systems, with optical tracking systems being the most common. In these systems cameras track the position of markers placed on the subject and use the data and algorithms to estimate the change in position, velocity, and acceleration during functional movements. Two main marker types are active and passive markers. Active markers emit their own light and are tracked by the cameras. For passive markers the camera system emits infrared light that is reflected by retroreflective markers and the cameras track their position over time. Pin markers are invasive and involve inserting pins, with attached markers, into the subjects.

In contrast, surface markers are attached and secured to subjects using tape and are much less invasive.

Surface markers are the common technique used in motion capture studies in many biomechanics labs; Vicon (Oxford, England) is a typical high-resolution motion capture optical tracking camera system. In the studies subjects have reflective markers placed on their segments of interest and the high-resolution cameras are positioned to track the markers during movement.[185] Individual cameras generate the 2-dimensional (2D) coordinates for each marker, expressed in the multiple camera image spaces (from all *n* cameras). However, the motion tracking algorithm may encounter ambiguities in the data. Proprietary software is used to analyze the data captured by all of the cameras to compute the 3-dimensional (3D) coordinates of the markers.[185] Due to the complexity of the motion capture analysis, 2D tracking is frequently supplemented with 3D tracking. At that level, the extrapolated 3D trajectory of the markers helps solving ambiguities by predicting future locations of markers in the camera plane. In many cases, these occlusions require manual intervention to identify lost markers.[186]

In addition to markers placed on segments, it is also common to use calibration markers on joints of interest (e.g. the knee joint) to improve the accuracy of the estimation of the joint's axis of rotation. While the knee joint if often considered a simple hinge joint, in reality it is characterized by the femur both sliding and rolling on the tibia, and there is no single point that acts as a hinge axis of rotation.[187] A common method to estimate the geometric center of the joint as the joint center is the midpoint between the femoral condyles. The procedure for locating the joint center of the knee suggests identifying where the knee joint axis passes through the lateral side of the knee by finding the lateral skin surface that comes closest to remaining fixed in the thigh. The marker is then placed 1.5 cm above the joint line on the lateral aspect of the knee joint, where the lower leg appears to rotate. However, this method does not determine the true kinematic or rotational joint center; it merely provides a reproducible reference point to analyze the joint moments. It is possible to define a kinematic joint center using instantaneous center of rotation for sagittal plane analysis or an instantaneous helical axis for general 3D analysis.[187]

One issue when using surface retroreflective markers is the motion of the markers on the body. Skin artifact motion can have significant impacts on the reliability and accuracy of motion capture. When applied to measuring knee joint kinematics based on the position of the tibia and femur, the accuracy of these measurements is prone to error due to skin movement artifact.[188] It is critical that the relative movement between markers and underlying bone should be minimal.[189,190] According to Benoit et al.[188] skin movement artifact is inherent in the measurement technique, therefore the standard error of measurement should be accounted for and reported. While the bones of the lower extremity move during locomotion, as captured by gait analysis, the limitation of the high-speed video is overestimating skeletal motion, related to the markers moving off the bone joint center because of soft tissue, such as skin, muscle, and fat.[191] According to Manal et al.[191] this soft tissue moves relative to the bones as the subject walks, and consequently so will the skin markers, resulting in kinematic estimates of peak knee abduction/adduction and internal/external rotation that differ from peak values by as much as 50 and 100% respectively.

Multibody mechanical modeling techniques typically model the limb segments as rigid bodies. Various estimation algorithms are used to obtain an optimal estimate of the rigid body motion. However, as discussed previously, markers placed directly on skin will experience nonrigid body movement.[185] Various techniques can be applied to lessen the effect of deformation between any two-time steps, such as using a minimum mean square error approach.[185] An additional technique includes utilizing a cluster of markers placed on each segment to minimize the effects of skin movement artifact. This technique can be extended to minimize skin movement artifact by optimal weighting of the markers according to their degree of deformation.

The marker cluster technique also corrects for error induced by segment deformation associated with skin marker movement relative to the underlying bone. This is accomplished by extending the transformation equations to the general deformation case, modeling the deformation by an activity-dependent function, and smoothing the deformation over a specified interval to the functional form. A limitation of this approach is the time-consuming placement of additional markers.[185]

When comparing skin versus pin markers, the relationship between skin- and pin-derived kinematic profiles observed across subjects differed considerably, because as discussed previously, skin movement artifact is inherent in motion analysis using surface markers.[188] Within-subject data revealed repeatable error when using either the skin- or pin-mounted markers for both the walk and cut, while error associated with skin movement artifact differed widely across subjects.[188] Skin movement of the thigh and shank may be large enough to mask the actual movements of the underlying bones, thus making reporting of knee joint kinematics using skin markers potentially uncertain.[188] Comparing kinematic data collected simultaneously from surface markers and bone-embedded marker systems fixed to an external fixation device, Cappozzo et al.[189] reported skin-marker movement of 1–3 cm on the shank and thigh, which was a slightly higher rotational error than found in work by Manal et al.[191] Both Benoit et al. and Manal et al.'s studies found that knee joint estimates may be more sensitive to soft tissue movement of the shank (especially at tibial rotation), and careful consideration should be given to skin marker placement in order to reduce the effect of soft tissue movement.[188,191] However, there is still debate as to what is optimal placement.

In addition to the artifacts originating from skin-marker movement, another major factor contributing to variability in gait analysis results is the reproducibility of the marker placement across sessions (test-retest) and across testers (inter-tester).[190] Maynard et al.[192] demonstrated that differences in identification of landmarks for marker placement can impact the results of motion capture. This was especially prevalent at the hip, which may be due to the difficulty in identifying the hip axis of rotation. The agreement in data was better at the ankle and knee when compared to the hip but was still a concern for accurate analysis. A study which looked at the variation in motion capture between different lab sites identified differences in marker placement by different examiners as the most likely source of variability in results between the sties. Having well-defined and detailed protocols and training programs can help reduce this variability but will not eliminate it.[193] Cappello et al.[194] reported that high levels of test-retest and inter-tester reliability can be obtained by standardizing marker placement methods and procedures.

Ground reaction force. In order to estimate joint loads in biomechanical models the ground reaction force (GRF) is an important variable to measure. The GRF is used as an input in inverse dynamic calculations and is typically captured using force plates during human motion, such as walking. There are 2 main types of force plates available: strain-gauge and piezoelectric.[195] Strain-gauge force plates are less expensive and have good static capabilities while piezoelectric models have greater range and sensitivity.

The data from GRF data can be used to analyze normal and pathological movement and analyzing the vertical GRF data is a common technique. The vertical GRF data estimate the acceleration of the body's center of mass during walking and the curve typically has an M shape as seen in Figure7. The first half of the curve is the load acceptance phase of gait during which the foot is striking the ground; the second part of the curve is the propulsion phase when the lower extremity is pushing off the ground.

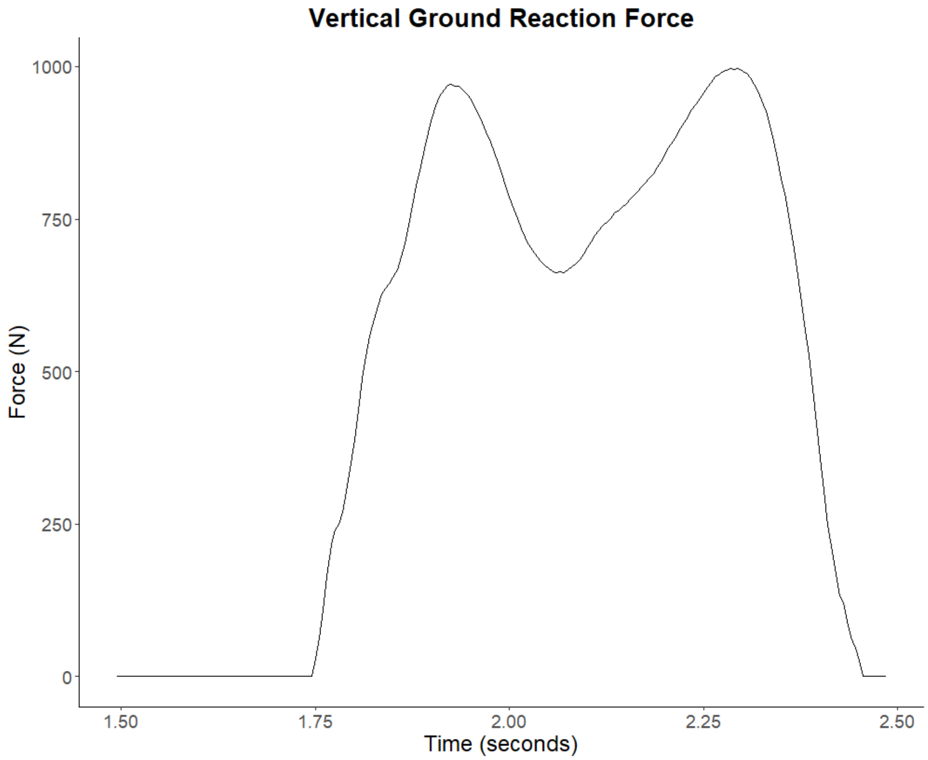

Figure 7. Vertical Ground Reaction Force Curve

Electromyography. One of the primary approaches used to study the function of lower extremity muscles in vivo is EMG, which measures the electrical activity in skeletal muscles and can be used to estimate the activation levels and recruitment patterns during functional movements. Two main techniques in EMG are surface and intramuscular. Surface EMG uses electrodes placed on the skin to measure electrical activity on the surface of the muscle whereas intramuscular EMG uses fine wire electrodes inserted into a muscle body. While surface EMG is less invasive, it cannot accurately measure activity in deep muscles and can experience crosstalk between adjacent muscles. In contrast, fine wire EMG can access deep muscles but is more invasive and difficult to work with. EMG is used to assess the function of muscles in a variety of tasks such as squats, jumping, landing, walking, and running. These studies are done in both healthy and pathological populations and can identify functional deficits in injury that can help inform approaches and techniques to optimize rehabilitation.[196-200] A study that used EMG to compare muscle activation between healthy and ACL-deficient participants found that coactivation of the quadriceps and gastrocnemius muscles was important for knee stability in the squat exercise.[201]

An early study that used surface EMG in gait found that at preferred walking speed the rectus femoris was more active during the swing-to-stand transition,[115] however a later study using fine wire EMG of the rectus femoris found that it was active in both the stance and swing phases of the gait cycle.[120] The study using fine wire EMG only to investigate the rectus femoris muscle did not measure activity in the vasti muscles. A study using both surface and fine wire EMG found that at normal walking speed the rectus femoris was active only during the stance-to-swing transition while at the fastest speed it had some activity during the terminal stance phase.[202] The authors concluded that the rectus femoris is active only during stance-to-swing transition and they attributed the activity during the swing-to-stance transition, identified in previous research, as possibly due to crosstalk from the vastus intermedius.[202]

Much of the work investigating the contribution of the quadriceps muscles to gait involves using EMG to measure some combination of the rectus femoris, vastus lateralis, and vastus medialis.[113-120,122,124,202,203] The vastus intermedius is a powerful knee extensor with a cross-sectional area nearly 4 times that of the rectus femoris.[204] The lack of study of the vastus intermedius has been attributed to the difficulty in measuring its activity using surface EMG.[115] There is conflicting evidence as to the precise contribution of the rectus femoris during gait, with some research attributing surface EMG activity in the muscle to crosstalk from the vastus intermedius.[202] Therefore, gaining a greater understanding of the role of the vastus intermedius during gait is an important topic of interest.

Biomechanical modeling and simulation. In human movement research it is common to build multibody mechanical models in order to analyze the effects of forces and motion on joints and bodies. These models can be configured to match a variety of systems, such as the shoulder joint, the ankle joint, or the entire human body. Kinematic and kinetic data can be applied to these dynamic models to simulate complex motion and provide estimates for forces and moments at different model segments. The joints in the models constrain the motion and can be configured to mimic a variety of motions observed in human joints. Table 1 summarizes typical joints used in multibody modeling.[205] While it is not impossible to measure forces in vivo the techniques are often invasive and challenging to implement.[206] Since it is impractical to directly measure forces in intact joints, in vivo modeling and simulation has become a widely used and popular approach for estimating these loads in human movement.[206-208] It should be noted that recent advances in noninvasive techniques show promise but they require specialized equipment, and further experiments and validation are needed before they can be widely adopted.[208]

Table 1. Multibody Mechanical Model Joint Types

Joint Type	Degrees of Freedom	Relative Motion	Motion Type
Helical	1	helical	spatial
Revolute	1	circular	planar
Prismatic	1	linear	planar
Cylindric	2	cylindric	spatial
Spheric	3	spheric	spheric
Flat	3	planar	spatial

Many models also include physiological models of muscles to predict muscle forces' action on the bodies and joints during movement. Musculoskeletal physiology is used to describe the effect of muscle contraction on joint motion and the hill type muscle model is frequently used.[182,209] Once a model is built the laws of physics and engineering are used to formulate equations of motion for these models and computers can be used to iteratively solve the equations to estimate the motion and forces of the system over time.[209] A key assumption of these models is that the bodies are rigid and do not experience deformation under loading. In order to estimate joint loading and metrics such as stress and strain, other models are typically used, such as finite element models.[207] These types of models can accurately represent complex geometries but require material properties, such as tissue density, as well as detailed imaging, to create 3D meshes that represent complex anatomical and musculoskeletal structures to be analyzed.[210] Initial conditions are then used to estimate metrics such as joint contact pressure, deformation, stress, and strain.

In rigid body modeling the mass properties of the system's elements are abstracted with the center of mass of each body acting as the "point mass" for that element. Linkages between bodies are made by joints with specified degrees of freedom. For example, a revolute joint between 2 bodies will have 1 degree of freedom and allow motion in 1 plane. These models are frequently used to analyze a variety of systems including robots, automobile suspension systems, spacecraft solar panels, and human musculoskeletal systems. They are useful to model and simulate the position, velocity, acceleration, forces, and moments of the system.[205]

These models are typically solved using inverse or forward dynamics approaches.[54,211] In inverse dynamics the position, velocity, and acceleration of the segments, typically collected from subjects in a lab, are used to calculate the forces and moments that would have been required to create those positions. This approach can provide estimates of joint moments and JRF in subjects performing a wide variant of tasks like walking, running, stepping up, jumping, or squatting.[181,212-218] In forward dynamics the muscle forces and moments are used to drive the calculation of the position, velocity, and acceleration of the body segments. A forward dynamics modeling approach was actually used to identify a subject-specific gait modification that minimized both the first and second joint moments during walking.[33] The subject-specific modification was implemented on the study subject and provided joint moment reductions of 39% to 50% in the first peak and 37% to 55% in the second peak after gait retraining sessions, which were consistent with predictions from the model.[33] Another forward simulation study that minimized KAM showed the model would increase LTL, toe-out, and step width.[219]

Within the field of biomechanics 2 common software tools used in analysis are Visual3D (C-Motion, Germantown, Maryland (MD), USA) and OpenSim.[55,220] Visual3D is a commercial software package that allows for the kinematic and kinetic analysis of 3D motion capture data as well as data management for biomechanical data.[220] The tool allows users to create 6 degree of freedom models of human subjects and calculate various biomechanical variables from imported motion capture data. Examples of common calculations include gait speed, stride length, stride width, joint angles, joint moments, and signal filtering. The tool uses inverse dynamics in its kinetic calculations and also allows users to export processed data into OpenSim-compatible files.

OpenSim is a free open source tool used for modeling, simulation, and analysis that was developed at Stanford University.[55,183] Similar to Visual3D, it can take captured biomechanical data and conduct analysis such as calculating joint angles and moments. However, it also has additional capabilities not available in Visual3D; for example, in addition to inverse dynamics, it can also conduct forward dynamics simulations where model motion is determined by internal forces and moments simulated by the tool and propagated forward to create motion.[55,183] This is in contrast to inverse dynamics where recorded motion is used to determine internal forces and moments that match the captured motion trajectories. For simulating movement there are several techniques available to calculate the muscle force estimates needed to reproduce movement trajectories: static optimization (SO), computed muscle control (CMC), and neuromusculoskeletal tracking (NMT). OpenSim has options for both SO and CMC; research comparing these techniques suggests that SO is a robust and efficient method for estimating forces in human locomotion.[214,221,222] SO is an extension to inverse dynamics that resolves net joint moments estimated by inverse dynamics into individual muscle forces at each time point by solving a constrained optimization problem with the objective function minimizing the sum of the activation levels of the muscles raised to a power.

$$J = \sum_{m=1}^{n} (a_m)^p$$

In the above equation n is the number of muscles in the OpenSim model, a_m is the activation of muscle m at a time point, and p is the power that the activations are raised to, which is typically 2. The algorithm, as described in the user documentation, is constrained by the measured position, velocity, and acceleration data collected on subjects and by the force-length-velocity properties of the muscles in the associated OpenSim model. Research has shown that results from SO provide reasonably good estimates when compared to EMG-to-force muscle forces.[215,222] However, an early study that looked at EMG and SO results found that the correlations for the knee were not as strong as other joints, such as at the ankle.[222] Other studies have also found that there was great individual variation in muscle activation ranges during walking that did not always resemble previous activation ranges in the literature or results from SO or CMC algorithms.[212,222] In contrast to that work, a recent study that compared muscle activations from level walking to EMG signals suggested that output from OpenSim SO had good agreement with collected EMG data.[215]

Researchers are able to extend the functionality of OpenSim software by creating custom plug-ins, extensions, and models which can be posted on a website (https://simtk.org/), allowing users to search and download the extensions. An important example of this work is the synergy optimization plug-in which allows users to modify the default OpenSim SO by adding weights to muscles, either individually or in coupled pairs.[213,223,224] When adding weights individually to the model the objective function equation for weighted SO includes an additional parameter, w_m, that is the weight applied to muscle m in the model.

$$J = \sum_{m=1}^{n} w_m * \ (a_m)^p$$

The result of adding weights is the optimization function tries to reduces the activation, and force, output from the muscles and shifts the force to other muscles while still meeting the kinematics of the motion. For example, Figure 8 shows the effect of adding a weight to the medial and lateral gastrocnemius on the force generated by the muscle during a simulation of normal walking. The black and blue lines represent the medial and lateral gastrocnemius force generated by the default SO while the green and yellow lines represent the results from the weighted SO. The result of adding the weights reduces the force output from the medial gastrocnemius and shifts the force to other muscles, such as the lateral gastrocnemius, while still meeting the kinematics of the motion.

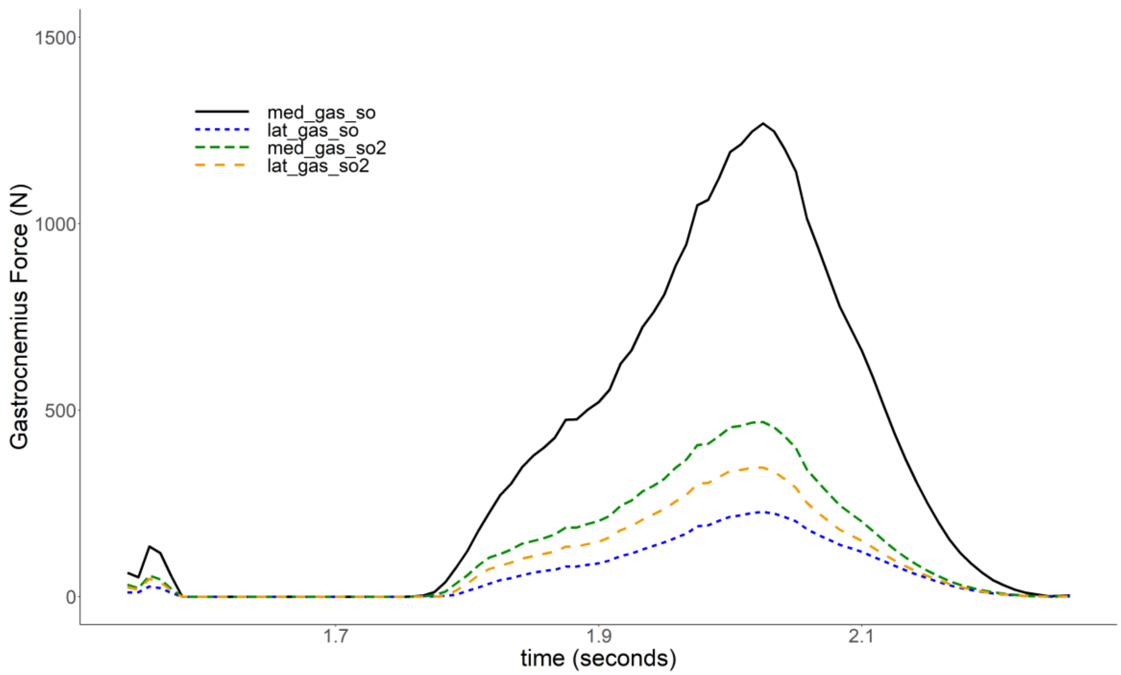

Figure 8. Representative Demonstration of How Weighted Static Optimization (SO), from the OpenSim Synergy Optimization Plug-in, Can Be Used to Shift Distribution of Force Between the Medial and Lateral Gastrocnemius

The black and blue lines represent the medial and lateral gastrocnemius force generated by the default SO; the green and yellow lines represent the results from the weighted SO.

In the default SO calculation muscle forces and activations are resolved, as described above, by solving an optimization problem that minimizes the sum of squared muscle activations for every muscle in the model. For example, gait2392.osim is a commonly used model that includes 92 muscles that are used to drive movement in forward and inverse dynamic simulations. The value “p” in the objective function is a variable that can be set by the user but has a default value of 2. The variable “a” is a matrix of all the muscles in the model; as a default in OpenSim there is a weight of 1 for each muscle. When SO is run a value for “a” is determined by the software and exported into output files. With the synergy optimization plug-in a custom weight can be defined for each muscle, or group of muscles. Adding a weight induces a “penalty” for using that muscle and the software’s minimization algorithm attempts to reduce the use of that muscle by shifting the activation and force levels to other muscles that can induce similar motions in the model. As an example, if a weight is placed on the rectus femoris muscle when the simulation requires knee extension, the algorithm will increase the activation of some combination of the vastus lateralis, vastus medialis, and vastus intermedius muscles to account for the reduced input from the rectus femoris. Weights are added, and modified, via a matrix in an OpenSim XML setup file that is used as input by the software for running static optimization. An example OpenSim workflow used for this project is shown in Figure 9. In the final step of the workflow the muscle force files output from SO are used as input in the Joint Reaction analysis, which provides a value for joint reaction forces and moments between any 2 consecutive bodies present in the model. Joint reaction differs from inverse dynamics calculations in that it also considers compressive forces between joints as a result of muscle forces acting across that joint.

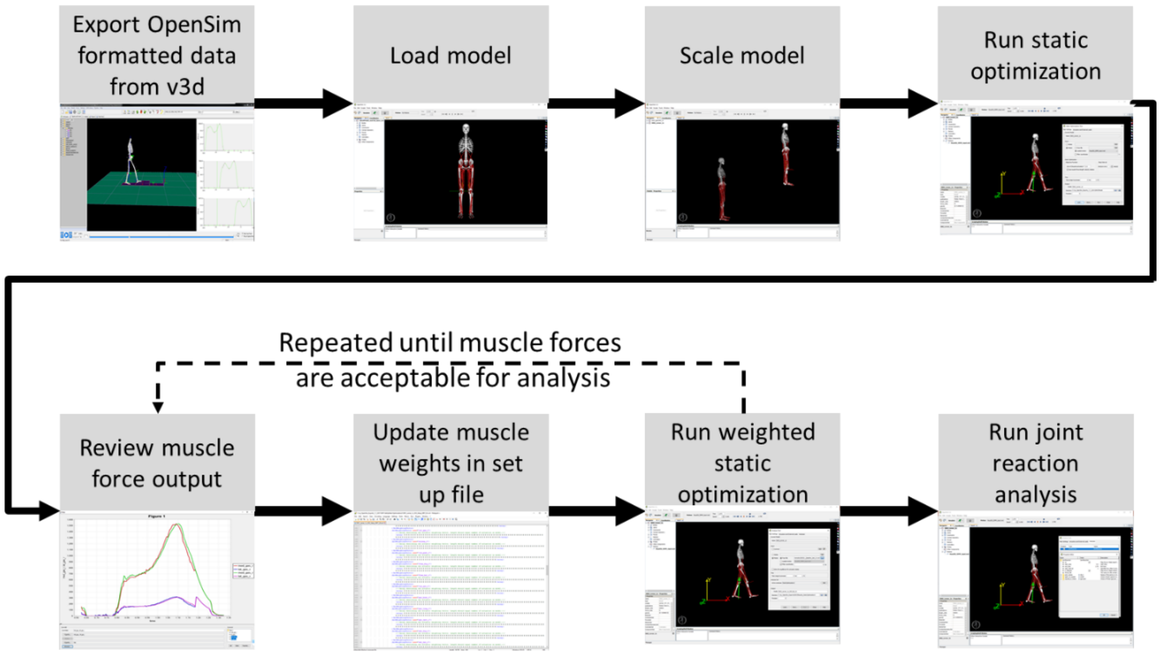

Figure 9. Typical OpenSim Workflow Used for this Project[183]

Several studies have looked at the impact of various muscles on the estimated JRF in OpenSim modeling of gait, with a consistent finding that the overestimation of the JRF in the knee during the second half of stance is often driven by large forces generated by SO of the gastrocnemius muscle.[56,106,107,181,213,218,225,226] Other studies have also identified individual variation in muscles that lead to overestimation of JRF in the knee and these include the hamstring muscles[56,181] and the quadriceps.[181,225] This work provides evidence that uniform weighting of muscles is not a good approach: It is important to find a strategy to identify the specific muscles and associated weights for SO that need to be used for each subject in a simulation study.

Another important addition to the field is work by Lerner et al.[56] which provided an update to the gait2392.osim model which includes an enhanced knee joint that is able to resolve the joint reaction forces in both the medial and lateral compartments of the knee. The improved model, known as the Lerner model, is able to be customized to individual subjects by modifying the angles of the alignment of the knee between the femur (Θ_1) and tibia (Θ_2) as well as specifying the specific contact locations between the femur and tibia in the medial (d_1) and lateral (d_2) sides of the joint.[56] Figure 10 shows a diagram of the knee joint model with the alignment and contact location parameters. Studies have found that variation in knee alignment and contact locations impact estimation of JRF in the knee and are an important factor for improved estimation of JRF in the knee.[56,99,140,227-229] Validation of the Lerner model demonstrated that the ability to adjust the model to match the anatomical alignment of the knee and the contact locations between the femur and tibia decreased the error in estimated knee JRF when model output was compared to in vivo data.[56]

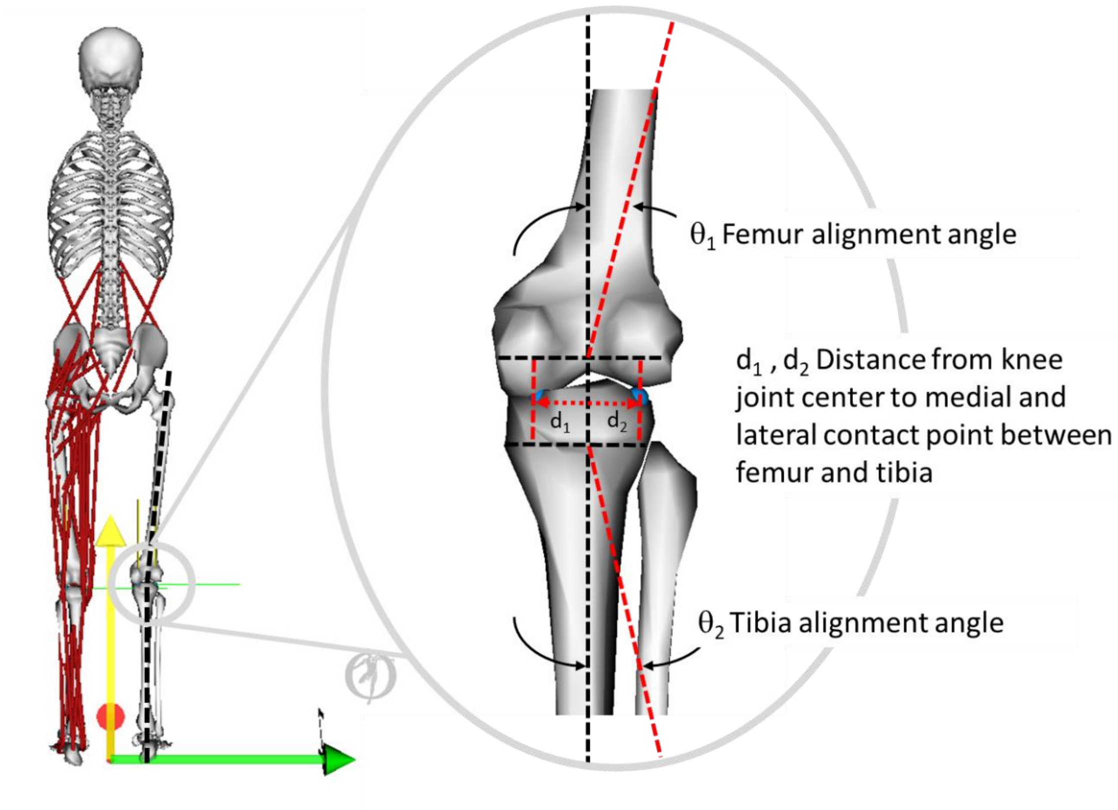

Figure 10. Lerner Enhanced Knee Joint Model for OpenSim[56]

Chapter 3. Study 1: Estimating Medial and Lateral Tibiofemoral Joint Reaction Forces in Common Gait Interventions via OpenSim

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Current Status: Submitted to PeerJ

Prebble M, Wei Q, Martin J, Cortes N. Estimating medial and lateral tibiofemoral joint reaction forces in common gait interventions via OpenSim.

Abstract

Background. Gait modifications, such as medial knee thrust or lateral trunk lean, have been investigated to reduce knee joint moments which are associated with joint loads and the progression of knee osteoarthritis. Musculoskeletal models have been developed that can estimate the medial and lateral tibiofemoral compartment joint reaction forces. These models have been validated with subjects using a normal gait pattern but have not yet been validated with data from subjects using gait modifications. To address this gap in knowledge, we tested a model that incorporates subject-specific parameters using 2 common gait modifications and compared our results with results from normal gait patterns.

Methods. Three-dimensional simulations for the stance phase of gait were created for a subject with an instrumented knee implant using OpenSim and the Lerner knee model. The medial and lateral joint reaction forces were calculated for 3 gait conditions: normal gait, medial knee thrust, and lateral trunk lean.

Results. The optimal percentage errors in the medial compartment for the first peak force were 8.1% for normal gait, 6.8% for medial knee thrust, and 3.8% for lateral trunk lean. In the second peak of the medial compartment, the optimal percentage errors were 16.1% for normal gait, 26.8% for medial knee thrust, and 23.7% for lateral trunk lean. For the lateral compartment for the first peak the values were 23.7% for normal gait, 11.2% for medial knee thrust, and 18.7% for lateral trunk lean. In the second peak of the lateral compartment the percentage errors were 22.8% for normal gait, 43.4% for medial knee thrust, and 30.1% for lateral trunk lean.

Discussion. The joint reaction force estimates for the 2 gait modifications tested had percentage errors that were comparable to normal gait estimates. Estimates for the medial compartment joint reaction force tend to be more accurate than the lateral compartment estimates. Estimates for the first peak of the stance phase in both the medial and lateral compartments were better than estimates in the second peak. The second peak estimates are affected by estimates of muscle force needed to match movement kinematics. Using a weighted static optimization with the OpenSim, joint reaction analysis provides improved estimates over the built-in OpenSim static optimization for the medial compartment. Our results provide support for the use of the Lerner knee model with weighted static optimization to estimate joint reaction forces in gait with the medial knee thrust and lateral trunk lean gait modifications.

Keywords: Gait retraining, osteoarthritis, knee joint reaction forces

Introduction

Osteoarthritis (OA) of the knee is a major cause of disability worldwide and affects more than 19% of the US adult population over the age of 45.[4,9] Excessive knee loads have been implicated in the development and progression of knee OA.[47,230] Evidence suggests that gait modifications are a viable noninvasive intervention that may slow the progression of knee OA.[40,45,231] Several gait modifications have been identified to reduce medial compartment knee loads.[33,40,41,45,164,171,231-234] The most common modifications investigated include medial knee thrust (MKT), lateral trunk lean (LTL), and altered foot progression angle (e.g. toe-in or toe-out).[33,41,43,45,219,235,236] Many studies investigating gait modifications rely on surrogate measures to assess knee loads (i.e., knee adduction and flexion moment).[49,50,233,237-243] However, with advancements in computing power, computational models are becoming a common approach to estimate the joint reaction forces in the knee during functional tasks, such as walking.[54-56,181,229,244-246]

While it is currently not practical to measure knee loads in intact knees, computational models are capable of estimating knee loads during functional movements.[111,181,207,218,229,247] Some researchers have developed custom-built models to estimate biomechanical parameters and respective forces, stress, and strain on muscles, ligaments, tendons, and other anatomical structures.[33,248-250] Previous research has evaluated the accuracy of model estimates for joint reaction forces for gait modifications such as MKT or LTL by comparing in vivo results in subjects with instrumented knee implants to computational estimates.[251] OpenSim is an open-source software application for modeling, simulating, and analyzing movement.[55] It provides a flexible and robust tool that can be used to simulate how altered movement patterns can affect internal joint loading.[55,56,157,179,181,205,229,244-246,252-258] While there are default musculoskeletal models that can be used with OpenSim, the software also allows for models that can be customized to more closely match subject-specific parameters.[56,181,229,244-246] Subject-specific models have shown to improve the accuracy of predictions in joint loading over generic models.[56,259] A common finding in previous studies is that a weighted static optimization (SO) approach provides improved results over the default OpenSim SO.[56,181,218] Many of these studies use in vivo data from instrumented knee implants to optimize their model estimates, but this is not a feasible approach when trying to estimate the effects of gait modifications in healthy and pathological subjects where no in vivo data is available.

Lerner et al. developed an OpenSim model capable of resolving the joint reaction forces in the knee into medial and lateral components.[56] The model's knee alignment and tibia/femoral contact positions can be modified to match subject-specific parameters. The model was tested on a subject with an instrumented knee joint using a normal walking gait and was shown to provide improved estimates over previous OpenSim models.[56] However, we are not aware of previous research that has applied the model on subjects using common gait modifications found in the literature. Therefore, the purpose of this study was to compare the accuracy of the model predictions for normal gait with 2 common gait modifications: MKT and LTL. A secondary purpose of the study was to evaluate a strategy to choose the parameters for a weighted SO approach that is often used when estimating joint reaction forces using OpenSim.

Methods

Experimental data. Experimental data from a subject with an instrumented knee replacement (left knee, female, mass 78.4 kg, height 1.67 m) were used to generate dynamic simulations of walking. These data have been made available by the Grand Challenge Competition to Predict in Vivo Knee Loads.[260] Kinematic, kinetic, and instrumented implant data were simultaneously collected using various gait strategies including normal gait (NG), MKT, and LTL. For the instrumented knee joint, validated regression equations were used to calculate separate medial and lateral tibiofemoral compartment contact forces.[261]

Musculoskeletal simulation of walking. Three-dimensional simulations for the stance phase of gait were created for the subject using OpenSim. C3D files provided by the Grand Challenge Competition to Predict in Vivo Knee Loads were used to export OpenSim-compatible format files from Visual3D software. As part of the export process Visual3D runs Inverse Kinematics on the data and provides a kinematic and a kinetic .mot file for each trial. The gait2392 model was scaled to the subject’s height and weight before running SO in OpenSim.

Default static optimization. In order to calculate muscle forces required to reproduce the measured kinematics and kinetics, the default SO was run on the data using OpenSim 3.2. The SO function resolves the net joint moments into individual muscle forces at each time step by minimizing a cost function, which is the sum of the muscle activations squared.[55] The results of SO allow identifying extreme values that may lead to increased estimates of vertical joint reaction forces. A muscle force was considered an extreme value if it was 2 to 3 times larger than the majority of other forces calculated as part of SO. After the default SO was completed, a weighted SO function was run.

Weighted static optimization. After completion of the default SO process, the data were iteratively run through a weighted SO function based on previously described methods.[56,181,218] The weighted SO objective function minimizes the sum of squared muscle activations while incorporating individual muscle weighting values.[218] OpenSim 3.2 was used for SO because the weighted SO plug-in was built to be compatible with this version of the software.[213] In order to identify muscles and corresponding weights the results of SO were visually inspected to identify any muscles that would contribute to increased estimates of vertical joint reaction forces in the knee (e.g. quadriceps, hamstrings, and calves). The heuristic used to identify potential muscles was to identify those that had a force 2 to 3 times greater in magnitude than the estimated forces from the other lower extremity muscle groups. A weight of 2 was initially applied to that muscle group; a weighted SO was run and the results visually inspected to determine the effect of the weight on the muscle force outputs. In the event that there were multiple muscles with extreme force estimates, muscles were weighted and evaluated in a set order for all gait intervention trials. The order used was to apply a weight to the gastrocnemius (GAS) muscles; then weights were applied to the GAS and the vastus lateralis (GAS/VL) muscle; then to the GAS, VL, and vastus intermedius/vastus medialis (GAS/VI/VL/VM) muscles; and lastly to the GAS, VL, VI, VM, and the rectus femoris

(GAS/VI/VL/VM/RF) muscles. The muscle weight values started at 2 and were systematically increased by 1 until the muscle force output values from the weighted SO did not show any large spikes in the weighted SO output. A summary of the weights used for the study is shown in Table 2.

Table 2. Muscle Weights Used for Weighted Static Optimization

	Muscle Weights					
Intervention	**MGAS**	**LGAS**	**VL**	**VL/VI/VM**	**VL/VI/VM 2nd iteration**	**RF**
Normal gait	2	1	1	1/1/1	1/1/1	1
Medial knee thrust	2	1	2	2/2/2	4/2/2	2
Lateral trunk lean	2	1	1	1/1/1	1/1/1	1

Abbreviations: MGAS, medial gastrocnemius; LGAS, lateral gastrocnemius; VL, vastus lateralis; VL/VI/VM, vastus lateralis, vastus intermedius, vastus medialis; RF, rectus femoris.

After the default SO and the weighted SO were completed the knee joint reaction forces for the medial and lateral compartment were computed using the OpenSim JointReaction analyses on the scaled Lerner model using OpenSim 3.3.

Statistical analysis. For each modeling approach we compared the first and second peak values from the simulation to the in vivo measurements and calculated the average percent error; 95% confidence intervals were calculated to determine if statistically significant differences existed for first and second peak vertical joint reaction forces between model predictions and the in vivo measurements. The total root-mean-square errors (RMSE) between the predicted and measured contact forces were calculated for the medial and lateral vertical joint reaction force estimates during the stance phase of gait. MatLab, version R2018b (MathWorks, Inc., Natick, MA) was used to perform the statistical analyses.

Results

The summary of the percentage error between the in vivo data and simulated data is provided in Figure 11. For NG, the GAS weighted SO model provided a lower percentage error than the default SO for the first (8.1% vs. 15.8%) and second (16.1% vs. 75.4%) peaks in the medial compartment. For the lateral compartment, the default SO had slightly lower percentage error for NG (first peak: 23.7% vs. 26.8%; second peak: 22.8% vs. 23.4%).

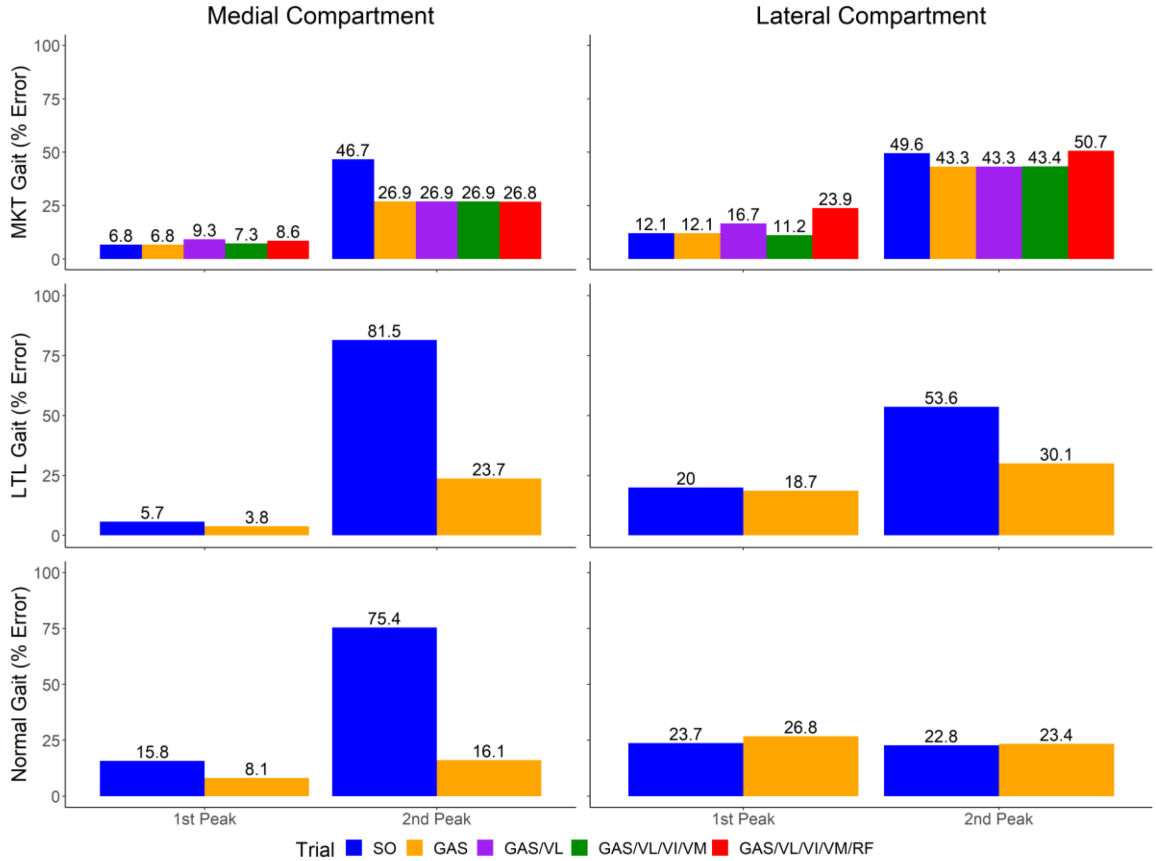

Figure 11. Percentage Error Between In Vivo and Simulation Joint Reaction Forces for Medial Knee Thrust (MKT) Gait, Lateral Trunk Lean (LTL) Gait, and Normal Gait
Abbreviations: SO, static optimization; GAS, gastrocnemius; GAS/VL, gastrocnemius and vastus lateralis; GAS/VL/VI/VM, gastrocnemius, vastus lateralis, vastus intermedius, and vastus medialis; GAS/VL/VI/VM /RF, gastrocnemius, vastus lateralis, vastus intermedius, vastus medialis, and rectus femoris.

For the MKT condition, the default SO and the GAS weighted SO model provided a lower percentage error for the first peak in the medial compartment (6.8%), while in the second peak the default SO had the highest percentage error with the other weighted SO models providing similar results (~26.8%). For the first peak in the lateral compartment the GAS/VL/VI/VM model provided the smallest error (11.2%) but it was not substantially different than the default or GAS model (both 12.1%). For the second peak in the lateral compartment there were no notable differences between the GAS, GAS/VI, GAS/VI/VM, and GAS/VI/VM/VL models (~43.3%), while the default SO (49.6%) and GAS/VI/VM/VL/RF (50.7%) had higher percentage errors.

For the LTL condition, the GAS weighted SO model error percentage was slightly lower than that of the default SO for the first peak in the medial compartment (3.8% vs. 5.7%). For the second peak in the medial compartment the GAS weighted SO was substantially lower than the default SO (23.7% vs. 81.5%). For the lateral compartment the GAS model was slightly lower in the first peak (18.7% vs. 20.0%) and much lower in the second peak (30.1% vs. 53.6%). Table 3 summarizes the 95% confidence intervals for the medial and lateral compartments for the first and second peak vertical joint reaction forces.

For the MKT and LTL conditions, the percentage errors for the first peak in the medial compartment were lower than the NG error (NG 8.1%; MKT 6.8%; LTL 3.8%). However, the second peak errors were higher when compared to the NG condition (NG 16.1%; MKT 26.8%; LTL 23.7%). Similarly, for the lateral compartment percentage error in the first peak the MKT and LTL conditions were lower than the NG error (NG 26.8%; MKT 11.2%; LTL 18.7%). For the second peak the percentage error for MKT and LTL were larger than for NG (NG 22.8%; MKT 43.3%; LTL 30.1%).

The subject in our study had higher in vivo estimates for medial compartment vertical joint reaction forces in both the first and second peak while also having slightly lower values for estimates in the lateral compartment. Significant differences between in vivo and simulation differences are summarized in Table 3. For NG there were statistically significant differences between in vivo results and all simulation results in the medial compartment for the second peak, and between the in vivo results and the default SO results in the second peak for the lateral compartment. For MKT there were statistically significant results between in vivo and all simulation results for the second peak in the lateral compartment. For LTL the default SO had a statistically significant difference from the in vivo measurement.

Table 3. 95% Confidence Intervals of Medial and Lateral Compartment 1st and 2nd Peak Joint Reaction Forces

	1st Peak (N)		**2nd Peak (N)**	
	Medial	**Lateral**	**Medial**	**Lateral**
Normal gait				
In vivo	1336.9-1451.8	449.4-553.0	1351.9-1536.0	463.4-545.3
SO	1244.2-1791.7	431.9-720.3	**2318.4-2729.4**[a]	**341.9-457.4**
GAS	1271.1-1497.5	478.8-751.5	1508.2-1794.6	343.7-498.0
Medial knee thrust				
In Vivo	1981.6-2352.7	1000.6-1295.0	1317.0-1511.3	615.1-959.4
SO	1985.1-2465.5	878.8-1381.3	882.4-2417.5	**259.1-520.8**
GAS	1984.7-2465.3	978.8-1381.4	651.7-1619.2	**277.1-599.4**
GAS/VL	2112.8-2606.5	719.0-1196.9	653.3-1619.0	**276.8-598.9**
GAS/VL/VI/VM	1978.5-2486.4	837.2-1308.4	651.0-1619.3	**276.5-598.4**
GAS/VL/VI/VM/RF	1973.3-2559.3	657.7-1090.0	627.3-1552.1	**189.7-581.8**
Lateral trunk lean				
In Vivo	1386.4-1863.9	354.4-843.9	1013.8-1394.7	533.5-960.2
SO	1367.8-1936.2	399.0-780.5	**1837.2-2506.8**	**214.2-486.6**
GAS	1327.3-1925.1	416.1-779.5	1196.6-1721.1	285.3-776.8

Abbreviations: SO, static optimization; GAS, gastrocnemius; GAS_VL, gastrocnemius-vastus lateralis; GAS/VL/VI/VM, gastrocnemius/vastus lateralis/vastus intermedius/vastus medialis; GAS/VL/VI/VM/RF, gastrocnemius/vastus lateralis/vastus intermedius/vastus medialis/rectus femoris.
[a] Bolded values represent a statistically significant difference from the in vivo data.

Figure 12 provides average ensemble curves comparing the in vivo vertical joint reaction forces to the simulated joint reaction forces from the simulation models for the 3 gait conditions. The weighted SO approach provided improvements in RMSE for all 3 gait conditions over the default SO approach. For MKT, adding weights to muscles in addition to the GAS did not improve RMSE values. Table 4 summarizes the RMSE results for the medial and lateral compartments. For the first peak in the medial compartment for the NG, MKT, and LTL, the weighted SO model provided similar percentage errors to the default SO. However, for the second peak the weighted SO provided lower percentage errors for NG, MKT, and LTL. In the NG and LTL conditions both the default SO and weighted SO overestimated the vertical joint reaction forces. For the MKT in the medial compartment the default SO overestimated the values while the weighted SO underestimated the values.

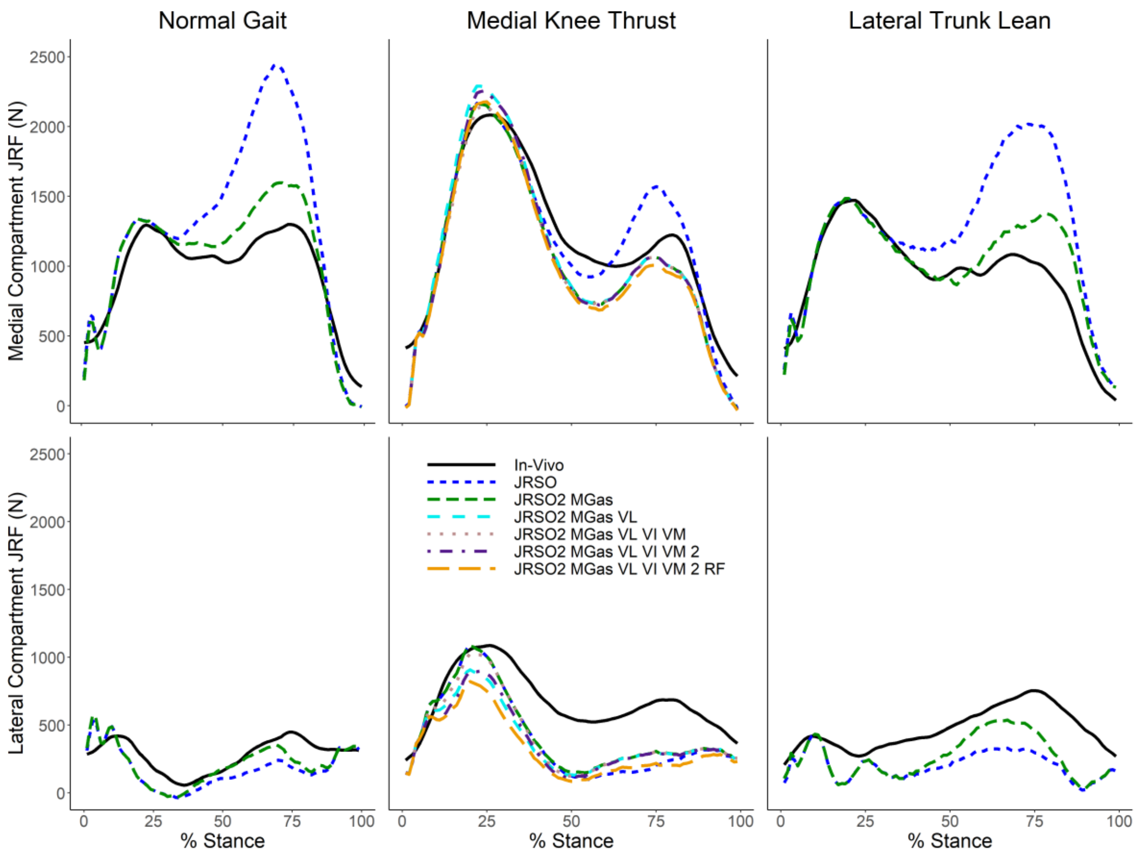

Figure 12. Medial (Top) and Lateral (Bottom) Compartment Tibiofemoral Joint Reaction Forces During Stance for Normal Gait (Column 1), Medial Thrust Gait (Column 2), and Lateral Trunk Lean Gait (Column 3)
Abbreviations: JRF, joint reaction forces; JRSO, joint reaction static optimization; JRSO2 joint reaction weighted static optimization; MGAS, medial gastrocnemius; VL, vastus lateralis; VI, vastus intermedius; VM, vastus medialis; VM2, vastus medialis 2?; RF, rectus femoris.

In the first peak of the lateral compartment the default and weighted SO models provide similar results for NG and LTL. For the lateral compartment first peak the default SO, MGAS weighted SO, and MGAS/VL weighted SO provided similar estimates to the in vivo data. The other weighted SO models for MKT had increased error and underestimated the forces in the first peak of the lateral compartment. For the second peak in the lateral compartment both the default and weighted SO simulation models underestimated the vertical joint reaction forces for all gait conditions, with MKT having the largest error. The results in the lateral compartment for NG are similar to what was found in NG in the previous research.[56]

Table 4. Medial and Lateral Compartment Joint Reaction Force Root Mean Square Error (RMSE) Over the Stance Phase of Gait

Gait		**Default SO (N)**	**GAS (N)**	**GAS/ VI (N)**	**GAS/VI/ VM (N)**	**GAS/VL/ VI/VM (N)**	**GAS/VL/ VI/VM/ RF (N)**
NG	medial	568.2	251.4	N/A	N/A	N/A	N/A
	lateral	176.1	157.8	N/A	N/A	N/A	N/A
MKT	medial	447.5	347.6	349.6	353.0	351.5	356.9
	lateral	346.6	316.9	344.1	325.1	343.6	401.8
LTL	medial	528.1	258.8	N/A	N/A	N/A	N/A
	lateral	312.4	256.6	N/A	N/A	N/A	N/A

Abbreviations: SO, static optimization; GAS, gastrocnemius; GAS/VI, gastrocnemius/vastus intermedius; GAS/VI/VM, gastrocnemius/vastus intermedius/vastus medialis; GAS/VL/VI/VM, gastrocnemius/vastus lateralis/vastus intermedius/vastus medialis; GAS/VL/VI/VM/RF, gastrocnemius/vastus lateralis/vastus intermedius/vastus medialis/rectus femoris; NG, normal gait; MKT, medial knee thrust gait; LTL, lateral trunk lean gait.

Discussion

Our study provided support for the use of the Lerner knee model to estimate knee vertical joint reaction forces in 2 gait modifications commonly seen in the literature. The secondary purpose of our study was to investigate a strategy to identify appropriate weighting factors that can be used in the OpenSim weighted SO step of the simulation workflow. Our approach provided improved results over the built-in default SO function while also providing results comparable to previous studies that used direct measurement of in vivo forces from subjects with instrumented knee implants. Overall, our results suggest that the Lerner model can be used to estimate vertical joint reaction forces in the MKT and LTL gait modifications but with some limitations. If comparing the effect of the MKT gait intervention on vertical joint reaction forces to NG, one issue that may confound statistical results is that MKT may underestimate the vertical joint reaction forces in the second peak while those values are overestimated in NG. This could lead to significant results in statistical tests that do not exist but are due to the over- versus under-estimation of the respective models. There is also a relatively large percentage error for MKT in the second peak (> 40% in our data) that may reduce the confidence in the model estimates. For the LTL modification our results provided similar percentage errors for both the first and second peak when compared to NG. The models for NG and LTL gait conditions both overestimated the vertical joint reaction forces, so comparisons between NG and LTL may be more consistent with what is being experienced in vivo, versus the comparison between NG and MKT.

Using weighted SO, the percentage error in the lateral compartment was larger than in the medial compartment for all 3 gait modifications. In addition, the models underestimated the forces for all gait modifications. This suggests the model performs better at estimating the vertical joint reaction forces in the medial compartment compared to the lateral compartment. Any research interested in the effect of gait modifications on the lateral compartment of the knee should take this into consideration when looking at the simulation results.

The RMSE was better using the weighted SO versus the default SO for all 3 gait conditions. Results are summarized in Table 2 and Table 3. For the Grand Challenge

Competition to Predict in Vivo Knee Loads competition, results for both blinded and unblinded prediction were calculated.[260,262] In the blinded condition the competitors did not have access to the in vivo results to "tune" their model, and after reporting their results they were "unblinded" and could then use the in vivo results to help improve their model predictions. The data for the subject in our study came from the third iteration of the Grand Challenge Competition to Predict in Vivo Knee Loads; there were 2 winners chosen for that year's challenge by their results in a single trial (the best 1 out of 5 trials) for both the NG and MKT conditions. For our study we calculated the average RMSE values for 5 trials and compared them to the blinded and unblinded results for the 2 winning teams in the competition.

For the blinded results our average RMSE predictions for NG were between the values for the winning teams for the medial compartment (NG 251.4 ± 102.7 vs. Team 1 237 and Team 2 285). For MKT in the medial compartment our results were in line with the winning teams' estimates (MKT 347.6 ± 217.0 vs. Team 1 351 and Team 2 330). For the blinded lateral predictions in NG (NG 157.8 ± 44.2 vs. Team 1 144 and Team 2 243) and MKT (MKT 316.9 ± 90.6 vs. Team 1 332 and Team 2 241), our results were better than 1 team but worse than the other. For the unblinded results our average RMSE predictions were higher for both the medial (NG 251.4 ± 102.7 vs. Team 1 130 and Team 2 216; MKT 347.6 ± 217.0 vs. Team 1 291 and Team 2 242) and lateral predictions (NG 157.8 ± 44.2 vs. Team 1 173 and Team 2 112; MKT 316.9 ± 90.6 vs. Team 1 288 and Team 2 198).[262] Our results are comparable to previous research; however, it should be noted that our values are the average of multiple trials, whereas the results reported for the competition used the best output from a single trial.[260,262] This suggests our approach does provide acceptable estimations for vertical joint reaction forces across the stance phase for the gait modifications examined.

For the NG condition in the medial compartment the percentage error in the first peak using weighted SO was lower than the error for the alignment-informed model from previous research (8.1% vs. ~25%). The error in the second peak was also lower in our results than in the alignment-informed model from the previous study (16.1% vs. ~20.0%).[56] For NG in the lateral compartment the error in our model was higher for the first peak (23.7% vs. ~15%) but lower than previous research for the second peak (22.8% vs. ~40.0%) for the alignment-informed model.[56] It is likely that using the default contact locations may have influenced the output, and including that in future work may improve the results—especially in the second peak. In previous research the addition of subject-specific contact locations to the subject-specific alignment improved model percentage error in the first peak by about 2% but decreased the percentage error in the second peak by about 12%.[56] Overall, our results for NG were consistent with previous research that validated the model estimates using in vivo data.

The first peak is associated with early stance, where muscles are primarily acting to prevent buckling of the supporting limb and are eccentrically contracting. Thus the forces estimated by SO in the first peak are driven by estimates of eccentric contraction, the model's anatomical alignment, and the vGRF measured during individual trials.[218,263] Including anatomical alignment has been shown to improve the estimates of knee joint reaction forces from simulation.[56] The second peak is associated with the late stance phase of gait, when the muscles are actively contracting to generate forces to continue the propulsion of the body forward. For the second peak in the medial compartment our simulation models tended to overestimate the vertical joint reaction forces in NG and LTL, and underestimate the vertical joint reaction forces when using weighted SO for the MKT condition. During late stance the muscles are shifting from eccentric to concentric action in order to generate propulsive forces for continued gait, thus concentric muscle activity estimated by SO is contributing to force estimates in the second peak.[181,218,263] The differences in estimate quality between the first and second peak may be driven by differences in the model estimates of eccentric versus concentric forces contributing to joint reaction force calculations. Previous research has looked at including subject-specific modifications to the maximum voluntary isometric contraction (MVIC) values in the computer models, which may be something that could improve output estimates.[181] Previous research has suggested that increased first peak forces are associated with higher risk of knee OA progression, while there has been less clinical relevance established for increased forces in the second peak.[91,138,264,265] Therefore, our results provide support for using the model to investigate the effect of gait interventions on the joint reaction forces in the first peak during early stance phase.

It was inconclusive if our weighting strategy provides a viable option to determine how to choose which muscles to weight when implementing weighted SO. For our subject, weighting only the MGAS provided the optimal results, which differed from previous research that required weights on either, or both, the quadriceps and/or the hamstring muscle groups to provide improved vertical joint reaction force estimations.

Previous research has indicated that weighting may differ between subjects[181] and this study suggests weighting may need to be tailored to specific gait modifications as well. Since implementing this type of simulation in healthy or pathological populations cannot be validated with in vivo data during the intervention, more research is needed to determine an optimal approach to choose which muscles require weights and the magnitude of those weights. It may be possible that the weighting strategy could differ depending on whether estimates in the medial or lateral compartments of the knee are the outcome of interest.

There are several limitations of this study. We only used a single subject because we needed data from a subject with an instrumented knee implant and that included data for walking trials using specific gait modifications. While previous research reported the percentage error for an uninformed model, an alignment-informed model, a contact-point informed model, and a fully-informed model,[56] our study used only the default contact locations because we did not have imaging data that would have allowed us to adjust that parameter, which may have contributed to error in the results. We also did not include subject-specific contact locations in the knee which may have increased the error in our simulation estimate outputs. Likewise, we did not include subject-specific MVIC values or EMG data which could have been used to further customize the model to the specific study participant.

Conclusion

This study provides support for using the Lerner Knee model in estimating vertical joint reaction forces in the MKT and LTL gait modifications. When implemented with weighted SO, the model can provide reasonably accurate estimates of the first peak vertical joint reaction forces in both the medial and lateral compartments of the knee in NG, MKT, and LTL. The second peak estimates have larger percentage errors but weighted SO provides improved performance over the default SO provided with OpenSim, especially for the NG and LTL conditions. However, the lateral compartment errors for vertical joint reaction forces in the second peak for MKT may be large and typically underestimate the vertical joint reaction forces; this should be considered if comparing the MKT to NG.

Acknowledgements

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Chapter 4. Study 2: Simulated Tibiofemoral Joint Reaction Forces for Three Previously Studied Gait Modifications in Healthy Controls

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Current Status: Submitted to *Journal of Biomechanical Engineering*

Prebble M, Wei Q, Martin J, Eddo O, Lindsey B., Comparing simulated tibiofemoral joint reaction forces for four common gait interventions.

Abstract

Background. Gait modifications, such as lateral trunk lean (LTL), medial knee thrust (MKT), and toe-in gait (TIG), are frequently investigated interventions used to slow the progression of knee osteoarthritis. The Lerner knee model was developed to estimate the tibiofemoral joint reaction forces in the medial and lateral compartments during gait. This model may be useful for estimating the effects on the joint reaction forces in the knee as a result of common gait modifications. We hypothesized that all 3 gait modifications would decrease the joint reaction forces compared to a normal baseline gait.

Methods. Twenty healthy individuals volunteered for this study (26.7 ± 4.7 years, 1.75 ± 0.1 m, 73.4 ± 12.4 kg). Ten trials were collected for a normal baseline gait as well as for each of the 3 gait modifications: LTL, MKT, and TIG. Gait modifications were individualized based on participants' baseline mean and standard deviation values. The data were then used to estimate the joint reaction forces in the first and second peaks for the medial and lateral compartments of the knee via OpenSim using the Lerner knee model.

Results. No significant difference from baseline was found for the first peak in the medial compartment for any of the studied gait modifications. Statistically significant effects from baseline were found for the medial second peak as well as the first and second peaks in the lateral compartment.

Discussion. Our results did not support our hypothesis. While there was a decrease in joint reaction forces in the medial compartment during the loading phase of

gait for both TIG and LTL modifications, the differences were not statistically significant. MKT showed an increasing joint reaction force in the medial compartment but was also not significant. These nonsignificant results could be due to the small sample size not being able to detect differences between the gait modifications and the baseline gait, or may be due to a limitation of the Lerner knee model. The model lacks a degree of freedom in the frontal plane so it may not be accurately capturing small biomechanical changes in the motion of the knee during the modifications tested.

Keywords: Gait modification, knee osteoarthritis, joint reaction forces

Introduction

Osteoarthritis (OA) of the knee is a major cause of disability and affects more than 19% of the adult population over the age of 45 in the United States.[4,9] Excessive joint reaction forces (JRF) have been implicated in the development and progression of knee OA.[47,230] Gait modifications are a common noninvasive intervention used to reduce JRFs in the knee, which evidence suggests may slow progression of the disease.[40,45,231]

A number of gait modifications have been identified that may help reduce the joint loads in the medial compartment of the knee. Three common modifications investigated include lateral trunk lean (LTL),[35,40,43,45,164,219,236,265,266] medial knee thrust (MKT),[33,45,164,171,233,235,236,265,267] and toe-in gait (TIG).[45,164,233,236,264,265] Many of the studies investigating gait modifications rely on surrogate measures to assess knee loads such as the knee adduction moment (KAM) and the knee flexion moment (KFM).[49,50,233,237-243] However, with advancements in computing power computational models are becoming a common approach to directly estimate the JRFs in the knee during gait.[54-56,181,229,244-246]

Many studies use real-time feedback as a way to help subjects implement gait interventions. Typical feedback methods include visual,[40,45,164,232,233] auditory,[45] and haptic.[234] The LTL modification has been shown to reduce the KAM when a large enough trunk angle is used,[40,41,164,234] but one study reported that the modification could lead to discomfort in the spine and ipsilateral knee and hip joints.[40] MKT with real-time visual feedback has also been shown to reduce the KAM in healthy subjects.[41,164,171,232] A patient-specific simulation study on a subject with grade 2 medial OA suggested that

MKT could reduce both the first and second knee adduction torque peaks.[33] After gait retraining, the subject was able to closely reproduce the knee adduction torque reductions, calculated by the simulation study, while walking in a laboratory setting.[33] TIG using real-time visual feedback was able to reduce peak KAM in one study,[233] however other research did not show a significant decrease in KAM when using TIG with real-time visual feedback.[164] Previous research has suggested that KAM can provide a reasonable indicator for the JRF at the first peak of stance, but that KFM is also a significant contributor to the medial JRF during the first peak.[138,264] However, the relationship between KAM and the joint contact force is not as strong for the second peak of stance.[138,264] Additionally, research in children and adolescents has indicated that KAM may not be a good predictor of knee joint contact force independent of leg alignment.[268]

While it is impractical to measure JRFs in vivo,[269] computational models are capable of estimating internal forces during functional movements (i.e. walking, running, crouch gait).[111,181,207,218,229,247,270] OpenSim is an open-source software application for modeling, simulating, and analyzing movement.[55] It provides a flexible and robust tool that can be used by researchers to simulate how altered movement patterns can affect internal joint loading.[55,56,157,179,181,205,229,244-246,252-258] While there are default musculoskeletal models that can be used with OpenSim, the tool also allows for models that can be customized to more closely match subject-specific parameters.[56,181,229,244-246] Research has demonstrated that subject-specific models can improve the accuracy of predictions in joint loading over generic models.[56,259] A common finding in past studies was that a weighted static optimization (SO) approach provides improved results over the default OpenSim static optimization. Many of these studies use in vivo data from instrumented knee implants to optimize their model estimates, which becomes infeasible when trying to estimate the effects of gait interventions in healthy and pathological subjects where no in vivo data is available.

The purpose of this study was to compare the effects of the LTL, MKT, and TIG gait on estimated JRFs in a group of heathy participants. We hypothesized that all 3 gait modifications would decrease the JRFs compared to baseline. We also hypothesized that the MKT would provide the greatest reduction in JRF from baseline.

Methods

Participants. Twenty healthy participants volunteered for this study and their dominant limb was identified as the preferred leg in a kicking task.[271] Eligibility criteria included being free from knee, hip, and back pain that required treatment within the prior 6 months, and no history of lower limb or back surgery. Participants were excluded if they had any neurological or musculoskeletal impairment that would affect gait or any cognitive impairment that would inhibit motor learning. The study was approved by the Institutional Review Board (IRB) of George Mason University (Appendix A) and all participants gave written informed consent (Appendix B) prior to participation. Participant demographics are presented in Table 5.

Table 5. Participant Characteristics

Characteristics	Mean (SD)
N	20
Gender (M/F)	12/8
Dominant Limb (R/L)	18/2
Age (yrs)	26.7 (4.7)
Height (m)	1.75 (0.1)
Mass (kg)	73.4 (12.4)
BMI	23.9 (3.0)

Abbreviation: BMI, body mass index.

Instrumentation. Prior to data collection, 53 retroreflective markers were attached to the trunk and lower extremities of participants. Six clusters (31 markers) were placed bilaterally on the lower back, thigh, shank, and foot segments with 12 tracking markers placed on various anatomical locations as shown in Figure 13. Ten calibration markers were attached during static and dynamic calibration trials. Eight high-speed motion analysis cameras (Vicon, Oxford, England) sampling at 200 Hz were used to track marker trajectories during the dynamic trials. Ground reaction force (GRF) was collected using 4 floor-embedded force plates sampling at 1000 Hz (Bertec, Columbus, OH) which were aligned in a single row 2.4 m long. A static calibration trial was conducted by having participants stand on a force plate with their feet parallel to the anterior–posterior axis of the laboratory. A dynamic calibration was collected to estimate hip joint center by having participants complete 3 clockwise rotations of the pelvis.[272] From the static trial, a kinematic model was created for each participant using Visual3D software (C-Motion, Germantown, MD, USA) which included the trunk, pelvis, thigh, shank, and foot segments. Calibration markers were removed before the trials.

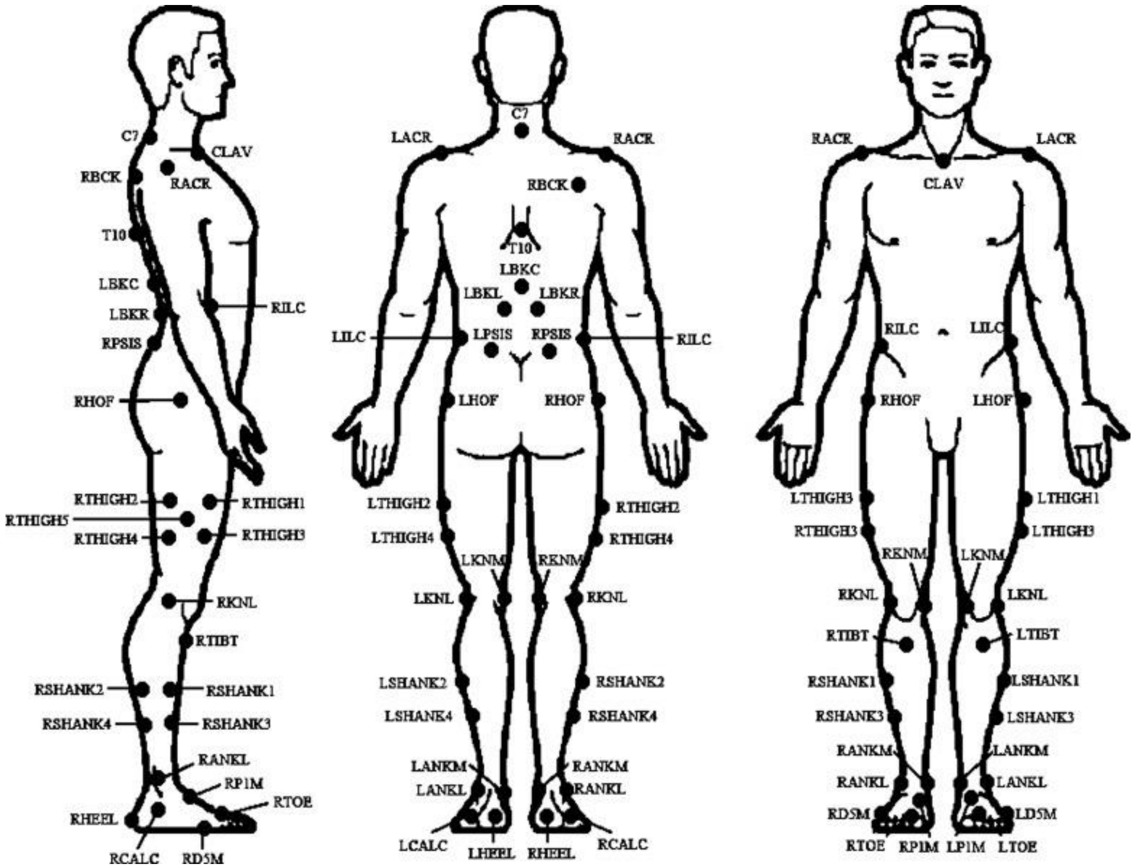

Figure 13. Experimental Marker Placement

Four tracking clusters (18 markers) were placed on the lateral aspect of each thigh and shank; 22 additional tracking markers were attached to the manubrium, 7th cervical vertebrae, right scapula, 10th thoracic vertebrae, and bilaterally to the following locations: posterior and lateral calcaneus, 5th distal metatarsal, 1st proximal metatarsal, 2nd metatarsophalangeal joint, tibial tuberosity, lateral iliac spine, posterior superior iliac spine, and acromion. Three tracking markers, arranged to form a triangular cluster, were attached to the lower back. Ten additional calibration markers were attached bilaterally to the following anatomical landmarks: lateral and medial malleoli, lateral and medial knee joint lines, and greater trochanters.[164]

Data collection. Two sets of data collection trials were conducted for the study. We first conducted baseline trials of normal walking and then collected data for the gait modification trails. The data was then used to create musculoskeletal simulations of walking for each participant.

Baseline trials. Participants walked along a 6-meter laboratory walkway using a self-selected gait speed. Timing gates (Brower Timing Systems, Draper, UT, USA) positioned at the start and end of 4 in-line force plates (2.4 meters long) were used to measure the average walking speed per trial. For a trial to be valid, 1 full contact with a force plate by the dominant limb was required. Participants completed 10 valid trials.

Gait modification trials. Gait modification parameters were individualized for each participant using their mean and standard deviation (SD) from baseline trials. Modification ranges were created so that gait parameters fell within a range of 1–3 SD greater (toe-in and lateral trunk lean) or lesser (knee adduction) than baseline for the first 5 trials and 3–5 SD greater or lesser than baseline for the second 5 trials. The 1–3 SD range was considered a small modification while the 3–5 SD range was considered a large modification. In total 6 target ranges were calculated for each participant: small and large LTL, small and large MKT, and small and large TIG.

Ten trials were completed for each of the 3 gait modification strategies using real-time visual biofeedback. The visual feedback was delivered by a line graph projected on a wall in front of the lab walkway as shown in Figure 14. The graph displayed the angle of the current gait modification parameter over stance and was updated during each step of the dominant limb. A range representing the lower and upper limits of the gait modification parameter (1–3 or 3–5 SD) was displayed on the graph (i.e. the green band in Figure 14). Participants were instructed to walk with the gait modification so that the line representing the gait parameter fell within the prescribed range. Participants were instructed to observe where the line fell during each trial and adjust their gait on the subsequent trial if needed.

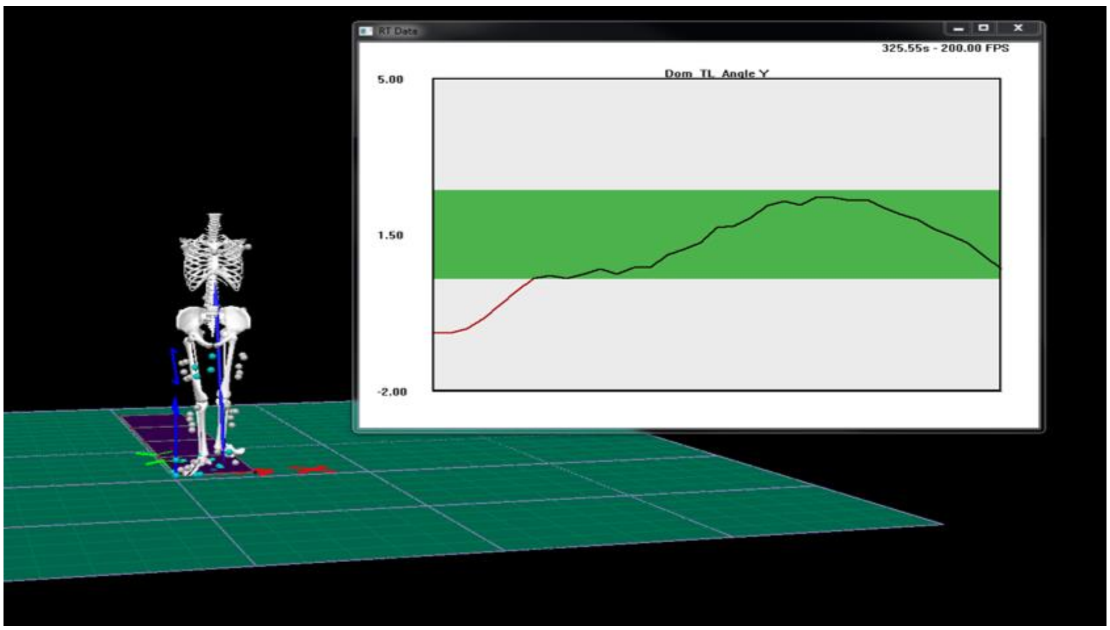

Figure 14. Example of Visual Feedback Graph for Participants Projected Onto the Laboratory Wall During Each Trial

The graph displays the angle of the current gait modification parameter over stance, updated during each step of the dominant limb. The green band is the range representing the lower and upper limits of the gait modification parameter (1–3 or 3–5 SD). Participants were instructed to walk with the gait modification so that the line representing the gait parameter fell within the prescribed range.

Standardized verbal instructions, as described in previous research,[273] were provided before implementing each modification. Participants were allowed to complete as many practice trials as needed to become comfortable with each modification, and additional verbal feedback was provided during practice trials as needed. Gait modification trials were completed in the following order: LTL, MKT, and TIG. Successful trials required at least 1 clean foot contact of the dominant limb within a force plate and average gait speed ± 5% relative to the baseline average speed. Only successful trials counted towards the 10 required for each modification.

Musculoskeletal simulation of walking. Recorded data were first exported to Visual3D (C-Motion, Germantown MD, USA) for preprocessing and then OpenSim-compatible format files were exported from Visual3D. Prior to export, Visual3D runs Inverse Kinematics on the data and provides a kinematic and a kinetic .mot file for each trial. The exported files were used to create three-dimensional simulations for the stance phase of gait using OpenSim. In order to simulate muscle forces required to reproduce the measured kinematics and kinetics, static optimization (SO) was run on the data using OpenSim 3.2. Prior to SO, the gait2392 model was scaled to each subject's height and weight. In addition to the default SO cost function for minimizing the sum of the muscle activations squared,[55] the data were also iteratively run through a weighted SO function based on previously described methods.[56,181,218] OpenSim 3.2 was used in this part because the weighted SO plug-in was built to be compatible with this version of the software and has not yet been updated to work with the latest version of OpenSim.[213]

Previous research has identified muscle forces as a major determinant of simulated compressive tibiofemoral contact forces,[247,274] thus variations in muscle activity greatly influence the accuracy of knee JRF predictions.[247] The weighted SO objective function minimizes the sum of squared muscle activations while incorporating individual muscle weighting values using the method described in previous research,[218] in which the models were tuned to find an optimal match between in vivo data and simulated knee JRFs by varying the weighting constants for the quadriceps, hamstrings, and/or plantar flexor muscle groups. However, in clinical settings this approach is not feasible so another strategy was chosen. In order to identify muscles and corresponding weights, the results of SO were visually inspected to identify any muscles identified in previous research that contributed to increased knee load estimates (e.g. quadriceps, hamstrings, calves), and that had a force that was 2 to 3 times greater than estimated forces from other lower extremity muscle groups. A weight of 2 was initially applied to that muscle group and a weighted SO was rerun; the results were visually inspected to determine the effect of the weight on the muscle force outputs. The weight was increased until the weighted SO output for the identified muscle fell within a comparable range to the other lower extremity muscles.

If there were multiple muscles with extreme force estimates, muscles were weighted and evaluated in a set order for all gait intervention trials. The order was to apply a weight to the gastrocnemius (GAS) muscles; then weights were applied to the GAS and the vastus lateralis (GAS/VL) muscles; then to the GAS, VL, vastus intermedius, and vastus medialis (GAS-VI-VL-VM) muscles; and lastly to the GAS, VL, VI, VM, and the rectus femoris (GAS/VI/VL/VM/RF) muscles. The muscle weight values started at 2 and were systematically adjusted until the muscle force output values from the weighted SO did not show any large spikes in the SO output. Final weights used for the model for each participant are located in Appendix C.

After the default SO and the weighted SO were completed, the knee JRFs for the medial and lateral compartment were computed using the OpenSim JointReaction analyses on the scaled Lerner model using OpenSim 3.3. The Lerner et al. model is capable of resolving the JRFs in the knee into medial and lateral components.[56]

Statistical analysis. Descriptive statistics were calculated and a within-group repeated measures analysis of variance (RM ANOVA) was used to compare JRF of participants' dominant limb across the 3 different gait modifications. RM ANOVA was used in both the medial and lateral JRF for the first and second peaks during the stance phase of gait. If results were significant, pairwise comparisons were calculated. Statistical analyses were performed using the ggstatsplot[275] package in R version 4.1.0 (R Foundation, Vienna, Austria, https://www.R-project.org) with an alpha level set at 0.05 *a priori*.

Results

Mean JRF by gait conditions for the first and second peaks in both the medial and lateral knee compartment are shown in Table 6. Post hoc analysis of the data indicated that the averages for JRF in both the small and large conditions did not differ significantly from each other, so the results were combined into a single average across the 3 interventions for the statistical analysis. Previous analysis indicated that subjects had a difficult time getting the modification to accurately fall within the prescribed bandwidth, but were generally able to meet the lower bound of the prescribed modification.[164]

Table 6. Peak Mean Joint Reaction Forces During Gait

Gait	Medial compartment 1st Peak _FY Mean (±SD)	Medial compartment 2nd Peak _FY Mean (±SD)	Lateral compartment 1st Peak _FY Mean (±SD)	Lateral compartment 2nd Peak _FY Mean (±SD)
Baseline	1761.84 (±166.40)	1734.88 (±170.65)	867.50 (±122.46)	1145.19 (±88.48)
LTL	1674.86 (±185.31)	1745.93 (±228.67)	950.56 (±164.65)	1228.96 (±143.37)
MKT	1807.02 (±249.57)	1605.32 (±245.75)	1134.84 (±183.07)	1091.33 (±161.62)
TIG	1645.65 (±159.61)	1835.33 (±182.29)	862.05 (±107.33)	1137.85 (±100.73)

Abbreviations: *N*, number of total trials; FY, vertical joint reaction force; TIG, Toe-in gait; MKT, medial knee thrust gait; LTL, lateral trunk lean gait.

The main effects of the RM ANOVA for the vertical JRFs are presented in Figure 15, Figure 16, Figure 17, and Figure 18. For the first peak JRF in the medial compartment there was no significant difference between conditions ($F(1.7, 32.3) = 1.70$, $p = .20$). For the second peak in the medial compartment there was a statistically significant difference between conditions ($F(1.8, 34.4) = 4.71$, $p = 0.02$). Pairwise comparisons indicated that the TIG condition was different from baseline ($p = 0.04$). The data failed the Mauchly's test of sphericity for both conditions (med $p = 0.002$; lat $p = 0.0002$) so a Greenhouse-Geisser correction was used in the interpretation of the data.

For the first peak JRF in the lateral compartment there was a statistically significant difference between conditions ($F(1.8, 34.7) = 10.56$, $p = 0.0004$). Pairwise comparisons indicated a difference between the MKT and baseline ($p = 0.01$). The data failed the Mauchly's test of sphericity for this condition ($p = 0.001$) so a Greenhouse-

Geisser correction was used in the interpretation of the data. For the second peak in the lateral compartment there was a statistically significant difference between conditions ($F(3.0, 57.0) = 3.81$, $p = 0.01$). However, pairwise comparisons indicated no significant difference between any condition and baseline.

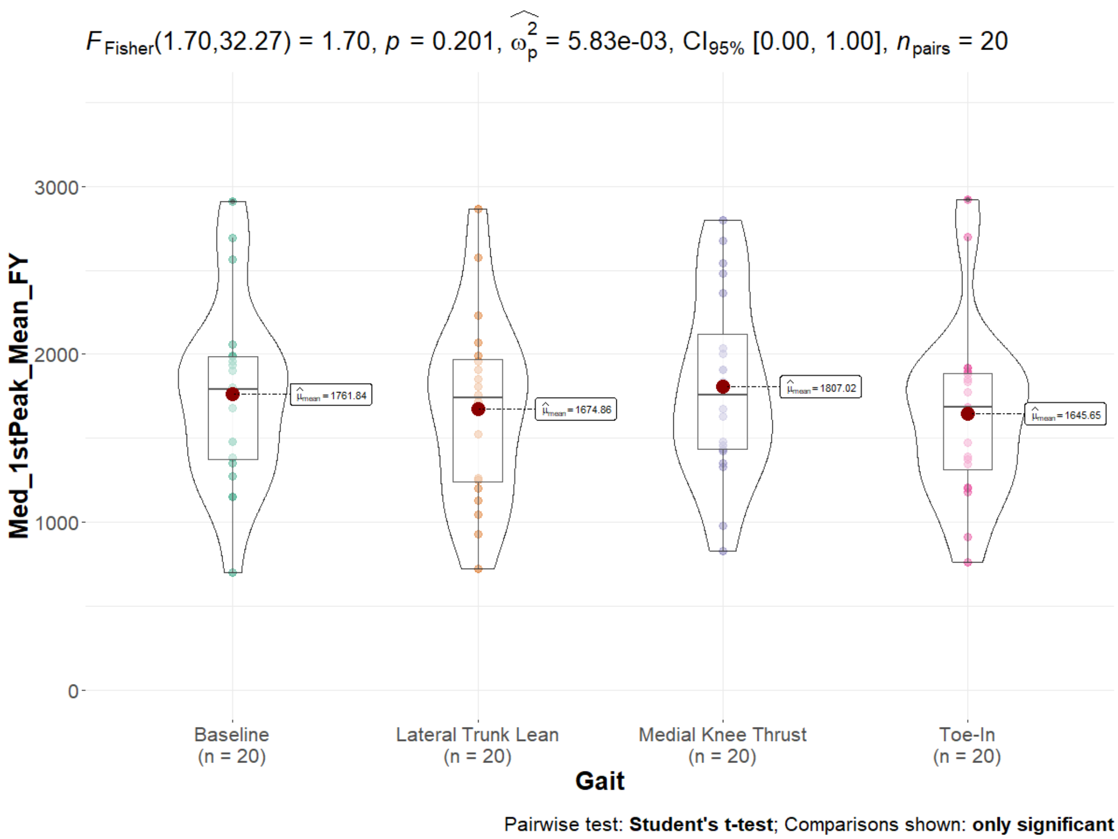

Figure 15. Repeated Measures ANOVA for the Mean Joint Reaction Force (N) in the 1st Peak in the Medial Compartment for Baseline, Lateral Trunk Lean, Medial Knee Thrust, and Toe-in Gait

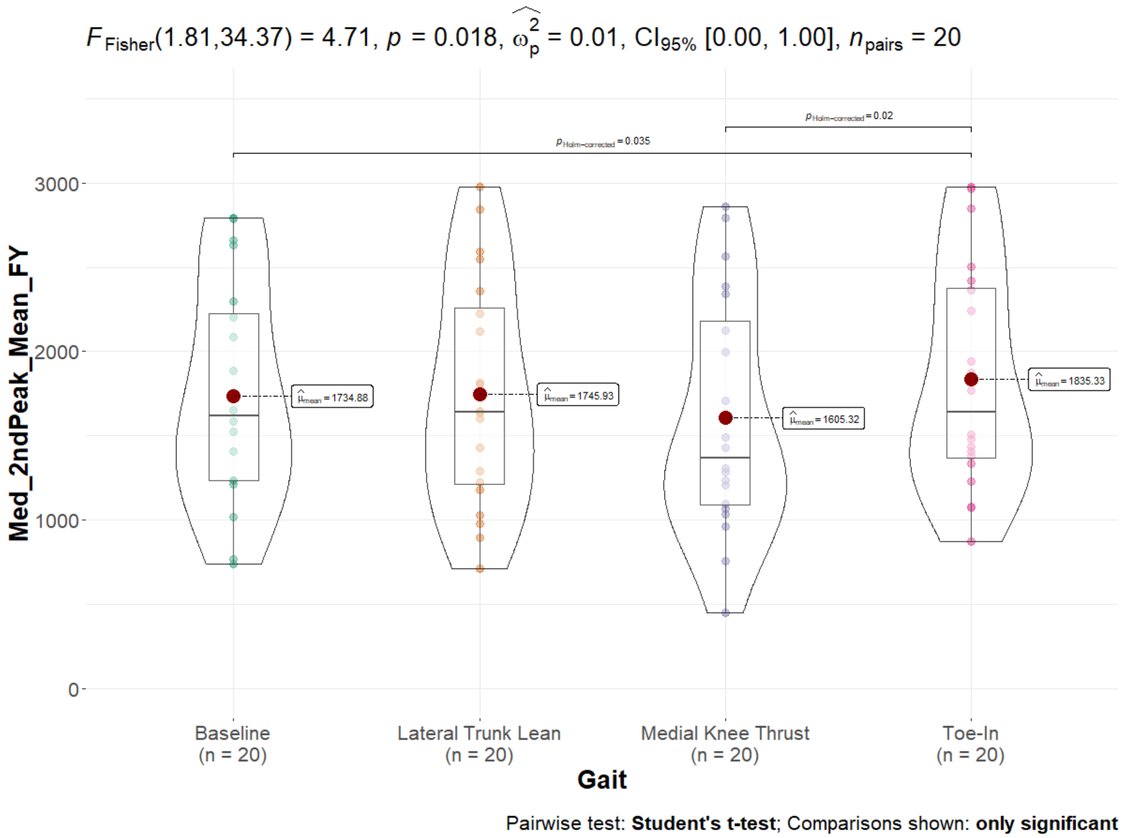

Figure 16. Repeated Measures ANOVA for the Mean Joint Reaction Force (N) in the 2nd Peak in the Medial Compartment For Baseline, Lateral Trunk Lean, Medial Knee Thrust, and Toe-in Gait

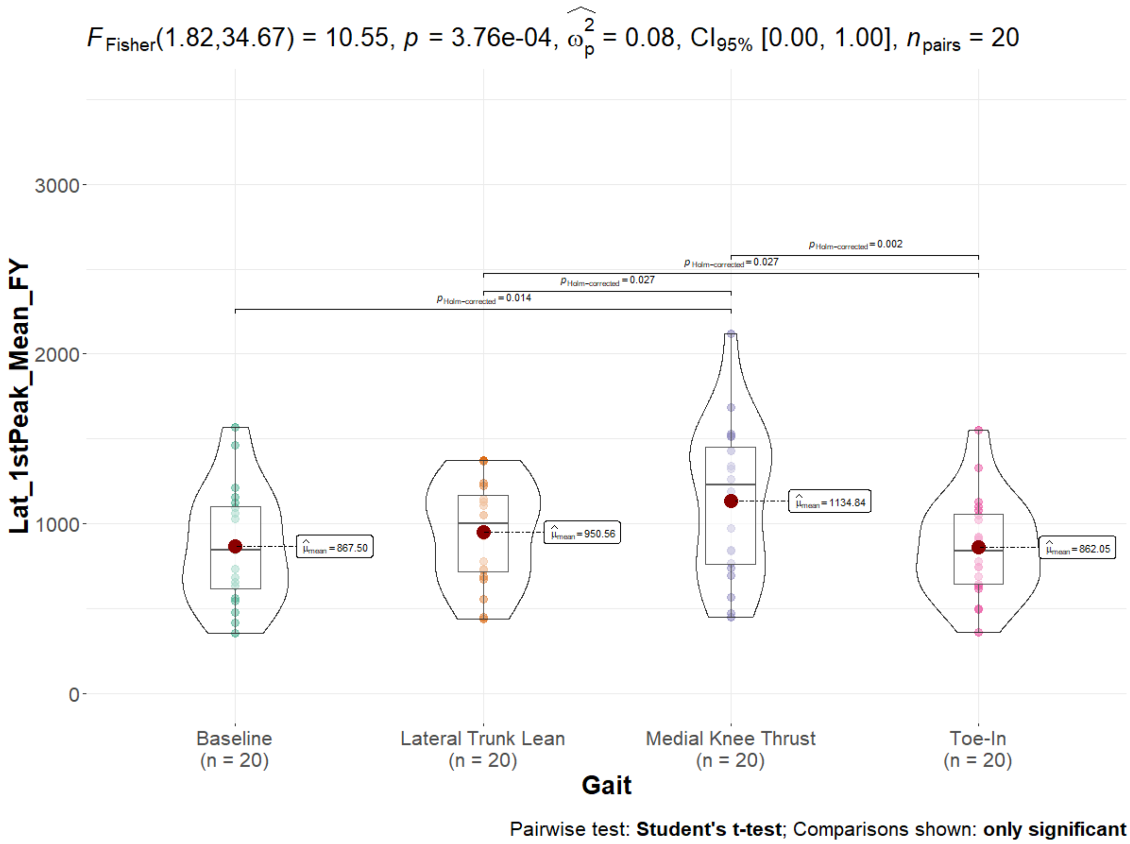

Figure 17. Repeated Measures ANOVA for the Mean Joint Reaction Force (N) in the 1st Peak in the Lateral Compartment for Baseline, Lateral Trunk Lean, Medial Knee Thrust, and Toe-in Gait

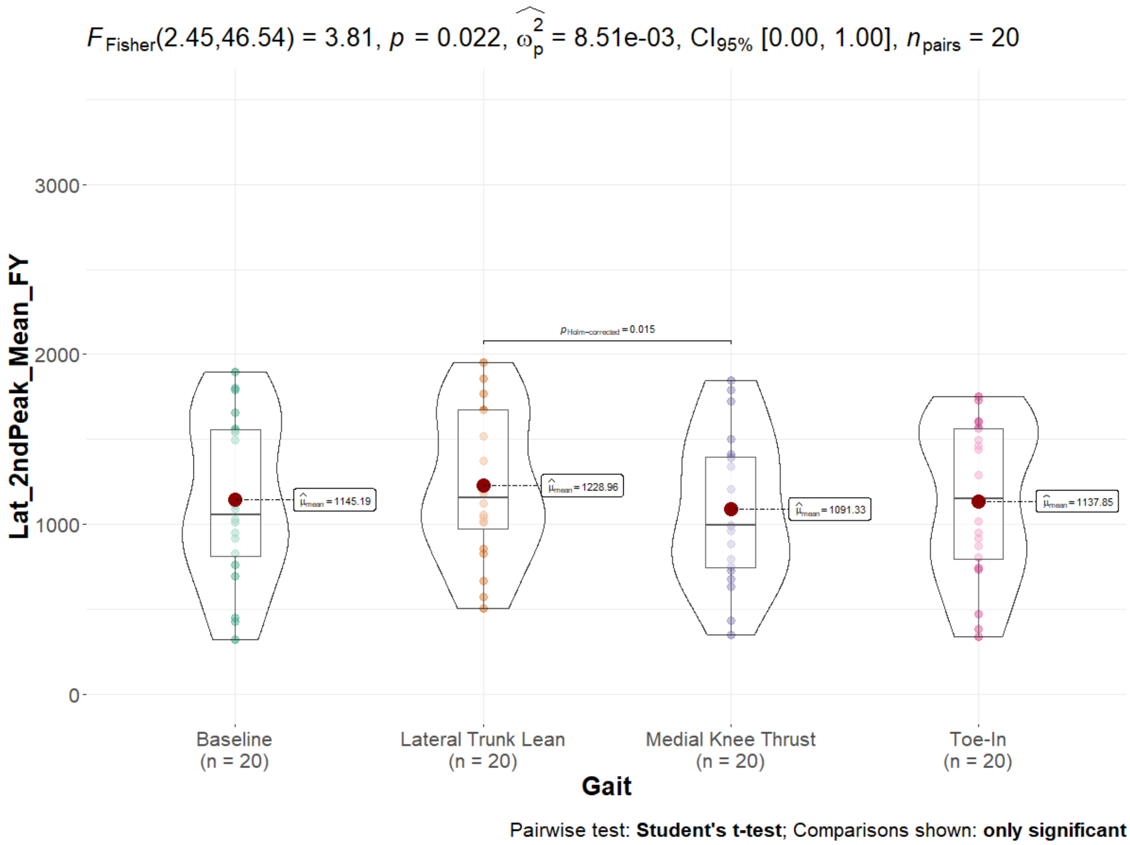

Figure 18. Repeated Measures ANOVA for the Mean Joint Reaction Force (N) in the 2nd Peak in the Lateral Compartment for Baseline, Lateral Trunk Lean, Medial Knee Thrust, and Toe-in Gait

The mean JRF normalized by body weight, during the stance phase of gait, across the 4 gait conditions in both the medial and lateral compartments, is shown in Figure 19.

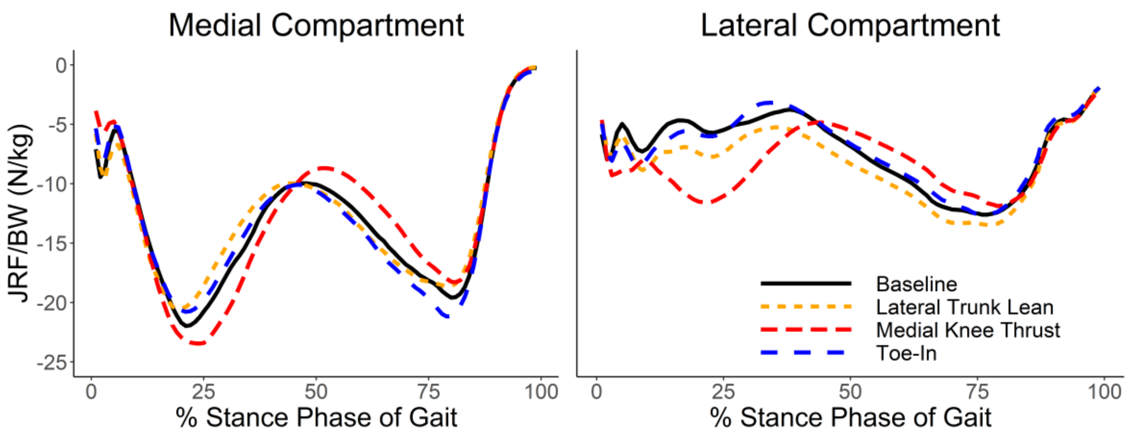

Figure 19. Mean Joint Reaction Force (JRF) Normalized by Body Weight (BW) in the Medial and Lateral Knee Compartments for Baseline, Lateral Trunk Lean, Medial Knee Thrust, and Toe-in Gait

Discussion

This study compared the effects of 3 gait modifications on the simulated JRFs in the medial and lateral compartments of the knee in healthy participants. The primary purpose was to determine if TIG, LTL, and MKT reduced the JRFs in the medial compartment of the knee in healthy individuals. Our hypothesis was not supported by the data, which showed no statistically significant difference between baseline and any of the gait interventions in the medial compartment during the loading phase (e.g. first peak) of gait.

For individuals at risk for, or diagnosed with, medial compartment knee OA, reducing the JRF in the first peak is generally thought to be of high importance, and gait interventions are commonly found to reduce either KAM or JRF in the first peak. Previous research on TIG has been inconclusive, but some studies have found that the modification can reduce KAM in both healthy and pathological populations.[38,42,276-278]

However, there is a lack of published data on how TIG affects the simulated JRF in subjects. While the data for this study exhibited decreasing JRF with TIG, the results were not statistically significant and had a small effect size. Data from a previous research project[279] suggests that our modeling approach can provide relatively robust results for simulated JRFs in the medial compartment during the loading phase, so 2 possible explanations for lack of results are either a sample size that was too small to detect the differences, or the intervention does not have a large effect on JRFs in the knee during the first peak.

The LTL modification has been shown to reduce the KAM in both healthy and pathological populations,[43,170,280] and while there was decreasing JRF in our study, the results were not statistically significant. In contrast to the LTL, the MKT modification showed an increasing JRF but it was also not significant. MKT has been shown to decrease both KAM and estimated JRF in previous studies.[33,164,171,281,282] One issue related to MKT is that of the 3 studied gait modifications, MKT was the most difficult for participants to adopt; a possible explanation for lack of results in our study is inconsistent implementation of the MKT intervention.[164] If some participants were not able to correctly implement MKT, it could have led to spurious results that obscured the results of the entire group. Overall, our results for MKT contradict previous research;[146,170,282] one possible explanation is that the outcome of gait interventions can be subject-specific[164,278] and may be influenced by parameters such as anatomical alignment,[283,284] body mass index,[285,286] and individual gait biomechanics.[278]

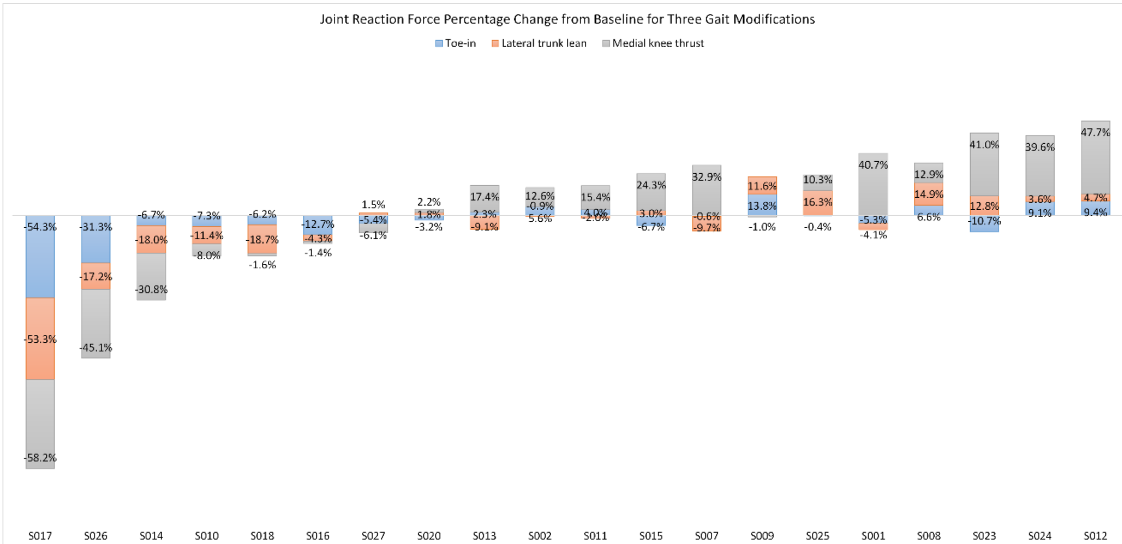

Figure 20. Percentage Reduction in Joint Reaction Force from Baseline Values, by Individual Participant, for Toe-in Gait, Lateral Trunk Lean, and Medial Knee Thrust

Figure 20 shows a summary of the responses to each intervention as a percentage increase or decrease from baseline JRF values by study participant. A couple participants had large (i.e. > 30%) reductions in their baseline values while others had large increases. In addition, some individuals showed an increase from baseline for some gait modifications but a decrease for others. Previous research has reported a similar finding when evaluating KAM in all 3 modifications.[164] Other research showed individual variation in the response to toe-in gait[278] and toe-out gait.[276] We compared our responses to participants' static knee alignment (estimated from Visual3D) and BMI, but there was no clear relationship between these variables and the responses to the modifications. One limitation to this analysis was our lack of imaging data, which did not allow us to accurately determine static knee alignment and contact locations. While we did attempt to estimate the values from Visual3D, the estimate of knee alignment calculation from the software differs from the approach described by Lerner et al.[56,190] It is also possible that no single variable contributes to an individual's response, but rather that it is a combination of several variables. For example, a participant's response may be affected by the level of strength in their leg muscles interacting with static knee alignment, BMI, and/or other variables.

While the second peak in the medial compartment is less important for subjects with knee OA, our data indicated a statistically significant difference between conditions for the propulsion phase of gait in the medial compartment (p = .02). The post-hoc pairwise comparisons indicated that TIG in the second peak produced a greater JRF than baseline (p = .04). Previous research on TIG has found inconclusive results on the effect of TIG on KAM, so this is not necessarily unexpected.[265] As shown in previous research, the Lerner knee model may overestimate the JRF in the second peak of the medial compartment when using a MKT or LTL gait.[56] While the weighted SO can reduce the error greatly, as found in previous research,[56,279] the errors can still be 20% or larger, as compared to less than 10% error in the medial compartment for MKT and LTL gait.

One of the main goals of these gait interventions is to reduce the JRF in the medial compartment; however, a consequence may be that the load is transferred to another region. While our data did not find statistically significant reductions in JRFs in the medial compartment, there was a statistically significant difference from baseline in the lateral compartment for both the first (p = .004) and second (p = .01) peaks. Post hoc tests indicated that the MKT differed from baseline (p = .02) in the first peak but there were no differences from baseline in the second peak. One factor to consider for this data is that the model used for the study was found to overestimate JRF in the lateral compartment to a greater extent than in the first peak of the medial compartment, especially when applied to MKT and LTL interventions. Therefore, the results in the lateral compartment may be skewed as a result of the model.

Conclusion

This study did not find the hypothesized decrease in simulated JRF in the medial compartment of the knee for TIG, LTL, or MKT. Possible reasons for the lack of results include a small sample size or individual variation in response to gait modifications. Future work should be done to develop a greater understanding of how different factors contribute to individual responses in JRFs as a result of gait modifications.

Chapter 5. Study 3: Simulating the Effect of a Gait Modification Intervention on the Joint Reaction Forces in Participants with Medial Compartment Knee Osteoarthritis

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Current Status: To be submitted

Prebble M, Wei Q, Martin J, Eddo O, Lindsey B., Simulating the effect of a gait modification intervention on the joint reaction forces in participants with medial compartment knee osteoarthritis

Abstract

Background. Knee osteoarthritis (OA) is a leading causes of disability with excessive joint reaction forces (JRF) in the tibiofemoral joint considered to be major factor in its development and progression. Gait interventions, such as LTL, aim to reduce JRF in the knee; evidence suggests these interventions may slow disease progression. This study investigated whether an LTL gait intervention using RTB would lead to reduced estimates of JRF in participants with medial compartment knee OA. We hypothesized that the treatment group would have decreased vertical JRF in the medial compartment of their symptomatic knee compared to a control group.

Methods. Eight individuals diagnosed with medial compartment knee OA completed the 10-week RCT before it was shut down due to the COVID-19 pandemic (62.0 ± 12.6 years, 1.66 ± 0.12 m, 78.4 ± 21.2 kg). The study includes a pre-test, post-test, and 8-week training period. Participants were randomly assigned to a control (n = 5) or treatment group (n = 3). OpenSim and the Lerner model were used to estimate the JRF during gait in the medial compartment.

Results. There were no statistically significant differences in JRF between the control group and treatment group (p-value = .08). There was an increase in estimated JRF in 2 of the 3 participants in the treatment group that warrants further investigation.

Discussion. The preliminary results demonstrate the ability for gait modification with RTB to be successfully implemented in a population with symptomatic knee OA. Further research is needed to identify whether LTL is leading to reduced JRF in the medial compartment of the knee, or if it is increasing JRF in some individuals.

Introduction

Osteoarthritis (OA) of the knee is a major public health concern and one of the leading causes of disability in the world.[4] The prevalence of the disease rises with age and has a number of risk factors including aging, obesity and a history of joint trauma.[11] In the United States knee OA is estimated to affect more than 19% of the adult population over the age of 45, and the lifetime risk of developing symptomatic knee OA was estimated to be ~40% in men and 47% in women.[4,9,287] There is no cure for knee OA and once diagnosed it will continue to progress until a partial or total joint replacement may be required. Excessive forces in the tibiofemoral joint have been implicated in the development and progression of knee OA.[47,230] A commonly studied intervention that may slow the progression of the disease is modified gait training, which is a noninvasive intervention used to reduce joint reaction forces (JRF) in the knee. Evidence suggests that gait modifications that reduce joint loading may slow the progression of the disease.[35,40,43,45,164,170,280,288] A number of gait modifications are commonly studied; 2 common interventions are altered foot progression angle (FP) and lateral trunk lean (LTL).[33,40,41,43,45,164,171,219,233,235,236,278]

FP gait modification involves changing the natural angle of the foot during gait and includes what are commonly referred to as toe-in gait (TIG) and toe-out gait (TOG). TIG is where the foot is rotated in towards the center of the body while in TOG the foot is rotated outward. One of the benefits of FP is that it is relatively easy for subjects to adopt, so may enable successful long-term adoption due to the relatively minor changes needed to implement it.[164] Previous studies have reported conflicting results on the FP strategy, with some research finding that it increased loading at the knee.[42,75,276-278]

The LTL modification has also been shown to reduce joint loading in both healthy and pathological groups.[33,43,164,170,171,280-282] Similar to FP, it is relatively easy to adopt; however, it involves a more noticeable change in gait that may lead to less compliance in participants long term. Some research has also suggested that the LTL can induce pathological issues at other joints, such as the lower back, which could reduce compliance and benefits from the modification.[273,289]

The LTL modification has been shown to reduce KAM in a number of studies, some of which have found it to be superior to other modifications, such as medial knee thrust, while others have found it to be less effective.[35,40,41,164,170,234] One study reported a reduction in peak KAM by as much as 65%[266] while another reported a dose response relationship between the LTL angle and KAM with larger angles leading to greater reductions in KAM.[43] However, it has also been reported that the modification could lead to some discomfort in the spine and ipsilateral knee and hip joints, and the modification may be difficult for some participants to adopt.[40,288]

Many studies that investigate gait interventions also use real-time biofeedback (RTB) as a way to help subjects implement the interventions.[40,45,172,242,290-292] RTB is used to provide immediate feedback to participants learning gait modifications and helps them calibrate the magnitude of the change they should incorporate. Typical types of feedback studied include visual, auditory, and haptic.[40,45,164,231-234] Gait interventions with real-time visual feedback have been shown to reduce the knee adduction moment (KAM) in healthy subjects.[41,164,171,172,232]

The KAM is a key indirect measure for the distribution of load in the medial and lateral tibiofemoral joint. A strong relationship has been identified between KAM and the progression of knee OA.[45,47,139] While KAM is a frequently used metric in knee OA research, some research has suggested that a combination of KAM and the knee flexion moment (KFM) may be a better predictor of medial joint reaction forces in the knee.[267] One study found that KAM may have a greater influence on femoral cartilage changes, while KFM may have a greater impact on tibial cartilage changes.[141] However, another study found no impact for KFM on medial knee OA progression.[150] The lever arm at the knee is a key component in the calculation of KAM; one study suggested that individuals with knee OA have an increased lever arm and that interventions that reduce the magnitude of the lever arm may be beneficial in reducing the progression of knee OA.[293] Modified gait strategies are thought to reduce the lever arm at the knee and decrease KAM.[280]

Most studies investigating gait modifications rely on surrogate measures, such as KAM and KFM, to assess knee loads.[49,50,233,237-243] However, with advancements in computing power, computational models are becoming a common approach used to estimate the JRF in the knee during gait.[54-56,181,229,244-246] While it is currently impractical to directly measure JRF in vivo, in intact knees, these computational models are capable of estimating internal forces during functional movements such as walking.[111,181,207,218,229,247] OpenSim is an open-source software application for modeling, simulating, and analyzing movement.[55] It provides a flexible and robust tool that can be used by researchers to simulate how gait modifications can affect internal joint loading.[55,56,157,179,181,205,229,244-246,252-258] While there are default OpenSim musculoskeletal models, the tool also allows for models that can be customized to more closely match subject-specific parameters.[56,181,228,229,244-246] Research has demonstrated that subject-specific models can improve the accuracy of estimates of joint loading when compared to generic models.[56,181,228,259] Lerner et al. developed an OpenSim model with a knee joint whose alignment and contact locations could be adjusted to match subject-specific parameters. The model is also capable of resolving the joint reaction forces in the knee into medial and lateral components.[56] When it was tested on a subject with an instrumented knee joint using a normal walking gait, the model was shown to provide improved estimates of JRF when compared to generic OpenSim models. In preparation for this study we validated the use of the Lerner knee model using 2 commonly researched gait modifications: MKT and LTL. Our results, in Chapter 3 of this dissertation, demonstrated the model provided reliable estimates in the medial compartment of the knee during the loading phase of gait for both interventions.

While there has been a significant amount of research on the effect of gait interventions in both healthy and pathological populations, a limited number of longitudinal randomized controlled trials (RCT) have looked at the effect of gait interventions in pathological populations over an extended period of time.[276] These types of interventions are important to determine the efficacy of gait interventions in reducing the joint loads in the knee over time and can help better understand how gait modifications can alter the progression of knee OA. RCTs can also improve the understanding of participants' ability to effectively incorporate gait modifications into their daily lives outside of a laboratory setting.

The purpose of this study was to investigate whether a long-term gait modification intervention using RTB would lead to reduced estimates of JRF in participants with medial compartment knee OA. We hypothesized that participants in the treatment group would have decreased vertical JRF in the medial compartment of their symptomatic knee compared to a control group, as calculated using OpenSim and the Lerner knee model.

Methods

Study design. The study was a nonblinded RCT to compare the pre- and postintervention joint kinetics and kinematics in the affected limb of participants diagnosed with medial compartment knee OA. Proportionate stratification sampling was used. The study period was 10 weeks in length with a pre-test, an 8-week intervention, followed by a postintervention assessment (post-test). Participants performed a baseline assessment (pre-test) during which their typical gait data were processed and analyzed to identify which of 2 possible gait intervention strategies—altered foot progression (FP) or lateral trunk lean (LTL)—maximizes their reduction in KAM during walking. Following the pre-test participants were randomly assigned into either the control group (CO) or 1 of the 2 previously identified intervention groups. The kinetic and kinematic data from the study were processed and analyzed using Visual3D to estimate the joint moments and OpenSim was used to estimate the joint reaction forces in the medial and lateral compartments of the affected knee. A within-groups comparison was done between the pre- and post-test data as well as a between-groups comparison looking at differences between the groups (CO, FP, LTL).

Participants. Participants diagnosed with symptomatic medial compartment knee OA, with radiographic evidence, and self-reported knee pain at least 1 day per week during the month prior to recruitment, were eligible for the study. Presence of knee OA was confirmed using a radiographic atlas, and was defined by greater medial osteophyte presence or greater medial joint space narrowing in the case of equal osteophyte grades (Kellgren & Lawrence [K/L] Grade). The leg with diagnosed OA was used for analyses. Participants were recruited from local physical therapy and orthopedic clinics and written informed consent was obtained for all participants. Participant demographics, to date, at baseline are presented in Table 7.

Table 7. Participant Characteristics

Characteristics	**Mean (SD)**
N	8
Sex (M/F)	2/6
Age (yrs)	62.0 (± 12.6)
Height (m)	1.66 (± 0.12)
Mass (kg)	78.4 (± 21.2)
BMI	27.9 (± 3.3)

Abbreviations: M, male; F, female; BMI, body mass index.

***Inclusion and exclusion criteria*.** To be eligible for inclusion, the participant needed to meet the following criteria:

1. are between the ages of 18 and 80,
2. have symptomatic medial compartment knee OA,
3. are able to walk unaided for a minimum of 60 minutes, and
4. have self-reported knee pain at least once per week during the month prior to recruitment.

Participants were excluded for any of the following reasons:

1. body mass index (BMI) greater than 35;
2. history of lower back, hip or, knee surgery during the previous 2 years;
3. knee arthroscopy or injection in the previous 6 months;
4. neurological or musculoskeletal conditions affecting ambulation;
5. cognitive impairment that would inhibit motor learning; and/or
6. use of gait aid, orthotic shoe inserts, or hinged knee brace.

If an individual presented with bilateral knee OA, the limb with the highest score on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire was used for the intervention.[294,295] This registered randomized controlled trial (NCT03663790) was conducted according to the Declaration of Helsinki guidelines; all procedures were approved by George Mason University's Institutional Review Board (IRB) for use of human subjects in research (Appendix D), and all participants gave written informed consent prior to participation (Appendix E).

Sample size. An a priori sample size was calculated using G*Power (G*Power 3.1.9.3)[296,297] with a power of 0.80, an alpha of 0.05, and an effect size of .072 which was estimated from previously reported literature. Specifically, the effect size was calculated using data from 3 previous studies that implemented gait retraining to reduce peak KAM.[46,232,298] The effect sizes ranged from 0.31 to 1.24 and the average value of 0.72 was used for the sample size calculation. The results of the analysis indicated 51 participants were necessary to complete the study.

Procedures. Upon arrival to the lab, all participants are required to read and sign the informed consent form. Height and mass were measured with height being recorded to the nearest 0.1 cm using a stadiometer, and mass to the nearest 0.1 kg. The experimental leg was defined as the leg diagnosed with symptomatic knee OA. Prior to both baseline testing and post-testing, participants will complete the WOMAC and rate their recent pain levels using the numeric rating scale (NRS) from 0 to 10, where 0 represents no pain and 10 the highest level of pain.

Pre-test. During week 0 participants were instructed to walk along a 6-meter walkway in the laboratory at a self-selected speed, with 4 floor-embedded force plates located along the middle 2.4 meters of the walkway. Timing gates (Brower Timing Systems, Draper UT, USA) positioned at each end of the force plates were used to record walking time, which was used to estimate the walking speed for each trial. Participants completed 5 baseline walking trials at their preferred speed. For a trial to be deemed successful, full contact with the foot of the experimental limb on 1 of the force plates was required. Force plate contact was confirmed visually. Upon completing the 5 trials, recorded kinetic and kinematic data were reconstructed, labeled, and trimmed to remove superfluous frames before exporting to Visual3D where the mean and SD for kinematic gait parameters (foot progression and trunk lean) were calculated. Foot progression angle was defined as the offset between the lines formed by the posterior calcaneus and 2nd metatarsophalangeal joint markers, and the anterior-posterior laboratory axis. Trunk lean angle was the frontal plane deviation of the straight line made by the 7th cervical and 10th thoracic markers from the vertical laboratory axis.[40]

Individualization phase. Before the start of the intervention, each participant performed baseline trials of the foot progression and lateral trunk lean gait modifications to identify which strategy was most effective in reducing their frontal plane knee moment. The order in which the trials was completed was randomized to prevent an order effect. To prevent any task transfer between the 2 strategies, participants were required to return to the lab within 1 week to complete the trials for the second gait modification strategy. Normal walking (baseline) trials were collected prior to implementing the second strategy (during the return visit), following the protocol used previously. This controlled for errors in comparisons across days as a result of marker placement.

For the foot progression condition, participants performed 5 trials each of small (1-3 SD from baseline mean) and large (3-5 SD from baseline mean) of the toe-in gait modifications totaling 10 trials. During the LTL condition, participants performed 5 trials each of small (1-3 SD from baseline mean) and large (3-5 SD from baseline mean) increases in trunk angle for a total of 10 trials.

Participants received standardized verbal instructions on how to achieve the instructed gait modification. Participants were then provided haptic RTB to ensure that they successfully achieved the required magnitudes of gait modification. Kinematic data collected in Vicon (Oxford, England) was streamed to MatLab (MathWorks, Natick, MA) for real-time computation. For FP trials participants received feedback from tactile sensors attached either to the lateral or medial aspect of the fibula. For the LTL modification vibration motors were placed on the scapula of the symptomatic side and just lateral to the spine at the same vertical level. For LTL trials, if participants did not meet the minimum or maximum angle for the LTL intervention, the motor device would provide haptic feedback so that on the next step they could correct their modification magnitude. If a participant did not lean enough to be within the prescribed range, the motor on the scapula would vibrate, prompting them to increase their lean on the subsequent step. If they leaned too much and were outside the range, the motor just lateral to the spine would vibrate, prompting them to decrease the amount of lean on the next step. Feedback was provided on each step and no vibration indicated that no correction was needed. A trial was only considered valid if the participant fully contacted the force plates twice with the foot of the experimental limb, and the modified parameter was in the prescribed target range. Additionally, participants were required to maintain an average gait speed relative to baseline gait speed for trials to be considered successful. Patient-specific gait modifications were determined based on the magnitude and strategy (foot progression or lateral trunk lean) that most reduced KAM compared to baseline gait trials. Participants were then randomly assigned to either their patient-specific gait modification (FP or LTL) group or CO group using proportionate stratification sampling as previously discussed. The study randomization process is shown in Figure 21.

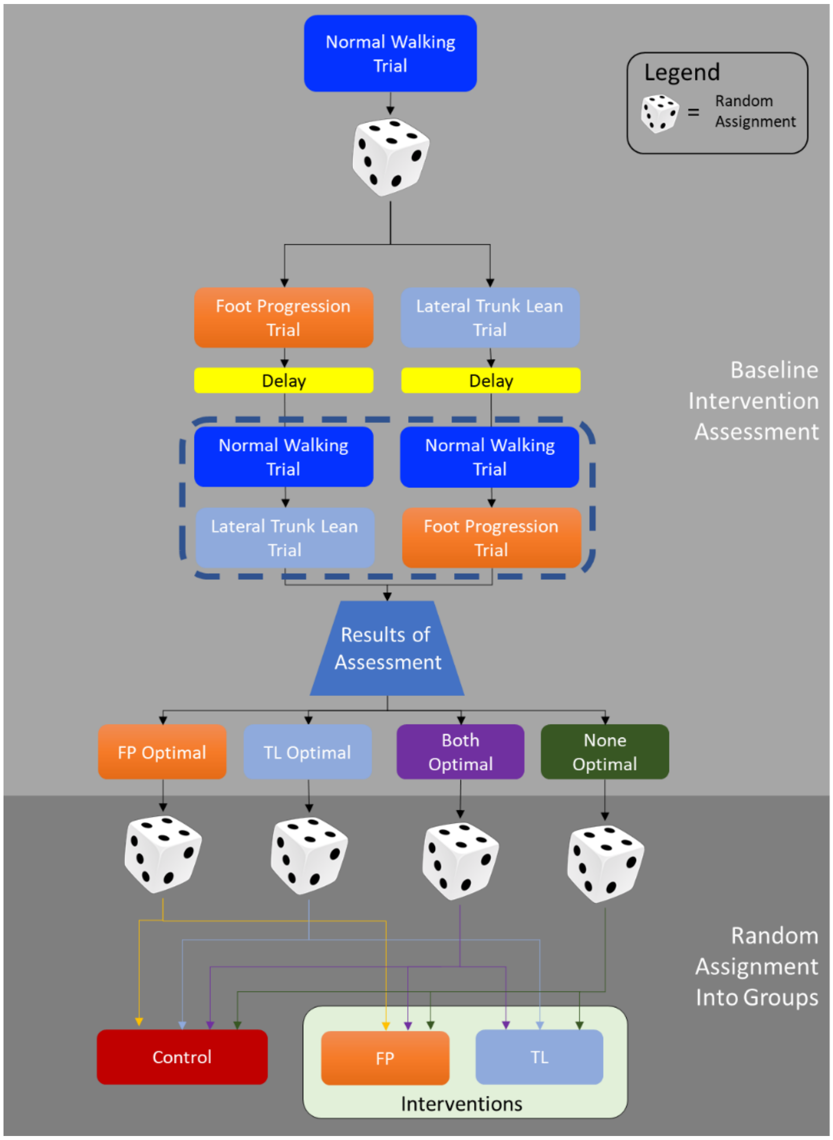

Figure 21. Flow Chart of Study Randomization Process

Gait-retraining phase. Eight gait-retraining sessions using patient-specific gait modifications (FP and LTL) or normal gait (CO) were performed once a week over 8 weeks. During gait-retraining sessions, participants walked on a Woodway Desmo treadmill (Woodway, Waukesha, WI) placed in the center of a calibrated volume area (approximately 0.5 x 1.5 meters). A 8-camera high-speed motion analysis system (Vicon, Oxford, England) sampling at 200 Hz was used to record gait kinematics. For the gait-retraining sessions, only 4 markers were used: 7th cervical vertebrae, 10th thoracic vertebrae, posterior calcaneus, and 2nd metatarsal phalangeal joint. The indicated anatomical landmarks were marked with an ultraviolet pen, which allowed for visibility for a week, and were reapplied at subsequent visits. This was done to improve marker placement repeatability during the gait-retraining phase. For the LTL group, frontal plane trunk angle was defined using the 7th cervical and 10th thoracic vertebrae markers. Foot progression angle was defined using the posterior calcaneus and 2nd metatarsal phalangeal joint markers for the FP group.

Adequate dynamic warm-up was provided prior to the commencement of each gait-retraining session; participants then walked with their individualized gait modification strategy for 20 minutes. Participants were provided with haptic feedback in the same manner outlined during the individualization phase (FP and LTL) or continued to walk without feedback (CO). A fading feedback design was implemented across sessions, as depicted in Figure 22, in order to gradually integrate task acquisition and transfer and to facilitate the internalization of the skill.[299] During the first 2 weeks, RTB was delivered on every step. For the third and fourth week, feedback was provided on the first 3 foot strikes by the experimental leg and withheld on the fourth, a 75% rate of feedback. During the fifth and sixth week, feedback was provided on alternating foot strikes, a 50% rate of feedback delivery. For the final 2 weeks of gait retraining, no feedback was provided on the first 3 steps but delivered on the fourth, a 25% rate of feedback.

Between gait-retraining sessions, subjects were instructed to practice the prescribed gait strategy on their own, which occurred in the absence of feedback. They were instructed to practice at least 10 min per day, and were provided weekly activity logs to record time of day and duration practiced each day during the 8 weeks of gait retraining. Practice logs were submitted weekly. As part of the waitlist control design, at the end of 10 weeks, patients assigned to the CO group were reassigned to their previously determined patient-specific gait modification intervention. The goal was to minimize attrition and increase the effective sample size.

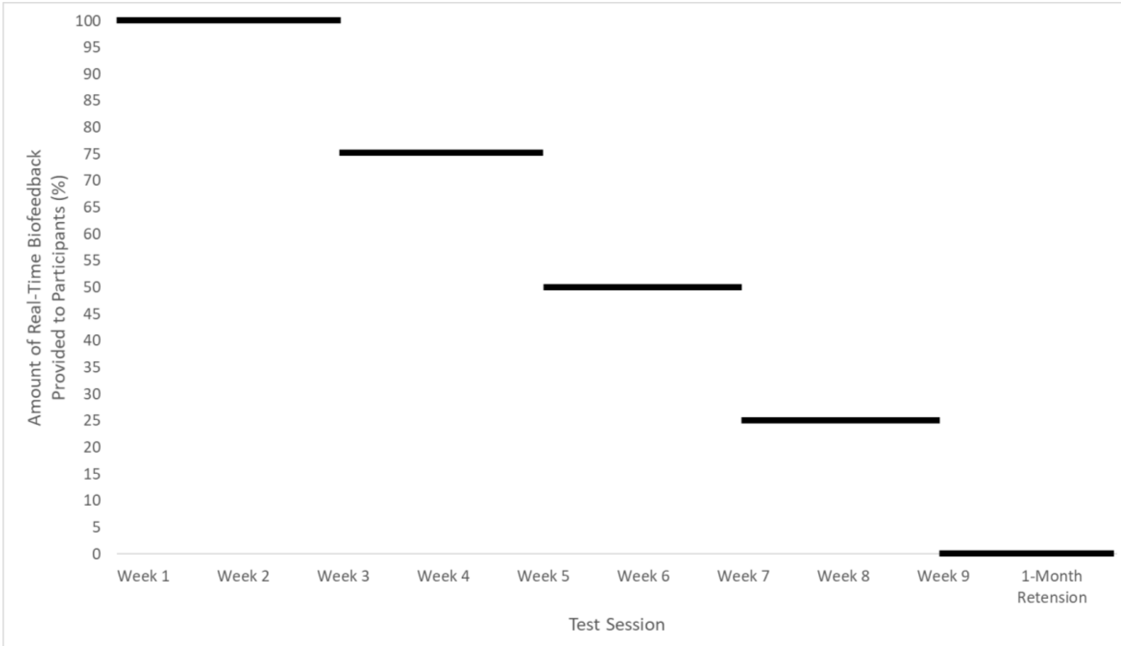

Figure 22. Percentage of Real-Time Feedback Given During Each Gait Retraining Session

Post-test. Over-ground gait analysis was performed at week 9 and 1 month postintervention to measure the effect and retention of the prescribed gait modification. This testing was similar to the baseline trials; however, participants were instructed to walk only using their tailored gait modification strategy. No feedback was provided during any of the post-testing.

Instrumentation. The following procedures and instrumentation were used to capture data during both the pre- and postgait-retraining assessment sessions.

Markers. Fifty-three reflective markers were attached to the participant's trunk and lower extremities. Tracking markers were attached to the following sites: posterior/ lateral calcaneus, tuberosity of the 5th metatarsal, 1st proximal metatarsal, 2nd metatarsal phalangeal joint, left/right anterior superior iliac spine, left/right posterior superior iliac spine, left/right acromion, mid clavicle, 7th cervical vertebrae, right scapula, and 10th thoracic vertebrae. Cluster shells were attached to the shank and thigh segment. Three markers arranged to form a cluster were attached to the lower back. Tracking markers were secured with double-sided tape and power flex tape. Thigh and shank clusters were secured using pre-wrap, athletic tape, and powerflex tape. Ten markers were used for calibration purposes only and were removed after the static and functional hip capture. The calibration markers were attached, using double sided tape, bilaterally to the greater trochanter, medial and lateral knee joint axis center, and malleoli.

Motion capture. Kinematic data were captured by tracking marker trajectories using 8 high-speed motion analysis cameras (Vicon, Oxford, England), sampling at 200 Hz, while participants walked along the lab walkway. Prior to the dynamic tasks a standing static trial and a functional hip trial were obtained to improve the estimation of hip joint centers.[300,301] For the static trial participants stood in anatomic position on a force plate at the center of the capturing volume with their feet aligned with the anterior-posterior axis of the laboratory. They were instructed to have their arms adducted 90 degrees and to hold motionless for static capture. For the functional hip trial their feet remained in the same orientation and their arms were adducted 90 degrees; participants were instructed to perform 3 hula circles with the hip traveling in a clockwise direction.[301] The final hula circle needed to terminate at the same location that the participant initiated the motion.

Force plates. GRF was measured at 1000 Hz using 4 floor-embedded force plates (Bertec, Columbus, OH), placed in a single row, located on the laboratory walkway.

Data processing. From the standing trial, a kinematic model was created for each participant which included the pelvis, thigh, shank, and foot, using Visual3D software (C-Motion, Germantown, MD, USA). This kinematic model was used to quantify the motion at the hip, knee, and ankle joints with rotations being expressed relative to the standing position. A cardan angle sequence was used to calculate joint angles,[302] and an inverse dynamics analysis was conducted to synthesize the trajectory and vertical GRF data for internal joint moment estimation.[303] Both force and kinematic and kinetic data were filtered at 8 Hz to reduce the effects of artifacts.[304,305] EMG signal data were high-pass filtered using a cutoff frequency of 500 Hz, rectified, and then low-pass filtered using a cutoff frequency of 20 Hz using a second order Butterworth filter. The EMG data from each muscle were normalized to their peak amplitude across all gait cycles.[306,307] All internal joint moments were normalized to mass and height, and all gait trials were normalized to 100% of stance.[308]

Computational model. Kinetic and kinematic data were exported from Visual3D into OpenSim-compatible format for joint contact force analysis. Prior to export a virtual lab reference frame was added to the data to align with the OpenSim software reference frame. Participant data were then imported into OpenSim. The OpenSim Lerner model was scaled to participant anatomical parameters (height and mass). Joint reaction forces in the medial and lateral compartments of the affected knee were estimated using inverse dynamics, weighted static optimization, and the OpenSim joint reaction analysis. Mean and standard deviation values were computed and used for statistical analyses.

Musculoskeletal simulation of walking. Participant kinematic and kinetic data were first exported to Visual3D for preprocessing and then OpenSim-compatible format files were exported from Visual3D. Prior to export, Visual3D runs Inverse Kinematics on the data and provides a kinematic and a kinetic .mot file for each trial. The exported files were used to create three-dimensional simulations for the stance phase of gait using OpenSim. In order to simulate the muscle forces required to reproduce the measured kinematics and kinetics static optimization (SO) was run on the data using OpenSim 3.2. Prior to SO, the gait2392 model was scaled to subject height and weight. In addition to the default SO cost function for minimizing the sum of the muscle activations squared,[55] the data were also iteratively run through a weighted SO function based on previously described methods.[56,181,218] OpenSim 3.2 was used in this part of the process because the weighted SO plug-in was built to be compatible with this version of the software and has not yet been updated to work with newer versions.[213]

Previous research has identified muscle forces as a major determinant of compressive tibiofemoral contact forces,[247,274] thus variations in muscle activity greatly influence the accuracy of knee joint reaction force predictions.[247] The weighted SO objective function minimized the sum of squared muscle activations while incorporating individual muscle weighting values using the method described in previous research,[218] in which the models were tuned to find an optimal match between in vivo data and simulated knee joint reaction forces by varying the weighting constants for the quadriceps, hamstrings, and/or plantar flexor muscle groups. However, in clinical settings this approach is not feasible, so another strategy was chosen. In order to identify muscles and corresponding weights, the results of SO were visually inspected to identify any muscles identified in previous research to contribute to increase knee load estimates (e.g. quadriceps, hamstrings, calves) that had a force that was 2 to 3 times greater than the estimated forces from the other lower extremity muscle groups. A weight of 2 was initially applied to that muscle group, a weighted SO was run, and the results visually inspected to determine the effect of the weight on the muscle force outputs. The weight was increased iteratively until an acceptable force was identified via visual inspection of the force output data.

If there were multiple muscles with extreme force estimates then muscles were weighted and evaluated in a set order for all gait intervention trials. The order was to apply a weight to the gastrocnemius (GAS) muscles; then weights were applied to the GAS and the vastus lateralis (GAS/VL) muscles; then to the GAS, VL, and vastus intermedius/vastus medialis (GAS/VI/VL/VM) muscles; and lastly to the GAS, VL, VI, VM, and the rectus femoris (GAS/VI/VL/VM/RF) muscles. The muscle weight values started at 2 and were systematically adjusted until the muscle force output values from the weighted SO did not show any large spikes in the SO output. A summary of the weights for each participant is provided in Appendix F.

After the default SO and the weighted SO were completed the knee joint reaction forces for the medial and lateral compartment were computed using the OpenSim JointReaction analyses on the scaled Lerner model using OpenSim 3.3. Postprocessing of the data included normalizing the trials to 100% of the stance phase of gait and exporting data for statistical analysis. Postprocessing was completed using MatLab (Version R2018b, The Math Works, Inc., www.mathworks.com/).

Statistical analysis. There were 4 steps to the statistical analysis: Data cleaning, assumption testing, descriptive statistics, and inferential analysis.

Data cleaning. An Excel file of raw data and descriptive statistics for joint angle and moments was generated for each participant and each session. Each variable of interest was inspected to ensure data integrity and to identify missing or abnormal values. Abnormal values or extreme outliers were visually inspected and investigated to determine if they were valid values or errors in the data file.

Testing of assumptions. Data were tested to ensure multilevel model assumptions of normality, linearity, homogeneity of variance, and normal distribution of residuals of the model were met. The model residuals were plotted against the predictors to determine if the pattern observed was nonrandom. To test the assumption of homogeneity of variance, an analysis of variance of the residuals was completed at the individual level. QQ plots were used to investigate the distribution of the residuals and the normal quantiles along a straight line were inspected.

Descriptive analysis. Descriptive statistics were calculated to describe the study sample: age, sex, height, mass, and BMI. In addition, descriptive statistics for gait speed, medial, and lateral knee JRF were computed.

Inferential analysis. Descriptive statistics were calculated and vertical JRF were normalized by subject's body weight (BW) measured at the time of data collection.[309,310]

Two types of statistical tests were run on the data: an analysis of covariance (ANCOVA) and a hierarchical linear model (HLM). For the ANCOVA the group served as the independent variable (within-between interactions) and the vertical JRF at baseline was the covariate. Peak medial and lateral compartment vertical JRF for the limb with knee OA were compared across the control and intervention groups at the post-test 2 time point.

The HLM was used to estimate the effect of the intervention across all time points (baseline, posttest 1, posttest 2, and posttest 3) while accounting for different sources of variation. This model was used to assess changes in mean vertical JRF, normalized by body weight, in the medial compartment across sessions and intervention groups via fixed effects, while also accounting for variability across the participants in baseline vertical JRF values and the changes in JRF from baseline to posttests via random effects. This allowed estimating the effect of the LTL intervention while accounting for variability across both sessions and participants. This model is as follows:

$$y_{ijk} = \beta_0 + u_{0j} + \beta_g group_{ijk} + (\beta_1 + u_{1j})Time1_{ijk} + (\beta_2 + u_{2j})Time2_{ijk} + (\beta_3 + u_{3j})Time3_{ijk} + \beta_{I1} group_{ijk} Time1_{ijk} + \beta_{I2} group_{ijk} Time2_{ijk} + \beta_{I3} group_{ijk} Time3_{ijk} + \epsilon_{ijk}$$

where y_{ijk} is the observed JRF/BW value for participant j on the i^{th} trial of the k^{th} session, $group_{ijk}$ is an indicator variable for the intervention group such that $group_{ijk} = 1$ if the j^{th} participant is in the LTL intervention group and $group_{ijk} = 0$ if the j^{th} participant is in the control group. $TimeN_{ijk}$ is an indicator variable for the post-tests during the intervention training sessions such that $Time1_{ijk} = 1$ if the i^{th} trial of j^{th} participant corresponds to post-test 1 and $Time1_{ijk} = 0$ otherwise, $Time2_{ijk} = 1$ if the i^{th} trial of the j^{th} participant corresponds to post-test 2 and $Time2_{ijk} = 0$ otherwise, and $Time3_{ijk} = 1$ if the i^{th} trial of the j^{th} participant corresponds to post-test 3 and $Time3_{ijk} = 0$ otherwise. β_0 is a fixed global intercept term; β_g is the fixed intervention effect at baseline; β_1 , β_2 and β_3 are fixed coefficients representing the estimated change in mean JRF/BW values from baseline to post-tests 1, 2, and 3 respectively for the control group; β_{I1} , β_{I2} and β_{I3} are fixed coefficients representing the additional change in mean JRF/BW values from baseline for the intervention group for post-tests 1, 2, and 3 respectively; u_{0j} is the random intercept term for participant j and u_{1j}, u_{2j} and u_{3j} are random effects for changes in mean JRF/BW values from baseline to post-tests 1, 2, and 3 respectively for participant j. It was assumed that the random effects followed a multivariate normal distribution and with normally distributed error terms.

Statistical analyses were performed using R: A language and environment for statistical computing (Version 4.1.0, R Foundation for Statistical Computing, Vienna, Austria: URL http://www.R-project.org/) and RStudio (Version 1.4.1717 Integrated Development for R, RStudio, PBC, Boston, MA: http://www.rstudio.com/) with an alpha level set at 0.05 a priori. For the HLM model the nlme package in R version 4.1.0 (R Foundation, Vienna, Austria, https://www.R-project.org) was used.[311]

Results

To date 8 participants have completed the training and follow-up post-testing and are included in this analysis. Participant demographic information is provided in Table 8. Of the 8 participants, 3 were randomized into the intervention group using the LTL gait.

For those 3 the baseline assessment determined that the large LTL condition was the optimal choice so it was used in the training sessions and post-testing.

Table 8. Mean (SD) Baseline Participant Characteristics

Descriptive data	**Control group (*n* = 5)**	**Trunk lean group (*n* = 3)**
Age	67.6 (7.5)	52.7 (15.3)
Sex (M/F)	0/5	2/1
Height (m)	1.62 (0.06)	1.73 (0.18)
Body mass (kg)	67.8 (6.2)	95.2 (28.7)
Body mass index (kg/m^2)	25.7 (1.3)	31.2 (2.6)

Attendance at the training sessions was high and participants were able to achieve trunk lean angles prescribed in the baseline assessment. Time series graphs of the vertical JRF in both the medial and lateral compartments of the knee are presented in Figure 23. Table 9 provides a summary of key variables for each time point in the study.

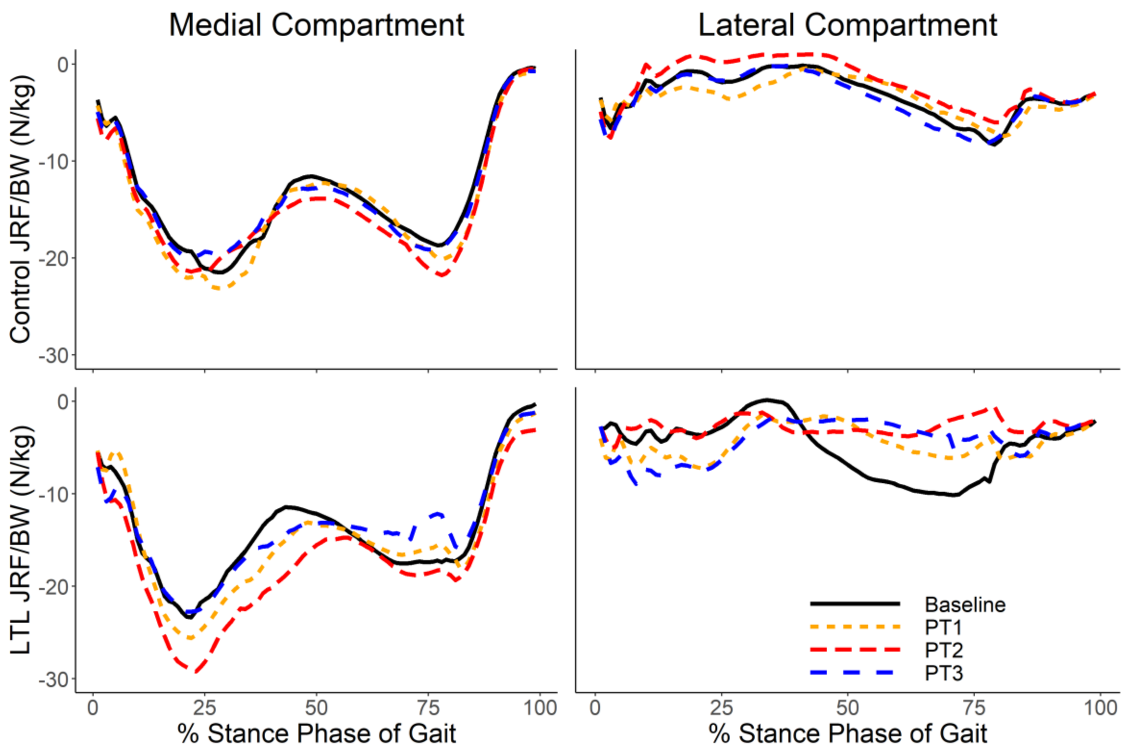

Figure 23. Simulated Vertical Joint Reaction Forces in the Medial and Lateral Compartment of the Symptomatic Knee, Normalized by Participant Body Weight, for Baseline, Posttest 1, Posttest 2, and Posttest 3
Abbreviations: LTL, lateral trunk lean; JRF, joint reaction force; BW, body weight, PT, posttest.

Table 9. Mean (SD) Data by Group Across All Time Points for Gait Speed, and Vertical Joint Reaction Forces in the Medial and Lateral Compartments for Both the First and Second Peak During the Stance Phase of Gait

	Baseline		**Post-test 1**		**Post-test 2**		**Post-test 3**	
	Control (*n* = 5)	**LTL (*n* = 3)**	**Control (*n* = 5)**	**LTL (*n* = 3)**	**Control (*n* = 5)**	**LTL (*n* = 3)**	**Control (*n* = 5)**	**LTL (*n* = 2)**
Gait Speed (m/s)	1.28 (0.13)	1.25 (0.11)	1.30 (0.12)	1.27 (0.07)	1.30 (0.09)	1.30 (0.12)	1.31 (0.14)	1.27 (0.11)
Medial 1st Peak JRF/BW	23.80 (9.56)	22.72 (6.51)	23.18 (7.52)	25.95 (2.51)	21.78 (5.84)	34.56 (9.23)	20.45 (7.61)	25.47 (4.51)
Medial 2nd Peak JRF/BW	20.44 (5.06)	20.32 (4.3)	19.27 (9.59)	22.05 (5.77)	22.16 (6.02)	26.45 (6.22)	19.96 (7.73)	19.78 (3.77)
Lateral 1st Peak JRF/BW	8.48 (2.23)	10.29 (2.53)	9.92 (4.3)	8.93 (3.3)	9.25 (5.52)	8.58 (2.81)	9.96 (4.19)	9.7 (2.38)
Lateral 2nd Peak JRF/BW	10.4 (4.47)	11.61 (4.53)	10.91 (4.37)	8.51 (1.96)	9.35 (4.39)	6.27 (2.76)	12.02 (4.77)	8.46 (3.57)

Abbreviations: LTL, lateral trunk lean; JRF, joint reaction force; BW, body weight.

Boxplots of the vertical JRF, normalized by body weight, are provided in Figure 24. The boxplots show both the medial (left column) and lateral (right column) vertical JRF for the first peak (first row) and second peak (second row) for the control and LTL groups. The figure also provides the data for baseline and each of the post-test time points.

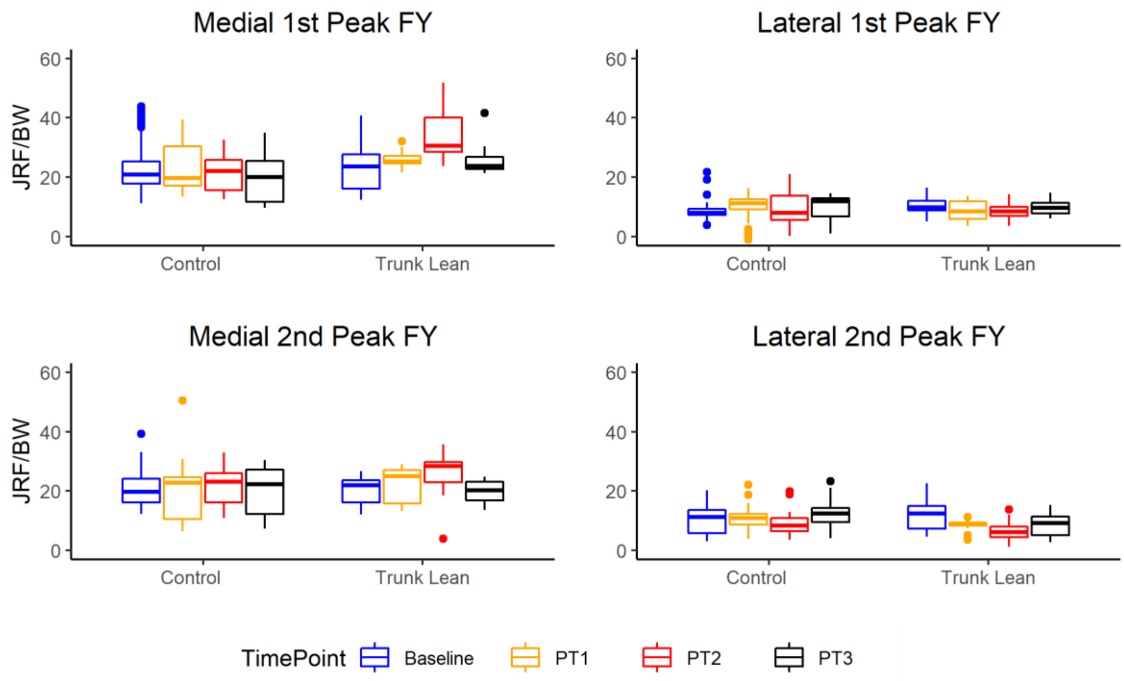

Figure 24. First and Second Peak Vertical Joint Reaction Forces in the Medial and Lateral Compartment of the Symptomatic Knee, Scaled by Participant Body Weight, for Baseline, Posttest 1, Posttest 2, and Posttest 3
Abbreviations: FY, ---; JRF, joint reaction force; BW, body weight; PT, posttest.

An ANCOVA was conducted to determine differences between groups (control and intervention) in their vertical JRF at posttest 2 while controlling for baseline vertical JRF. Tests were run for JRF in both the medial and lateral compartments of the symptomatic knee and for the first and second peak of the stance phase of gait. The results of the tests are summarized in Table 10. The data did not provide any statistically significant results for the first peak ($F(1,5) = 4.86$, $p = 0.08$) nor the second peak ($F(1,5) = 0.47$, $p = 0.53$) of the medial compartment in the intervention group.

Table 10. ANCOVA Results for Differences in Peak Vertical Joint Reaction Forces (Normalized for Body Weight) in the Medial and Lateral Compartments of the Knee Between the Control and Lateral Trunk Lean Groups at Post Test 2

	Medial		**Lateral**	
	F	***p***	***F***	***p***
Vertical 1st Peak	$F(1,5) = 4.86$	$p = 0.08$	$F(1,5) = 0.10$	$p = 0.76$
Vertical 2nd Peak	$F(1,5) = 0.47$	$p = 0.53$	$F(1,5) = 2.08$	$p = 0.21$

In addition to the ANCOVA, an HLM was run on the data for the first peak JRF in the medial side using all time points (baseline, post-test 1, post-test 2, and post-test 3). Table 11 provides a summary of the results. As with the ANCOVA none of the results were statistically significant.

Table 11. Hierarchical Linear Model for First Peak Joint Reaction Force Normalized by Body Weight

Fixed effects			
Parameter	**Estimate (SE)**	***p*-value**	**95% Confidence Interval**
Intercept	24.45 (23.04)	0.00	(17.59, 29.30)
Post-test 1	1.99 (2.04)	0.33	(-1.96, 5.93)
Post-test 2	-0.54 (3.32)	0.87	(-6.96, 5.87)
Post-test 3	-0.94 (2.04)	0.64	(-4.87, 2.99)
Intervention Group	1.56 (4.96)	0.76	(-10.31, 13.43)
Post-test 1* Intervention Group	0.00 (3.45)	0.99	(-6.67, 6.67)
Post-test 2* Intervention Group	8.20 (5.45)	0.13	(-2.31, 18.71)
Post-test 3* Intervention Group	2.72 (3.53)	0.44	(-4.09, 9.54)
Random effects			
Parameter	**Standard Deviation**		**95% Confidence Interval**
Intercept	6.49		(3.89, 10.83)
Post-test 1	4.08		(2.20, 7.60)
Post-test 2	7.03		(4.15, 11.91)
Post-test 3	4.06		(2.13, 7.74)

Point estimates, *p*-value, and 95% confidence intervals are provided for the effect of changes in groups and sessions on the joint reaction forces normalized by body weight values. Asterisks indicate statistically significant difference (* = <0.05).

Discussion

This study assessed the effect of a 10-week gait modification study on the vertical JRF in participants diagnosed with medial compartment knee OA via a RCT. It provides evidence to support that a LTL gait intervention performed over an 8-week training period with RTB can be completed by participants with symptomatic knee OA.

While there were no statistically significant results for either the ANCOVA or the HLM, inspection of the data and graphs appears to suggest the potential for an increase in the vertical JRF in the medial compartment of the knee during the first peak in the LTL group. Previous research that studied the LTL typically found a reduction in

KAM,[40,146,164,219,234] so an increase in the vertical JRF would be a concerning finding and counter to expectations.

Figure 25 shows the interaction plot of the data with an increase at post-test 2 in the intervention group. The potential for the LTL intervention to increase the JRF in the medial compartment during the first peak was also identified in the pilot study discussed in Chapter 3. Figure 12 from that chapter shows that the individual with an instrumented knee implant had an increased JRF during the loading phase (first peak) of gait during both the MKT and the LTL trials when compared to their normal gait. That data also suggested a decreased JRF during the propulsion phase (second peak) for the in vivo data that was not captured by the model output. However, further data needs to be collected to verify whether this result is an outlier or representative of the LTL intervention.

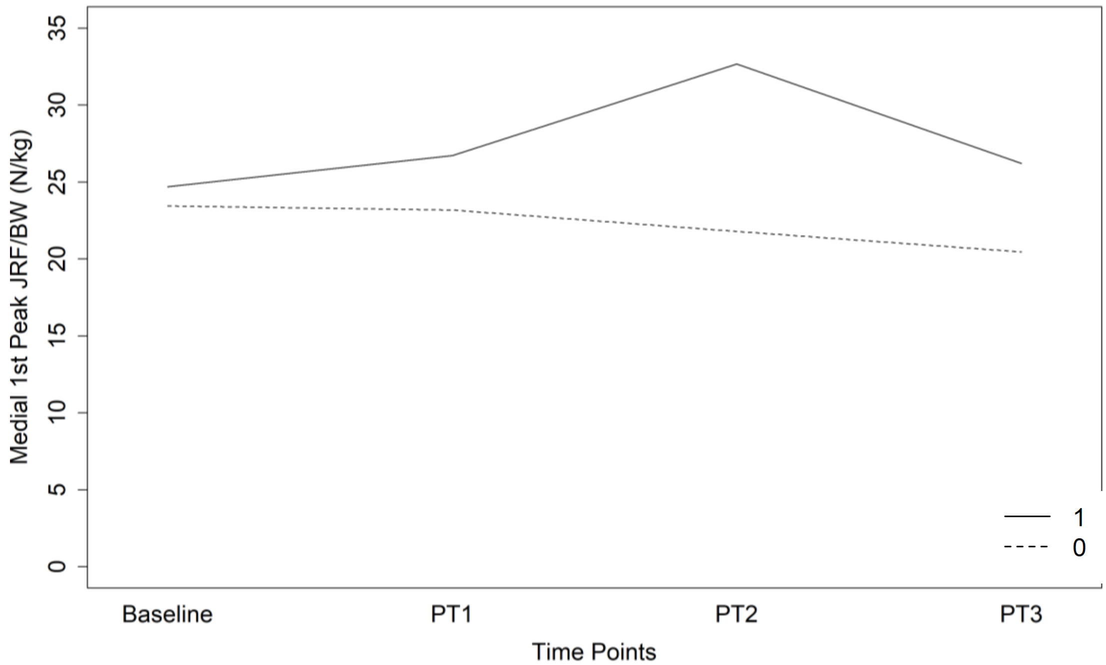

Figure 25. Interaction Plot of Intervention (1) and Control (0) Groups Across Time Points
Abbreviations: JRF, joint reaction force; BW, body weight, PT, posttest.

In order to better understand the peak in the LTL group from Figure 23, Figure 24, and Figure 25, Figure 26 shows the mean for the vertical JRF across the time points for each participant separately. The right column is the data for the intervention group and shows that 1 individual had a clear decrease in their vertical JRF. However, the other 2 participants in the group had increased vertical JRF compared to their baseline normal walking gait values. One possible explanation for this finding is erroneous output from the simulation models that are not accurately reflecting what is occurring in vivo. However, the pilot work discussed in Chapter 3, which investigated the modeling methodology, suggested that for the LTL gait modification the simulation models provided estimated vertical JRF with very low error (< 5%) in the medial compartment for the first peak in a subject with an instrumented knee implant. This raises the question of whether a subject with an instrumented implant is representative of the forces experienced in the knees in healthy individuals or those with knee OA.

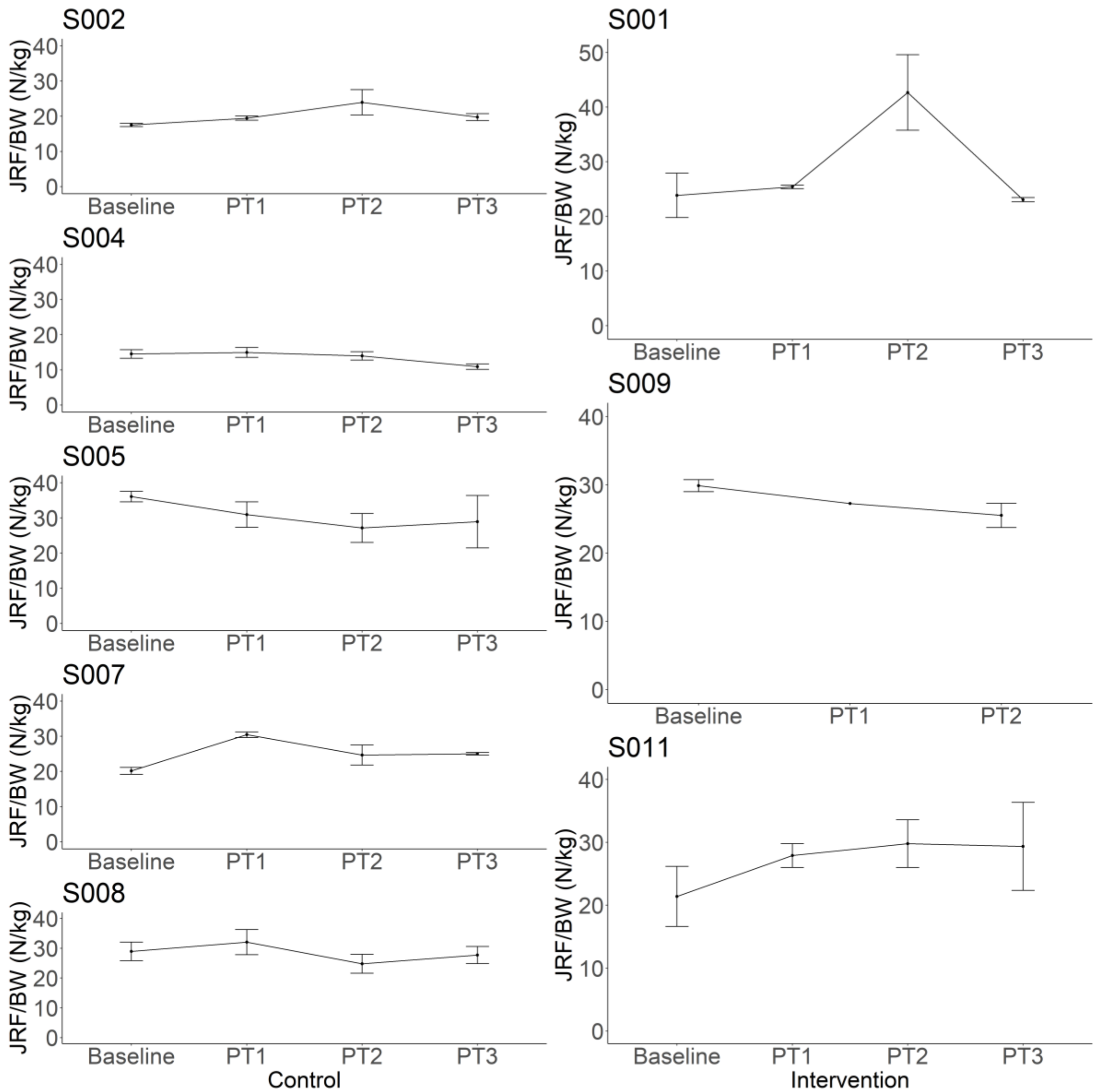

Figure 26. Mean and Standard Deviation of the Vertical Joint Reaction Forces at Each Time Point for Individual Participants
Abbreviations: S, subject; JRF, joint reaction force; BW, body weight, PT, posttest.

Another possibility is that there is variability in how individuals respond to the intervention, and that while the vertical JRF in the medial compartment decreases in some individuals, in others the intervention may actually cause it to increase. This was discussed in previous research by Lindsey et al.[164] that investigated the individual response in KAM for 3 commonly studied gait interventions and broke down the variation in response by participant. The study suggested a wide range of outcomes including some who experienced a decrease in KAM, some who experienced an increase in KAM and others with little response to the interventions.[164] Other studies have also suggested that there is variance in how individuals respond to gait interventions and suggest the need to tailor interventions to subjects based on individual responses to gait modification interventions.[172,228]

In addition to individual variables in responding to the LTL, it is possible that the increase in JRF may be related to the physics of the intervention. The goal of the LTL gait is to shift the center of mass over the leg, thus reducing the moment arm, and decreasing the KAM. However, this shift of the center of mass would also lead to an increase in the vertical component of the GRF and a decrease in the horizontal component, as shown in Figure 27. This increased vertical GRF may lead to an increase in the vertical JRF at the knee. In theory this could be leading to an increasing compressive force at the knee with decreasing shear forces. The trade-off between compressive and shear forces in the knee may warrant further investigation.

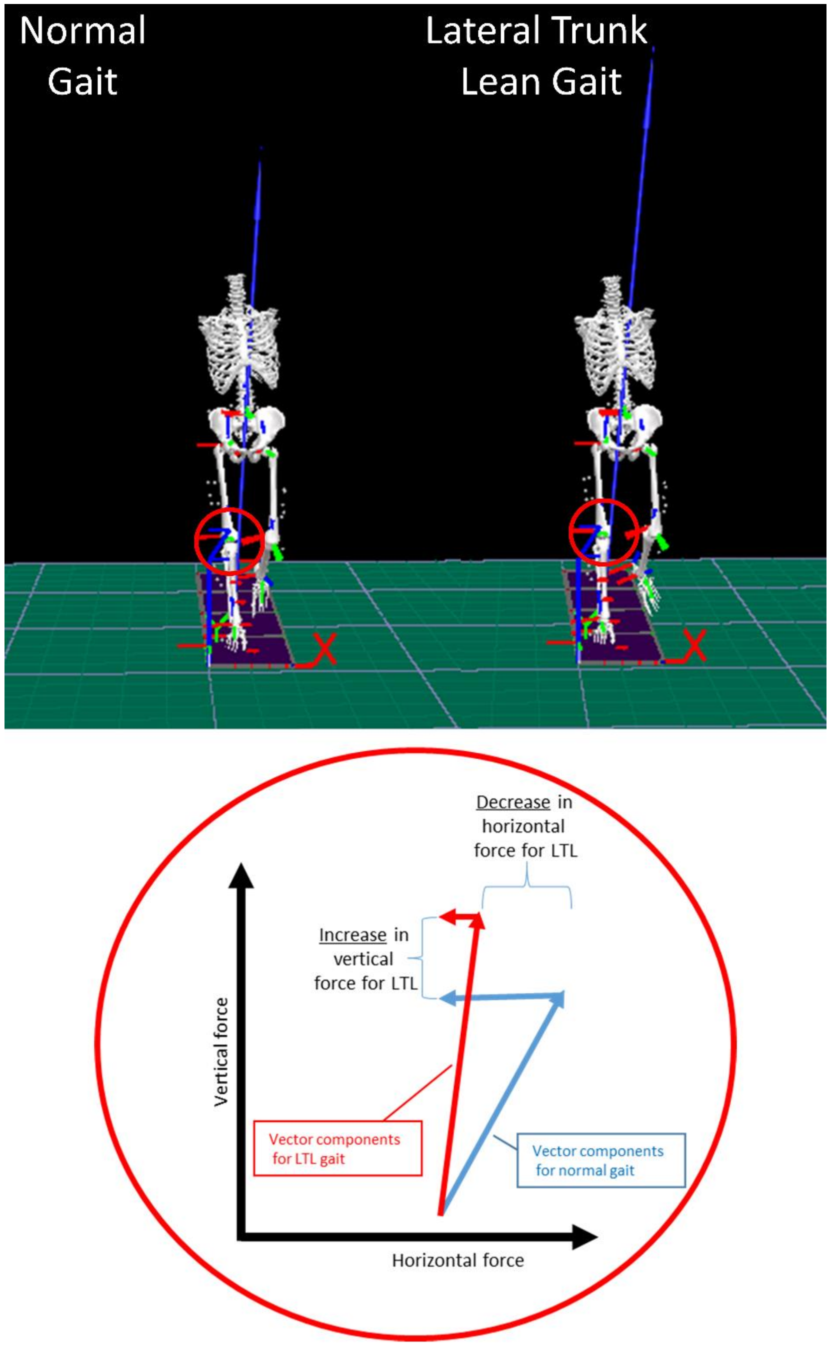

Figure 27. Changes in Vertical and Horizontal Joint Reaction Force between Normal Gait and Lateral Trunk Lean Gait

Chapter 6. General Discussion

Discussion

The purpose of this PhD dissertation was to calculate the effect of gait interventions on the estimated JRF in the knee via computer simulation. As part of the project the Lerner knee model was validated for use in 2 commonly researched modified gait strategies: MKT and LTL. The data collection methods and simulation approach were also validated in a study on healthy controls that assessed the effect of 3 common gait interventions on the estimated JRF in the knee: toe-in gait, medial knee thrust, and lateral trunk lean. Lastly, a preliminary 10-week RCT was conducted to determine if a LTL gait with RTB would reduce the estimated JRF in the medial compartment in participants diagnosed with medial compartment knee OA. The following sections provide a comprehensive overview of the main findings as they related to the research questions for the 3 studies completed as well as summaries of the main findings from each individual study. This is followed by a discussion on the limitations and suggestions for future research.

Main Findings

The main goal of this dissertation was to assess the effectiveness of gait interventions in lowering the vertical JRF in the medial compartment of the knee. Gait modifications are a common, noninvasive, clinical intervention intended to slow the progression of knee OA by reducing the forces experienced in the joint and the subsequent degradation of the joint tissue exposed to those forces. While a preponderance of literature describes the effect of various gait interventions on the KAM[20,21,34,47,91,141,145,150,152,163,267,312] and KFM,[50,141,142,150,152,243,264,313-316] fewer studies have estimated the effect of these modifications on the JRF,[33,236,317] and none to the best of our knowledge used the Lerner knee model.[172,228] One of the main contributions of this study was validating use of the Lerner knee model to estimate the JRF in subjects performing modified gait strategies, specifically the MKT and LTL interventions. When comparing the simulation output to in vivo data, the error for both interventions was less than 10% for the first peak in the medial compartment and was in line with error estimates from previous studies that implemented the model in normal gait.[56] The results of this and other studies highlight the importance of being able to individualize models to the participants in a study. Factors such as knee alignment and femoral-tibial contact locations contribute to improved estimates of JRF and matching the model to subject-specific parameters increases the accuracy of model estimates.[56,227] Several studies support this and also suggest improvements can be made by adding variables such as subject-specific strength[181] or improvements to how muscle forces are estimated.[318]

A second finding from the research was the potential for both the MKT and the LTL to increase the vertical JRF in the medial compartment of the knee. This is counter to the research that has provided support for MKT and LTL lowering KAM and KFM, and would be a concerning outcome if it holds up in further studies. Another possibility is that these results were due to a large variation in individual responses to gait interventions, which suggests that while some individuals may be able to reduce the vertical JRF as a result of a particular intervention, others may experience increases in their vertical JRF.[164,172,228] While this idea is gaining wider acceptance, more research needs to be done to further identify the factors that lead to the variation in outcomes among individuals. However, it does lend support to our approach in the RCT that gait interventions are not one-size-fits-all and should be tailored to each patient to provide them the best intervention for their specific anatomical and physiological parameters.

As discussed in Chapter 5, and shown in Figure 27, for the LTL it is possible that the increase in vertical JRF is due to the increased vertical component of the GRF and a related reduction in the horizontal GRF. This leads to a question: Has enough attention has been paid to horizontal shear forces in studies of knee OA, and is there a relationship or a trade-off between compressive forces and shear forces? An early simulation study suggested that the curves of shear forces had similar turning points when compared to compressive forces and knee moments during normal walking.[206] Few simulation studies in humans have investigated shearing forces in the knee during walking, but one study that used a drop-jump task found that these forces were underestimated in early OpenSim models.[319] However, studies in animals and cadavers have found that shear forces cause damage to cartilage.[320-323] One study found a strong correlation between KAM and the lateral-medial shear force[75] while another suggested a similar relationship between KAM and shear forces in FP gait modifications.[38] The detrimental effects of shear forces on cartilage seem likely and it may be that increasing them could lead to, or contribute to, the development of knee OA.[38,75,324] Some researchers have even suggested that shear forces may be more related to cartilage loss in the knee than KAM.[137,324] At the very least, more work is needed to unpack the question about which forces contribute more to the initiation and/or progression of Knee OA, compressive or shear forces. Determining which are worse for OA and identifying any trade-offs in shifting forces between compression and shear may be important research questions for future study.

Study 1. I tested the hypothesis that the Lerner knee model would provide reliable estimates of vertical JRF in the knee when compared to in vivo measurements in 2 common gait interventions. Results provided support for using the model to estimate the JRF in the knee in both the MKT and LTL gaits. When comparing the model output to the in vivo data from a subject with an instrumented knee implant, the model provided reliable estimates of the vertical JRF in the medial compartment of the knee, especially during the loading phase of gait. Using a weighted static optimization approach during the loading phase, or first peak, the error for both normal gait and MKT was less than 10% while the error for the LTL was found to be less than 5%. These results are similar to errors from the model estimated in normal walking gait.[56]

Unfortunately the error for the propulsion phase, or second peak, of gait, as well as for both phases in the lateral knee compartment, was much higher and may be an issue for accurately modeling the effect of these gait interventions in these regions of the knee. The model in this case did not perform as well as when tested in normal gait. However, the weighted static optimization approach used for the study generally provided improved results over the default static optimization method in OpenSim. Researchers should be aware that the weighted static optimization did lead to underestimation of JRF in the medial compartment in the MKT gait intervention and both the default and weighted static optimization led to underestimation of vertical JRF in the lateral compartment for all 3 gait strategies studied.

Study 2. For the second study it was hypothesized that all gait modifications would decrease the vertical JRF, estimated by OpenSim using the Lerner knee model, when compared to a normal baseline gait. Results demonstrated the use of the Lerner knee model to simulate the vertical JRF in healthy controls implementing 3 commonly studied gait interventions: TIG, MKT, and LTL. Contrary to published research that identified statistically significant reductions in KAM as a result of the interventions,[164] the study found no reduction in the simulated vertical JRF in the medial compartment for any of the 3 gait interventions.

For the TIG intervention there are conflicting results in the literature with respect to reductions in KAM,[42,75,276-278] an often-used proxy for vertical JRF, and this study lends support to the idea that TIG may not be effective in reducing medial compartment vertical JRF in healthy subjects. This study found no difference in the vertical JRF in the medial compartment for the first peak when compared to normal gait. However, there was a statistically significant increase in vertical JRF in the medial compartment for the second peak for the TIG modification. Results from Study 1 do indicate that there is larger error in the second peak which may lead to the significant results.

Previous research has suggested that both MKT and LTL may lead to decreased KAM,[33,43,164,170,171,280-282] however we found no statistically significant differences between neither MKT nor LTL with normal gait. The result was surprising since in the pilot study the model generated good estimates for both modifications, during the loading phase of gait, in the medial compartment. One possibility is that the subject used in the pilot study may not be representative of a younger healthy population and thus the model may or may not be providing accurate results of this population. More work needs to be done to further validate the model's accuracy and applicability in different populations and gait strategies.

Study 3. For the final study in this dissertation a randomized controlled trial was used to investigate whether a 10-week gait intervention, using RTB, could reduce the vertical JRF in a population diagnosed with medial compartment knee OA. We hypothesized that participants in the intervention group would have decreased vertical JRF in the medial compartment of their symptomatic knee compared to a control group, as calculated using OpenSim and the Lerner knee model. While the study data is incomplete, due to the COVID-19 pandemic, we were able to show that 8 participants with knee OA are capable of successfully completing a 10-week gait intervention study. While none of the results were statistically significant, we did highlight concerning increases in the vertical JRF as a result of the LTL gait intervention and identified potential causes and issues with the intervention. This finding warrants further work to expand on the results and determine if these increases are in fact occurring or are just spurious results.

Limitations

There are several limitations of the studies. To validate the Lerner knee model, discussed in Chapter 3, we only used a single subject because we needed in vivo data from a subject with an instrumented knee implant, and that included data for walking trials using specific gait modifications of interest. While previous research reported the percentage error for an uninformed model, an alignment-informed model, a contact-point-informed model, and a fully informed model, our study used only the default contact locations.[56] This was done because we did not have the necessary imaging data that would have allowed us to adjust that model parameter, which may have contributed to increased error in the results. Additionally, in the other studies, neither the healthy controls nor the RCT study included subject-specific contact locations in the knee, due to lack of necessary imaging data, which may have also increased the error in our simulation estimate outputs. Some researchers also augment their simulation studies with subject-specific MVIC values or EMG data, which could have been used to further customize the model to the specific study participants and may have further improved simulation results.

One potential limitation of the Lerner knee model is that it does not have a degree of freedom in the frontal plane. The goal of many interventions is to shift forces laterally to offload the medial compartment. An intact knee joint can rotate a few degrees in the frontal plane and therefore it is possible that the model is not capturing small rotations from medial to lateral that may be occurring in study participants. Since the knee joint in the model does not possess a degree of freedom in this plane, it may be that the force estimates are higher than what is being experienced in vivo. However, previous research has indicated a knee joint model with a single degree of freedom can provide robust estimates of JRF, so this may not be of great concern.[318] The results from Chapter 3 that compared in vivo joint reaction force with data from the Lerner knee model, in a participant with an instrumented knee implant, suggested the model is capable of estimating knee joint reaction force in the medial compartment for both MKT and LTL with less than 10% error in the first peak. Recent research has identified the single-segment foot in common OpenSim models, such as the gait2392 and Lerner models, as another source of measurement error.[325] The study found that including the toes, via a 2-segment foot model, improved estimates of knee flexion angles, knee joint torques, and decreased the vGRF peak during stance.

Limitations for our second and third study are similar to the first in that we did not have imaging data to maximize the customization of the model nor did we have MVIC or EMG data to help tailor the model to the healthy controls. For the RCT study we were not able to collect data on the full 51 participant sample size due to the COVID-19 pandemic so the statistical power was not sufficient and may have contributed to the lack of statistical significance in the analysis.

Recommendations for Future Research

There are several directions for future research in both the clinical and modeling aspects of the dissertation. First, completing the randomized controlled trial with the full sample size is an important step to gather information about the effect of personalized gait interventions on simulated JRF in participants. This information could provide further evidence about whether the LTL intervention decreases the JRF in individuals or if it actually can lead to increased JRF in the medial compartment of the knee in all or only certain participants.

A second area of interest involves the question of whether or not larger KAM or JRF is necessarily bad. It may be that there is a minimum and maximum threshold of forces that provide for healthy development and maintenance of cartilage in the knee, and that when these forces and/or moments fall below or above this range problems arise. Research that has looked at runners has found that they are not at greater risk for knee OA even though they often experience much higher forces in their knees than nonrunners.[81,326] An early study on knee OA found only the subject with the highest value of KAM progressed to OA,[75] while a study in ACL patients found that unloading of the knee after surgery could increase their risk of developing OA.[106]

For the modeling and simulation aspects of the dissertation, further work to validate and understand the causes of errors in the model can help improve simulation outputs, especially in the second peak, during the propulsion phase of gait, and in the lateral side of the knee. Part of this research could include gaining a better understanding of the impact of weighted static optimization on the simulation output, especially during the propulsion phase of stance. Improving on the strategies to identify appropriate weights for the weighted static optimization could potentially reduce the error in the second peak and improve model output across the entire stance phase of gait.

It is also important to further investigate how individualizing the models to more closely match study participants may improve simulation results. For example, Rajagopal et al.[182] also developed a new OpenSim full body model that has improved muscle properties that were derived from 21 cadaver lower limbs and MRI images of 24 young adult subjects. The Stanford Research group which manages the OpenSim software has been working to create a new model that is a combination of the Lerner model and the Rajagopal model which could potentially offer improved ability to tailor a model's muscle properties to individuals. Incorporating either or both MVIC and EMG data into the modeling process could be investigated to determine if that offers improved results, especially with the updated Rajagopal/Lerner combined model. Lastly, recent research has also investigated if adding in dynamic toe elements to OpenSim gait models can lead to improved estimation of forces in the joints.[325]

Chapter 7. Conclusion

This dissertation validated the Lerner knee model for use in studies that use modified walking gait, such as the MKT and LTL. It also demonstrated implementing the simulation approach in a clinical setting that assessed the impact of several modified gait strategies and their estimated effects on the vertical JRF in the knee. I further demonstrated the use of the Lerner model combined with weighted static optimization in RCT which aimed to reduce the forces experienced in the knee in participants diagnosed with medial compartment knee OA. While we did not find data to support the hypothesized reduction in JRF as a result of the LTL gait modification, we did provide evidence to support the possibility that the intervention may actually lead to increased, as opposed to decreased, forces in some participants who use the intervention. Future work should further improve on the model validation and collect more data to determine whether the increased JRF from LTL is in fact a valid finding; is due to individual variation (i.e. differences in knee alignment, joint laxity, variations in strength of knee flexors/extensors) in response to gait modifications, like LTL; or if it was a spurious result.

Appendix A. IRB Approval Letter for Study 2

IRB Approval Letter: Osteoarthritis in the ACL reconstructed knee: A Multifactorial Approach

GEORGE MASON UNIVERSITY

Office of Research Development, Integrity, andAssurance

Research Hall, 4400 University Drive, MS 6D5, Fairfax, Virginia 22030 Phone: 703-993-5445; Fax 703-993-9590

DATE: August 1, 2019

TO: Nelson Cortes
FROM: George Mason University IRB

Project Title: [477645-9] Osteoarthritis in the ACL reconstructed knee: A multifactorialapproach
Reference: 8095
SUBMISSION TYPE: Continuing Review/Progress Report

ACTION:
APP
ROVED APPROVAL DATE:
Aug
ust 1, 2019
EXPIRATION DATE: July 31, 2020
REVIEW TYPE: Expedited Review

REVIEW TYPE: Expedited review categories 4, 7

Thank you for your submission of Continuing Review/Progress Report materials for this project. The George Mason University IRB has APPROVED your submission. This submission has received Expedited Review based on applicable federal regulations.

Please remember that all research must be conducted as described in the submitted materials.

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Please remember that informed consent is a process beginning with a description of the project and insurance of participant understanding followed by a signed consent form unless the IRB has waived the requirement for a signature on the consent form or has waived the requirement for a consent process.
Informed consent must continue throughout the project via a dialogue between the researcher and research participant. Federal regulations require that each participant receives a copy of the consentdocument.

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

All UNANTICIPATED PROBLEMS involving risks to subjects or others and SERIOUS and UNEXPECTEDadverse events must be reported promptly to the IRB office. Please use the appropriate reporting forms for this procedure. All FDA and sponsor reporting requirements should also be followed (if applicable).

All NON-COMPLIANCE issues or COMPLAINTS regarding this project must be reported promptly to the IRB.

The anniversary date of this study is July 31, 2020. This project requires continuing review by this committee on an annual basis. You may not collect data beyond this date without prior IRB approval.

A continuing review form must be completed and submitted to the IRB at least 30 days prior to the anniversary date or upon completion of this project. Prior to the anniversary date, IRBNet will send you a reminder regarding continuing review procedures.

Please note that all research records must be retained for a minimum of five years, or as described inyour submission, after the completion of the project.

Please note that department or other approvals may be required to conduct your research in addition toIRB approval.

If you have any questions, please contact Bess Dieffenbach at 703-993-5593 or edieffen@gmu.edu. Please include your project title and reference number in all correspondence with this committee.

GMU IRB Standard Operating Procedures can be found here: https://rdia.gmu.edu/topics-of-interest/human-or-animal-subjects/human-subjects/human-subjects-sops/

This letter has been electronically signed in accordance with all applicable regulations, and a copy is retained within George Mason University IRB's records.

Appendix B. Consent Form for Study 2

Consent Form

Osteoarthritis in the ACL reconstructed: A multifactorial approach

INFORMED CONSENT FORM

RESEARCH PROCEDURES

This research is being done to evaluate the mechanisms for osteoarthritis development in individuals that have a history of anterior cruciate ligament (ACL) reconstruction. If you agree to participate, you will be asked to perform a number of tests to determine your muscle strength, muscle characteristics, muscle activity, and movement patterns while jumping, walking, and running. We will measure your height, and weight, and you will fill a questionnaire with questions pertaining to your injury history, and quality of life.

- We will then measure your muscle size using ultrasound imaging. For this you will sit on a table, relax your legs, and we will place a cold water base gel on your legs to then place the ultrasound probe. We will be able to visualize your muscles.
- Your muscle strength will be measure with a dynamometer. We will ask you to sit on a chair and resist a static object. At the same time we will be measure the amount of force you are applying to resist the object.

After those measures are obtained, we will ask you to jump, walk and run at different times for us to assess your movement patterns:

- We will then collect your muscle activity using surface electrodes. These non-invasive surface electrodes will attached over your thigh and calf muscles and over the flat part of the shinbone. We will prepare the skin above these areas by it shaving and wiping with alcohol swabs. The surface electrodes will be connected to wires that lead to a computer that measures muscle activity. These methods are commonly used for collecting muscle activity data.
- You will have a 10-minute warm-up period that will consist of running and stretching. Thereafter, forty (40) reflective markers will be placed on specific areas on your body. A measurement tape will be used to measure your leg length. The measurement will be taken from your hip to your ankle.
- You will then have time to familiarize yourself with the jumping, walking and running tasks.
- After you familiarize yourself with the tasks, we will ask you to jump from a box, placed at different heights (26, 30, and 40 cm). After, we will ask you to walk across a path and/or on a treadmill at your preferred speed. Lastly, we will ask you to run on that same path (or treadmill) at your preferred speed. While you perform these tasks we will be measuring your muscle activity, muscle contraction velocities, and movement patterns.

All tasks will be videotaped; this will allow us to evaluate differences between jumping, walking, and running. If you say YES, then your participation will last for approximately 90 minutes at the SMART Lab, Room 215, in the Freedom Aquatic Center.

George Mason University
Office of Research Integrity & Assurance

IRB: For Official Use Only

Project Number: 477645-6
Date Approved: 1/5/17
Approval Expiration Date: 1/4/18

Page 1 of 3

Approximately 20 females and 20 males with knee osteoarthritis will be participating in this study, as well as 40 healthy individuals.

RISKS

There are no known risks of using ultrasound imaging, EMG, and strength devices that will be used during this protocol. You may feel increased pain on the knee with osteoarthritis when performing the dynamic tasks, and minimally increase cartilage degeneration in that same knee. You may experience increased instability in the knee with osteoarthritis. The foreseeable risks or discomforts include ankle sprain, knee injury, muscle pain, and muscle soreness. The researcher has tried to reduce these risks by providing clear directions on how to jump from a box, and walk and run. You could also experience muscle injury, inappropriate changes in blood pressure or heart rhythm, a heart attack, stroke or death during the exercise tests. The risk of these events is very low in individuals who are physically active and apparently healthy. The risk is likely no greater than what you experience during walking, walk downstairs or step down on a sidewalk. There is also a risk of too much exposure to x-rays, since you will need to have a radiograph done prior to participate if you are in the injured group. If you experience knee pain while performing our protocol, we request that you inform any of the researchers immediately. Finally, as with any research, there is some possibility that you may be subject to risks that have not yet been identified. In case of injury, the investigators or George Mason University are not liable for an injury and cannot cover any expenses related to treatment of an injury. In case of that rare event, you should seek medical help.

BENEFITS

There are no benefits to you as a participant other than to further research in lower extremity injury prevention.

CONFIDENTIALITY

All data in this study will be confidential. The researchers will take reasonable steps to ensure confidentiality is upheld. The researchers will store all questionnaires, videotapes, and laboratory findings in a locked file cabinet prior to processing. The results of this study may be used in reports, presentations and publications, but the researcher will not identify you.

PARTICIPATION

Your participation is voluntary, and you may withdraw from the study at any time and for any reason. The age range for participation is 21 to 46 years old. If you decide not to participate or if you withdraw from the study, there is no penalty or loss of benefits to which you are otherwise entitled. There are no costs to you or any other party.

CONTACT

This research is being conducted by Dr. Nelson Cortes, and Dr. Siddhartha Sikdar from the SMART Laboratory at George Mason University. They may be reached at 703-993-9257 for questions or to report a research-related problem. You may contact the George Mason University

Office of Research Subject Protections at 703-993-4121 if you have questions or comments regarding your rights as a participant in the research.

This research has been reviewed according to George Mason University procedures governing your participation in this research.

CONSENT

I have read this form and agree to participate in this study.

_______ I agree to audio (video) taping.

_______ I do not agree to audio (video) taping

____

Name

____

Date of Signature

Appendix C. Final Muscle Weights Used for Weighted Static Optimization for Study 2

		Muscle Weights					
Participant	Gait	MGAS	LGAS	VL	VI	VM	RF
1 (S001)	Normal (Baseline)	2	1	1	1	1	1
1 (S001)	Toe-In	2	1	4	2	2	2
1 (S001)	Medial Knee Thrust	2	1	1	1	1	1
1 (S001)	Lateral Trunk Lean	2	1	1	1	1	1
2 (S002)	Normal (Baseline)	5	2	1	1	1	1
2 (S002)	Toe-In	5	2	1	1	1	1
2 (S002)	Medial Knee Thrust	5	2	1	1	1	1
2 (S002)	Lateral Trunk Lean	5	2	1	1	1	1
3 (S007)	Normal (Baseline)	5	2	1	1	1	1
3 (S007)	Toe-In	5	2	1	1	1	1
3 (S007)	Medial Knee Thrust	5	2	3	2	2	2
3 (S007)	Lateral Trunk Lean	5	2	1	1	1	1
4 (S008)	Normal (Baseline)	16	6	1	1	1	1
4 (S008)	Toe-In	16	6	1	1	1	1
4 (S008)	Medial Knee Thrust	16	6	1	1	1	1
4 (S008)	Lateral Trunk Lean	16	6	1	1	1	1
5 (S009)	Normal (Baseline)	20	3	3	2	2	1
5 (S009)	Toe-In	20	3	3	2	2	1
5 (S009)	Medial Knee Thrust	20	3	3	2	2	1
5 (S009)	Lateral Trunk Lean	20	3	3	2	2	2
6 (S010)	Normal (Baseline)	18	6	3	2	2	8
6 (S010)	Toe-In	18	6	3	2	2	8
6 (S010)	Medial Knee Thrust	18	6	3	2	2	8
6 (S010)	Lateral Trunk Lean	18	6	3	2	2	8
7 (S011)	Normal (Baseline)	5	2	1	1	1	1
7 (S011)	Toe-In	5	2	1	1	1	1
7 (S011)	Medial Knee Thrust	5	2	1	1	1	1
7 (S011)	Lateral Trunk Lean	5	2	1	1	1	1
8 (S012)	Normal (Baseline)	15	3	1	1	1	1
8 (S012)	Toe-In	15	3	1	1	1	1
8 (S012)	Medial Knee Thrust	15	3	3	2	2	2
8 (S012)	Lateral Trunk Lean	15	3	1	1	1	1
9 (S013)	Normal (Baseline)	5	2	1	1	1	1
9 (S013)	Toe-In	5	2	1	1	1	1
9 (S013)	Medial Knee Thrust	5	2	1	1	1	1
9 (S013)	Lateral Trunk Lean	5	2	1	1	1	1

		Muscle Weights					
Participant	**Gait**	**MGAS**	**LGAS**	**VL**	**VI**	**VM**	**RF**
10 (S014)	Normal (Baseline)	17	2	1	1	1	10
10 (S014)	Toe-In	17	2	1	1	1	10
10 (S014)	Medial Knee Thrust	17	2	1	1	1	10
10 (S014)	Lateral Trunk Lean	17	2	1	1	1	10
11 (S015)	Normal (Baseline)	17	2	3	2	2	4
11 (S015)	Toe-In	17	2	3	2	2	4
11 (S015)	Medial Knee Thrust	17	2	3	2	2	4
11 (S015)	Lateral Trunk Lean	17	2	3	2	2	4
12 (S016)	Normal (Baseline)	10	2	3	2	2	8
12 (S016)	Toe-In	10	2	3	2	2	8
12 (S016)	Medial Knee Thrust	10	2	3	2	2	8
12 (S016)	Lateral Trunk Lean	10	2	3	2	2	8
13 (S017)	Normal (Baseline)	2	1	1	1	1	5
13 (S017)	Toe-In	2	1	1	1	1	1
13 (S017)	Medial Knee Thrust	2	1	1	1	1	1
13 (S017)	Lateral Trunk Lean	2	1	1	1	1	1
14 (S018)	Normal (Baseline)	2	1	1	1	1	1
14 (S018)	Toe-In	2	1	1	1	1	1
14 (S018)	Medial Knee Thrust	2	1	1	1	1	1
14 (S018)	Lateral Trunk Lean	2	1	1	1	1	1
15 (S020)	Normal (Baseline)	5	1	1	1	1	1
15 (S020)	Toe-In	5	1	1	1	1	1
15 (S020)	Medial Knee Thrust	5	1	1	1	1	1
15 (S020)	Lateral Trunk Lean	5	1	1	1	1	1
16 (S023)	Normal (Baseline)	3	1	1	1	1	1
16 (S023)	Toe-In	3	1	1	1	1	1
16 (S023)	Medial Knee Thrust	3	2	3	2	2	1
16 (S023)	Lateral Trunk Lean	3	1	1	1	1	1
17 (S024)	Normal (Baseline)	3	2	1	1	1	1
17 (S024)	Toe-In	3	2	1	1	1	1
17 (S024)	Medial Knee Thrust	3	2	1	1	1	1
17 (S024)	Lateral Trunk Lean	3	2	1	1	1	1
18 (S025)	Normal (Baseline)	3	1	1	1	1	1
18 (S025)	Toe-In	3	1	1	1	1	1
18 (S025)	Medial Knee Thrust	3	1	3	2	2	2
18 (S025)	Lateral Trunk Lean	3	1	1	1	1	1
19 (S026)	Normal (Baseline)	8	4	1	1	1	1
19 (S026)	Toe-In	8	4	1	1	1	1
19 (S026)	Medial Knee Thrust	8	4	1	1	1	1
19 (S026)	Lateral Trunk Lean	8	4	1	1	1	1
20 (S027)	Normal (Baseline)	8	3	1	1	1	1
20 (S027)	Toe-In	8	3	1	1	1	1
20 (S027)	Medial Knee Thrust	8	3	1	1	1	1
20 (S027)	Lateral Trunk Lean	8	3	1	1	1	1

Abbreviations: MGAS, medial gastrocnemius; LGAS, lateral gastrocnemius; VL, vastus lateralis; VI, vastus intermedius; VM, vastus medialis; RF, rectus femoris; S, subject.

Appendix D. IRB Approval Letter for Study 3

IRB Approval Letter: Comparison of the Effects of Gait Modification Strategies on Knee Adduction Moment in Patients with Medial Knee Osteoarthritis:Randomized Controlled Trial

GEORGE MASON UNIVERSITY

Office of Research Integrity and Assurance

Research Hall, 4400 University Drive, MS 6D5, Fairfax, Virginia 22030 Phone: 703-993-5445; Fax: 703-993-9590

DATE:	June 22, 2020
TO:	Nelson Cortes
FROM:	George Mason University IRB
Project Title:	[1315238-8] Comparison of the Effects of Gait Modification Strategies on Knee Adduction Moment in Patients with Medial Knee Osteoarthritis:Randomized Controlled Trial
SUBMISSION TYPE:	Continuing Review/Progress Report
ACTION:	APPROVED
APPROVAL DATE:	June 22, 2020
EXPIRATION DATE:	June 21, 2021
REVIEW TYPE:	Expedited Review
REVIEW TYPE:	Expedited review categories #4 & 7

Thank you for your submission of Continuing Review/Progress Report materials for this project. The George Mason University IRB has APPROVED your submission. This submission has received Expedited Review based on applicable federal regulations.

You are required to follow the George Mason University Covid-19 research continuity of operations guidance. You may not begin or resume any face-to-face interactions with human subjects until (i) Mason has generally authorized the types of activities you will conduct, or (ii) you have received advance written authorization to do so from Mason's Research Review Committee. In all cases, all safeguards for face-to-face contact that are required by Mason's COVID policies and procedures must be followed.

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Please remember that all research must be conducted as described in the submitted materials.

Please remember that informed consent is a process beginning with a description of the project and insurance of participant understanding followed by a signed consent form unless the IRB has waived the requirement for a signature on the consent form or has waived the requirement for a consent process.
Informed consent must continue throughout the project via a dialogue between the researcher and research participant. Federal regulations require that each participant receives a copy of the consentdocument.

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

All UNANTICIPATED PROBLEMS involving risks to subjects or others and SERIOUS and UNEXPECTEDadverse events must be reported promptly to the IRB office. Please use the appropriate reporting forms for this procedure. All FDA and sponsor reporting requirements should also be followed (if applicable).

All NON-COMPLIANCE issues or COMPLAINTS regarding this project must be reported promptly to the IRB.

The anniversary date of this study is June 21, 2021. This project requires continuing review by this committee on an annual basis. You may not collect data beyond this date without prior IRB approval.
A continuing review form must be completed and submitted to the IRB at least 30 days prior to the anniversary date or upon completion of this project. Prior to the anniversary date, IRBNet will send you a reminder regarding continuing review procedures.

Please note that all research records must be retained for a minimum of five years, or as described inyour submission, after the completion of the project.

Please note that department or other approvals may be required to conduct your research in addition toIRB approval.

If you have any questions, please contact Katie Brooks at (703) 993-4121 or kbrook14@gmu.edu. Pleaseinclude your project title and reference number in all correspondence with this committee.

GMU IRB Standard Operating Procedures can be found here: https://rdia.gmu.edu/topics-of-interest/human-or-animal-subjects/human-subjects/human-subjects-sops/

This letter has been electronically signed in accordance with all applicable regulations, and a copy is retained within George Mason University IRB's records.

Appendix E. Consent Form for Study 3

COMPARISON OF THE EFFECTS OF GAIT MODIFICATION STRATEGIES ON KNEE ADDUCTION MOMENT IN PATIENTS WITH MEDIAL KNEE OSTEOARTHRITIS: RANDOMIZED CONTROLLED TRIAL

INFORMED CONSENT FORM

RESEARCH PROCEDURES

This study involves experimental research being done to evaluate and identify the most effective gait modification strategy for reducing estimated knee joint loads in patients with medial compartment osteoarthritis (OA) of the tibiofemoral joint (TFJ). An additional goal of this research is to measure the retention of kinematic changes that have occurred as a result of gait modification over time. If you agree to participate you will be asked to visit the laboratory on a periodic schedule, which includes 2 baseline measurement sessions, 8 weeks of gait retraining, 2 testing sessions during the 10 weeks of the intervention, and 4 retention tests (1, 3, 6 months, and 1 year) for a total of 16 sessions. The study procedures are outlines below:

Week 1:

- Your mass and height will be recorded and pain and function will be assessed by completing the Western Ontario and McCaster Universities Arthritis (WOMAC), a numeric scale rating (NRS) of pain, and the Timed Up & Go (TUG) test. You will be equipped with 4 surface electromyograms (sEMG) placed on the thigh of your affected limb after which 53 retroreflective markers will be attached to your trunk and lower extremity. An ultraviolet marker pen will be used to mark the location of the retroreflective markers to aid in the repeatability of accurate marker placement.

- After a static and dynamic calibration trial, you will perform 5 normal walking trials along a 6m walkway followed by 12 minutes of walking on a treadmill.
- You will then perform either 6 trials of altered foot progression gait or 3 trials of trunk lean gait using real-time haptic feedback in the form of vibratory feedback from sensors attached to your leg or trunk. This session will last approximately 2 hours.
- You will visit the lab again in the same week to complete an additional 5 normal walking trials and 6 altered foot progression gait (if trunk lean gait was performed in the first visit) or 3 trunk lean gait (if altered foot progression gait was performed in the first visit) trials using the same methods from visit 1. This session will last approximately 2 hours.
- Following the second baseline session, you will be randomly assigned to either the control or intervention group; there is a 50/50 chance (like the flipping of a coin) that you would be assigned to either the control group or treatment group. If you are assigned to the intervention group you will be further split into either the altered foot progression gait group or trunk lean group, based on which modification most reduced knee load at baseline.

Weeks 2-11:

- Over the following 10 weeks, you will perform 8 gait retraining sessions (once per week) with the exception of week 6 and 11 where you will perform testing sessions.
- During retraining sessions, you will walk on a treadmill for 20 minutes performing either your assigned modification using haptic feedback if you are in the intervention group (using the same method during baseline) or using normal walking if you are in the control group. These sessions will last approximately 1 hour.

- Over the course of the intervention, haptic feedback will be reduced week by week to encourage learning and reduce reliance on the feedback.
- Between gait retraining sessions, you will be asked to practice your acquired gait modification strategy outside of the laboratory for a minimum of 10 minutes per day and record your practice in a weekly activity log.
- During weeks 6 and 11, you will be tested in a similar manner to the baseline sessions. You will be asked to perform 5 normal walking trials followed by 5 trials of either your assigned gait modification or normal walking (depending on your group) ending with 12 minutes of walking on the treadmill. Unlike baseline, you will not receive any haptic feedback during these testing sessions. Testing sessions will last approximately 2 hours.

Follow-up testing:

- You will be asked to return for follow-up testing at one, three, and six months as well as one-year post-intervention to measure effects of the intervention over time.
- This testing will take the same form as the testing during week 6 and 11 and will last approximately two hours.

If you agree, then you will participate in 12 sessions over the course of 11 weeks with an additional 4 follow-up sessions occurring at 1, 3, and 6 months and 1 year after the end of the study for a total of 16 sessions. Eight sessions will be used for testing (including 4 following-up sessions) and last approximately 2 hours. The remaining 8 sessions will be used for training and will last approximately 1 hour. All testing will occur at George Mason University's Science & Technology Campus, Manassas, VA 20110.

RISKS

You may feel increased pain on the knee with osteoarthritis when performing the dynamic tasks. You may also experience increased instability in the knee with osteoarthritis. The foreseeable risks or discomforts include ankle sprain, and knee injury. The researcher has tried to reduce these risks by providing clear directions on how to operate a treadmill. You could also experience muscle injury, inappropriate changes in blood pressure or heart rhythm, a heart attack, stroke or death during the exercise tests. The risk of these events is very low in individuals who are physically active and apparently healthy. The risk is likely no greater than what you experience during walking, walk downstairs or step down on a sidewalk. If you experience knee pain while performing our protocol, we request that you inform any of the researchers immediately. Finally, as with any research, there is some possibility that you may be subject to risks that have not yet been identified. In case of injury during testing procedures, the GMU research team may provide basic first aid. If appropriate, the staff will call the emergency response team at 911. Neither George Mason University nor the investigators have funds available for payment of medical treatment for injuries that you may sustain while participating in this research. Should you need medical care, you or your insurance carrier will be responsible for payment of the expenses required for medical treatment.

BENEFITS

There are no direct benefits to you other than furthering research in gait modification for medial tibiofemoral joint osteoarthritis.

CONFIDENTIALITY

All data in this study will be confidential. You will be assigned a unique participant ID which will be used for all data collection and analysis. The researchers will take reasonable steps to ensure confidentiality is upheld. While it is understood that no computer transmission can be perfectly secure, reasonable efforts will be made to protect the confidentiality of your transmission. The researchers will store all questionnaires, and laboratory findings in a locked file cabinet prior to processing and all digital data (including videotapes) will be stored on a password-protected computer in the SMART lab. The results of this study may be used in reports, presentations and publications, but the researcher will not identify you. Identifiers will be removed from the data (video recorders will be below the waist only) and the de-identified data could be used for future research without additional consent from participants. All data will be deleted 5 years from the end of your participation in the study.

PARTICIPATION

Your participation is voluntary, and you may withdraw from the study at any time and for any reason. The age range for participation is 18 to 80 years old. If you decide not to participate or if you withdraw from the study, there is no penalty or loss of benefits to which you are otherwise entitled. There are no costs to you or any other party. Financial compensation will be available in the form of $50 and $100 gift cards which will be provided at the completion of the week 6 testing session and the 1-month follow-up session, for a total of $150. At the completion of the 10-week intervention study you will also be eligible for compensation in the form of one assessment of your choice at George Mason University's SMART Lab on the Science & Technology campus in Manassas, VA. These assessments include V02 max, resting metabolic rate, and body composition.

TAX RESPONSIBILITIES

If required by the federal law, the compensation for research/survey participation will be reported to the Internal Revenue Service (IRS) either on 1099-MISC, or on 1042-S tax form. It is the responsibility of the research participant to inform the investigator of the nonresident tax status, so that the compensation for the research/survey participation would be reported on the appropriate IRS form.

CONTACT

This research is being conducted by Dr. Nelson Cortes (Division of Health and Human Performance) at George Mason University. He may be reached at 703-993-9257 for questions or to report a research-related problem. You may contact the George Mason University Institutional Review Board office at 703-993-4121 if you have questions or comments regarding your rights as a participant in the research.

This research has been reviewed according to George Mason University procedures governing your participation in this research.

CONSENT

I have read this form and agree to participate in this study.

_______ I agree to audio (video) taping.

_______ I do not agree to audio (video) taping

Name________________________

Date of Signature_______________

Appendix F. Final Muscle Weights Used for Weighted Static Optimization for Study 3

Participant	Gait Type	Muscle Weights MGAS	LGAS	VL	VI	VM	RF	BFLH	BFSH
1 (S001)	Normal (Baseline)	8	1	1	1	1	50	1	1
(S001)	Lateral Trunk Lean	8	1	1	1	1	50	1	1
2 (S002)	Normal (Baseline)	4	2	1	1	1	1	2	1
3 (S004)	Normal (Baseline)	2	1	1	1	1	1	1	1
4 (S005)	Normal (Baseline)	2	1	1	1	1	20	1	1
5 (S007)	Normal (Baseline)	2	1	1	1	1	10	1	1
6 (S008)	Normal (Baseline)	4	1	1	1	1	10	1	2
7 (S009)	Normal (Baseline)	50	20	1	1	1	1	1	10
(S009)	Lateral Trunk Lean	50	20	1	1	1	1	1	10
8 (S011)	Normal (Baseline)	2	1	3	2	2	2	1	1
(S011)	Lateral Trunk Lean	2	1	3	2	2	2	1	1

Abbreviations: MGAS, medial gastrocnemius; LGAS, lateral gastrocnemius; VL, vastus lateralis; VI, vastus intermedius; VM, vastus medialis; RF, rectus femoris; BFLH, biceps femoris long head; BFSH, biceps femoris short head; S, subject.

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Biography

Matthew Prebble graduated from J.E.B High School, Falls Church, Virginia, in 1992. He received a Bachelor of Science in Mathematical Sciences from Virginia Commonwealth University in 1997. Matt was a 4-year letter winner in track and field at VCU, was all-conference in the high jump and triple jump, and a member of 4 conference championship teams. He went on to receive a Master of Science Degree in Operations Research from George Mason University in 2004, a Master of Science in Exercise, Fitness, and Health Promotion from George Mason University in 2007, a Master of Engineering in Mechanical and Aerospace Engineering from the University of Virginia in 2010, a Master of Science in Industrial and Systems Engineering from the University of Florida in 2013, and a Master of Public Health from the University of Florida in 2016.