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Mitigating Risk Factors for Disease Progression in Patients with Varus Gonarthrosis

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A thesis submitted in partial fulfillment of the requirements for the degree in Doctor of Philosophy

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(Thesis format: Integrated Article)

by

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Abstract

Knee osteoarthritis (OA) is a leading cause of disability worldwide. Its growing burden is related to an aging population, obesity and physical inactivity. The progression of knee OA involves both biomechanical and systemic mechanisms. Known risk factors that might be altered through interventions include lower limb alignment, the distribution of loads across the knee during walking, body composition and muscular strength. The overall purpose of this thesis was to evaluate the effects of combined rehabilitative and surgical interventions that target different risk factors for disease progression in patients with medial compartment knee OA and varus mal-alignment (varus gonarthrosis). The thesis included three studies. Study 1 demonstrated that patients with substantial bilateral varus alignment who underwent unilateral medial opening wedge high tibial osteotomy (HTO) experienced large decreases in the external knee adduction moment during walking two years after surgery. However, they also experienced increased knee adduction moments in the mal-aligned, non-operated limb, explained most by increases in both body mass and gait speed. Study 2 demonstrated that body composition measurements in patients with knee OA using air displacement plethsmography (BodPod®) had excellent test-re-test reliability. It also provided estimates of measurement error and minimal detectable change to be used when evaluating body composition changes in individual patients with knee OA. Study 3 was a proof of principle study that demonstrated multi-modal physiotherapy (operationally defined as functional range of motion, strengthening and neuromuscular control exercises plus patient education with a focus on nutritional counseling) combined with medial opening wedge HTO decreased fat mass, increased muscular strength, decreased knee adduction moments and varus mal-

alignment in patients with varus gonarthrosis. Rehabilitative intervention was required to improve body composition and strength, whereas surgical intervention was required to improve alignment and knee adduction moments. Overall, the results of these studies suggest that a combination of treatment approaches that target different risk factors for knee OA are necessary. Multi-modal rehabilitative and surgical intervention for patients with varus gonarthrosis is recommended.

Keywords

Keywords: Knee Osteoarthritis, Varus Mal-alignment, High Tibial Osteotomy, Gait Biomechanics, body composition, Physiotherapy, Strengthening

Co-Authorship

Chapter 1 was written solely by Angelo Boulougouris. Chapter 2 was written by Angelo Boulougouris and was co-authored by Trevor Birmingham, Rebecca Moyer and Kristyn Leitch, all from the Wolf Orthopaedic Biomechanics Laboratory, Western University. Chapter 3 was written by Angelo Boulougouris and was co-authored by Trevor Birmingham, T. Dylan Olver and Peter Lemon, all from the Faculty of Health Sciences, Western University. Chapter 4 was written by Angelo Boulougouris and was co-authored by Trevor Birmingham and T. Dylan Olver. Chapter 5 was written solely by Angelo Boulougouris.

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List of Abbreviations

ACL	Anterior Cruciate Ligament
ADL	Activities of Daily Living
ADP	Air Displacement Plethysmography
AP	Anteroposterior
BMI	Body Mass Index
BW	Body Weight
CI	Confidence Interval
cm	Centimeters
GRF	Ground Reaction Force
Ht	Height
ICC	Intraclass correlation coefficient
Kg	Kilogram
KL	Kellgren and Lawernce (grade of OA severity)
KOOS	Knee Injury and Osteoarthritis Outcome Score
L	Liters
MAA	Mechanical Axis Angle
MCID	Minimal Clinically Important Difference
MDC	Minimum Detectable Change
MPT	Multi-modal Physiotherapy
MRI	Magnetic Resonance Imaging
m/s	Meters per second
N	Newtons
Nm	Newton-meters
Nms	Newton-meters-second
OA	Osteoarthritis
OR	Odds Ratio
RCT	Randomized Control Trial
ROM	Range of Motioin
SD	Standard Deviation
SEM	Standard Error of Measurement
WOMAC	The Western Ontario and McMaster Universities Arthritis Index
3D	Three dimensional
°	Degrees
%	Percent
%BW*Ht	Percentage of the product of body weight and height

Chapter 1

1 Introduction and Background

1.1 Osteoarthritis

Osteoarthritis (OA) is a common joint disorder that affects almost 10% of Canadian adults (Health Canada).[1] Cardinal signs and symptoms include pain (frequently characterized as activity-related and often insidious in onset), reduced function, stiffness (typically of short duration after a period of inactivity), joint instability (described as buckling or giving way), decreased range of motion, bony deformity, swelling, and crepitus.[2] The OA disease process includes the softening and loss of articular cartilage, sclerosis of subchondral bone, osteophyte formation along the joint margins and subchondral cysts.[3] Eventually, all the tissues of the joint are involved including the synovium, periartiulcar muscles, nerves, ligaments and, in the case of the tibio-femoral joint, the meniscus.[3]

Osteoarthritis is typically initiated by some form of mechanical insult related to either abnormal anatomy (such as congenital deformities), excessive loading (that might occur from an acute injury or in chronic conditions such as mal-alignment and obesity), or a combination of the two.[4] Joints with OA have shown markers of inflammation, such as synovitis or pro-inflammatory cytokines that are present in the cartilage matrix. Joint trauma, whether caused by an acute injury or chronic abnormal loading, may work independently to cause joint damage, and the resulting inflammatory process may accelerate this degenerative process.[4] Ultimately, the OA process is a failed attempt to

repair the damage caused by abnormal joint loading due to the underlying mechanical stressors.[3,4]

The knee joint is the most common weight-bearing joint affected by OA, with over 200 million people afflicted worldwide.[5-7] Commonly reported risk factors include advanced age, joint injury, obesity, muscle weakness, mal-alignment and female gender (See Fig.1.1).

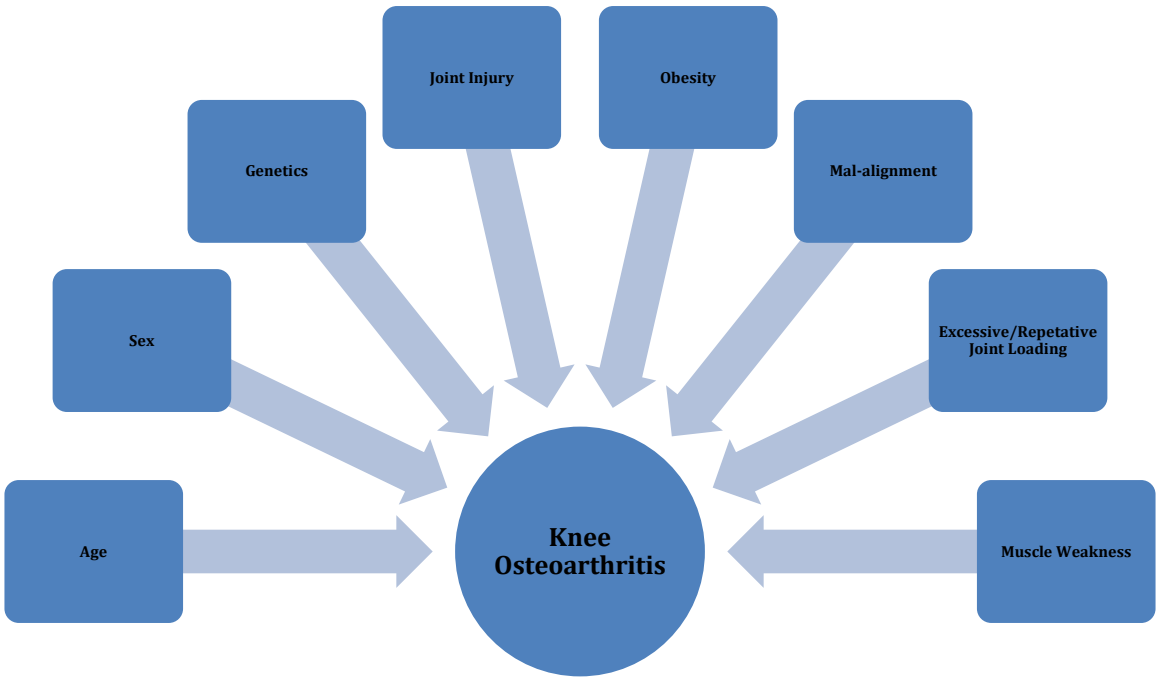

Figure 1.1 Diagram demonstrating the interplay of multiple risk factors and their possible contribution to the knee osteoarthritis disease process

The development of knee OA is likely caused by the interplay of several of these factors. However, the focus of interventions has been on those that are modifiable, such as muscle weakness, obesity and mal-alignment. Several clinical practice guidelines[8-10] have been published that provide clinicians with evidence-based criteria for treating patients with knee OA. These guidelines generally propose a multi-modal approach to treatment and

suggest interventions that improve symptoms and attempt to mitigate risk factors for disease progression such as muscle weakness and obesity. Importantly, treatment benefits may depend on individual patient characteristics. In particular, patients who are in varus alignment and have medial compartment knee OA (i.e. varus gonarthrosis) appear to respond differently to traditional rehabilitative interventions.[11] Varus alignment (measured on radiographs; see Fig.1.2) is a well-established, independent risk factor for the onset and progression of medial compartment knee OA.[12-15] Therefore, without changes in alignment, interventions targeting other risk factors may not be as effective for these patients. The external knee adduction moment calculated through 3-D gait analysis is related to mal-alignment and is an indicator of the distribution of load across the knee during walking. It is also an established, independent a risk factor for the onset of future knee pain[16] and knee OA progression[17,18]. This next section will focus on known modifiable biomechanical risk factors for knee OA progression, including; obesity, muscle weakness, lower limb alignment, and a high knee adduction moment.

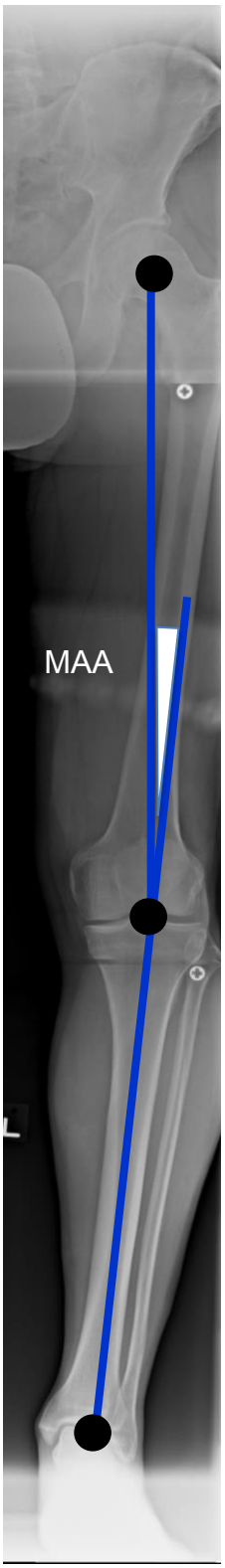

Figure 1.2: The Mechanical Axis Angle (MAA) obtained from full-limb standing anteroposterior radiographs of a patient in varus alignment.

1.2 Risk Factors for Knee Osteoarthritis

1.2.1 Obesity

Obesity has a strongly established link to the incidence and progression of knee OA.[19-23] In fact, individuals who are obese (BMI>30) are four times more likely to develop knee OA than those who are considered to be of normal weight (BMI≤25).[24] Coggon et al[25] estimated the risk for incident knee OA was almost seven times greater in patients that were obese compared to a control group of normal weight individuals. Furthermore, in a prospective cohort study, Felson et al[26] found that a 5 kg reduction in body mass over the course of a decade was able to reduce the odds of incident knee OA by 50%. With the link between knee OA and obesity firmly established, it is concerning that obesity rates in Canada and around the world are rising and are expected to continue to rise with an aging population that is becoming increasingly inactive.[5,27]

The knee joint is subjected to loads 2-4 times a person's body weight such that increases in body weight would exponentially increase the compressive loads at the knee.[28-30] Increased joint loading is considered the primary mechanism that leads to knee OA in patients who are overweight.[4] Specifically, cartilage breakdown occurs due to the increase in compressive load which leads to joint damage, and body mass which tends to increase with age, propagates the structural deterioration of the joint.[4] This abnormal joint loading may trigger a local inflammatory response leading to further articular damage.[4,31,32] Furthermore, patients who are obese have higher levels of adipose tissue which may lead to an pro-inflammatory state and thus continue to exacerbate the disease process.[33-35]

Interventions targeting weight loss in patients with knee OA have been successful in reducing body mass and demonstrating improvements in pain and function.[36-38] For example, Messier et al,[37] randomized patients with radiographic knee OA into four groups (1.control, 2.diet, 3.exercise, 4.diet plus exercise) and demonstrated that patients who underwent both diet and exercise had significant, clinically important improvements in pain and function more so than those who had diet or exercise alone. Christensen et al[36] also completed a randomized controlled trial (RCT) comparing patients with knee OA undergoing a low energy diet to a control group. Patients in the low energy diet group lost an average of 4% of their baseline weight and achieved significantly greater improvements in the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC). Further, there was an association with body composition, suggesting an almost 10% improvement in total WOMAC score for each percent of body fat lost. Additionally, a meta-analysis[39] demonstrated that in patients with knee OA, a minimum of 5% loss in body mass was required to experience a reduction in knee OA symptoms. A 10% reduction in body mass resulted in moderate to large effects in self-reported disability.[39]

There is a strong link between body mass and knee OA, with individuals who are overweight or obese having a significant risk of incident knee OA and a faster rate of progression compared to those who are of normal weight. There is also evidence that demonstrates those patients with knee OA who are overweight or obese can significantly improve their function and reduce pain after interventions to reduce body mass. This is likely mediated through a combination of mechanistic pathways.

1.2.3 Muscular Strength

Muscle strength is also an important factor in knee OA, especially the quadriceps muscle group.[40] This is a particularly important for patients with knee OA who have been shown to be 20-40% weaker in relative quadriceps strength compared to healthy controls.[41-43] This may be related to a decrease in muscle cross-sectional area and/or muscle inhibition.[44,45] Muscle inhibition is a consequence of pain and/or joint effusion, while the loss of muscle cross-sectional area could be related to sarcopenia or disuse atrophy.[40]

Research regarding quadriceps strength and its importance in knee OA disease onset is unclear. A longitudinal study in women demonstrated that baseline knee extensor strength was significantly lower in women who developed radiographic knee OA 30 months later compared to women who did not develop any radiographic changes.[46] However, Segal et al,[47] demonstrated quadriceps weakness did not lead to disease onset, but that quadriceps strength was protective against symptoms. Furthermore, quadriceps strength was not related to MRI measures of OA progression after 30 month follow up.[48] Despite inconsistent results regarding the association between strength and structural disease onset or progression, muscle strengthening may have a greater role in managing symptoms and preventing functional declines in knee OA.

The basis of recommending strengthening exercise as a part of rehabilitation regimen in patients with knee OA comes from several systematic reviews and meta-analyses demonstrating significant self-reported improvements in pain and function.[49-51] Patients with knee OA who undergo muscle strengthening interventions have significant gains in muscle strength compared to control groups.[51] Furthermore, the strength gains

lead to improved voluntary muscle activation which account for almost 50% in the improvement in quadriceps strength in patients with knee OA.[45] Therefore, it seems possible that deficits in activation due to muscle inhibition can be addressed in rehabilitation programs targeting changes in muscle strength.

1.2.3 Alignment

Knee alignment is best measured using full-limb (hip to ankle) radiographs. The mechanical axis angle (MAA) is determined by the angle formed between a line drawn from the centre of the hip to the centre of the knee, and a line drawn from the centre of the knee to the centre of the ankle (see Fig.1.2). Negative MAA values are associated with knees in varus alignment ("bow-legged") and positive values are associated with valgus alignment ("knock-kneed").

Alignment affects the load distribution within the knee compartments. Even in neutral alignment 60-70% of the force during stance phase of gait is on the medial compartment.[52] In a varus knee during the stance phase of gait, the line of action of the ground reaction force passes even more medial to the knee, thereby producing a larger external adduction moment about the tibiofemoral joint and therefore, even greater loads on its medial compartment relative to its lateral compartment.[52-54]

Recent studies suggest that varus and valgus alignment are risk factors for both the incidence and progression of compartment specific knee OA.[12-15] Varus alignment appears to be particularly important. For example, Sharma et al[14] followed a large cohort and showed that after only 30 months, varus alignment at baseline was associated with incident medial compartment cartilage damage measured on MRI [OR 3.59 (95%CI 1.59, 8.10)].

It is important to note that radiographic alignment provides only a two dimensional, static impression of the knee joint. However, during normal walking, multiple forces act upon the knee joint and these forces occur in several planes of movement acting at the same time. During the stance phase of gait, the ground reaction force acting on the limb passes medial to the knee joint towards the centre of mass located just above the umbilicus. The perpendicular distance from this force vector to the centre of the knee joint (i.e. lever arm) creates an adduction moment about the knee (See fig 1.3). In a varus aligned knee, the peak knee adduction moment is expected to increase (due to a larger lever arm), thereby further increasing the load across the medial tibiofemoral compartment. Static radiographs cannot precisely predict the type of dynamic loading that occurs about the knee. Three-dimensional (3D) gait analysis is better able to quantify the distribution of loads across the medial and lateral compartments of the knee during walking.

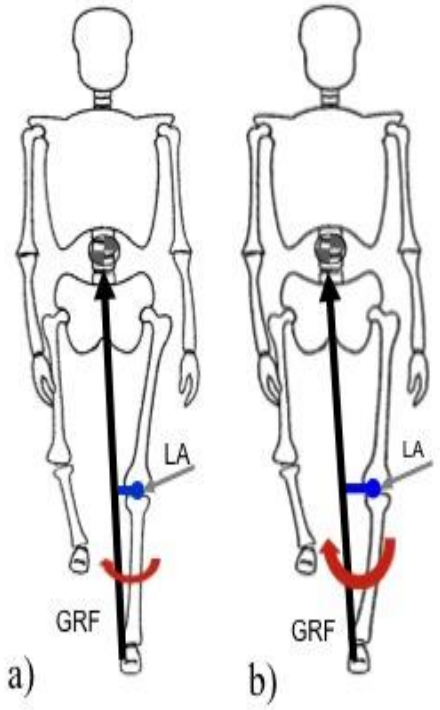

Figure 1.3: Diagram depicting the ground reaction force, frontal plane lever arm and the external knee adduction moment. The knee adduction moment acts to "inwardly turn" the lower limb and compresses the medial compartment. Diagram a) Neutral lower limb alignment. Diagram b) Varus lower limb alignment. Note the moment is larger in Diagram (b) due to the increased frontal plane lever arm of a varus lower limb.

1.2.4 Knee Adduction Moment

The knee adduction moment normally exists during walking and is often used as a surrogate measure for the mediolateral distribution of dynamic loads across the knee.[55] The knee adduction moment is calculated primarily as the product of the ground reaction force (GRF), and the lever arm, defined as the perpendicular distance from the centre of the knee to the GRF in the frontal plane (See Fig. 1.3). The larger the knee adduction moment, the higher the compressive loads on the medial compartment of the knee. High knee adduction moments can be exacerbated by patient characteristics such as varus mal-alignment and high body mass.[56-59] Unbalanced compartmental loading, is likely the main reason medial tibiofemoral compartment knee OA is more prevalent compared to the lateral compartment.[52]

The knee adduction moment typically presents with two peaks, the first (early stance) often being larger than the second (late stance) (see fig. 1.4). The peaks correspond to different phases of stance during the gait cycle that reflect the GRF. The first peak corresponds with the load acceptance phase of gait and the second peak occurs during late stance. Often, the larger of the two peaks is reported in the literature, which reflects the highest load bourn by the medial compartment of the tibiofemoral joint. The magnitude of the first peak knee adduction moment has been associated with the onset of future pain,[16] and progression of structural degeneration.[18] It has also been associated with levels of pain[60] and disease severity[61]. Patients with medial compartment knee OA can have higher peak knee adduction moments compared to age matched controls without knee OA[62] (See Fig. 1.4). Therefore, reducing the knee adduction moment is a common goal of several intervention strategies for patients with medial compartment knee OA.

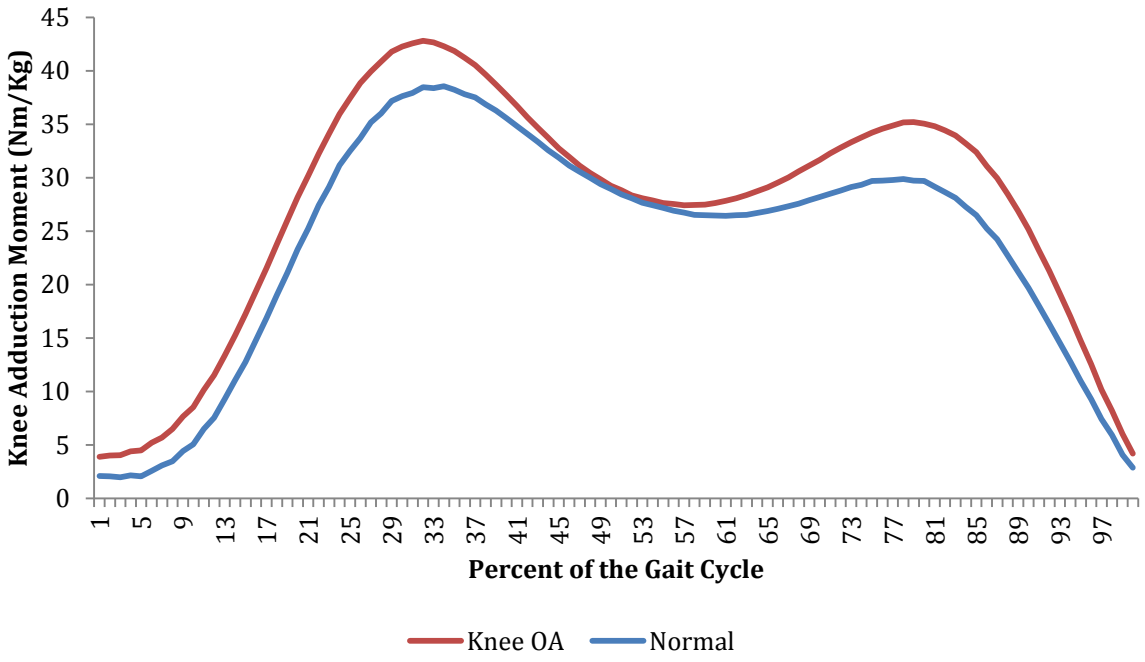

Figure 1.4: The Knee adduction moment represented over 100% of stance. The larger moment (red line) represents a patient with medial compartment knee OA. The smaller moment (blue line) represent a patient without knee OA.

Reductions in the knee adduction moment can theoretically be achieved through reductions in the GRF directly, and/or through reductions in the frontal plane lever arm. Orthoses (knee braces and shoe inserts) can alter the knee adduction moment through a combination of proposed mechanisms.[63-66] Valgus producing knee braces have been reported to decrease the knee adduction moment by approximately 13-20% depending on the degree of correction.[63] Lateral wedge insoles have been reported to decrease the knee adduction moment by approximately 5%.[64,65] Furthermore, the combination of a valgus knee brace and a lateral wedge insole used concurrently may provide greater reductions in the knee adduction moment compared either device on their own.[66] Reductions in the GRF can be achieved by decreasing body mass or gait speed. Reductions in the frontal plane lever arm can be changed by bringing the GRF closer to the centre of the knee

through gait modifications such as trunk leaning over the stance limb[67], or changing toe-out progression angle[67]. Although, rehabilitation efforts often focus on weight loss and muscle strengthening as core components, its effects on the knee adduction moment are currently unclear.

Messier et al[57] demonstrated that for every 1 kg of body mass lost by overweight or obese patients there was a 0.5Nm reduction in the knee adduction moment. Although not a large decrease in of itself, when multiplied by the number of steps taken per day, the overall reduction in medial compartment loading is substantial. Very similar reductions were reported in another weight loss study[68]. Moreover, increased body mass can have the opposite effect. Moyer et al[58] demonstrated that for every 1 kg gain in mass there was a 0.4Nm increase in the peak knee adduction moment. Consequently, patients who gain weight will likely experience substantial increases in medial compartment loading.

The association between the knee adduction moment and muscle strengthening is not clear. The quadriceps muscles are commonly the focus of rehabilitation programs because they are thought to behave as buffers to joint loading and act to stabilize the knee.[69] Several RCTs investigating the changes in joint loading and the role of strengthening interventions have failed to find an association between quadriceps strengthening and the knee adduction moment, despite improvements in strength, pain and function.[11,70,71] Lim et al[11] compared quadriceps strengthening in patients with knee OA who were stratified according to alignment (more varus or more neutral) and then randomized into a 12-week home-based quadriceps strengthening group or a control group that did not have any intervention administered. The knee adduction moment did

not change in either the varus or neutral aligned group, despite similar increases in strength. However, there were significant reductions in pain for the neutral group, but not for the varus-aligned group. The authors suggested that strengthening patients with varus gonarthrosis could potentially increase medial compartment loading by altering the line of action of the quadriceps and thus increasing medial tibiofemoral compressive forces.

Weakness of the hip abductors of the stance limb is thought to increase medial compartment loading by leading to a pelvic drop on the contralateral limb thereby shifting the GRF line of action away from the stance limb.[72] This theoretically would increase the frontal plane lever arm and consequently the knee adduction moment.[73] However, several randomized controlled trials[70,74,75] targeting strength changes to the hip abductors failed to demonstrate any changes to the knee adduction moment even though patients increased hip abductor strength.

A more recent concept in muscle rehabilitation for patients with knee OA termed neuromuscular training is suggested to improve sensorimotor control and functional stability through controlled movement and coordinated joint stability.[76,77] Neuromuscular training has been demonstrated to be feasible in patients with knee OA and may be incorporated into general strengthening programs to improve muscle function.[76] The emphasis of neuromuscular training is to create a better biomechanical environment for the quadriceps to function and this may contribute to reductions in knee joint loading.[78] A RCT is currently underway evaluating the effects of a neuromuscular training program on the knee adduction moment.[78]

1.3 Surgical Re-alignment

The goal of surgical lower limb re-alignment for knee OA is to decrease the load on the more diseased tibiofemoral compartment by transferring load towards the opposite compartment. Patients who undergo surgical re-alignment are generally younger and more active than patients considering arthroplasty. Unlike disproportionately high medial compartment loads in the presence of even minor varus alignment, extreme degrees of valgus alignment are required (≥7degrees MAA) before the lateral compartment accepts the majority of load.[79] Therefore, the following section will focus on varus-correcting surgical re-alignment as a treatment for patients with varus gonarthrosis.

The medial opening wedge HTO technique corrects varus alignment by creating a cut in the medial, proximal tibia, which is opened to a pre-determined amount (see fig. 1.5). As described by Fowler et al,[80] a vertical incision is made along the tibia from the medial aspect at a point bisecting the anterior tibial tubercle and the posteromedial border of the tibia approximately 5cm distal from the medial joint line. Using fluoroscopy, a guide pin is inserted through the proximal tibia in medial to lateral direction. The guide pin is obliquely oriented approximately 4cm below the medial joint line to approximately 1cm below the lateral joint line. The osteotomy is carried out using an oscillating saw and the medial cortex is cut parallel and just below the guide pin. Using a previously calibrated wedge inserted into the osteotomy, it is advanced slowly until the proper osteotomy size is reached in order to achieve the appropriate alignment. A fixation plate is then used to support the osteotomy gap. The plate is secured through cancellous screws, and fluoroscopic imaging is used to confirm screw position avoiding intra-articular placement. Bone grafting is recommended for any osteotomies that are greater

than 7.5mm in order to prevent delayed or non-union. For osteotomies less than 7.5mm bone grafting is up to the discretion of the surgeon.

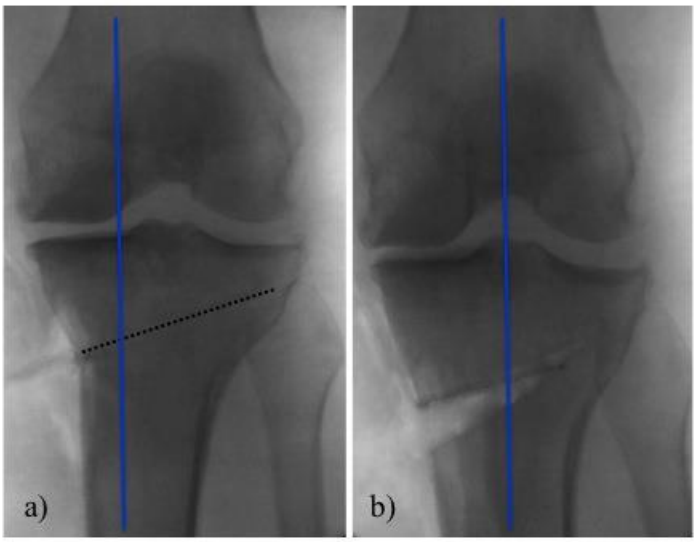

Figure 1.5: Medial opening wedge High Tibial Osteotomy (HTO). Panel a) and b) demonstrate how surgery can correct mal-alignment by shifting the weight bearing line (i.e. the line connecting the centre of the hip to the centre of the ankle).

Surgical re-alignment for patients with varus gonarthrosis has demonstrated long-term benefits in normalizing dynamic joint loading and improvements in patient self-report measures such as pain and function.[81-85] Birmingham et al[81] showed significant improvements in radiographic, gait and patient self-report measures two years after surgery in patients who underwent medial opening wedge HTO. Patients in this group were relatively young (mean age 47.5), overweight, with a mean BMI of 29.5 and with

significant varus alignment with a (mean MAA = -7.5º). The mean MAA after surgery was 0.05º, and the first peak knee adduction moment was reduced by almost 50% from 2.99%BW*Ht to 1.62%BW*Ht. Patient self-report measures all showed significant improvements in the knee injury and osteoarthritis outcome scores (KOOS) that evaluates five domains including; pain, function, activities of daily living, quality of life and sport and recreation. Other studies evaluating the knee adduction moment have also shown significant reductions in the knee adduction moment after re-alignment surgery.[82-85]

1.4 Thesis Outline

The overall purpose of this thesis was to evaluate the effects of a combined, multi-modal rehabilitative and surgical interventions that targeted different risk factors for disease progression in patients with varus gonarthrosis. Targeted risk factors were lower limb mal-alignment, the knee adduction moment, body composition and muscular strength. The thesis contains three studies reporting data obtained from radiographs, 3D gait biomechanics, air displacement plethysmography, and isokinetic dynamometry. Patient-reported outcomes were also assessed using the KOOS. All participants were recruited from the Fowler Kennedy Sport Medicine Clinic at Western University. All testing took place in the Wolf Orthopaedic Biomechanics Laboratory, and in the Exercise and Nutrition Laboratory both located in the 3M Centre at Western University.

Study 1: Patients who are in substantial varus alignment bilaterally are at increased risk for medial knee OA progression and functional decline. The purpose of study 1 (Chapter 2) was to examine changes in gait in both limbs two years after unilateral medial opening wedge HTO. The results of this study provided impetus for planning and completing studies 2 and 3 (Chapters 3 and 4)

Study 2: Patients with knee OA are typically overweight or obese. Several interventions have targeted changes in weight and/or body mass index in order to reduce symptoms in knee OA. However, few studies have addressed changes in body composition, especially the importance of losing fat mass while preserving fat-free (lean) mass. The purpose of study 2 (chapter 3) was to examine the test-retest reliability and quantify the minimum detectable change in body density, fat mass, lean mass and percent fat in patients with knee OA. The results of this study aided in the evaluation of changes following the intervention in study 3 (chapter 4).

Study 3: Interventions aimed at limiting progression of knee OA focus on known risk factors that are modifiable. Different interventions typically target different risk factors. The primary objective of this proof of principle study was to evaluate the cumulative effects of combined physiotherapy and medial opening wedge HTO on body composition, muscular strength, the knee adduction moment, lower limb mal-alignment and KOOS scores. The secondary objective was to evaluate the effects of each intervention separately.

The final chapter (Chapter 5) provides a general discussion of the studies, including a summary of their most important findings, limitations and recommendations for future research.

1.5 References

1. Health Canada. Arthritis in Canada. An ongoing challenge. Ottawa: Health Canada, 2003.
2. Hunter DJ, McDougal JJ, Keefe FJ. The symptoms of osteoarthritis and the genesis of pain. Rheum Dis Clin N Am. 2008;34:623-643.
3. Brandt KD, Dieppe P, Radin E. Etiopathogenesis of osteoarthritis. Med Clin N Am. 2009;93:1-24.
4. Felson DT. Osteoarthritis as a disease of mechanics. Osteoarthritis Cart. 2013;21:10-15.
5. Horton R. GBD 2010: understanding disease, injury, and risk. Lancet. 2012;380:2053-2054. DOI 10.1016/S0140-6736(12)62133-3.
6. Felson DT, Zhang Y, Hannan MT, Naimark A, Weissman BN, Aliabadi P, et al. The incidence and natural history of knee osteoarthritis in the elderly: the Framingham Osteoarthritis Study. Arthritis Rheum. 1995;38:1500-5.
7. Felson DT & Radin EL. What causes knee osteoarthrosis are different compartments susceptible to different risk factors? J Rheumatol 1994:21;181-183.
8. Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis. Part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis Cart. 2008;16(2): 137-62.
9. Hochberg MC, Altman RD, Toupin Aril K, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res. 2012;64(4):465-74.
10. National Collaborating Centre for Chronic Conditions. Osteoarthritis: national clinical guideline for care and management in adults. London: Royal College of Physicians, 2008.
11. Lim BW, Hinman RS, Wrigley TV, Sharma L, Bennell KL. Does malalignment mediate the effects of quadriceps strengthening on knee adduction moment, pain, and function in medial knee osteoarthritis? A randomized Controlled Trial. Arthritis Rheum. 2008;59:943-951.
12. Brouwer GM, van Tol AW, Bergink AP, Belo JN, Bernsen RM, Reijman M Pols HA, et al. Association between valgus and varus alignment and the development and progression of radiographic osteoarthritis of the knee. Arthritis Rheum. 2007;56:1204-1211.
13. Sharma L, Song J, Felson DT, Cahue S, Shamiyeh E, Dunlop DD. The role of knee alignment in disease progression and functional decline in knee osteoarthritis. JAMA. 2001;286:188-195.
14. Sharma L, Chmiel JS, Almagor O, et al. The role of varus and valgus alignment in the initial development of knee cartilage damage by MRI: the MOST study. Ann Rheum Dis. 2013;72:235-240.
15. Sharma L, Song J, Dunlop D, Felson D, Lewis CE, Segal N, Torner J et al. Varus and valgus alignment and incident and progressive knee osteoarthritis. Ann Rheum Dis. 2010;69:1940-1945.

16. Amin S, Leupongsak N, McGibbon CA, LaValley MP, Krebs DE, Felson DT. Knee adduction moment and development of chronic knee pain in elders. Arthritis Rheum. 2004;51:371-376.
17. Bennell KL, Bowles K, Wang Y, Cicuttini F, Davies-Tuck M, Hinman RS. Higher dynamic medial knee load predicts greater cartilage loss over 12 months in medial knee osteoarthritis. Ann Rheum Dis. 2011;70:1770-1774.
18. Miyazaki T., Wada M., Kawahara H., Sato M., Baba H., Shimada S. Dynamic load at baseline can predict radiographic disease progression in medial compartment knee osteoarthritis. Ann Rheum Dis. 2002;61:617-622.
19. Blagojevic M, Jinks C, Jeffery A, Jordan KP. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. Osteoarthritis Cart. 2010;18:24-33.
20. Felson DT, Zhang Y, Hannan MT, Naimark A, Weissman B, Aliabadi P et al. Risk factors for incident radiographic knee osteoarthritis in the elderly. The Framingham study. Arthritis Rheum. 1997;40:728-733.
21. Felson DT, Anderson JJ, Naimark A, Walker AM, Meenan RF. Obeisty and knee osteoarthritis. The Framingham Study. Ann Intern Med. 1988;109;18-24.
22. Niu J, Zhang YQ, Torner J, et al. Is obesity a risk factor for progressive radiographic knee osteoarthritis? Arthritis Rheum. 2009;61:329-335.
23. Yusuf E, Bijsterbosh J, Slagboom PE, Rosendaal FR, Huizinga TWJ, Kloppenburg M. Body mass index and alignment and their interaction as risk factors for progression of knees with radiographic signs of osteoarthritis. Osteoarthritis Cart. 2011;19:1117-1122.
24. Anderson JJ & Felson DT. Factors associated with osteoarthritis of the knee in the first national health and nutrition examination survey (HANES I). Evidence for an association with overweight, race, and physical demands of work. Am J Epidemiol. 1988;121:179-189.
25. Coggon D, Reading I, Croft P, McLaren M, Barrett D, Cooper C. Knee osteoarthritis and obesity. International Journal of obesity and related metabolic disorders. Int J Obes. 2001;25:622-627.
26. Felson DT, Zhang Y, Anthony JM, Anderson JJ. Weight loss reduces the risk for symptomatic knee osteoarthritis in women. The Framingham study. Ann Int Med. 1992;116:535-539.
27. Tjepkema M. Adult obesity. Health Rep. 2006;17:9-25.
28. Shelburne KB, Torry MR, Pandy MG. Contributions of muscles, ligaments, and the ground-reaction force to tibiofemoral joint loading during normal gait. J Orthop Res. 2006;24:1983-1990.
29. Zhao D, Banks SA, Mitchell KH, D'Lima DD, Colwell CW Jr, Fregly BJ. Correlation between the knee adduction moment torgue and medial contact force for a variety of gait patterns. J Orthop Res. 2007;25:789-797.
30. Winby CR, Lloyd DG, Besier TF, Kirk TB. Muscle and external load contribution to knee joint contact loads during normal gait. J Biomech. 2009;42:2294-2300.

31. Griffin TM & Guilak F. The role of mechanical loading in the onset and progression of osteoarthritis. Exerc and sport sci rev 2005;33:195-200.
32. Loeser RF Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis a disease of the joint as an organ. Arthritis Rheum. 2012;64:1697-1707.
33. Berry PA, Jones SW, Cicuttini FM, Wluka AE, Maciewicz RA. Temporal relationship between serum adipokines, biomarkers of bone and cartilage turnover, and cartilage volume loss in population with clinical knee osteoarthritis. Arthritis Rheum 2011;63:700-707.
34. Pottie P, Presle N, Terlain B et al. Obesity and osteoarthritis: more complex than predicted! Ann Rheum Dis 2006;65:1403-1405.
35. Toda Y, Toda T, Takemur S et al. Change in body fat, but not body weight or metabolic correlates of obesity, is related to symptomatic relief of obese patients with knee osteoarthritis after a weight control program. J Rheumatol 1998;25:2181-2186.
36. Christensen R, Astrup A, Bliddal H. Weight loss: the treatment of choice for knee osteoarthritis? A randomized trial. Osteoarthritis Cart. 2005;13:20-27.
37. Messier SP Loeser RF, Miller GD, Morgan TM, Rejeski J, Sevick MA, Ettinger WH, Pahor M, Williamson JD. Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis. Arthritis Rheum. 2004;50:1501-1510.
38. Messier SP, Mihalko SL, Legault C, Miller GD, Nicklas B, DeVita P, Beavers DP et al. Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis. The IDEA randomized clinical trial. JAMA. 2013;310:1263-1273.
39. Christensen R, Bartels EM, Astrup A, Bliddal. Effect of weight reduction obese patients diagnosed with knee osteoarthritis: a systematic review and meta-analysis. Ann Rheum Dis. 2007;66:433-439.
40. Bennell KL, Wrigley TV, Hunt MA, Lim BW, Hinman RS. Update on the role of muscle in the genesis and management of knee osteoarthritis. Rheum Dis Clin N Am. 2013;39:145-176.
41. Slemenda C, Brandt KD, Heilman DK, Mazzuca S, Braunstein EM, Katz BP, Wolinsky FD. Quadriceps weakness and osteoarthritis of the knee. Ann Int Med. 1997;127:97-104.
42. Hinman RS, Hunt MA, Creaby MW, Wrigley TV, McManus FJ, Bennell KL. Hip muscle weakness in individuals with medial knee osteoarthritis. Arthritis Care Res. 2010;62:1190-1193.
43. Messier SP, Loeser RF, Hoover JL, Semble EL, Wise CM. Osteoarthritis of the knee: effects on gait, strength, and flexibility. Arch Phys Med Rehab. 1992;73:29-36.
44. Petterson SC, Barrance P. Buchanan T, Binder-Macleaod S, Snyder-Mackler L. Mechanisms underlying quadriceps weakness in knee osteoarthritis. Med Sci Sport Ex. 2008;40:422-427.

45. Pietrosimone BG, Hertel J, Ingersoll CD, Hart JM, Saliba SA. Voluntary quadriceps activation deficits in patients with tibiofemoral osteoarthritis: a meta-analysis. Pm & R. 2011;153-162.
46. Slemenda C, Heilman DK, Brandt KD, Katz BP, Mazzuca SA, Braunstient EM Byrd D. Reduced quadriceps strength relative to body weight: a risk factor for knee osteoarthritis for women? Arthritis Rheum. 19989;41:1951-1959.
47. Segal NA, Torner JC, Felson DT, Niu J, Sharma L, Lewis CE, Nevitt M. Effect of thigh strength on incident radiographic and symptomatic knee osteoarthritis in a longitudinal cohort. Arthritis Rheum. 2009;61:1210-1217.
48. Amin S, Baker K, Niu J, Clancy M, Goggins J, Guermazi A, Grigoryan M, Hunter DJ, Felson DT. Quadriceps strength and the risk of cartilage loss and symptom progression in knee osteoarthritis. Arthritis Rheum. 2009;60:189-98.
49. Fransen M, McConnell S. Exercise for osteoarthritis of the knee. Cochrane Database of Systematic Reviews 2008, Issue 4. Art. No.:CD004376. DOI: 10.1002/14651858.CD004376.pub2.
50. Roddy E, Zhang W, Doherty M. Aerobic walking or strengthening exercise for osteoarthritis of the knee? A systematic review. Ann Rheum Dis. 2005;64:544-548.
51. Lange AK, Vanwanseele B, Fiatarone Singh MA. Strength training for treatment of osteoarthritis of the knee: a systematic review. Arthritis Rheum. 2008;59:1488-1494.
52. Andriacchi TP. Dynamics of knee malalignment. Orthop Clin North Am. 1994;25:395-403.
53. Hunt MA, Birmingham TB, Giffin JR, Jenkyn TR. Associations among knee adduction moment, frontal plane reaction force, and lever arm during walking in patients with knee osteoarthritis. J Biomech. 2006;39:2212-2220.
54. Schipplein OD, Andriacchi TP. Interaction between active and passive knee stabilizers during level walking. J Orthop Res. 1991;9:113-119.
55. Andriacchi TP. Valgus alignment and lateral compartment knee osteoarthritis: a biomechanical paradox or new insights into knee osteoarthritis? Arthritis Rheum. 2013;65:310-313.
56. Hurwitz De, Ryals AB, Case JP, Block JA, Andriacchi TP. The knee adduction moment during gait in subjects with knee osteoarthritis is more closely correlated with static alignment than radiographic disease severity, toe out angle and pain. J Orthop Res. 2002;20:101-107.
57. Messier SP Gutekunst DJ, Davis C, DeVita P. Weight loss reduces knee-joint loads in overweight and obese older adults with knee osteoarthritis. Arthritis Rheum. 2005;52:2026-2032.

58. Moyer RF, Birmingham TB, Chesworth BM, Kean CO, Giffin JR. Alignment, body mass and their interaction on dynamic knee joint load in patients with knee osteoarthritis. Osteoarthritis Cart. 2010;18:888-893.
59. Sharma L, Song J, Felson DT, Cahue S, Shamiyeh E, Dunlop DD. The role of knee alignment in disease progression and functional decline in knee osteoarthritis. JAMA. 2001;286:188-195.
60. Thorp LE, Sumner DR, Wimmer MA, Block JA. Relationship between pain and medial knee joint loading in mild radiographic knee osteoarthritis. Arthritis Rheum. 2007;51:1254-1260.
61. Sharma, Hurwitz DE, Thonar EJ, Sum JA, Lenz ME, Dunlop DD, Schinitzer TJ et al. Knee adduction moment, serum hyaluronan level, and disease severity in medial tibiofemoral osteoarthritis. Arthritis Rheum. 1998;41:1233-1240.
62. Baliunas AJ, Hurwitz DE, Ryals AB, Karrar A, Case JP, Block JA, Andriacchi TP. Increased knee joint loads during walking are present in subjects with knee osteoarthritis. Osteoarthritis Cart. 2002;10:573-579.
63. Pollo FE, Otis JC, Backus SI, Warren RF Wickiewicz TL. Reduction of meidal compartment loads with valgus bracing of the osteoarthritic knee. Am J Sports Med. 2002;30;414-421.
64. Hinman RS, Payne C, Metcalf BR, Wrigley TV, Bennell KL. Lateral wedges in knee osteoarthritis: What are their immediate clinical and biomechanical effects and can these predict a three-month clinical outcome? Arthritis Rheum. 2008;59:408-415.
65. Jones RK, Chapman GJ, Findlow AH, Forsythe L, Parkes MJ Sultan J, Felson DT. A new approach to prevention of knee osteoarthritis: Reducing medial load in the contralateral knee. J Rheumatol. 2013;40:309-315.
66. Moyer RF, Birmingham TB, Dombroski CE, Walsh RF, Leitch KM, Jenkyn TR, Giffin JR. Combined effects of a valgus knee brace and lateral wedge foot orthotic on the exernal knee adduction moment in patients with varus gonarthrosis. Arch Phys Med Rehab. 2013;94:103-112.
67. Simic M, Hinman RS, Wrigley TV, Bennell KL, Hunt MA. Gait modification strategies for altering medial knee joint load: A systematic review. Arthritis Care Res. 2011;63:405-426.
68. Aaboe J, Bliddal H, Messier SP, Alkjaer T, Henrikson M. Effects of an intensive weight loss program on knee joint loading in obese adults with knee osteoarthritis. Osteoarthritis Cart. 2001;19:822-828.
69. Mikesky AE, Meyer A, Thompson KL. Relationship between quadriceps strength and rate of loading during gait in women. J Orthop Res. 2000;18:171-175.
70. Foroughi N, Smith RM, Lange AK, Baker MK, Fiatarone Singh MA, Vanwasnseele B. Dynamic alignment and its association with knee adduction moment in medial knee osteoarthritis. Knee. 2010;17:210-216.

71. McQuade KJ & de Oliveira AS. Effects of progressive resistance strength training on knee biomechanics during single leg step-up in persons with mild knee osteoarthritis. Clin Biomech. 2011;26:741-748.
72. Chang A, Hayes K, Dunlop D, Song J, Hurwitz D, Cahue S, Sharma L. Hip abduction moment and protection against medial tibiofemoral osteoarthritis progression. Arthritis Rheum. 2005;52:3515-3519.
73. Takacs J, Hunt MA. The effect of contralateral pelvic drop and trunk lean on frontal plane knee biomechanics during single limb standing. J Biomech. 2012;45:2791-2796.
74. Bennell KL, Hunt MA, Wrigley TV, Hunter DJ, McManus FJ, Hodges PW, Li L, et al. Hip strengthening reduces symptoms but not knee load in people with medial knee osteoarthritis and varus malalignment: a randomized controlled trial. Osteoarthritis Cart. 2010;18:621-628.
75. Sled EA, Khoja L, Deluzio KJ, Olney SJ, Culham EG. Effect of a home program of hip abductor exercises on knee joint loading, strength, function, and pain in people with knee osteoarthritis: A Clinical Trial. Phys Ther. 2010;90:895-904.
76. Ageberg E, Link A, Roos EM. Feasibility of neuromuscular training in patients with severe hip or knee OA: the individualized goal-based NEMEX-TJR training program. BMC Musculoskelet Disord. 2010;11:126.
77. Stensrud S, Roos EM, Risberg MA. A 12-week exercise therapy program in middle-aged pateitns with degenerative meniscus tears: A case series with 1-year follow-up. J Orthop Sports Phys Ther. 2012;42:919-931.
78. Bennell KL, Egerton T, Wrigley TV, Hodges PW, Hunt M, Roos EM, Kyriakides M et al. Comparison of neuromuscular and quadriceps strengthening exercise in the treatment of varus malaligned knees with medial knee osteoarthritis: a randomized controlled trial protocol. BMC Musculo Dis. 2011;12:276.
79. Leitch KM, Birmingham TB, Dunning CE, Giffin JR. Changes in valgus and varus alignment neutralize aberrant frontal plane knee moments in patients with unicompartmental knee osteoarthritis. J Biomech. 2013;46:1408-1412.
80. Fowler PJ, Tan JL, Brown GA. Medial opening wedge high tibial osteotomy: How I do it. Oper Tech Sports Med. 2000;8:32-38.
81. Birmingham TB, Giffin JR, Chesworth BM, et al. Medial opening wedge high tibial osteotomy: A prospective cohort study of gait, radiographic and patient-reported outcomes. Arthritis Rhem. 2009;61:648-657.
82. DeMeo PJ, Johnson EM, Chiang PP, Flamm AM, Miller MC. Midterm follow-up of opening-wedge high tibial osteotomy. Am J Sports Med. 2010;38:2077-2084
83. Lind M, McClelland J, Wittwer JE, Whitehead TS, Feller JA, Webster KE. Gait analysis of walking before and after medial opening wedge high tibial osteotomy. Knee Surg Sports Traumatol Arthrosc. 2013.21;1:74-81.

84. Prodromos CC, Andriacchi TP, Galante JO. A relationship between gait and clinical changes following high tibial osteotomy. J Bone Joint Surg Am. 1985;67:1188-1194.
85. Wada M, Imura S, Nagatani K, Baba H, Shimada S, Sasaki S. Relationship between gait and clinical results after high tibial osteotomy. Clin Orthop. 1998;354:180-188.

Chapter 2

2 Bilateral Changes in Gait Two Years after High Tibial Osteotomy

2.1 Summary

Patients with substantial varus alignment bilaterally are at greater risk for disease progression and functional declines. Large decreases in the surgical limb knee adduction moment during walking are observed after HTO, but changes in the non-surgical limb are unclear. The objectives of this study were: 1) To compare the pre- to postoperative change in external knee adduction moments during walking after unilateral medial opening wedge high tibial osteotomy (HTO) in both limbs of patients with substantial bilateral varus, and 2) To test whether observed changes in walking characteristics and patient characteristics are related to changes in the non-surgical limb knee adduction moment. Sixty-seven patients (mean age 48±7 years) with bilateral mechanical axis angles ≤ -5º were included. Three-dimensional gait analysis using inverse dynamics, and hip-to-ankle weight-bearing radiographs, were completed before and 2 years after surgery. External knee adduction moments (as well as ground reaction forces and frontal plane lever arms) were compared using two-factor time-by-limb analysis of variance. All outcomes were compared before and after surgery using paired t-tests. Multiple linear regression tested whether significant changes in walking characteristics (speed, lateral trunk lean and progression angle) and patient characteristics (lower limb alignment and mass) were significantly related to increases in the non-surgical limb knee adduction moment. There was an expected large decrease in the surgical limb peak knee adduction moment (-30.09Nm; 95%CI -33.84, -26.34Nm), yet a small increase in the non-surgical

limb (5.6Nm; 95%CI 3.3, 8.0Nm). Lateral trunk lean decreased (bilaterally) and walking speed and body mass increased ($p<0.01$). While controlling for other variables that changed significantly, increases in speed (unstandardized beta coefficient (B) = 17.7; 95%CI 1.0, 34.3, p=0.04) and mass (B=0.55; 95%CI 0.05, 1.1, p=0.03) were related to the increase in the non-surgical limb peak knee adduction moment. These findings suggest that patients with substantial bilateral varus alignment experience a large decrease in medial compartment loading of the surgical knee during walking, yet a small increase in medial compartment loading of the non-surgical knee, two years after unilateral HTO. The present findings suggest the increase in the non-surgical limb is explained most by walking faster and by gaining weight after surgery.

2.2 Introduction

Knee osteoarthritis (OA) more commonly involves the medial compartment of the tibiofemoral joint, largely because of biomechanical factors related to how the knee is loaded during walking[1]. During the stance phase of gait, the line of action of the ground reaction force typically remains medial to the weight-bearing knee, thereby producing a lever arm in the frontal plane, an external adduction moment about the tibiofemoral joint and greater loads on its medial compartment relative to its lateral compartment[1-3] The knee adduction moment reflects the mediolateral distribution of load across the knee during walking,[1,3] and a high knee adduction moment is a risk factor for medial knee OA progression.[4,5]

A knee adduction moment normally exists during walking, yet is exacerbated substantially by patient characteristics such as varus mal-alignment and high body mass.[6-8] These finding are consistent with varus alignment and obesity being risk factors for the

development of and progression of medial knee OA.[9-12] The knee adduction moment can also be altered by several walking characteristics, such as speed,[8,13] lateral trunk lean,[14,15] and progression angle,[16-18] among others, presumably due to their effects on the ground reaction force and the lever arm in the frontal plane about the knee.

Individuals with medial knee OA in one limb are at high risk of having medial knee OA in their contralateral limb, either concurrently or in the future.[12,19-23] For example, 90% of participants in the longitudinal Framingham Osteoarthritis Study with medial radiographic knee OA either had concurrent contralateral medial knee OA, or developed it within 10 years.[19] This risk is particularly important for individuals with varus alignment, where those with substantial bilateral varus (≥-5º) are at greatest risk for disease progression and functional declines.[12]

Medial opening wedge high tibial osteotomy (HTO) is a surgical intervention for patients with medial knee OA and varus alignment.[24] The goal of HTO is to decrease aberrant loads on the medial compartment by correcting varus alignment. Various HTO procedures can indeed produce large, sustained decreases in the knee adduction moment during walking.[25-31] Other gait characteristics, including gait speed, lateral trunk lean over the stance limb, and progression angle can also change significantly after surgery.[25]

Given that the non-surgical limb is already at risk preoperatively, it is important to understand how HTO may affect that limb to tailor rehabilitation and continued treatment efforts accordingly. There is limited research evaluating the effect of HTO procedures on the non-surgical limb.[25,27,31] Reported findings have been inconsistent, with a suggested decrease[31], increase[27] and no change[25] in various gait characteristics including the knee adduction moment. Given their more general objectives, these prior studies reported

limited data on the non-surgical limb.[25,27,31] These studies have not evaluated alignment or disease status in that limb and did not investigate potential mechanisms such as gait speed, trunk lean and progression angle that impact the knee adduction moment and may explain the discrepancies reported in the literature. The effect of HTO on the knee adduction moment on the non-surgical limb of patients who are at greatest risk for disease progression and functional declines is presently unclear.

Objectives of the present study were: 1) To compare the pre- to postoperative change in external knee adduction moments during walking after unilateral medial opening wedge high tibial osteotomy in both limbs of patients with substantial bilateral varus, 2) To test whether observed changes in walking characteristics and patient characteristics are related to changes in the non-surgical limb knee adduction moment. To provide further context when interpreting these objectives, we also evaluated Knee injury and Osteoarthritis Outcome Scores.

Based on pilot data,[32] we hypothesized that**:** 1) the expected decrease in knee adduction moment in the surgical limb pre to postoperatively would be accompanied by an increase in the non-surgical limb knee adduction moment, and that the differences between limbs in the pre- to postoperative changes would be due to differing effects of the ground reaction force and frontal plane lever arm, and 2) that the increase in the non-surgical limb would be related to changes in walking characteristics (increased speed and decreased trunk lean) and patient characteristics (increased mass) observed after surgery.

2.3 Methods

2.3.1 Participants

Patients in the present study are a subgroup of participants in an ongoing observational cohort study of medial opening wedge HTO. To address the present study's objectives, we evaluated all patients from the cohort with preoperative bilateral varus alignment of mechanical axis angle ≤-5° and therefore at greatest risk for disease progression and functional declines.[12] All patients were referred for treatment of knee pain located primarily in the medial compartment of the tibiofemoral joint. Patients were referred from family physicians, rheumatologists and primary care sports medicine specialists for consultation with an orthopaedic surgeon. Inclusion criteria consisted of mechanical varus alignment and a clinical diagnosis of knee OA according to the American College of Rheumatology classification criteria[33] in at least one limb, with the greatest severity in the medial compartment of the tibiofemoral joint. Patients with concomitant disease in the lateral compartment were considered eligible as long as pain and radiographic disease were more severe in the medial compartment. For patients with bilateral joint disease, only the more symptomatic knee underwent surgery. Patients with concomitant chronic anterior cruciate ligament (ACL) deficiency undergoing simultaneous ACL reconstruction were included. Patients ≥60 years of age with grade 4 degenerative changes in ≥2 knee compartments (widely accepted as better candidates for total knee arthroplasty), infectious arthritis of the knee, or advanced symptomatic patellofemoral disease (i.e. substantial anterior knee pain and degenerative changes identified on x-ray or diagnostic arthroscopy) were not considered appropriate candidates for HTO. We excluded patients with prior HTO on the contralateral extremity, multi-

ligamentous instability, major neurologic deficit that would affect gait, major medical illness with a life expectancy <2 years or with an unacceptably high operative risk, pregnancy, inability to speak or read English, and psychiatric illness that limited informed consent.

2.3.2 Intervention

Patients underwent medial opening wedge HTO surgery using techniques described previously.[25] The desired angle of correction was calculated preoperatively with the goal of achieving neutral-to-slight valgus alignment. Patients were placed in a hinged knee brace and instructed on crutch-walking with feather weight-bearing (very slight weight through the foot). Partial weight-bearing (up to 50% bodyweight) commenced when x-rays showed signs of union (approximately 6 weeks) and continued until approximately 10-12 weeks, while progressively increasing weight-bearing as tolerated. Hip, knee and ankle range of motion (ROM) exercises, and isometric quadriceps exercises, were started on the first day post-operatively. Patients removed the brace for daily rehabilitation. Concentric exercises using weighted resistance were added at approximately 8 weeks. Weight-bearing, functional exercises with emphasis on balance, and gait re-training, were initiated at approximately 12 weeks. Other than exercises involving both limbs (such as squatting, lunging and leg press), no interventions on the non-surgical limb were attempted. Rehabilitation continued until both the therapist's expected outcomes and the patient's functional goals were adequately met. Rehabilitation typically lasted from 6 to 9 months.

2.3.3 Radiographic Measurements

Standing, hip-to-ankle anteroposterior (AP) radiographs for both limbs were obtained by a musculoskeletal x-ray technologist using methods previously described to be reliable.[34] The mechanical axis angle (MAA) was determined by identifying the geometric centre of the femoral head using a circular template,[34] the centre of the knee was identified as the midpoint of the tibial spines extrapolated inferiorly to the surface of the intercondular eminence, and the centre of the ankle was defined as the mid-width of the tibia and fibula at the level of the tibial plafond. The MAA was defined as the angle formed between the line drawn from the centre of the hip to the centre of the knee and the line from the centre of the knee to the centre of the ankle. Valgus alignment was reported as a positive value and varus alignment was reported as a negative value.

Two investigators (AB and RM) measured the mechanical axis angle and assessed the tibiofemoral joint Kellgren and Lawrence (KL) grade of OA severity.[35] For any mechanical axis angle measures that differed between assessors by ≥2 degrees, the film was re-measured by both assessors and their mean value recorded. For any KL grade that differed by ≥1 grade, the film was re-assessed by both assessors concurrently to reach consensus.

2.3.4 Gait Analysis

Patients' walking gait was analysed using an eight-camera motion capture system (Eagle EvaRT; Motion Analysis Corporation, Santa Rosa, CA) synchronized with a floor-mounted force platform (Advanced Mechanical Technology, Watertown, MA). We used a modified Helen Hayes 22 passive-reflective marker set.[36] A static trial was first completed with four additional markers placed over the medial knee joint line and medial

malleolus bilaterally to determine positions of joint centres of rotation for the knee and ankle. Patients stood on the force platform during this static trial to determine body mass. The four extra markers were removed prior to gait testing.

Patients walked barefoot at their self-selected pace across the length of the laboratory's 8m floor, enabling data collection during the middle of several strides for each limb. Patients were instructed to walk at their normal pace and to ignore the force plate. Walking trials were repeated until five clean force plate strikes (initial contact to pre-swing; one foot completely on the plate) from each limb were obtained. Force plate data were sampled at 1,200Hz while camera data were sampled at 60Hz. Moments about the knee were calculated from the kinematic and kinetic data using inverse dynamics (Orthotrak 6.0; Motion Analysis Corporation, Santa Rosa, CA, USA) and custom post-processing and data reduction techniques.[2,17] Knee moments were expressed as external moments relative to the tibial anatomical frame of reference.

For each patient, the knee adduction moment was plotted over 100% percent of stance. The first and second peaks were identified if immediately preceded by five continuously ascending values and followed by five continuously descending values. The higher of the first or second peaks was also recorded to ensure one peak (maximum) knee adduction moment value for all patients. We also integrated the entire adduction portion of the knee frontal plane moment waveform with respect to time to calculate the angular impulse.[37] The peak vertical ground reaction force and lever arm about the knee in the frontal plane were also calculated to help explain observed changes in the knee adduction moment.[1,2,18] The frontal plane lever arm was defined as the maximum perpendicular

distance between the knee joint centre of rotation and the resultant frontal plane ground reaction force.[2]

Specific walking characteristics associated with the knee adduction moment were also defined from the three-dimensional gait data, including gait speed, progression angle and lateral trunk lean.[2,8,13,15-18] Walking speed was calculated as the average walking speed between successive foot contacts of the tested limb. The progression angle was calculated as the maximum angle between a line drawn between the centre of the ankle and the head of the second metatarsal and the forward progression of the body. Positive values corresponded to toeing-out while negative values corresponded to toeing-in. The lateral trunk lean angle was calculated as the maximum angle of a line drawn from the midpoint of the anterior superior iliac spines to the midpoint of the anterior tips of the acromion processes with respect to vertical. Positive angles corresponded to a shift in the body's centre of mass over the stance limb while negative angles corresponded to a shift in the body's centre of mass to the swing limb. Participants underwent radiographic assessments and gait analyses within 4 weeks before surgery and 24 months afterwards.

2.3.5 Patient-Reported Outcomes

To help interpret the potential clinical importance of the observed gait findings, participants also completed the Knee Injury and Osteoarthritis Outcome Score (KOOS) before and 2 years after surgery.[38] The KOOS includes five separately reported domains of pain, other symptoms, function in daily living, function in sports/recreation, and knee-related quality of life. Scores can range from 0-to-100 where higher scores represent less disability. A change of 10 points is considered clinically important.[38] The KOOS is highly responsive to change after HTO.[39]

2.3.6 Statistical Analysis

For each patient, we calculated the mean of five trials for each of the gait variables listed above and used the mean of the trials in all subsequent statistical analyses. For objective 1, external knee adduction moments before and after surgery in both limbs were compared using two-factor time-by-limb analysis of variance. We then repeated the analysis using vertical ground reaction force and frontal plane lever arm. For post-hoc analysis, we compared all variables before and after surgery using paired t-tests and 95% confidence intervals (CI) around the mean change. For objective 2, we performed multiple linear regression (least squares method) using the variables that significantly changed in the non-surgical limb after surgery. The dependent variable was the 2-year postoperative knee adduction moment. Independent variables were all entered into one model that included the preoperative knee adduction moment, pre and postoperative lateral trunk lean, pre and postoperative walking speed and pre and postoperative body mass. We used the peak (maximum) knee adduction moment regardless of whether it was observed in the first or second half of stance. We then repeated the analysis using the knee adduction impulse. For the regression models, we plotted a histogram of the standardized residuals to determine if they were normally distributed. We also plotted the studentized residuals against the predicted values for the dependent variable to confirm homogeneity of variance of the residuals.[40] An alpha level of 0.05 was used to denote statistical significance in all analyses. Statistical analyses were completed using SPSS 20.0 (SPSS Inc., Chicago, USA).

2.4 Results

Sixty-seven of the total 264 eligible participants in the larger study met the eligibility criteria and were included (Table 2.1). Of the 67 patients, 12 had combined medial opening wedge HTO and anterior cruciate ligament reconstruction.

Table 2.1: Demographics and Clinical Characteristics

Characteristic	Value[#]
Males, no. (%)	54 (81%)
Age, years	48 ± 7
Height, meters	1.75 ± 0.09
Mass, kilograms	87.8 ± 17.6
BMI, kg/m^2	28.4 ± 4.1
Non-surgical knee mechanical axis angle, degrees	-7.4 ± 2.4
Surgical knee mechanical axis angle, degrees	-10.6 ± 3.7
Non-surgical knee KL grade, no. (%)	
0	18 (26.9%)
1	28 (41.8%)
2	17 (25.4%)
3	4 (6.0%)
4	0 (0%)
Surgical knee KL grade, no. (%)	
0	0 (0%)
1	17 (25.4%)
2	26 (38.8%)
3	20 (29.9%)
4	4 (6.0%)

[*]BMI = body mass index. KL = Kellgren Lawerence grade of OA severity (0=no OA present, 1= doubtful narrowing of joint space and possible osteophytic lipping, 2=definite osteophytes, definite narrowing of joint space, 3=moderate multiple osteophytes, definite narrowing of joints space, some sclerosis and possible deformity of bone contour, 4=large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone contour.
#Mean ± Standard deviation where applicable

There was a significant interaction between time and limb for the peak knee adduction moment ($p<0.001$) and for the frontal plane lever arm ($p<0.001$), but not for the vertical ground reaction force ($p=0.85$) (Figure 2.1). There were significant main effects for time ($p<0.001$) and limb ($p<0.001$) for the vertical ground reaction force (Figure 2.1). Preoperative, postoperative, and mean change measures for all gait and radiographic variables are summarized in Table 2.2. There were large decreases in the surgical limb knee adduction moment measures ($p<0.001$), while there were small increases in the non-surgical limb knee adduction moment measures ($p<0.05$) (Table 2.2). There were also increases in walking speed ($p<0.001$), and body mass ($p=0.01$), and decreases in lateral trunk lean for both the surgical limb ($p=0.001$), and non-surgical limb ($p=0.006$) (Table 2.2). Importantly, the non-surgical limb lever arm ($p=0.69$) and mechanical axis angle ($p=0.17$) did not change significantly (Table 2.2), suggesting these variables did not cause the increase in knee adduction moment.

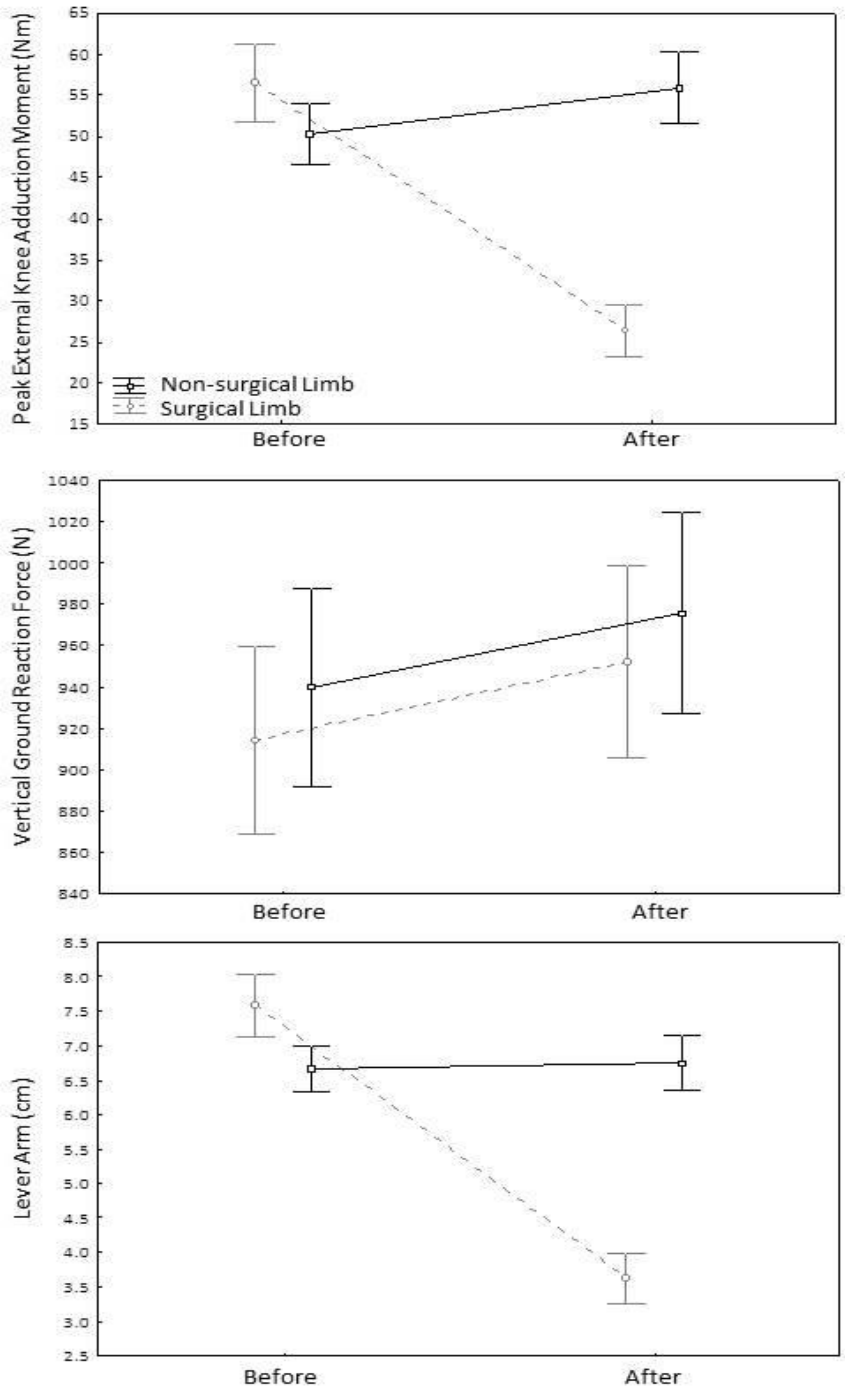

Figure 2.1: Means and 95% confidence intervals (n=67) for the surgical limb (dashed lines) and non-surgical limb (solid lines) peak external knee adduction moment (top), vertical ground reaction force (middle), and lever arm (bottom) before and 2 years after HTO. These findings suggest an increase in the non-surgical limb knee adduction moment ($p<0.001$) because of an increase in ground reaction force ($p<0.001$) without an increase in lever arm ($p=0.69$), and a decrease in the surgical limb knee adduction moment ($p<0.001$) because of a decrease in lever arm ($p<0.001$) despite an increase in ground reaction force ($p<0.001$).

Table 2.2: Gait and Radiographic Outcome Measures

Outcome Measure	Baseline, mean ± SD	24 months, mean ± SD	Change, mean (95% CI)	Change, Min, Max
Gait				
Mass (kg)	87.8± 17.6	89.2± 17.9	1.4 (0.3, 2.6)*	-10.9, 25.0
1stPeak (Nm) ‡				
Non-surgical	47.5 ± 14.8	51.8 ± 16.7	4.3 (1.73, 6.8)*	-17.0, 37.8
Surgical	54.2 ± 17.8	23.9 ± 12.5	-30.3 (-33.8, -26.8)*	-78.9, -3.7
2ndPeak (Nm)§				
Non-surgical	45.7 ± 15.8	51.3 ± 18.	5.6 (3.3, 7.9)*	-14.8, 29.5
Surgical	52.1 ± 18.4	23.4 ± 11.5	-28.7 (-33.1, -24.3)*	-63.4, 2.6
Peak (Nm)				
Non-surgical	50.3 ± 15.3	55.9 ± 15.3	5.6 (3.3, 7.9)*	-14.8, 31.3
Surgical	56.5 ± 19.2	26.4 ± 13.0	-30.1 (-33.8, -26.3)*	-78.9, -0.9
Impulse (Nms)				
Non-surgical	24.0 ± 8.1	25.2 ± 8.6	1.2 (0.04, 2.4)*	-8.9, 14.5
Surgical	27.3 ± 10.8	11.4 ± 6.3	-15.9 (-18.2, -13.7)*	-54.7, 3.8
Peak VGRF (N)				
Non-surgical	939.7 ± 195.3	975.9 ± 200.1	36.2 (23.80, 48.60)*	-65.5, 215.1
Surgical	914.2 ± 185.2	952.1 ± 190.0	37.9 (22.72, 53.04)*	-133.4, 223.2
Lever Arm (cm)				
Non-surgical	6.7 ± 1.4	6.8 ± 1.6	0.1 (-0.3, 0.5)	-4.8, 6.8
Surgical	7.6 ± 1.9	3.6 ± 1.5	-4.0 (-4.5, -3.4)*	-9.9, 1.6
Speed (m/s)				
Non-surgical	1.09 ± 0.18	1.16 ± 0.19	0.07 (0.03, 0.10)*	-0.43, 0.44
Surgical	1.09 ± 0.18	1.16 ± 0.19	0.07 (0.03, 0.10)*	-0.43, 0.44
Lateral Trunk Lean (^{o})				
Non-surgical	2.5 ± 2.3	1.6 ± 1.4	-0.9 (-1.5, -0.3)*	-9.1, 3.4
Surgical	2.9 ± 2.6	1.8 ± 2.0	-1.1 (-1.8, -0.5)*	-8.0, 5.8
Toe-out (^{o})				
Non-surgical	12.9 ± 6.2	12.5 ± 5.8	-0.4 (-1.3, 0.5)	-7.9, 10.4
Surgical	12.5 ± 5.8	13.9 ± 6.6	1.4 (0.5, 2.3)*	-8.1, 9.5
Radiographic				
MAA (^{o})				
Non-surgical	-7.4 ± 2.4	-7.7 ± 2.4	-0.3 (-0.7, 0.1)	-14.0, -5.0
Surgical	-10.6 ± 3.7	1.0 ± 3.5	11.6 (10.5, 12.7)*	-20.0, -5.0

*$p<0.05$

‡One patient did not have a 1st peak for the non-surgical limb post-operatively.

§Eight patients at baseline and six patients post-operatively did not have a 2nd peak on the surgical limb

† 95% CI = 95% confidence interval; 1stPeak = first peak knee adduction moment; 2ndPeak = second peak knee adduction moment; Peak = peak knee adduction moment; Nm = Newton metres; Impulse = Knee Angular impulse; Nms = Newton metre seconds; VGRF = Vertical ground reaction force; N = Newton; cm = centimetres; m/s = metres per second; ^{0} = degrees; kg = kilograms.

However, the surgical limb had a significant reduction in both lever arm ($p<0.001$) and mechanical axis angle ($p<0.001$) resulting in the observed reduction in the knee adduction moment (Table 2.2). All KOOS domains (pain, symptoms, function in daily living, sport and recreation and quality of life) increased with even the lower ends of the 95% confidence intervals for mean changes exceeding suggested clinically important differences of approximately 10 points (Table 2.3)

Linear regression diagnostics confirmed normality and homoscedasticity of the residuals. Results of the regression analysis indicated that while controlling for the changes in the other independent variables, the increase in walking speed (unstandardized beta coefficient (B)=17.7; 95%CI 1.0, 34.3; p=0.04), and increase in body mass (B=0.55; 95%CI 0.05, 1.1; p=0.03) were significantly related to the increase in the non-surgical limb peak knee adduction moment, whereas the decrease in lateral trunk lean towards the non-surgical limb was not (B=-0.16; 95%CI -1.5, 1.8; p=0.85). When repeating the analysis using the knee adduction impulse, the increase in mass was significantly related to increase in adduction impulse (B=0.28; 95%CI 0.03, 0.51; p=0.03). Decrease in trunk lean (B=-0.04; 95%CI -0.86, 0.79; p=0.93) and increase in walking speed (B=-5.70; 95%CI -14.0, 2.6; p=0.17) were not.

Table 2.3: Knee Injury and Osteoarthritis Outcome Scores

Outcome Measure	Baseline, mean ± SD	24 months, mean ± SD	Change, mean (95% CI)
Pain	49.2 ± 19.6	69.9 ± 20.5	20.7 (15.5, 26.0)*
Other symptoms	49.1 ± 18.9	65.9 ± 19.5	16.8 (11.7, 21.8)*
Function in daily living	58.5 ± 20.2	76.9 ± 20.5	18.4 (13.4, 23.4)*
Sports/recreation	25.6 ± 18.8	44.8 ± 28.3	19.2 (12.9, 25.5)*
Quality of life	22.2 ± 16.2	48.0 ± 26.4	25.8 (19.9, 31.7)*

*$p<0.05$
† 95% CI = 95% confidence interval; ^{0} = degrees; KOOS = Knee injury and Osteoarthritis Outcomes Score; MAA = Mechanical Axis Angle

2.5 Discussion

The present findings are consistent with our hypothesis and suggest that patients with substantial bilateral varus mal-alignment who undergo unilateral medial opening wedge HTO experience large reductions in the external knee adduction moment in the surgical limb while the non-surgical limb had a small increase in the external knee adduction moment two years after surgery. Although exceptions can occur,[41] these findings suggest an increase in medial compartment loading of the non-surgical limb. The increase in mean peak knee adduction moment is relatively small (11% of the preoperative value) and might be considered negligible, particularly given the large decrease in the surgical limb knee adduction moment (53%) and the improvements in the KOOS scores. Alternatively, the observed increase in knee adduction moment in the non-surgical limb is similar in size to the decreases often observed after various conservative interventions suggested to be of potential benefit.[20] The argument typically presented is that changes in gait may be important due to the thousands of steps taken per day[7], and the knee adduction moment is a strong risk factor for disease progression.[4,5] Importantly, the present data show that the non-surgical limb peak knee adduction moments increased

2 years post-operatively to the level of the pre-operative surgical limb (Figure 2.1). With existing mal-alignment, advanced OA in the opposite (surgical) limb, and commonly being overweight or obese, these patients have multiple risk factors for disease progression in the non-surgical limb. Therefore, we suggest that even a small increase in the knee adduction moment of the non-surgical limb after HTO deserves attention. Given the potential for future degeneration, mechanisms for the observed increase in the knee adduction moment, and potential ways to mitigate them, should be explored.

Varus alignment of the non-surgical limb did not change after surgery in the present sample (Table 2.2) and therefore was not responsible for the observed increase in knee adduction moment. Rather, consistent with our hypothesis, the present findings suggest that other characteristics changed after surgery. Specifically, patients walked with increased speed and decreased trunk lean towards the stance limb. Although these walking characteristics suggest a more normal gait pattern, indeed increased walking speed is often a treatment goal and outcome measure of success after interventions, they contribute to higher peak knee adduction moments nonetheless.[8,13] Importantly, the present patients gained weight in the 2 years after surgery (Table 2.2), which also contributed to the increase in knee adduction moment on the non-surgical limb. The present data suggest that even while controlling for the decrease in trunk lean and increase in walking speed, a 1kg increase in mass was associated with a 0.55Nm increase in knee adduction moment. This is quite consistent with cross-sectional data from a larger sample of patients with substantial varus alignment, where a 1 kg increase in body mass was associated with a 0.4 Nm increase in peak knee adduction moment.[42] It is also quite consistent with previously reported prospective weight loss data, suggesting a 1kg

decrease in mass was associated with a 0.50 Nm decrease in knee adduction moment.[7] Overall, the literature suggest that mitigating weight gain after surgery should be an important goal of postoperative rehabilitation. Indeed, weight-loss would seem to be important to the health of both limbs after HTO.

Changes in the non-surgical limb after HTO have been documented in two previous studies. Weidenhielm et al.[31] evaluated 17 patients before and 1 year after undergoing either a closing wedge HTO (n=8) or unicompartmental knee replacement (n=9). For the combined group of patients, there were significant decreases in the mid-stance peak knee adduction moment (27%) and the frontal plane lever arm (19%). Conversely, Lind et al.[27] evaluated 11 patients before and 1 year after medial opening wedge HTO, and reported an increase in the mean maximum adduction moment in both early (24%) and late stance (36%). They also reported a significant increase in the maximum adduction angle of the non-surgical limb and an increase in self-selected gait speed. Although not specifically evaluated, both Weidenhielm et al.[31] and Lind et al.[27] hypothesized that the changes in the knee adduction moment in the non-surgical limb may occur because the patients adopt a more normal gait pattern. Our gait findings generally agree with those of Lind et al.[27] and suggest increases in gait speed and body mass after unilateral HTO may negatively impact the biomechanics of the non-surgical limb.

Limitations in the present study include the fact that patients responded to the patient-reported outcomes in reference to the surgical limb only. It is possible that patient-reported outcomes may have worsened in the non-surgical limb, but were not measured. We must also acknowledge that the present study design does not enable us to

determine with certainty whether the surgery contributed to the changes in the non-surgical limb, or if the changes were simply due to the passage of time. The present findings are somewhat consistent, however, with previous reports suggesting a degradation in biomechanical outcomes in the non-surgical limb, and emphasizing the importance of potential increases in body mass, after unilateral total knee arthroplasty.[43-45] More specifically, the present findings suggest that an increase in peak vertical ground reaction force of both limbs, due to increased gait speed and especially increased body mass, leads to an increase in the knee adduction moment of the non-surgical (and malaligned) limb, but not in the surgical limb with corrected alignment (Figure2.1). The importance of continuing to address impairments in the surgical limb after HTO has been previously established.[46,47] The present findings suggest that we also need to be cognizant of potential increased loads in the non-surgical limb. In that regard, several conservative strategies aimed at decreasing the knee adduction moment exist and should be considered during rehabilitation after HTO.[48] Lastly, we believe the present findings also underscore the importance of considering the effects of multi-modal interventions that address multiple contributors to aberrant joint loads bilaterally.

2.6 References

1. Andriacchi TP. Dynamics of knee malalignment. Orthop Clin North Am. 1994;25:395-403.
2. Hunt MA, Birmingham TB, Giffin JR, Jenkyn TR. Associations among knee adduction moment, frontal plane reaction force, and lever arm during walking in patients with knee osteoarthritis. J Biomech. 2006;39:2212-2220.
3. Schipplein OD, Andriacchi TP. Interaction between active and passive knee stabilizers during level walking. J Orthop Res. 1991;9:113-119.
4. Bennell KL, Bowles K, Wang Y, Cicuttini F, Davies-Tuck M, Hinman RS. Higher dynamic medial knee load predicts greater cartilage loss over 12 months in medial knee osteoarthritis. Ann Rheum Dis. 2011;70:1770-1774.
5. Miyazaki T., Wada M., Kawahara H., Sato M., Baba H., Shimada S. Dynamic load at baseline can predict radiographic disease progression in medial compartment knee osteoarthritis. Ann Rheum Dis. 2002;61:617-622.
6. Hurwitz De, Ryals AB, Case JP, Block JA, Andriacchi TP. The knee adduction moment during gait in subjects with knee osteoarthritis is more closely correlated with static alignment than radiographic disease severity, toe out angle and pain. J Orthop Res. 2002;20:101-107.
7. Messier SP, Gutekunst DJ, Davis C, DeVita P. Weight loss reduces knee-joint loads in overweight and obese older adults with knee osteoarthritis. Arthritis Rheum. 2005;52:2026-2032.
8. Robbins SMK, Maly MR. The effect of gait speed on the knee adduction moment depends on waveform summary measures. Gait Posture. 2009;30:543-546.
9. Blagojevic M, Jinks C, Jeffery A, Jordan KP. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. Osteoarthritis Cart. 2010;18:24-33.
10. Niu J, Zhang YQ, Torner J, et al. Is obesity a risk factor for progressive radiographic knee osteoarthritis? Arthritis Rheum. 2009;61:329-335.
11. Sharma L, Chmiel JS, Almagor O, et al. The role of varus and valgus alignment in the initial development of knee cartilage damage by MRI: the MOST study. Ann Rheum Dis. 2013;72:235-240.
12. Sharma L, Song J, Felson DT, Cahue S, Shamiyeh E, Dunlop DD. The role of knee alignment in disease progression and functional decline in knee osteoarthritis. JAMA. 2001;286:188-195.
13. Mundermann A, Dyrby CO, Hurwitz DE, Sharma L, Andriacchi TP. Potential strategies to reduce medial compartment loading in patients with knee osteoarthritis of varying severity. Arthritis Rheum. 2004;50:1172-1178.
14. Hunt MA, Birmingham TB, Bryant D, et al. Lateral trunk lean explains variation in dynamic knee joint load in patients with medial compartment knee osteoarthritis. Osteoarthritis Cart. 2008;16:591-599.

15. Mundermann A, Asay JL, Mundermann L, Andracchi TP. Implications of increased medio-lateral trunk sway for ambulatory mechanics. J Biomech. 2008;41:165-170.
16. Guo M, Axe MJ, Manal K. The influence of foot progression angle on the knee adduction moment during walking and stair climbing in pain free individuals with knee osteoarthritis. Gait Posture. 2007;26:436-441.
17. Jenkyn TR, Hunt MA, Jones IC, Giffin JR, Birmingham TB. Toe-out in patients with knee osteoarthritis partially transforms external knee adduction moment into flexion moment during early stance phase of gait: A tri-planar kinetic mechanism. J Biomech. 2008;41:276-283.
18. Shull PB, Shultz R, Sider A, et al. Toe-in gait reduces the first peak knee adduction moment in patients with medial compartment knee osteoarthritis. J Biomech. 2013;46:122-128.
19. Felson DT, Zhang Y, Hannan MT, et al. The incidence and natural history of knee osteoarthritis in the elderly: The Framingham osteoarthritis study. Arthritis Rheum. 1995;38:1500-1505.
20. Jones RK, Champman GJ, Findlow AH, et al. A new approach to prevention of knee osteoarthritis: reducing medial load in the contralateral knee. J Rheumatol. 2013;40:309-315.
21. Mazzuca SA, Brandt KD, Lane KA, Chakr R. Malalignment and subchondral bone turnover in contralateral knees of overweight/obese women with unilateral osteoarthritis: Implication for bilateral disease. Arthritis Care Res. 2011;63:1528-1534.
22. Mont MA Mitzner DL, Jones LC, Hungerford DS. History of the contralateral knee after primary knee arthroplasty for osteoarthritis. Clin Orthop Relat Res. 1995;321:145-150.
23. Spector TD, Hart DJ, Doyle DV. Incidence and progression of osteoarthritis in women with unilateral knee disease in the general population: the effect of obesity. Ann Rheum Dis. 1994:53:565-568.
24. Amendola A, Bonasia DE. Results of high tibial osteotomy: review of the literature. Int Orthop. 2010;34:155-160.
25. Birmingham TB, Giffin JR, Chesworth BM, et al. Medial opening wedge high tibial osteotomy: A prospective cohort study of gait, radiographic and patient-reported outcomes. Arthritis Rhem. 2009;61:648-657.
26. DeMeo PJ, Johnson EM, Chiang PP, Flamm AM, Miller MC. Midterm follow-up of opening-wedge high tibial osteotomy. Am J Sports Med. 2010;38:2077-2084.
27. Lind M, McClelland J, Wittwer JE, Whitehead TS, Feller JA, Webster KE. Gait analysis of walking before and after medial opening wedge high tibial osteotomy. Knee Surg Sports Traumatol Arthrosc. 2013.21;1:74-81.

28. Prodromos CC, Andriacchi TP, Galante JO. A relationship between gait and clinical changes following high tibial osteotomy. J Bone Joint Surg Am. 1985;67:1188-1194.
29. Wada M, Imura S, Nagatani K, Baba H, Shimada S, Sasaki S. Relationship between gait and clinical results after high tibial osteotomy. Clin Orthop. 1998;354:180-188.
30. Wang JW, Kuo KN, Andriacchi TP, Galante JO. The influence of walking mechanics and time on the results of proximal tibial osteotomy. J Bone Joint Surg. 1990;72-A:905-909.
31. Weidenhielm L, Svensson OK, Brostrom LA. Surgical correction of leg alignment in unilateral knee osteoarthrosis reduces the load on the hip and knee joint bilaterally. Clin Biomech. 1995;10:217-221.
32. Boulougouris A, Birmingham TB, Moyer R, Jones I, Giffin JR. Increased dynamic knee joint load on the non-operative limb after high tibial osteotomy. In: Proceedings of the World Congress on Osteoarthritis, San Diego, CA. 2011;19:S17.
33. Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. Arthritis Rheum. 1986;29:1039-1049.
34. Specogna AV, Birmingham TB, DaSilva JJ, et al. Reliability of lower limb frontal plane alignment measurements using plain radiographs and digitized images. J Knee Surg. 2004;17:203-210.
35. Kellgren JH, Lawrence JS. Radiological assessment of osteoarhtrosis. Ann Rheum Dis. 1957;16:494-502.
36. Kadaba MP, Ramakrishnan HK, Wootten ME. Measurement of lower extremity kinematics during level walking. J Orthop Res. 1990;8:383-392.
37. Thorp LE, Wimmer MA, Block JA, et al. Bone mineral density in the proximal tibia varies as a function of static alignment and knee adduction angular momentum in individuals with medial knee osteoarthritis. Bone. 2006;39:1116-1122.
38. Roos EM, Lohmander LS. The knee injury and osteoarthritis outcome score (KOOS): from joint injury to osteoarthritis. Helath Qual Life Outcomes. 2003;1:64.
39. W-Dahl A, Toksvig-Larsen S, Roos EM. A 2-year prospective study of patient-relevant outcomes in patients operated on for knee osteoarthritis with tibial osteotomy. BMC Musculoskelet Disord. 2005;6:18.
40. Kleinbaum DG, Kupper LL, Muller KE. Applied regression analysis and other multivariable methods. 2nd ed. Belmont, California: Duxbury Press;1998:185-196.

41. Walter JP, D'Lima DD, Colwell Jr. CW, Fregly BJ. Decreased knee adduction moment does not guarantee decreased medial contact force during gait. J Orthop Res. 2010;28:1348-1354.
42. Moyer RF, Birmingham TB, Chesworth BM, Kean CO, Giffin JR. Alignment, body mass and their interaction on dynamic knee joint load in patients with knee osteoarthritis. Osteoarthritis Cart. 2010;18:888-893.
43. Alnahdi AH, Zeni JA, Snyder-Mackler L. Gait after unilateral total knee arthroplasty: frontal plane analysis. J Orthop Res. 2011;29:647-652.
44. Farquhar S, Snyder-Mackler L. The Chitranjan Ranawat Award: The nonoperated knee predicts function 3 years after Arthroplasty. Clin Orthop Relat Res. 2010;468:37-44.
45. Zeni JA Jr., Snyder-Mackler L. Early postoperative measures predict 1- and 2-year outcomes after unilateral total knee arthroplasty: importance of contralateral limb strength. Phys Ther. 2010;90:43-54.
46. Kean CO, Birmingham TB, Garland SJ, Bryant DM, Giffin JR. Preoperative strength training for patients undergoing high tibial osteotomy: a prospective chort study with historical controls. J Orthop Sports Phys Ther. 2011;41:52-59.
47. Ramsey DK, Snyder-Mackler L, Lewek M, Newcomb W, Rudolph KS. Effect of anatomic realignment on muscle function during gait in patients with medial compartment knee osteoarthritis. Arthritis Rhem. 2007;57:389-397.
48. Simic M, Hinman RS, Wrigley TV, Bennell KL, Hunt MA. Gait modification strategies for altering medial knee joint load: A systematic review. Arthritis Care Res. 2011;63:405-426.

Chapter 3

3 Reliability of Body Composition Measures Using Air Displacement Plethysmography in Patients with Knee Osteoarthritis

3.1 Summary

The objective of the present study was to establish the reliability and minimal detectable change in air displacement plethysmography (ADP) measures of body density, fat mass, lean mass and percent body fat in a sample of overweight-to-obese patients with knee osteoarthritis (OA). Fourteen patients with knee OA (age; 54 ± 6, BMI; 32.5 ± 4.8) underwent two body composition tests 24-to-36 hours apart using air displacement plethysmography (BodPod®). Test-retest reliability was evaluated using Bland-Altman plots, intraclass correlation coefficients (ICC type 2,1) and standard errors of measurement (SEM). Minimum detectable change values were then calculated for various levels of confidence. All of the ICCs were very high (>0.98). Standard errors of measurement for density, fat mass, lean mass and percent body fat were ±0.2kg/L^{-2}, ±1.5kg, ±1.2kg and ±1.3%, respectively. Upon repeated testing 95% of stable patients would change by less than approximately 2% body fat and 75% of stable patients would change by less than 1% body fat. Air displacement plethysmography provides excellent test-retest reliability and minimum detectable change values for measures of body composition in overweight-to-obese patients with knee OA.

3.2 Introduction

Knee osteoarthritis (OA) is a leading cause of pain, disability and healthcare use worldwide, resulting in substantial personal and societal burden.[1-4] Over 250 million people have knee OA and it has become one of the fastest growing major health

conditions related to physical inactivity, obesity and an aging population. [2] Obesity is thought to contribute to knee articular cartilage degradation through both biomechanical and systemic factors, as excessive body mass places aberrant loads on the knee, and excessive adipose tissue promotes the release of adipokines that cause inflammation.[5,6] Accordingly, clinical practice guidelines consistently suggest that obesity is one of the most important, modifiable risk factors for the development and progression of knee OA and should be a focus of treatment .[7-9]

Most studies investigating obesity and knee OA measure body mass or body mass index (BMI) rather than specific measures of body composition.[10-12] This is less than ideal as several methods to assess body composition are available including skinfolds, bioelectrical impedance analysis, dillution techniques, air displacement plethysmography, dual energy X-ray absorptiometry, and magnetic resonance imaging.[13] Typically reported components include fat and lean mass (sometimes referred to as fat-free mass). Body fat is also often expressed as a percent of total body mass (i.e. percent body fat). [13]

Measures of body composition appear to be important when studying the progression and treatment of knee OA. For example, observational studies indicate that greater fat mass is associated with a decrease in tibial cartilage volume, and an increase in both tibiofemoral cartilage defects and eventual arthroplasty, while greater lean mass is associated with an increase in tibial cartilage volume.[14,15] Body mass reduction studies indicate that improvement in pain and function are best predicted by reductions in body fat.[16,17] Further, systematic reviews evaluating exercise interventions for knee OA suggest that improvements in pain and function are mediated by a reduction in fat mass or a gain in lean mass.[18,19]

The BodPod® (Life Measurement, Inc, Concord, CA), uses air displacement plethysmography (ADP) and body mass measures to determine body density from which estimates of fat mass, lean mass and percent body fat are possible.[20] The volume of an individual is measured as the litres of air displaced inside an enclosed chamber and mass with an accurate scale.[20] With both body volume and mass determined, body density is calculated.[20] Then, knowing the densities of fat and lean tissue from cadaver analyses body composition can be estimated reliably.[21]

Previous investigators have reported the reliability of BodPod® measures when repeated on the same testing day for a range of participants[20] and on different test days in a sample of young healthy individuals.[22] We are unaware of previous research reporting the test-retest reliability of body composition measures in a sample of patients with knee OA who are typically overweight or obese. Therefore, the measurement error and minimal detectable change of such measures that can be used to help interpret potential changes in fat or lean mass following interventions for patients with knee OA are currently unclear. The purpose of this study was to estimate the test-retest reliability of body composition measures of body density, fat mass, lean mass and percent body fat using ADP measured by the BodPod®, and to describe the results in terms of measurement error and minimal detectable change for overweight-to-obese patients with knee OA.

3.3 Methods

3.3.1 Participants

Fourteen patients (10 men, 4 women) with knee OA were recruited from a tertiary care center specializing in orthopedics. All patients had symptomatic knee OA with Kellgren and Lawrence grade ≥ 2 in the tibiofemoral joint.[23] Patient demographic and clinical characteristics are summarized in Table 3.1. Each patient attended two test sessions with at least 24 hours, and no more than 3 days, between sessions. Patients were advised to continue their current practices for managing their symptoms, but not to begin any new treatments between testing sessions. Ethics approval was provided by the institution's Research Ethics Board for Health Sciences Research Involving Human Subjects. All participants provided informed consent before testing.

Table 3.1: Demographics and Clinical Characteristics

Characteristic	Mean ± SD
Age, years	54 ± 6
Height, m	1.70 ± 0.10
Total Mass, kg	96.1 ± 19.5
Body mass index, kg/m^2	32.5 ± 4.8
Right knee KL grade of OA	No. of patients
0	0
1	3
2	7
3	0
4	4
Left knee KL grade of OA	
0	0
1	1
2	5
3	2
4	6

KL = Kellgren Lawerence grade of OA severity (0=no OA present, 1= doubtful narrowing of joint space and possible osteophytic lipping, 2=definite osteophytes, definite narrowing of joint space, 3=moderate multiple osteophytes, definite narrowing of joints space, some sclerosis and possible deformity of bone contour, 4=large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone contour.

3.3.2 Body Composition

Each patient had his/her body volume measured through air displacement plethysmography using the BodPod® and software version 1.69 as outlined by the manufacturer. The testing procedures followed those suggested by Noreen & Lemon[20] to maximize reliability. Before testing, the scale was calibrated using two 10-kg weights, and the Bod Pod® chamber was calibrated using a cylinder of known volume. The patient's height was measured using a stadiometer. Each patient was weighed wearing only a tight-fitting swimsuit or undergarments and an acrylic swim cap. Patients sat in the chamber and body volume measurements were taken. This measurement was done in

duplicate, with each test lasting approximately 40 seconds. If both measures were within 150mL of each other, the mean was taken and used in subsequent calculations. If the two measurements differed by >150ml, a third measurement was performed. If two of the three measurements were within 150ml of each other, the mean of those two were taken and used, but if the three measurements were not within 150ml of each other, the entire process, including the calibration steps, was repeated. The measured body volume was adjusted for lung volume and body surface area artifact using prediction equations. This corrected body volume was used in combination with the body mass to determine body density (body density = body mass/body volume). The resultant body density was used in the Siri equation[21] [(%fat = 495/body density)-450] to estimate body composition values for fat mass, lean mass and percent fat. All calculations were done using the system software. This entire procedure was repeated for the second test session. The total time to calibrate the BodPod® was approximately 20 minutes and data collection took approximately 5 minutes per individual.

3.3.3 Statistical Analysis

Test-retest data were first examined graphically for each body composition measure (i.e. density, fat mass, lean mass and percent fat) using Bland-Altman plots in which the difference between test sessions was plotted against the mean of the two test sessions.[24] Test sessions were compared using a paired t-test and mean differences with 95% CIs were calculated. Test-retest reliability of each measure was evaluated using the intraclass correlation coefficient (ICC type 2,1) and the standard error of measurement (SEM). The ICC provided an indication of how well the body composition measure distinguished among patients (relative reliability), whereas the SEM provided an

expression of the measurement error in the original units (absolute reliability).[25] The SEM was then used to estimate the error in an individual patient's body composition measure at one point in time by multiplying the SEM by the z-value associated with various confidence levels. The estimated error at one point in time was then multiplied by the square root of 2 (to account for measurement error on 2 test sessions) to estimate the minimal detectable change using those same confidence levels.[25]

3.4 Results

Within each test session, the mean of two body volume measurements was used (i.e. a third measurement was not required as the values did not differ by greater than 150ml). Bland-Altman plots suggested no obvious biases between days in density (Figure 3.1A), fat mass (Figure 3.1B), lean mass (Figure 3.1C), or percent body fat (Figure 3.1D). There were also no statistically significant differences between test sessions for density, fat mass, lean mass or percent fat. Mean differences were very small and 95%CIs around the differences were narrow (Table 3.2). All of the ICCs were very high, with even the lower ends of the 95%CIs greater than 0.98, while the SEMs were very low (Table 3.2). Estimates of the error associated with an individual patient's fat mass, lean mass and percent fat at one point in time, and the minimal detectable change upon reassessment, are reported for various confidence levels in Table 3.3.

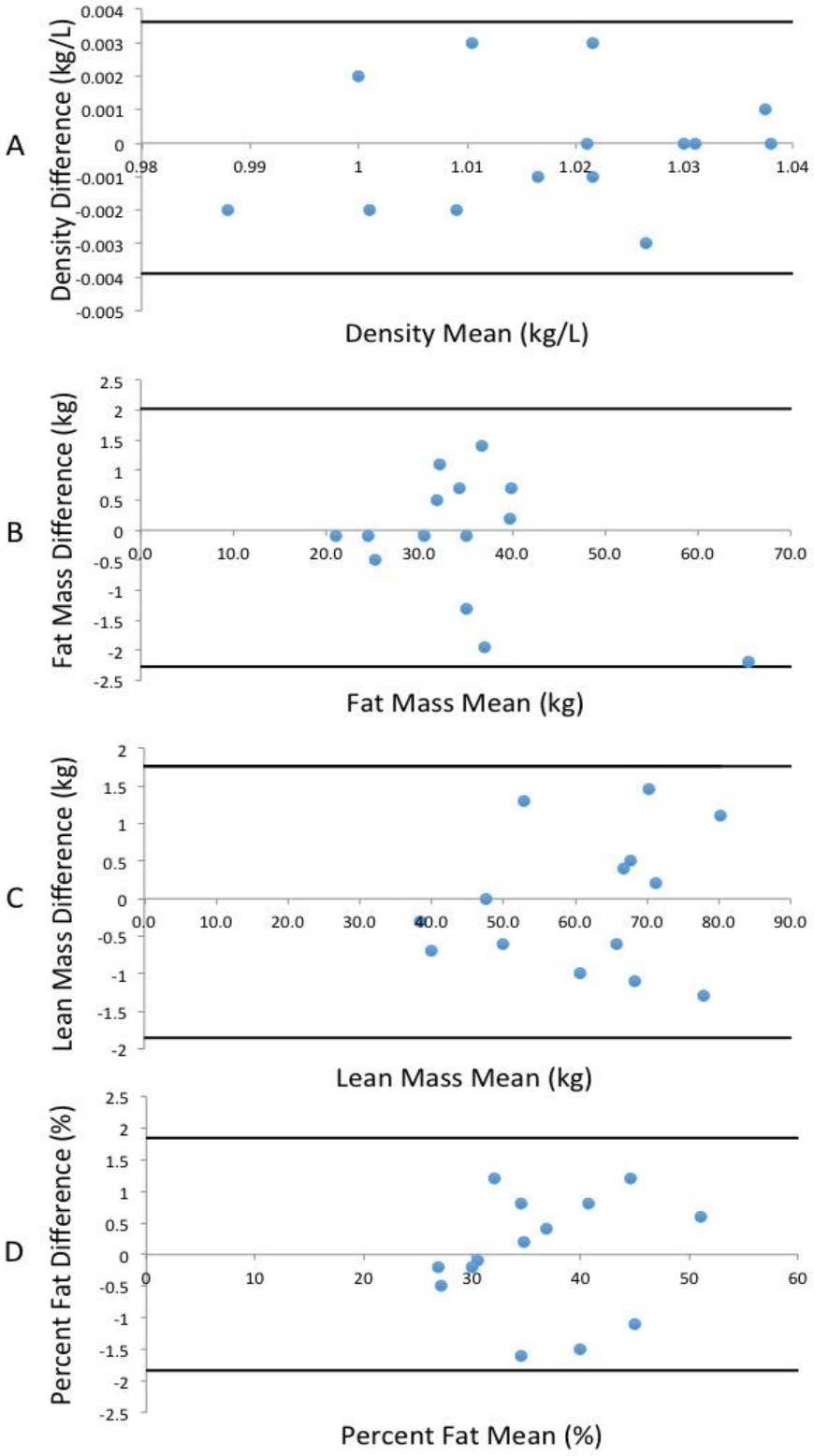

Figure 3.1: Bland-Altman plots showing the difference between the test and retest (y-axis) versus the mean of the test and retest (x-axis) for A. Density, B. Fat Mass, C. Lean Mass and D. Percent Fat. Horizontal lines represent ±2 Standard Deviations

Table 3.2: Mean ± SD Values for Body Composition Measures for Day 1 and Day 2

Outcome Measure	Test 1 Mean ± SD	Test 2 Mean ± SD	Mean Difference (95% CI)	ICC (95%CI)	SEM
Density(kg/L)	1.02 ± 0.02	1.02 ± 0.02	$-0.01^{-2}(-0.1^{-2},0.09^{-2})$	0.99 (0.977,0.998)	0.12^{-2}
Fat Mass (kg)	34.9 ± 10.2	35.0 ± 10.7	-0.13 (-0.7, 0.5)	0.99 (0.985, 0.998)	0.74
Lean Mass (kg)	61.2 ± 13.4	61.3 ± 13.3	0.05 (-0.6, 0.5)	0.99 (0.993, 0.999)	0.60
Percent Fat (%)	36.3 ± 7.2	36.3 ± 7.1	-0.0001(-0.5, 0.5)	0.99 (0.976, 0.998)	0.64

95% CI = 95% confidence interval; ICC = intraclass correlation coefficient;
SEM = Standard Error of Measurement = SD√1-ICC

Table 3.3: Measurement Error and Minimal Detectable Change for Density, Fat mass, Lean mass and Percent Fat for Various Confidence Intervals

Body Composition		Confidence level (%)					
		95%	90%	85%	80%	75%	50%
Density $(kg/L)^{-2}$	Measurement error *	0.24	0.20	0.18	0.16	0.14	0.08
	Minimal detectable change **	0.34	0.29	0.25	0.23	0.20	0.12
Fat Mass (kg)	Measurement error *	1.5	1.2	1.0	0.9	0.8	0.5
	Minimal detectable change**	2.1	1.7	1.5	1.3	1.2	0.7
Lean Mass (kg)	Measurement error *	1.2	1.0	0.9	0.8	0.7	0.4
	Minimal detectable change**	1.7	1.4	1.2	1.1	1.0	0.6
Percent Fat (%)	Measurement error *	1.3	1.1	0.9	0.8	0.7	0.4
	Minimal detectable change**	1.8	1.5	1.3	1.2	1.0	0.6

*Standard Error of Measurement x Z value
**Standard Error of Measurement x Z value x √2

3.5 Discussion

The observed ICCs suggest excellent test-retest reliability of the BodPod® for evaluating body composition measurements in patients with knee OA. A high ICC implies that the between-patient variability in the studied sample is high relative to the within-patient variability. Therefore, the present, very high ICCs indicate that BodPod® measurements of fat mass, lean mass and percent fat are highly reliable for use in studies measuring changes in groups of patients with knee OA undergoing treatments aimed at altering body composition.

The SEM provides more clinically relevant information about how to interpret an individual patient's body composition measures. For example, based on the information provided in Table 3 and using the SEM with the confidence level of 95%, an individual patient's true density, fat mass, lean mass and percent fat could vary by ±0.2kg/L^{-2}, ±1.5kg, ±1.2kg, and ±1.3%, respectively. Note that smaller estimates of measurement error are determined if a lower level of confidence is chosen (Table 3).

Importantly, the SEM also allows for estimates of the minimum detectable change in these measures. For example, the values presented in Table 3 suggest that in almost all (95%) of stable patients undergoing repeated testing**,** body density would change by <0.3kg/L^{-2}, fat mass would change by <2.1kg, lean mass would change by <1.7kg and percent body fat would change by <1.8%. In the vast majority (75%) of stable patients, body density would change by <0.2kg/L^{-2}, fat mass would change by <1.2kg, lean mass would change by <1.0kg and percent body fat would change by <1.0%. Therefore, when evaluating change in body composition in an individual knee OA patient with a BMI ≥25, we could be quite confident of a true change occurring if the patient lost or gained at least

approximately 1kg fat mass, 1kg lean mass or 1% body fat. Alternatively, if the patient lost or gained lesser amounts we cannot be very confident that a true change has occurred (Table 3).

Although one's true body composition is unlikely to change significantly in 24-36 hours, variation in measurements between test days could be explained by measurement error. For example, if an individual's level of hydration changed between test days, this could impact density measures. A change in temperature above the skin is a potential source of error. This was minimized in the present study by the use of tight fitting clothing. If the temperature around the skin is warm it causes it to be more compressible therefore underestimating body volume.[20] It is also possible that metabolic rate could affect the temperature of the air layer above the skin and influence body volume measures. This was controlled in the present study by having the patients abstain from exercise for 2 hours prior to the testing. In addition, there is some evidence that BodPod® units used in different laboratories may provide data that are more variable due to the surrounding environmental conditions as opposed to the units themselves which may also contribute to this variability .[20,26] Room temperature was kept constant at 20° C for the present study.

It should be noted that the greatest variation in measurements between testing days occurred in two active individuals who were over 100kg and most likely to have variation in hydration levels. It is possible that lower minimum detectable change values may be more suitable for patients with lower body mass, and higher minimum detectable change values may be more suitable for patients with higher body mass. The present reliability estimates are only generalizable to patients with characteristics similar to the

present study's patients. The sample included middle-aged (54±6 years), overweight-to-obese (36.3±7.2% fat) patients with knee OA. Although these participants are representative of those patients where losses in body fat and gains in lean mass are primary treatment goals, the present estimates should only be used cautiously in individuals with other characteristics.

3.6 References

1. Badley EM. Arthritis in Canada: what do we know and what should we know? J Rheumatol 2005;32 Suppl:32-41
2. Horton R. GBD 2010: understanding disease, injury, and risk. Lancet 2012;380:2053-2054. DOI 10.1016/S0140-6736(12)62133-3.
3. Kadam UT, Croft PR. Clinical comorbidity in osteoarthritis: associations with physical function in older patients in family practice. J Rheumatol 2007;34:1899-904.
4. Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: part II. Arthritis Rheum 2008;58:26-35.
5. Berry PA, Jones SW, Cicuttini FM, Wluka AE, Maciewicz RA. Temporal relationship between serum adipokines, biomarkers of bone and cartilage turnover, and cartilage volume loss in population with clinical knee osteoarthritis. Arthritis Rheum 2011;63:700-707.
6. Pottie P, Presle N, Terlain B et al. Obesity and osteoarthritis: more complex than predicted! Ann Rheum Dis 2006;65:1403-1405.
7. Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis. Part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis Cartilage 2008;16(2): 137-62
8. Hochberg MC, Altman RD, Toupin Aril K, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res 2012;64(4):465-74.
9. National Collaborating Centre for Chronic Conditions. Osteoarthritis: national clinical guideline for care and management in adults. London: Royal College of Physicians, 2008.
10. Felson DT, Chaisson CE. Understanding the relationship between body weight and osteoarthritis. Baillieres Clin Rheumatol 1997;11:671-681.
11. Felson DT, Anderson JJ, Naimark A, Walker AM, Meenan RF. Obeisty and knee osteoarthritis. The Framingham Study. Ann Intern Med 1988;109;18-24
12. Messier SP Loeser RF, Miller GD, Morgan TM, Rejeski J, Sevick MA, Ettinger WH, Pahor M, Williamson JD. Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis. Arthritis Rheum 2004;50:1501-1510.
13. Lee SY & Gallagher D. Assessment methods in human body composition. Curr Opin Clin Nurtr Metab Care 2008;11:566-572.
14. Wang Y, Wluka AE, English DR, Teichtahl AJ, Giles GG, O'Sullivan R, et al. Body composition and knee cartilage properties in healthy, community-based adults. Ann Rheum Dis 2007;66:1244-1248.
15. Wang Y, Simpson JA, Wluka AE, Teichtahl AJ, English DR, Giles GG, Graves S, Cicuttini FM. Relationship between body adiposity measures and risk of primary knee and hip replacement for osteoarthritis: a prospective cohort study. Arthritis Res & Ther 2009;DOI:10.1186/ar2636.

16. Christensen R, Astrup A, Bliddal H. Weight loss: the treatment of choice for knee osteoarthritis? A randomized trial. Osteoarthritis Cartilage 2005;13:20-27
17. Toda Y, Toda T, Takemur S et al. Change in body fat, but not body weight or metabolic correlates of obesity, is related to symptomatic relief of obese patients with knee osteoarthritis after a weight control program. J Rheumatol 1998;25:2181-2186.
18. Fransen M, McConnell S. Exercise for osteoarthritis of the knee. Cochrane Database of Systematic Reviews 2008, Issue 4. Art. No.:CD004376. DOI: 10.1002/14651858.CD004376.pub2.
19. Roddy E, Zhang W, Doherty M. Aerobic walking or strengthening exercise for osteoarthritis of the knee? A systematic review. Ann Rheum Dis 2005;64:544-548.
20. Noreen EE, Lemon PW. Reliability of air displacement plethysmography in a large, heterogeneous sample. Med Sci Sports Exerc 2006;38:1505-1509.
21. Siri, WE. Body composition from fluid spaces and density: analysis of methods. In: Techniques for measuring Body Composition, J. Brozek and A. Henschel (Eds.). National Research Council, Washington, DC: National Academy of Sciences, pp. 223-244, 1961.
22. Anderson DE. Reliability of air displacement plethysmography. J Strength Cond Res 2007;21:169-172.
23. Kellgren JH, Lawrence JS. Radiological assessment of osteoarthrosis. Ann Rheum Dis 1957;16:494-502.
24. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1:307-10.
25. Stratford PW, Binkley J, Solomon P, Finch E, Gill C, Moreland J. Defining the minimum level of detectable change for the Roland-Morris Questionnaire. Phys Ther 1996;76:359-365.
26. Collins AL, Saunders S, McCarthy HD, Williams JE, Fuller NJ. Within and between precision in the measurement of body volume using air displacement plethysmography and its effect on body composition assessment. Int. J. Obes. Relat. Metab. Disord. 28:80-90, 2004.

Chapter 4

4 Mitigating risk factors for disease progression in patients with varus gonarthrothis: A proof of principle study of combined rehabilitative and surgical interventions

4.1 Summary

Rehabilitative interventions for patients with knee osteoarthritis (OA) can substantially decrease body mass and increase muscular strength, but have limited effects on limb mal-alignment. High tibial osteotomy (HTO) can effectively correct mal-alignment, but can also lead to increased body mass and decreased muscular strength. The primary objective of the present study was to investigate the cumulative effects of combined physiotherapy and medial opening wedge HTO on multiple risk factors for OA progression in patients with varus gonarthrosis. In this proof of principle study, eight patients with varus mal-alignment and medial compartment knee OA completed a combined intervention consisting of medial opening wedge HTO and 8-weeks of rehabilitation with a focus on reducing fat mass and increasing muscular strength (multi-modal physiotherapy, MPT) repeated approximately 4 months before and 12 months after surgery. Outcomes included measures of body composition, isokinetic strength, radiographic lower limb alignment, the external knee adduction moment during walking, and the Knee injury and Osteoarthritis Outcome Score (KOOS). Repeated measures analysis of variance indicated significant ($p<0.05$) changes over time for all outcome measures with the exception of lean mass. Mean changes (95%CI) from the study baseline to its endpoint indicated that, overall, patients lost substantial fat mass [4.6 kg (-8.0, -1.2)], made modest improvements in isokinetic knee extension peak torque [7.2Nm (-45.0, 59.5)] and knee flexion peak torque [23.0Nm (-1.8, 47.7)], had mal-alignment

corrected from substantial varus to approximately neutral [8.6° (6.3, 10.8)], and experienced very large improvements in the peak knee adduction moment during walking [-27.7Nm (-43.1, -11.6)] and improved KOOS scores [e.g., decrease in pain = 31.4 (10.0, 52.8)]. Moreover, the MPT was required to produce the improvements in body composition and strength, whereas the HTO was required to produce the improvements in alignment and knee adduction moment. The present findings support the principle of using combined multi-modal rehabilitative and surgical interventions that target different risk factors to produce overall, cumulative effects for patients with varus gonarthrosis.

4.2 Introduction

Osteoarthritis (OA) is one of the leading causes of disability worldwide, creating substantial burden on individuals and societies.[1-4] The knee is the weight-bearing joint most commonly affected by OA, and most commonly involves the tibiofemoral medial compartment.[5,6] The OA disease process is driven by both biomechanical and systemic factors.[7-9] Accordingly, the incidence and prevalence of knee OA is increasing along with increasing levels of physical inactivity and obesity in an aging population.[2] Authorities emphasize the importance of establishing interventions aimed at limiting knee OA progression, operationally defined presently as multiple measures of deterioration of joint structure (e.g., radiographic and magnetic resonance imaging markers) and/or declines in patient-important outcomes (e.g., measures of pain and function).[10-13]

Several published clinical practice guidelines suggest evidence-based treatment options for knee OA.[14-16] These guidelines emphasize the importance of multi-modal interventions that include patient education, decreasing body mass and improving muscular strength.[14-16] The guidelines are consistent with respect to recommending

physiotherapy.[14-16] Recommendations regarding surgery for knee OA are less consistent, but generally suggest that operative procedures such as osteotomy, and especially total joint replacement, be considered only after non-operative treatments have failed.[14-16]

Interventions aimed at limiting progression of knee OA focus on its risk factors. Known risk factors for knee OA that may be modifiable include obesity[17-20], muscular weakness[21-24], lower limb mal-alignment[25-27] and measures representing the load on the knee during walking[28-29]. Several longitudinal studies link obesity and knee OA.[17-20,30-34] Greater fat mass is associated with a decrease in tibial cartilage volume, and an increase in both tibiofemoral cartilage defects and eventual arthroplasty.[33,34] Although less consistent than obesity, muscular weakness is also associated with knee OA[21-24], with greater quadriceps strength serving to protect against symptoms.[21,23] Several recent studies now link lower limb frontal plane mal-alignment with knee OA, including incident and progressive medial and lateral tibiofemoral structural changes[26,27,35], and functional declines[25]. The external knee adduction moment during walking, measured from three-dimensional (3D) gait analysis, is also associated with future knee pain[36] and knee medial compartment disease progression[28,29]. The knee adduction moment is correlated to frontal plane mal-alignment[37,38], but is also independently associated with radiographic and magnetic resonance imaging measures of OA progression[28,29].

The most commonly targeted modifiable risk factors for knee OA progression, often treated in combination, are obesity and lower extremity muscle weakness.[38-43] For example, two large randomized controlled trials demonstrate that interventions combining diet and exercise or diet alone produce improvements in pain, function and modelled measures of knee joint load during walking.[43,44] Systematic reviews evaluating

exercise interventions for knee OA also suggest that improvements in pain and function are related to reductions in fat mass and gains in lean mass.[45,46] Although the importance of diet and exercise for knee OA must not be under-estimated, those interventions do not address mal-alignment. Importantly, the evidence also suggests that lower limb mal-alignment may actually mitigate improvements in disability and pain despite improvements in muscle strength or reductions in body mass.[41] This may suggest that lower limb mal-alignment is a potent enough risk factor to progress knee OA despite successful reduction in weight and/or increase in muscular strength.

High tibial osteotomy (HTO) is a surgical re-alignment procedure that effectively corrects mal-alignment and can provide substantial decreases in the external knee adduction moment.[47-53] For example, for every 1° change towards valgus after osteotomy, there is a 1.6 Nms reduction in the knee adduction impulse.[38] Medial opening wedge HTO results in a sustained reduction in the peak knee adduction moment of approximately 50%.[47] However, paradoxically, patients undergoing HTO can also experience losses in muscular strength and neuromuscular function post-operatively[55-58] and many increase weight after surgery, presumably because of the prolonged recovery process after surgery.

Patients with varus mal-alignment and medial compartment knee OA (varus gonarthrosis) may benefit from both rehabilitative and surgical interventions that target several risk factors in combination. Therefore, the primary objective of the present study was to investigate the cumulative effects of multi-modal physiotherapy and medial opening wedge HTO in patients with varus gonarthrosis. We hypothesized that when compared to baseline, patients would experience significant improvements in all of the

investigated outcome measures after completing the combination of interventions. Secondary objectives were to evaluate the change in outcome measures before and after each intervention separately. We hypothesized that the physiotherapy intervention would improve measures of body composition, strength, pain and function, without changing the knee adduction moment. We also hypothesized that medial opening wedge HTO would improve mal-alignment and the knee adduction moment, but lessen the preoperative improvements in body composition and strength.

4.3 Methods

4.3.1 Study Design

In this proof of principle study, patients with varus gonarthrosis completed an 8-week multi-modal physiotherapy intervention (MPT) approximately 4 months before undergoing medial opening wedge HTO, and again at approximately 12 months after surgery. Outcomes included measures of body composition, isokinetic strength, the external knee adduction moment during walking, radiographic lower limb alignment and the Knee injury and Osteoarthritis Outcome Scores (KOOS). With the exception of radiographic alignment, all outcome measures were tested before and after each intervention. The measurements completed after the first physiotherapy intervention also served as the pre-operative HTO measurements (Figure 4.1).

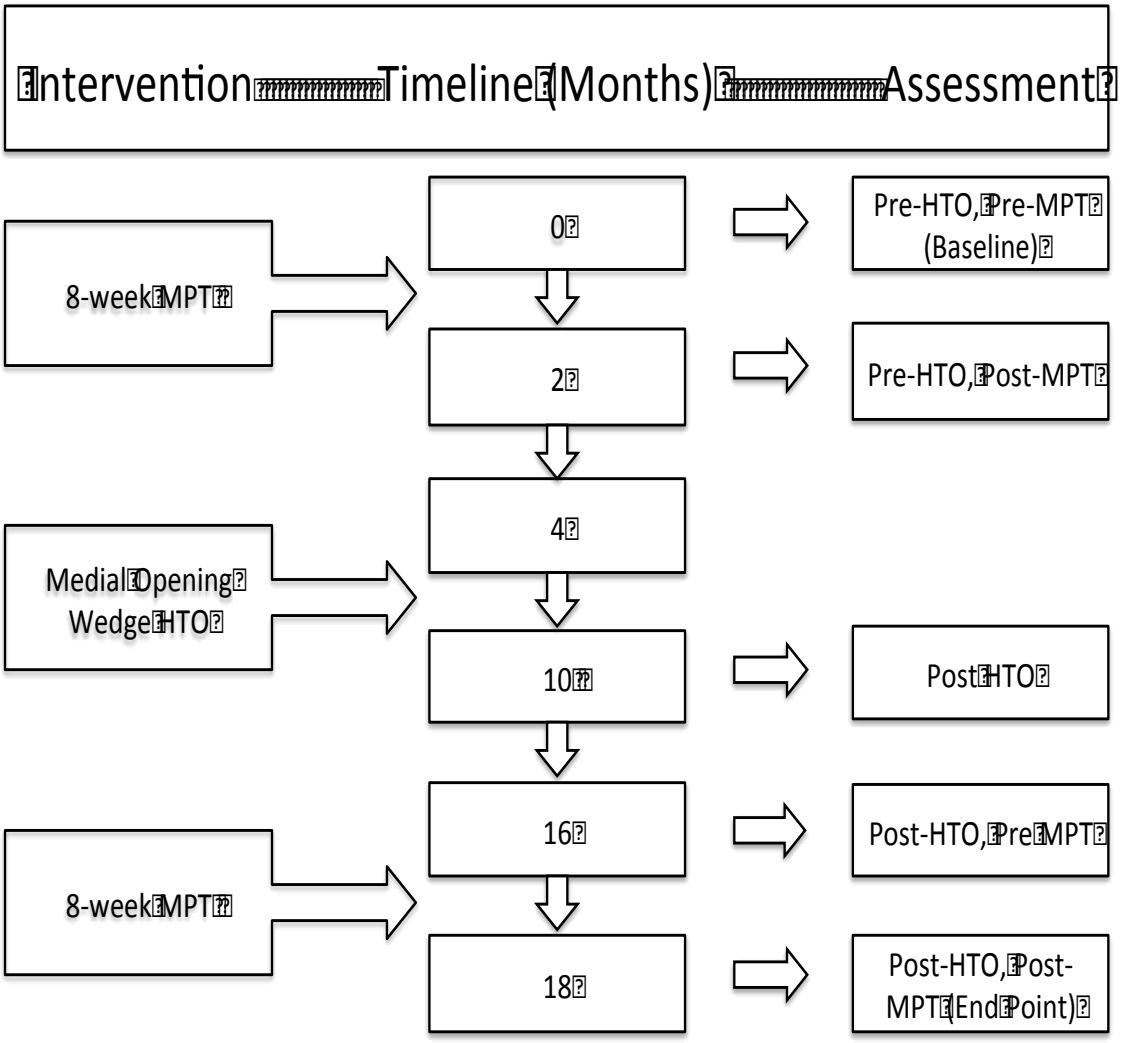

Figure 4.1: Summary of interventions, timeline and assessments. Patients underwent baseline testing immediately before starting the 8-week multi-modal physiotherapy (MPT), which was approximately 4 months before high tibial osteotomy (HTO) (i.e. Pre-HTO, Pre-MPT). Four follow-up assessments were completed at: 2-months (i.e. Pre-HTO, Post-MPT), approximately 10-months (i.e. 6 months Post-HTO), approximately 16 months (i.e. 12 months Post-HTO, Pre-MPT), and again at the study endpoint of approximately 18 months (i.e, 14 Months Post HTO, Post MPT). The timing of the second, post-operative 8-week MPT intervention (Post HTO, Pre MPT) varied among patients, with a mean of approximately 12 months post HTO.

4.3.2 Patients

Ten patients (8 males, 2 females) were recruited from a tertiary care centre specializing in orthopaedics. Participants were enrolled in the study after being assessed by an orthopaedic surgeon to determine their suitability for HTO. These patients were referred by primary care physicians due to long-standing complaints of primarily medial knee pain. All patients met the Altman criteria for knee OA[58], had varus alignment of the lower limb, and radiographic evidence of OA with the medial compartment of the tibiofemoral joint most affected. Patient demographic and clinical characteristics are summarized in Table 4.1.

Table 4.1: Baseline demographics and clinical characteristics

Characteristic	Value
Age, years	52 ± 4
Height, meters	1.8 ± 0.09
Mass, kilograms	100.2 ± 11.2
BMI, kg/m^2	31.5 ± 2.3
Mechanical axis angle,^{o}	-7.0 ± 1.3
KL grade, no.	
2	1
3	7

*BMI = body mass index. KL = Kellgren Lawrence grade of OA severity (0=no OA present, 1= doubtful narrowing of joint space and possible osteophytic lipping, 2=definite osteophytes, definite narrowing of joint space, 3=moderate multiple osteophytes, definite narrowing of joints space, some sclerosis and possible deformity of bone contour, 4=large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone contour.

4.3.3 Interventions

Multi-modal Physiotherapy (MPT): Patients completed a physiotherapist-developed and supervised program with a focus on patient education, muscular strengthening and postural control (i.e. open and closed kinetic chain strengthening exercises that also incorporated concepts from previous research related to neuromuscular control).[59,60] Participants attended two 45-60 minute sessions per week for 8 weeks, and were provided with a home program (including images and written instructions) to be completed three times per week. Patients were monitored either individually or in group sessions by a physiotherapist and were required to complete a record sheet during each session indicating the intensity, frequency and rating of perceived exertion for each exercise. They were asked to rate their current knee pain using a visual analog scale prior to and after each session. They were asked to record any adverse events that may have occurred during each session. Feedback was provided by the physiotherapist pertaining to the quality of movement, with the goal of maintaining neutral alignment of the knee compared to the hip and foot during each exercise.[59,60] Patients were instructed to work at a level between 15-18 on a rating of perceived exertion scale (hard to very-hard).[61-63] Progression was deemed appropriate when patients reported their exertion level below 15. See Appendix A, Table 1A for a description of each exercise performed during the supervised sessions.

The MPT also included a "body re-composition coaching program" where participants attended a seminar-based session once per week for the same 8 weeks. Each session was divided equally between an education and a practical application component. Nutrition education consisted of a Powerpoint presentation (~25 minutes) focused on

specific nutrition-related topics (i.e. energy balance, energy stores, macronutrients, nutrient timing and food awareness). For example, topics included the timing of food consumption and when activity should take place in relation to eating to maximize the use of fat stores in the body. There was also feedback and discussion regarding the macronutrient composition of meals (i.e. fat and protein or carbohydrate and protein versus fat and carbohydrate). The program did not emphasize the reduction in calorie consumption, rather it emphasized making better food choices and the timing of meals and exercises.. This was followed by an "interactive knowledge exchange" where a discussion of how course materials can be incorporated into daily eating habits (e.g., strategies to increase vegetable consumption). During the final ten-minutes of each seminar, participants were provided with (and encouraged to share their own) healthy recipes and successful healthy eating tips. Participants also had access to an exclusive body re-composition online-community for the duration of the study, including videos, recipes, coaching, and an online forum for questions and feedback.

Medial opening wedge HTO: The surgical procedure has been described in detail in previous publications.[47,64-66] The aim was to shift the weight-bearing line (centre of femoral head to centre of talus) laterally to a point ≤62.5% of the width of the tibial plateau from medial to lateral cortex. This approach emphasizes avoiding over-correction while still creating a substantial shift in the mediolateral distribution of load across the biofemoral joint.[64-66] All patients followed the same general postoperative guidelines. Individualized progression depended on the radiographic and clinical evidence of osteotomy site healing, based on clinic appointments at 2, 6, and 12 weeks post-operatively. Patients were placed in a hinged knee brace on the day of surgery. They were

instructed to use crutches with feather-touch weight-bearing for the first 2 weeks, with progressively increasing partial weight-bearing from 2-to-6 weeks. Patients commenced range of motion on the day after surgery, and completed non weight-bearing active assisted flexion and extension exercises at home twice per day until the two-week clinic appointment. Exercises were progressed from 2-6 weeks, with the goal of commencing weight-bearing exercises by 6 weeks post-operatively.

4.3.4 Outcome Measures

Body Composition: Each patient had their body volume measured through air displacement plethysmography using the BodPod® and software version 1.69 as outlined by the manufacturer. Before testing, the scale was calibrated using two 10-kg weights, and the Bod Pod® was calibrated using a cylinder of known volume. The patient's height was measured using a stadiometer. Each patient was weighted wearing only a tight-fitting swimsuit or undergarments and an acrylic swim cap. Patients were required to sit in the chamber while body volume measurements were taken. This measurement was done in duplicate, with each test lasting approximately 40 seconds. If both measures were within 150mL of each other, the mean was taken and used in subsequent calculations. If the two measurements differed by >150ml, a third measurement was performed. If two of the three measurements were within 150ml of each other, the mean of those two were taken and used, but if the three measurements were not within 150ml of each other, the entire process, including the calibration steps, was repeated. The measured body volume was adjusted for lung volume and body surface area artifact using prediction equations. This corrected body volume used in combination with body mass was used to determine body density (body density = body mass/body volume). The resultant body density was used in

the Siri equation[67] [(%fat = 495/body density)-450] to estimate body composition. All calculations were done using the system software. Calibration took approximately 20 minutes, Data collection took approximately 5 minutes. Fat mass (kg), percent fat, and lean mass (kg) were calculated. The minimal detectable change (MDC) for each body composition measure at various confidence intervals was reported for patients with knee OA in Chapter 3.

Muscular strength: Peak torque during knee extension and flexion were assessed at 60°/sec using the Biodex System 3 isokinetic dynamometer and accompanying software. Prior to each test, participants performed three sub-maximal (50-65%) repetitions and one maximum contraction to allow for familiarization with the task. Following these trial repetitions, participants completed five repetitions at maximum effort. The mean of the three highest trials was calculated. The MDC at the 90% confidence level for isokinetic extensor strength for patients with knee OA is 33.9Nm or 0.27Nm/kg.[68]

External Knee Adduction Moment during Walking: Gait was assessed using an eight-camera motion capture system (Eagle EvaRT; Motion Analysis Corporation, Santa Rosa, CA) synchronized with a floor-mounted force platform (Advanced Mechanical Technology, Watertown, MA). We used a modified Helen Hayes 22 passive-reflective marker set.[69] A static trial was first completed with four additional markers placed over the medial knee joint line and medial malleolus bilaterally to determine positions of joint centres of rotation for the knee and ankle. Patients were required to stand on the force platform during this static trial to determine body mass. The four extra markers were removed prior to gait testing.

Patients walked barefoot at their self-selected pace across the laboratory while three-dimensional kinetic (sampled at 1,200 Hz) and kinematic (sampled at 60 Hz) data were recorded during the middle of several strides for at least five trials. Patients were instructed to walk at their normal pace and to ignore the force plate. Walking trials were repeated until 5 clean force plate strikes (initial contact to preswing; one foot completely on the plate) were obtained. Moments about the knee were calculated from the kinematic and kinetic data using inverse dynamics (Orthotrak 6.0; Motion Analysis Corporation, Santa Rosa, CA, USA) and custom post-processing and data reduction techniques.[38] Knee moments were expressed as external moments relative to the tibial anatomical frame of reference. For each patient, the knee adduction moment was plotted over 100% percent of stance. The first and second peaks and the angular impulse were then determined.[70] The MDC for the peak knee adduction moment at the 95% confidence level is 1%BW*Ht.[71]

Radiographic Lower limb Alignment. Standing, hip-to-ankle anteroposterior (AP) radiographs for both limbs were obtained by a musculoskeletal x-ray technologist using methods previously described to be reliable.[72] The mechanical axis angle (MAA) was determined by identifying the geometric centre of the femoral head using a circular template,[72] the centre of the knee was identified as the midpoint of the tibial spines extrapolated inferiorly to the surface of the intercondular eminence, and the centre of the ankle was defined as the mid-width of the tibia and fibula at the level of the tibial plafond. The MAA was defined as the angle formed between the line drawn from the centre of the hip to the centre of the knee and the line from the centre of the knee to the centre of the ankle. Varus alignment was reported as a negative value.

Knee injury and Osteoarthritis Outcome Score: The KOOS includes five separately reported domains of pain, other symptoms, function in daily living, function in sports/recreation, and knee-related quality of life. Scores can range from 0-to-100 where higher scores represent less disability. A change of 10 points is considered clinically important for each domain of the KOOS.[73]

4.3.5 Statistical Analysis

Means and standard deviations were calculated for each outcome measure assessed at each time point. The change over time was evaluated using a one-factor repeated measures analysis of variance (anova), with statistical significance set a $p<0.05$. Mean changes with 95% confidence intervals (CI) were then calculated for the following periods: from the study baseline to its endpoint, before and after the pre-operative MPT intervention, before and after HTO, and before and after the postoperative MPT intervention. Also, data for individual patients were recorded and the number changing by greater than known MDCs were presented for body composition measures, knee extensor strength, the peak knee adduction moment and the mechanical axis angle. The number of patients changing by greater than the suggested MCID for the KOOS was also presented.

4.4 Results

Overall Changes

Two participants dropped out. One discontinued because s/he did not want to participate in the full pre-operative MPT intervention. One discontinued because s/he did not undergo HTO. Compliance during both MPT interventions was excellent. Attendance, ratings of perceived exertion and pain during MPT are reported in Appendix

A, Tables A.3-A.4. With the exception of lean mass, all outcome measures changed significantly (i.e. anovas indicated significant main effects for time; please see Figure 4.2). Mean changes using only the study baseline to endpoint data are reported in Table 4.2. These show substantial reductions in fat mass, without reductions in lean mass. Although there was a mean increase in strength, changes were highly variable among patients and the 95% confidence interval (CI) did not exclude zero, indicating no significant difference. The external knee adduction moment during walking was reduced by over 50%, consistent with a large change in lower limb alignment from substantial varus to slight valgus. All KOOS domains improved substantially. Changes in individual patients from study baseline to endpoint for all outcome measures are reported in Appendix A (Tables A.5-A.21). Most Importantly, 7 of the 8 patients experienced reductions in each of fat mass, varus alignment and knee adduction moment that are greater than the suggested MDCs and therefore we can be confident that they are true changes. Also 7 of the 8 patients experienced improvements in Pain, Function in Activities of Daily living, Sport and Recreation and Quality of Life that are greater than the suggested clinically important difference. With respect to the Symptoms domain 6 of the 8 patients experienced improvements greater than the suggested minimal clinically important difference.

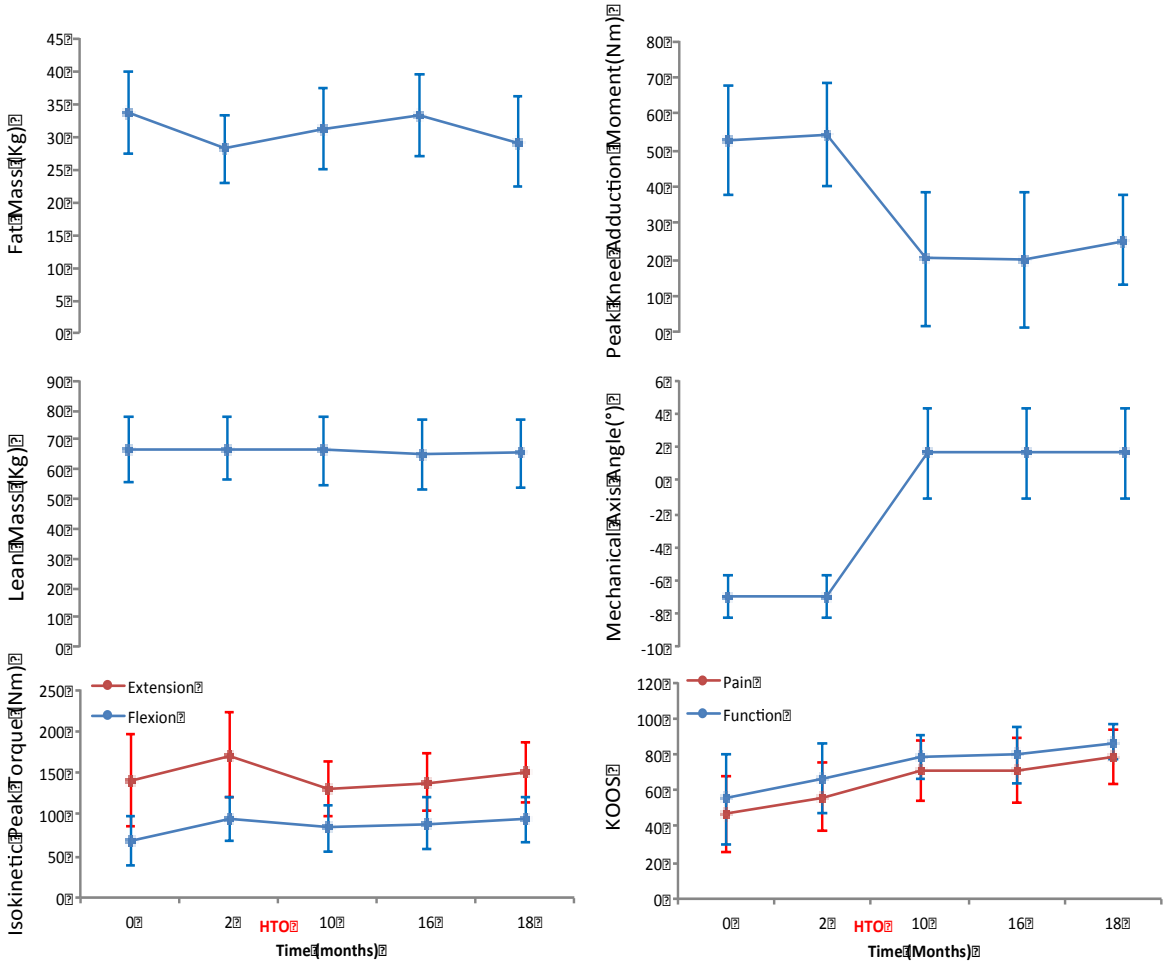

Figure 4.2: Means and standard deviations for each outcome measure at each time point. Only KOOS Pain and Function domains are reported for clarity. Other domains are included in Tables 4.2-to-4.5

Table 4.2: Overall Change in outcome measures from study baseline to endpoint. Values are means ± SD and mean change (95%CI)

	Baseline	Endpoint	Change (95%CI)
Body Composition			
Fat Mass (Kg)	32.7±6.2	28.2±6.9	-4.6 (-8.0, -1.2)
Percent Fat (%)	33.3±7.1	30.6±9.5	-2.8 (-5.6, 0.09)
Lean Mass (Kg)	66.3±1.7	65.4±12.6	-0.9 (-3.3, 1.5)
Muscular Strength			
Knee Extension Torque (Nm)	147.4±55.8	154.6±38.3	7.2 (-45.0, 59.5)
Knee Flexion Torque (Nm)	72.7±29.8	95.6±28.6	23.0 (-1.8, 47.7)
Knee Adduction Moment			
Peak (Nm)	53.0±16.4	25.6±13.1	-27.3 (-43.1, -11.6)
Impulse (Nms)	25.2±7.2	10.7±5.7	-14.5 (-21.4, -7.6)
Lower Limb Alignment			
Mechanical Axis Angle (°)	-7.0±1.3	1.6±2.7	8.6 (6.3, 10.8)
KOOS			
Pain	47.6±23.0	79.0±16.5	31.4 (10, 52.8)
Symptoms	44.9±22.9	62.3±10.1	17.4 (-2.5, 37.3)
Functions in ADL	54.8±27.4	88.7±8.7	33.9 (12.2, 55.5)
Sport and Recreation	23.6±15.7	57.9±26.9	34.3 (9.3, 59.2)
Quality of Life	31.3±19.1	59.9±29.6	28.7 (7.8, 49.5)

Kg=Kilogram, %=percent, Nm=Newton meters, Nms=Newton meters per second, °=degrees, KOOS=Knee Injury and Osteoarthritis Outcome Score, ADL=Activities in Daily Living

Changes in Outcome Measures during the Pre-operative Multi-modal Physiotherapy Intervention

Mean changes (95%CI) are reported in Table (4.3). There were large reductions in fat mass and percent fat, while lean mass did not change. Although there was a large mean increase in muscular strength, patient responses varied considerably and the 95%CI did not quite exclude zero. The peak knee adduction moment did not change. Although there were mean improvements in all domains of the KOOS, individual responses were also variable and the 95%CI did not exclude zero. Individual patient changes are reported in Appendix A.

Table 4.3: Change in outcome measures from pre to post MPT completed preoperatively. Values are mean ± SD and mean change (95%CI)

	Pre MPT	Post MPT	Change (95%CI)
Body Composition			
Fat Mass (kg)	32.7±6.2	27.3±5.1	-5.4 (-7.2, -3.6)
Percent Fat (%)	33.3±7.1	29.3±6.9	-4.0 (-4.9, -3.2)
Lean Mass (kg)	66.3±1.7	67.0±11.3	0.7 (-1.0, 2.4)
Muscular Strength			
Knee Extension Torque (Nm)	147.4±55.8	175.6±53.3	28.2 (-4.7, 61.1)
Knee Flexion Torque (Nm)	72.7±29.8	95.4±28.8	22.7 (-2.8, 48.2)
Knee Adduction Moment			
Peak (Nm)	53.0±16.4	54.7±15.2	1.8 (-5.1, 8.6)
Impulse (Nms)	25.2±7.2	25.0±5.9	-0.2 (-3.2, 2.8)
KOOS			
Pain	47.6±23.0	56.3±20.1	9.0 (-4.2, 21.6)
Symptoms	44.9±22.9	51.0±23.9	6.1 (-6.3, 18.6)
Function in ADL	54.8±27.4	67.0±21.0	12.2 (-5.1, 29.4)
Sport and Rec	23.6±15.7	31.4±27.3	7.9 (-12.6, 28.3)
Quality of Life	31.3±19.1	33.0±21.6	1.8 (-9.6, 13.2)

Kg=Kilogram, %=percent, Nm=Newton meters, Nms=Newton meters per second, KOOS=Knee Injury and Osteoarthritis Outcome Score, ADL=Activities in Daily Living

Changes in Outcomes Six Months After Medial Opening Wedge HTO

Mean changes (95%CI) are presented in Table 4.3. Six months after surgery there were mean *increases* in fat mass and percent body fat, with 95%CIs excluding zero. Mean decreases in lean mass and isokinetic peak torques were also observed, although the 95%CIs did not quite exclude zero. There were very large reductions in both knee adduction moment measures (~54%) and an increases in the mechanical axis angle (i.e. correction of mal-alignment). There was a mean improvement in all KOOS domains, although 95CIs included zero. Individual patient results are reported in Appendix A.

Table 4.4: Change in outcome measures from pre to post HTO. Values are mean ± SD and mean change (95%CI)

	Pre HTO	Post HTO	Change (95%CI)
Body Composition			
Fat Mass (kg)	27.3±5.1	30.4±6.3	3.1 (0.81, 5.5)
Percent Fat (%)	29.3±6.9	32.0±8.4	2.7 (0.34, 5.1)
Lean Mass (kg)	67.0±11.3	66.0±12.7	-1.0 (-3.3, 1.3)
Muscular Strength			
Knee Extension Torque (Nm)	175.6±53.3	132.2±34.3	-43.4 (-87.2, 0.51)
Knee Flexion Torque (Nm)	95.4±28.8	87.0±29.4	-8.4 (-19.8, 2.9)
Knee Adduction Moment			
Peak (Nm)	54.7±15.2	25.4±11.9	-29.3 (-42.0, -16.6)
Impulse (Nms)[¥]	25.0±5.9	10.3±4.7	-14.7 (-19.9, -9.4)
Lower Limb Alignment			
MAA(°)	-7.0±1.3	2.0±2.7	8.6 (6.3, 10.8)
KOOS			
Pain	56.3±20.1	71.0±18.6	14.7 (-9.2, 38.6)
Symptoms	51.0±23.9	63.3±22.7	12.2 (-18.9, 43.4)
Function in ADL	67.0±21.0	78.4±13.5	11.3 (-9.7, 32.4)
Sport and Rec	31.4±27.3	50.0±35	18.6 (-20.1, 57.2)
Quality of Life	33.0±21.6	49.1±30.5	16.1 (-4.7, 36.9)

Kg=Kilogram, %=percent, Nm=Newton meters, Nms=Newton meters per second, °=degrees, KOOS=Knee Injury and Osteoarthritis Outcome Score, ADL=Activities in Daily Living

[¥]One patient did not demonstrate an adduction impulse and was not included in analysis

Changes in Outcome Measures Demonstrated by the Post-operative Multi-modal Physiotherapy Intervention

Mean changes (95%CI) are presented in Table 4.4. Results were generally similar to those observed pre-operatively, although improvements in strength were not as large. Individual patient changes are reported in Appendix A.

Table 4.5: Change in outcome measures from pre to post MPT completed post-operatively. Values are mean ± SD and mean change (95%CI)

	Pre MPT	Post MPT	Change (95%CI)
Body Composition			
Fat Mass (kg)	32.8±6.6	28.2±6.9	-4.6 (-6.0, -3.2)
Percent Fat (%)	34.1±9.4	30.6±9.5	-3.6 (-5.2, -1.9)
Lean Mass (kg)	64.7±12.9	65.4±12.6	0.7 (-1.2, 2.6)
Muscular Strength			
Knee Extension Torque (Nm)	142.2±36.0	154.6±38.3	12.4 (-6.4, 31.3)
Knee Flexion Torque (Nm)	93.2±32.	95.6±28.6	2.5 (-7.0, 11.9)
Knee Adduction Moment			
Peak (Nm)	25.3±12.4	25.6±13.1	0.31 (-9.0, 9.6)
Impulse (Nms)[¥]	11.1±5.1	10.7±5.7	-0.4 (-5.0, 4.2)
KOOS			
Pain	71.8±20.0	79.0±16.5	7.2 (-2.5, 16.9)
Symptoms	64.3±24.9	62.3±10.1	-2.0 (-18.3, 14.4)
Function in ADL	79.6±17.1	88.7±8.7	9.1 (0.6, 17.5)
Sport and Rec	51.4±31.5	57.9±26.9	6.4 (-1.9, 14.8)
Quality of Life	51.8±36.0	59.9±29.6	8.1 (-7.8, 24.1)

Kg=Kilogram, %=percent, Nm=Newton meters, Nms=Newton meters per second, KOOS=Knee Injury and Osteoarthritis Outcome Score, ADL=Activities in Daily Living

[¥] One patient did not demonstrate an adduction impulse and was not included in analysis

4.5 Discussion

This study focused on the cumulative effects of combined physiotherapy and medial opening wedge HTO on known risk factors for patients with varus gonarthrosis. Overall, the results support the principle of using multi-modal interventions to address the multiple risk factors present in these patients. With the exception of observing no change in lean mass, the findings are generally consistent with our primary hypothesis. Specifically, the results suggest that decreases in fat mass (while maintaining lean mass), increases in muscular strength, correction of lower limb mal-alignment and decreases in the peak knee adduction moment during walking can all be achieved through the combination of rehabilitative and surgical intervention. Importantly, KOOS scores increased steadily throughout the study, suggesting that in addition to improvements in risk factors for disease progression, the participants also experienced improvements in outcomes that are clearly important to patients (Figure 4.2).

The size of the overall improvements observed is encouraging (Table 4.2). When expressed as standardized response means (i.e. mean change divided by standard deviation of the change), changes in fat mass, knee flexor strength, mechanical axis angle, knee adduction moment, and KOOS Pain, Function during ADL, Sport and Recreation and Quality of Life scores were all greater than 1.0 and can be described as very large. Overall, patients lost a mean of 4.6 kg (>10pounds) and 5% of their body mass. A previous systematic review with meta-analysis suggests that a 5% reduction in body mass is required to experience even a small improvement in pain and function for patients with knee OA.[75] When accompanied by the correction of lower limb mal-alignment and a decrease in knee adduction moment of over 50%, the changes in these

potent risk factors for disease progression are arguably impressive. The fact that 7 of the eight patients also changed by greater that the suggested MCID of 10 KOOS points on 4 of its five domains further supports the importance of the changes observed after the combined intervention.

It is important to note that the observed large mean loss in fat mass was not accompanied by a loss in lean mass. This likely relates to the present emphasis on muscular strengthening, including a combination of open and closed kinetic chain exercises. Also, patients exercised at a high intensity, according to the Borg rating of perceived exertion scale (Appendix A, Table A.4).[61-63] However, it is also important to note that although the patients ended up with similar or greater strength when compared to starting the study, substantial losses in strength were observed after surgery despite the substantial pre-operative gains (described in more detail below).

Our secondary objectives aimed to evaluate each intervention separately. Doing so provides insight into the different effects of MPT and HTO. Consistent with our hypotheses, the present findings clearly show different, even paradoxical, effects on the various risk factors. The MPT resulted in decreased fat mass and increased strength, but had no effect on alignment and actually increased the knee adduction moment in some patients, most likely due to increases in speed (the mean increase in gait speed after the MPT programs was approximately 0.1 m/sec). Previous studies have shown that reductions in body mass can result in a decrease the knee adduction moment and a decrease in modeled internal knee joint load in patients with knee OA.[43,44,75] As we did not observe similar reductions in the knee adduction moment, it may be that patients with substantial varus alignment respond differently.

Medial opening wedge HTO resulted in the correction of mal-alignment and a decrease in the knee adduction moment, but also resulted in increased fat mass and decreased muscular strength. Patients gained a mean of 3kg of fat mass after HTO. Patients are typically non-weight bearing for up to 6 weeks and then partial weight bearing for up to 12 weeks after HTO. This has consequences on muscle functioning and the ability for patients to perform exercises that can promote energy expenditure. Consistent with the present findings, several studies have demonstrated reductions in strength and neuromuscular function during recovery after HTO.[54-57] The period of decreased weight-bearing required to allow healing of the osteotomy, and inhibitory neuromuscular mechanisms (i.e. decreased recruitment of large motor neurons) that are common after knee surgeries, clearly have detrimental effects on knee extension strength. Further ways to mitigate these effects after HTO should be investigated and may include newer fixation plate technologies that enable earlier weight-bearing, and/or neuromuscular electrical stimulation in addition to resistance training.[76] Interestingly, the large improvements in all domains of the KOOS after HTO may demonstrate that varus mal-alignment and the medial to lateral distribution of knee joint loading during walking can strongly impact patient pain and function, despite the regression of pre-operative improvements in body composition and muscle strength.

The post-operative MPT intervention was again successful in reducing significant amounts of fat mass while maintaining lean mass. There was an overall 4% reduction in total body mass post-operatively. There was a small increase in strength for both knee extensor and flexor muscle groups; however, the mean changes made during the pre-operative MPT intervention generally exceeded those made during the post-operative

MPT intervention. It is possible that patients may still have been experiencing muscular inhibition and were unable to achieve the same gains post-operatively that were made pre-operatively in the same time frame. Overall, the knee adduction moment did not change after the post-operative MPT, which was similar to the pre-operative intervention. However, when looking at the individual data, there were two patients that experienced large *increases* in the peak knee adduction moment after completing the post-operative MPT. These large increases were not observed for the pre-operative MPT. One patient had an *abduction* moment at the start of the post-operative MPT which changed back to an adduction moment after the intervention. The second patient experienced an increase in peak knee adduction moment that was likely related to a large increase in gait speed. In fact, that patient's peak knee adduction moment increased such that it was greater than observed at the study baseline. If those two outliers are removed from the analysis, the post-operative MPT intervention in the six remaining patients resulted a 12% reduction in the peak knee adduction moment. Although future research may help explain those very different patient responses, the present sample size is far too small to draw any conclusions in that regard.

There are substantial limitations in this proof of principle study, the most obvious being the small sample size. Furthermore, we lack a control group, which does not allow us to fully elucidate the benefits of the combined intervention. We also cannot compare the present results to other interventions with somewhat similar goals, such as gait retraining, knee bracing and shoe modifications. Although the present MPT included postural control exercises, consistent with suggestions for exercises for patients with knee OA,[59,60] it did not directly target the knee adduction moment like other proposed

neuromuscular exercises.[39,41,77] Importantly, although the combined intervention targeted modifiable risk factors previously reported to contribute to disease progression, we did not quantify structural measures of disease progression. Indeed, no interventions, including those studied presently, have been shown to prevent the progression of OA. Nonetheless, the present results support the principle of using multiple interventions that primarily target different risk factors to achieve greater overall benefits. These findings suggest that future research should directly compare the effects combined rehabilitative and surgical intervention to competing treatment strategies and evaluate their effects on OA progression using the best available measures.

4.6 References

1. Badley EM. Arthritis in Canada: what do we know and what should we know? J Rheumatol. 2005;32 Suppl:32-41.
2. Horton R. GBD 2010: understanding disease, injury, and risk. Lancet. 2012;380:2053-2054. DOI 10.1016/S0140-6736(12)62133-3.
3. Kadam UT, Croft PR. Clinical comorbidity in osteoarthritis: associations with physical function in older patients in family practice. J Rheumatol. 2007;34:1899-904.
4. Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: part II. Arthritis Rheum. 2008;58:26-35.
5. Felson DT, Zhang Y, Hannan MT, Naimark A, Weissman BN, Aliabadi P, et al. The incidence and natural history of knee osteoarthritis in the elderly: the Framingham Osteoarthritis Study. Arthritis Rheum. 1995;38:1500-5.
6. Felson DT & Radin EL. What causes knee osteoarthrosis are different compartments susceptible to different risk factors? J Rheumatol 1994:21;181-183.
7. Felson DT. Osteoarthritis as a disease of mechanics. Osteoarthritis Cart. 2013;21:10-15.
8. Griffin TM & Guilak F. The role of mechanical loading in the onset and progression of osteoarthritis. Exerc and sport sci rev 2005;33:195-200.
9. Loeser RF Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis a disease of the joint as an organ. Arthritis Rheum. 2012;64:1697-1707.
10. Eyles J. Lucas BR, Hunter DJ. Targeting care: tailoring nonsurgical management according to clinical presentation Rheum Dis Clin North Am. 2013;39:213-233.
11. Waller C, Hayes D Block JE, London NJ. Unload it: the key to the treatment of knee. Knee Surg Sports Traummatol Arthrosc. 2011;19:1823-1829.
12. Roos WM, Herzog W, Block JA, Bennell KL. Muscle weakness, afferent sensory dysnfunction and exercise in knee osteoarthritis. Nat Rev Rheumatol. 2011;7:57-63.
13. Hunter DJ. Review risk stratification for knee osteoarthritis progression: a narrative review. Osteoarthritis Cart. 2009;17:1402-1407.
14. Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis. Part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis Cart. 2008;16(2): 137-62.
15. Hochberg MC, Altman RD, Toupin Aril K, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res. 2012;64(4):465-74.
16. National Collaborating Centre for Chronic Conditions. Osteoarthritis: national clinical guideline for care and management in adults. London: Royal College of Physicians, 2008.
17. Blagojevic M, Jinks C, Jeffery A, Jordan KP. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. Osteoarthritis Cart. 2010;18:24-33.

18. Felson DT, Anderson JJ, Naimark A, Walker AM, Meenan RF. Obeisty and knee osteoarthritis. The Framingham Study. Ann Intern Med. 1988;109;18-24.
19. Niu J, Zhang YQ, Torner J, et al. Is obesity a risk factor for progressive radiographic knee osteoarthritis? Arthritis Rheum. 2009;61:329-335.
20. Yusuf E, Bijsterbosh J, Slagboom PE, Rosendaal FR, Huizinga TWJ, Kloppenburg M. Body mass index and alignment and their interaction as risk factors for progression of knees with radiographic signs of osteoarthritis. Osteoarthritis Cart. 2011;19:1117-1122.
21. Amin S, Baker K, Niu J, Clancy M, Goggins J, Guermazi A, Grigoryan M, Hunter DJ, Felson DT. Quadriceps strength and the risk of cartilage loss and symptom progression in knee osteoarthritis. Arthritis Rheum. 2009;60:189-98.
22. Brandt KD, Heilman DK, Slemenda C, Katz BP, Mazzuca SA, Braunstein EM, Byrd D. Quadriceps strength in women with radiographically progressive osteoarthritis of the knee and those with stable radiographic changes. Journal of Rheum. 1999;26:2431-2437.
23. Segal NA, Torner JC, Felson DT, Niu J, Sharma L, Lewis CE, Nevitt M. Effect of thigh strength on incident radiographic and symptomatic knee osteoarthritis in a longitudinal cohort. Arthritis Rheum. 2009;61:1210-1217.
24. Slemenda C, Heilman DK, Brandt KD, Katz BP, Mazzuca SA, Braunstein EM, Byrd D. Reduced quadriceps strength relative to body weight: a risk factor for knee osteoarthritis in woment? Arthritis Rheum. 1998;41:1951-1959.
25. Sharma L, Song J, Felson DT, Cahue S, Shamiyeh E, Dunlop DD. The role of knee alignment in disease progression and functional decline in knee osteoarthritis. JAMA. 2001;286:188-195.
26. Sharma L, Chmiel JS, Almagor O, et al. The role of varus and valgus alignment in the initial development of knee cartilage damage by MRI: the MOST study. Ann Rheum Dis. 2013;72:235-240.
27. Sharma L, Song J, Dunlop D, Felson D, Lewis CE, Segal N, Torner J et al. Varus and valgus alignment and incident and progressive knee osteoarthritis. Ann Rheum Dis. 2010;69:1940-1945.
28. Bennell KL, Bowles K, Wang Y, Cicuttini F, Davies-Tuck M, Hinman RS. Higher dynamic medial knee load predicts greater cartilage loss over 12 months in medial knee osteoarthritis. Ann Rheum Dis. 2011;70:1770-1774.
29. Miyazaki T., Wada M., Kawahara H., Sato M., Baba H., Shimada S. Dynamic load at baseline can predict radiographic disease progression in medial compartment knee osteoarthritis. Ann Rheum Dis. 2002;61:617-622.
30. Baum T, Joseph GB, Nardo L, Virayavanich W, Arulanandan A, Alizai H, Carballido-Gamio J, et al. Correlation of magnetic resonance imaging-based knee cartilate T2 measurements and focal knee lesions with body mass index: thirty-six-month-followup data from a longitudinal, observational multicenter study. Arthritis Care Res. 2013;65:23-33.
31. Dougados M, Gueguen A, Nguyen M, Thiesce A, Listrat V, Jacob L, Nakache JP, et al. Longitudinal radiologic evaluation of osteoarthritis of the knee. Journal of Rheum. 1992;19:378-84.
32. Reijman M, Pols HA, Bergink AP, Hazes JM, Belo JN, Lievense AM, Bierma-Zeinstra SM. Body mass index associated with onset and progression of

osteoarthritis of the knee but not of the hip: the Rotterdam Study. Ann Rheum Dis. 2007;66:158-162.
33. Wang Y, Wluka AE, English DR, Teichtahl AJ, Giles GG, O'Sullivan R, et al. Body composition and knee cartilage properties in healthy, community-based adults. Ann Rheum Dis. 2007;66:1244-1248.
34. Wang Y, Simpson JA, Wluka AE, Teichtahl AJ, English DR, Giles GG, Graves S, Cicuttini FM. Relationship between body adiposity measures and risk of primary knee and hip replacement for osteoarthritis: a prospective cohort study. Arthritis Res & Ther. 2009;DOI:10.1186/ar2636.
35. Felson DT, Goggins J, Niu J, Zhang Y, Hunter DJ. The effect of body weight on progression of knee osteoarthritis is dependent on alignment. Arthritis Rheum. 2004;50:3904-3909.
36. Amin S, Leupongsak N, McGibbon CA, LaValley MP, Krebs DE, Felson DT. Knee adduction moment and development of chronic knee pain in elders. Arthritis Rheum. 2004;51:371-376.
37. Hurwitz De, Ryals AB, Case JP, Block JA, Andriacchi TP. The knee adduction moment during gait in subjects with knee osteoarthritis is more closely correlated with static alignment than radiographic disease severity, toe out angle and pain. J Orthop Res. 2002;20:101-107.
38. Leitch KM, Birmingham TB, Dunning CE, Giffin JR. Changes in valgus and varus alignment neutralize aberrant frontal plane knee moments in patients with unicompartmental knee osteoarthritis. J Biomech. 2013;46:1408-1412.
39. Bennell KL, Hunt MA, Wrigley TV, Hunter DJ, McManus FJ, Hodges PW, Li L, et al. Hip strengthening reduces symptoms but not knee load in people with medial knee osteoarthritis and varus malalignment: a randomized controlled trial. Osteoarthritis Cart. 2010;18:621-628.
40. Christensen R, Astrup A, Bliddal H. Weight loss: the treatment of choice for knee osteoarthritis? A randomized trial. Osteoarthritis Cart. 2005;13:20-27.
41. Lim BW, Hinman RS, Wrigley TV, Sharma L, Bennell KL. Does malalignment mediate the effects of quadriceps strengthening on knee adductioin moment, pain, and function in medial knee osteoarthritis? A randomized Controlled Trial. Arthritis Rheum. 2008;59:943-951.
42. Messier SP Loeser RF, Miller GD, Morgan TM, Rejeski J, Sevick MA, Ettinger WH, Pahor M, Williamson JD. Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis. Arthritis Rheum. 2004;50:1501-1510.
43. Messier SP, Mihalko SL, Legault C, Miller GD, Nicklas B, DeVita P, Beavers DP et al. Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis. The IDEA randomized clinical trial. JAMA. 2013;310:1263-1273.

44. Messier SP Gutekunst DJ, Davis C, DeVita P. Weight loss reduces knee-joint loads in overweight and obese older adults with knee osteoarthritis. Arthritis Rheum. 2005;52:2026-2032.
45. Fransen M, McConnell S. Exercise for osteoarthritis of the knee. Cochrane Database of Systematic Reviews 2008, Issue 4. Art. No.:CD004376. DOI: 10.1002/14651858.CD004376.pub2.
46. Roddy E, Zhang W, Doherty M. Aerobic walking or strengthening exercise for osteoarthritis of the knee? A systematic review. Ann Rheum Dis. 2005;64:544-548
47. Birmingham TB, Giffin JR, Chesworth BM, et al. Medial opening wedge high tibial osteotomy: A prospective cohort study of gait, radiographic and patient-reported outcomes. Arthritis Rheum. 2009;61:648-657.
48. DeMeo PJ, Johnson EM, Chiang PP, Flamm AM, Miller MC. Midterm follow-up of opening-wedge high tibial osteotomy. Am J Sports Med. 2010;38:2077-2084.
49. Lind M, McClelland J, Wittwer JE, Whitehead TS, Feller JA, Webster KE. Gait analysis of walking before and after medial opening wedge high tibial osteotomy. Knee Surg Sports Traumatol Arthrosc. 2013.21;1:74-81.
50. Prodromos CC, Andriacchi TP, Galante JO. A relationship between gait and clinical changes following high tibial osteotomy. J Bone Joint Surg Am. 1985;67:1188-1194.
51. Wada M, Imura S, Nagatani K, Baba H, Shimada S, Sasaki S. Relationship between gait and clinical results after high tibial osteotomy. Clin Orthop. 1998;354:180-188.
52. Wang JW, Kuo KN, Andriacchi TP, Galante JO. The influence of walking mechanics and time on the results of proximal tibial osteotomy. J Bone Joint Surg. 1990;72-A:905-909.
53. Weidenhielm L, Svensson OK, Brostrom LA. Surgical correction of leg alignment in unilateral knee osteoarthrosis reduces the load on the hip and knee joint bilaterally. Clin Biomech. 1995;10:217-221.
54. Kean CO, Birmingham TB, Garland SJ, Bryant DM, Giffin JR. Preoperative strength training for patients underoing high tibial osteotomy: a prospective cohort study with historical controls. J Orthop Sports Phys Ther. 2011;41:52-59.
55. Machner A, Pap G, Krohn A, Rohkohl K, Awiszus F. Quadriceps muscle function after high tibial osteotomy for osteoarthritis for the knee. Clin Orthop Relat Res. 2002;177-183.
56. Ramsey DK, Snyder-Mackler L, Lewek M, Newcomb W, Rudolph KS. Effect of anatomic realignment on muscle function during gait in patients with medial compartment knee osteoarthritis. Arthritis Rheum. 2007;57:389-397.
57. Kawazoe T, Takahashi T. Recovery of muscle strength after high tibial osteotomy. J Orthop Sci. 2003;8:160-165.

58. Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. Arthritis Rheum. 1986;29:1039-1049.
59. Ageberg E, Link A, Roos EM. Feasibility of neuromuscular training in patietns with severe hip or knee OA: the individualized goal-based NEMEX-TJR training program. BMC Musculoskelet Disord. 2010;11:126.
60. Stensrud S, Roos EM, Risberg MA. A 12-week exercise therapy program in middle-aged pateitns with degenerative meniscus tears: A case series with 1-year follow-up. J Orthop Sports Phys Ther. 2012;42:919-931.
61. Borg G. Psychophysical scaling with applications in physical work and the perception of exertion. Scand J Work Environ Health. 1990;16 suppl 1:55-58.
62. Borg G, Hassmen P, Lagerstrom M. Received exertion related to hart rate and blood lactate during arm and leg exercise. Eur J Appl Physiol. 1987;65:679-685.
63. Day ML, McGuigan MR, Brice G, Foster C. Monitoring exercise intensity during resitatnce training using the session RPE scale. J Strength Cond Res. 2004;18:353-358.
64. Amendola A, Bonasia DE. Results of high tibial osteotomy: review of the literature. Int Orthop. 2010;34:155-160.
65. Fowler PJ, Tan JL, Brown GA. Medial opening wedge high tibial osteotomy: How I do it. Oper Tech Sports Med. 2000;8:32-38.
66. Song EK, Seon JK, Park SJ, Seo HY. Navigated open wedge high tibial osteotomy. Sports Med Arthrosc Rev. 2008;16:84-90.
67. Siri, WE. Body composition from fluid spaces and density: analysis of methods. In: Techniques for measuring Body Composition, J. Brozek and A. Henschel (Eds.). National Research Council, Washington, DC: National Academy of Sciences, pp. 223-244, 1961.
68. Kean CO, Birmingham TB, Garland JS, Bryant DM, Giffin JR. Minimal detectable change in quadriceps strength and voluntary muscle activation in patients with knee osteoarthritis. Arch Phys Med Rehabil. 2010;91:1447-1451.
69. Kadaba MP, Ramakrishnan HK, Wootten ME. Measurement of lower extremity kinematics during level walking. J Orthop Res. 1990;8:383-392.
70. Thorp LE, Wimmer MA, Block JA, et al. Bone mineral density in the proximal tibia varies as a function of static alignment and knee adduction angular momentum in individuals with medial knee osteoarthritis. Bone. 2006;39:1116-1122.
71. Birmingham TB, Hunt MA, Jones IC, Jenkyn TR, Giffin JR. Test-retest reliability of the peak knee adduction moment during walking in patients with medial compartment knee osteoarthritis. Arthritis Rheum. 2007;57:1012-1017.

72. Specogna AV, Birmingham TB, DaSilva JJ, et al. Reliability of lower limb frontal plane alignment measurements using plain radiographs and digitized images. J Knee Surg. 2004;17:203-210.
73. Roos EM, Lohmander LS. The knee injury and osteoarthritis outcome score (KOOS): from joint injury to osteoarthritis. Helath Qual Life Outcomes. 2003;1:64.
74. Christensen R, Bartels EM, Astrup A, Bliddal. Effect of weight reductionin obese patients diagnosed with knee osteoarthritis: a systematic review and meta-analysis. Ann Rheum Dis. 2007;66:433-439.
75. Aaboe J, Bliddal H, Messier SP, Alkjaer T, Henrikson M. Effects of an intensive weight loss program on knee joint loading in obese adults with knee osteoarthritis. Osteoarthritis Cart. 2001;19:822-828.
76. Elboim-Gabyzon M, Rozen N, Laufer Y. Does neuromuscular electrical stimulation enhance the effectiveness of an exercise programme in subjects with knee osteoarthritis? A randomized controlled trial. Clin Rehab. 2013;27:246-257.
77. Bennell KL, Egerton T, Wrigley TV, Hodges PW, Hunt M, Roos EM, Kyriakides M et al. Comparison of neuromuscular and quadriceps strengthening exercise in the treatment of varus malaligned knees with medial knee osteoarthritis: a randomized controlled trial protocol. BMC Musculo Dis. 2011;12:276.

Chapter 5

5. Thesis Summary and General Discussion

5.1 Thesis Overview

Patients with knee OA have numerous, varied risk factors for OA disease progression. The overall purpose of this thesis was to evaluate the effects of multi-modal, rehabilitative and surgical interventions that target different risk factors in patients with medial compartment knee OA and varus mal-alignment (i.e. varus gonarthrosis). Main findings include:

Chapter 2: Patients with substantial bilateral varus (MAA<5°) pre-operatively experienced decreases in important risk factors for disease progression 2 years after undergoing unilateral medial opening wedge HTO. Specifically, varus mal-alignment and the external knee adduction moment during walking were improved substantially in the surgical limb. However, patients also gained weight and the knee adduction moment of the non-surgical limb increased slightly. The observed increase in the non-surgical limb was explained most by increased mass and increased gait speed experienced after the surgery.

Chapter 3: Given the importance of high body mass in patients with knee OA, both before and especially after HTO, further investigation of measures of body composition was warranted. Excellent test-retest reliability of air displacement plethysmography (ADP) measures of body density, fat mass, lean mass and percent body fat were established in a sample of overweight-to-obese patients with knee OA. Minimum detectable change values were reported for each of these measures at various confidence

intervals. Results suggested that, as a "rule of thumb" upon repeated testing, 95% of stable patients would change by less than approximately 2% body fat, and 75% of stable patients would change by less than 1% body fat.

Chapter 4: This proof of principle study investigated the cumulative effects of combined physiotherapy and medial opening wedge HTO in patients with varus gonarthrosis. The study demonstrated that combined, multi-modal intervention was required to mitigate the varied risk factors for disease progression. After the combination of medial opening wedge HTO and physiotherapy (with a focus on diet and functional strengthening, completed pre- and post-operatively), patients experienced improvements in fat mass, muscular strength, lower-limb mal-alignment and the knee adduction moment during walking. Patients also reported large improvements in all domains of the KOOS after completing all interventions. Importantly, HTO was required to correct mal-alignment and decrease the knee adduction moment, but also diminished the pre-operative improvements in fat mass and muscular strength. Indeed, physiotherapy was required to improve body composition and muscular strength. The findings provide support for future investigations comparing multi-modal rehabilitative and surgical intervention to other treatment strategies, including the comparative effects on multiple measures of OA progression.

5.2 The Role of Medial Opening Wedge HTO in Mitigating Risk Factors for Disease Progression in Patients with Varus Gonarthrosis

Findings from this thesis suggest that medial opening wedge HTO is quite successful in reducing some biomechanical risk factors for disease progression in patients with varus gonarthrosis, by producing substantial reductions in varus mal-alignment, the peak knee adduction moment and the knee adduction impulse. This is consistent with

previous research that has also reported large changes in the distribution of loads across the knee during gait after HTO.[1-5] However, unlike previous research, the present findings highlight the potential detrimental effects of surgery on other risk factors for knee OA progression. If increases in body mass and decreases in muscular strength are allowed to persist post-operatively, this will likely limit the future knee joint health of these patients, bilaterally. Clearly, ways of diminishing the postoperative increases in fat mass and decreases in strength are required. Although the present thesis focused on diet and exercise, other methods should also be considered. For example, the required period of partial weight-bearing after medial opening wedge HTO is problematic for both increases in fat mass and decreases in muscular strength.[6-9] As HTO fixation plate technology improves, the potential effects of earlier weight-bearing post-operatively should be evaluated. Additionally, other therapeutic interventions targeting neuromuscular deficits may also prove to be valuable before and/or after HTO.[10-12] Consistent with the general theme of this thesis, multi-modal interventions are likely required to better address the multiple risk factors.

Interestingly, the present patients demonstrated large improvements in all domains of the KOOS after surgery. This is also in line with others who have reported large, long-term improvements in patient-reported outcomes after HTO.[1,4,5] Although the importance of patient-reported outcomes should not be underestimated, findings from the present thesis emphasize that long-term impairments can exist after HTO, these would likely be missed if not specifically tested, and deserve further attention.

5.3 The Role of Multi-modal Physiotherapy in Mitigating Risk Factors for Disease Progression in Patients with Varus Gonarthrosis

The present thesis also demonstrated that some risk factors for OA progression could be improved in patients with varus gonarthrosis through rehabilitative intervention alone. Patients were able to reduce their fat mass, percent body fat and maintain their lean mass, while also demonstrating improvements in muscular strength. Despite these improvements in body composition and muscular strength, there were no associated reductions in the peak knee adduction moment or in the knee adduction impulse. It is possible that the present patients did not lose enough body mass to elicit changes in gait. For example, Messier et al[13] compared gait biomechanics in a group of patients with knee OA who lost more than 10% of their baseline weight with a group of patients who lost less than 5%. The researchers observed reductions in their modelled measure of total tibiofemoral compressive force in the higher weight loss group only. Also, Aaboe et al,[14] evaluated gait biomechanics in patients who lost 13.5% of their baseline weight. In that study, the peak knee adduction moment decreased by 12%, and the knee adduction impulse decreased by 13%, compared to baseline.

The present physiotherapy intervention included functional muscle strengthening exercises that targeted the entire lower limb bilaterally, including the hip and pelvis, and also incorporated postural control exercises. However, it should be acknowledged that, unlike other rehabilitative attempts to specifically alter the external knee adduction moment by controlling the relationship between the centre of pressure and the centre of mass, the present exercises were simply considered part of a thorough physiotherapy program. Although the existing evidence is mixed, the present results do not preclude the

possibility that other rehabilitation programs targeting the knee adduction moment may be successful.

5.4 The Role of Combined Physiotherapy and High Tibial Osteotomy in Mitigating Risk Factors for Disease Progression in Patients with Varus Gonarthrosis

Overall, the present thesis highlights the importance of attempting to mitigate the multiple risk factors for the progression of knee OA by administering multiple interventions. The present findings emphasize that different interventions target different risk factors. Some treatments, although quite successful in affecting some risk factors, are ineffective - even detrimental - to others.[6-9] Specifically, in patients with varus gonarthrosis, the ability of HTO to correct varus mal-alignment and produce very large reductions (>50%) in the external knee adduction moment during walking suggests strong benefits for future knee joint health. However, without offsetting the accompanying increases in fat mass and decreases in strength observed after surgery, the future benefits may not be fully realized. Alternatively, the large decrease in fat mass (almost 5kg, over 10 pounds) and modest gains in strength achieved in patients with varus gonarthrosis through physiotherapy alone, also suggest benefits to future knee joint health. However, despite those changes, patients experienced no change in lower limb mal-alignment and the knee adduction moment. Physiotherapy also resulted in smaller increases in KOOS scores compared to HTO. Only the combination of rehabilitative and surgical intervention was able to adequately affect change in the full spectrum of risk factors investigated. Therefore, results of the present thesis support the principle of using multi-modal interventions to produce cumulative benefits and mitigate several risk factors for the progression of OA in patients with varus gonarthrosis.

5.5 Overall Limitations and Future Research

1. The studies in this thesis measured the external knee adduction moment during walking to describe the biomechanical environment at the knee. The knee adduction moment is a good surrogate for the distribution of load across the knee during gait, and has been demonstrated repeatedly to be a strong risk factor for medial knee OA progression. However, it is possible that changes in the actual medial compartment load can occur without experiencing changes in the knee adduction moment (for example, through muscle co-contraction). Similarly, it is also theoretically possible that changes in the knee adduction moment can occur without true changes in the medial compartment compressive force.
2. Eight weeks may not be long enough to in achieve optimal gains in muscular strength, or to overcome potential inhibitory neuromuscular mechanisms after HTO. Extending the length of the described physiotherapy program and nutritional counseling may also lead to greater reductions of fat mass.
3. Although the present thesis measured known risk factors for the structural progression of medial compartment knee OA, it did not measure structural progression itself. Future studies incorporating magnetic resonance imaging, or longer term radiographic evaluations are required to more fully evaluate the effects of multi-modal, rehabilitative and surgical intervention.

4. The final chapter of this thesis was a proof of principle study with a low sample size. It was largely influenced by outliers. Although, the findings support the principle of using multi-modal interventions to mitigate multiple risk factors for the progression of OA in patients with varus gonarthrosis, future research with larger samples is both warranted and required.

5.6 References

1. Birmingham TB, Giffin JR, Chesworth BM, et al. Medial opening wedge high tibial osteotomy: A prospective cohort study of gait, radiographic and patient-reported outcomes. Arthritis Rhem. 2009;61:648-657.
2. DeMeo PJ, Johnson EM, Chiang PP, Flamm AM, Miller MC. Midterm follow-up of opening-wedge high tibial osteotomy. Am J Sports Med. 2010;38:2077-2084
3. Lind M, McClelland J, Wittwer JE, Whitehead TS, Feller JA, Webster KE. Gait analysis of walking before and after medial opening wedge high tibial osteotomy. Knee Surg Sports Traumatol Arthrosc. 2013.21;1:74-81.
4. Prodromos CC, Andriacchi TP, Galante JO. A relationship between gait and clinical changes following high tibial osteotomy. J Bone Joint Surg Am. 1985;67:1188-1194.
5. Wada M, Imura S, Nagatani K, Baba H, Shimada S, Sasaki S. Relationship between gait and clinical results after high tibial osteotomy. Clin Orthop. 1998;354:180-188.
6. Kean CO, Birmingham TB, Garland SJ, Bryant DM, Giffin JR. Preoperative strength training for patients underoing high tibial osteotomy: a prospective cohort study with historical controls. J Orthop Sports Phys Ther. 2011;41:52-59.
7. Machner A, Pap G, Krohn A, Rohkohl K, Awiszus F. Quadriceps muscle function after high tibial osteotomy for osteoarthritis for the knee. Clin Orthop Relat Res. 2002;177-183.
8. Ramsey DK, Snyder-Mackler L, Lewek M, Newcomb W, Rudolph KS. Effect of anatomic realignment on muscle function during gait in patients with medial compartment knee osteoarthritis. Arthritis Rheum. 2007;57:389-397.
9. Kawazoe T, Takahashi T. Recovery of muscle strength after high tibial osteotomy. J Orthop Sci. 2003;8:160-165.
10. Bennell KL, Egerton T, Wrigley TV, Hodges PW, Hunt M, Roos EM, Kyriakides M et al. Comparison of neuromuscular and quadriceps strengthening exercise in the treatment of varus malaligned knees with medial knee osteoarthritis: a randomized controlled trial protocol. BMC Musculo Dis. 2011;12:276.
11. Ageberg E, Link A, Roos EM. Feasibility of neuromuscular training in patients with severe hip or knee OA: the individualized goal-based NEMEX-TJR training program. BMC Musculoskelet Disord. 2010;11:126.
12. Stensrud S, Roos EM, Risberg MA. A 12-week exercise therapy program in middle-aged pateitns with degenerative meniscus tears: A case series with 1-year follow-up. J Orthop Sports Phys Ther. 2012;42:919-931.
13. Messier SP, Legault C, Loeser RF, Van Arsdale SJ, Davis C, Ettinger WH, et al. Does high weight loss in older adults with knee osteoarthritis affect bone-on-bone joint loads and muscle forces during walking? Osteoarthritis Cart. 2011;19:272-280.

14. Aaboe J, Bliddal H, Messier SP, Alkjaer T, Henrikson M. Effects of an intensive weight loss program on knee joint loading in obese adults with knee osteoarthritis. Osteoarthritis Cart. 2001;19:822-828.

6. APPENDICES

APPENDIX A: Individual Patient Changes Assessed During the Intervention in Study 3 (Chapter 4)

Table A.1: Summary of 8-week Physiotherapy Intervention

Warm-up – 10 minutes	Cycle ergometer: at 50rpm 1kp
Stretching – 5 minutes	Quadriceps, hamstrings, gastrocnemius, soleus
Physiotherapy Muscular Strengthening Program – 45 minutes	**1.Shuttle leg press**: Closed kinetic chain focusing on quadriceps strength. Patient in supine lying, with feet flat on a platform with knees flexed to 90 degrees. Patient maintains neutral knee alignment over foot and not allowing medial or lateral movement of the knee relative to the foot. Patient must extend knee against platform, which moves the "sled" that is attached to a frame with resistance bands. The patient must control the "sled" when returning to start position. **2.Shuttle calf press**: Closed kinetic chain focusing on gastrocnemius strength. Patient in supine lying, with knees extended and distal aspect of both feet supported on platform. Patient required to plantar flex against platform moving the "sled" attached to a frame with resistance bands. Patient instructed to control the "sled" when returning to start position. **3.Seated knee extension/flexion**: Open kinetic chain exercise focusing on quadriceps and hamstring strength. Resistance applied through hydraulics, both when extending and flexing the knee. Emphasis placed on moving through all available range. **4.Seated knee flexion**: Open kinetic chain exercise focusing on hamstring strength. Patient in a seated position with a resistance attached by pulley around ankle. Patient required to flex the knee from an extended position and control weight when returning to start position **5.Bungie-cord walking**: Neuromuscular control during walking. Resistance cord placed around pelvis and patient required to walk out as far as they can as long as they are able to maintain neutral knee, and no pelvic drop (i.e. trendelenburg type gait). Patient must also maintain control of knee and pelvis upon returning to start position. **6.Sidelying hip abduction**: Open kinetic chain exercise focusing of strength of the hip abductors. Patient in sidelying, required to abduct the hip. Patient must maintain neutral pelvis and hip such that ankle is in dorsiflexion and foot not allowed to "turn-in" to point to the floor or "turn-out" to point to the ceiling. **7.Supine ball bridge**: Strengthening exercise focusing on gluteals and hamstrings. Patient in supine lying with heels placed on exercise ball and arms placed on floor by side. Patient required to lift pelvis off floor by contracting gluteals and hamstrings. Hips must remain in a neutral position by not allowing either foot to rotate "inwards" or "outwards" while performing the task. The patient must control the decent of the pelvis back to the floor. **8.Postural stability**: Patient required to maintain postural stability while standing on an unstable board approximately 1 inch off the floor. Patient performs this exercise for 5 minutes attempting to keep board "level" for as long as possible. Patient instructed to keep pelvis "level" and a neutral knee position.

Table A.2: Rating of Perceived Exertion (RPE) Scale[62-64]

Value	Description
6	
7	Very, very light
8	
9	Very light
10	
11	Fairly light
12	
13	Somewhat hard
14	
15	Hard
16	
17	Very hard
18	
19	Very, very hard
20	Maximum exertion

Table A.3: Pre-operative and Post-operative Summary of Patient Attendance and Mean (±SD) Pain Ratings for Each Participant Prior (Pre) to engaging in the Physiotherapy Sessions and After Completing the Physiotherapy Sessions (Post)

	Pre-operative MPT Intervention			Post-operative MPT Intervention		
		Pain Ratings (0-10)			Pain Ratings (0-10)	
Patient	Attendance	Mean±SD (Pre)	Mean±SD (Post)	Attendance	Mean±SD (Pre)	Mean±SD (Post)
1	9/16	3±1	2±0.7	13/16	0.8±0.8	0.5±0.5
2	16/16	3.4±1.2	4.4±1.5	16/16	3.4±1.1	3.3±1.1
3	14/15	5.4±1.9	7.4±1.2	15/16	0±0	0±0
4	15/16	2.4±1.1	2.2±1.5	14/16	1.8±1.1	2.1±1.7
5	15/16	0±0	0±0	12/16	0±0	0±0
6	16/16	3.9±0.7	2.9±0.9	16/16	1.0±0	1.0±0
7	15/16	5.6±0.9	7.6±0.6	15/16	0.6±0.7	2.3±0.8
8	13/16	2.0±1.0	3.5±1.8	7/16	3.4±1.1	6.4±1.4

Pain rating: 0=no pain, 10=worst pain imaginable

Table A.4: Pre-operative and Post-operative Summary of Mean (±SD) Ratings of Perceived Exertion for each Exercise for each Individual Patient

Pre-operative	Patient							
*Exercise	1	2	3	4	5	6	7	8
1	13±1.2	15±1.9	16±1.8	16±1.1	17±2.5	15±2.3	17±1.5	18±2.2
2	15±2.0	15±1.1	17±1.3	15±1.1	18±1.5	15±2.1	18±1.4	19±1.2
4	15±1.2	15±1.1	16±1.5	15±1.2	17±1.7	17±1.7	16±2.0	19±2.8
3	14±1.1	15±1.2	17±1.7	15±1.2	16±2.3	16±1.7	17±1.8	18±1.6
5	14±1.2	14±1.3	16±1.5	15±1.2	16±2.5	15±2.0	16±1.8	18±1.5
6	16±0.7	15±1.4	18±0.8	15±1.0	18±1.3	15±1.7	18±1.5	19±0.9
7	15±1.2	15±1.1	16±1.7	13±0.8	16±1.8	14±1.4	16±1.9	18±1.2
8	14±1.8	14±1.0	17±2.2	13±0.6	16±2.6	14±2.5	16±1.9	16±2.6
Post-operative	Patient							
*Exercise	1	2	3	4	5	6	7	8
1	16±1.2	16±0.8	15±0.5	15±1.1	16±1.4	15±1.8	17±0.8	18±1.8
2	15±1.6	16±0.6	15±0.4	15±0.9	17±0.7	15±1.5	17±1.4	17±1.5
4	16±1.2	15±0.6	15±0.4	15±0.8	17±1.3	15±1.0	17±1.4	18±2.6
3	15±0.9	16±0.4	15±0.5	14±0.7	17±0.8	15±0.8	17±0.8	16±1.5
5	16±0.5	15±0.4	15±0.5	14±0.6	16±1.3	15±0.9	17±0.6	18±1.0
6	16±1.0	16±0.5	15±0.5	14±0.7	16±0.9	15±0.6	17±0.8	18±0.8
7	15±0.6	15±0.4	15±0.0	13±0.5	16±0.9	14±0.7	17±1.4	15±1.7
8	14±1.0	15±0.4	16±0.5	13±0.7	15±0	14±0.9	17±1.2	16±1.5

Rating of perceived exertion (RPE) scale 6-20

*See Table A.1 for description of exercise

Tables Comparing Overall Changes in Individual Patients from Endpoint to Baseline

Table A.5: Changes in Individual Patient Body Composition Measures Comparing Endpoint to Baseline

Patient	Body Composition	Baseline	Endpoint	Change
1	Fat mass(kg)	37.8	33.5	**-4.3**¥
	Percent Fat(%)	36.1	32.8	**-3.3**¥
	Lean Mass(kg)	66.8	68.5	**1.7**¥
2	Fat mass(kg)	36.3	37.8	**1.5**€
	Percent Fat(%)	45.3	48.7	**3.4**¥
	Lean Mass(kg)	43.8	39.8	**-4.0**¥
3	Fat mass(kg)	23.0	18	**-5.0**¥
	Percent Fat(%)	22.7	18.6	**-4.1**¥
	Lean Mass(kg)	78.3	78.5	0.2
4	Fat mass(kg)	31.4	29.7	**-1.7**♯
	Percent Fat(%)	34.1	32.9	**-1.2**∞
	Lean Mass(kg)	60.7	60.6	-0.1
5	Fat mass(kg)	25.6	20.8	**-4.8**¥
	Percent Fat(%)	27.6	23.9	**-3.7**¥
	Lean Mass(kg)	67.1	66.2	-0.9
6	Fat mass(kg)	38.0	29.3	**-8.7**¥
	Percent Fat(%)	35.3	29.2	**-6.1**¥
	Lean Mass(kg)	69.5	71.1	**1.6**♯
7	Fat mass(kg)	39.5	35.6	**-3.9**¥
	Percent Fat(%)	36.6	35.0	**-1.6**♯
	Lean Mass(kg)	68.6	66.2	**-2.4**¥
8	Fat mass(kg)	37.1	28.2	**-8.9**¥
	Percent Fat(%)	32.2	27.9	**-4.3**¥
	Lean Mass(kg)	77.9	73.0	**-4.9**¥

Values in bold exceeded the Minimum Detectable Change.
¥ Minimum Detectable Change surpassed at 95%CI
♯ Minimum Detectable Change surpassed at 90%CI
€ Minimum Detectable Change surpassed at 85%CI
∞ Minimum Detectable Change surpassed at 80% CI
§ Minimum Detectable Change surpassed at 75%CI

Table A.6: Changes in Isokinetic Knee Extension and Flexion for each Individual Patient Comparing Endpoint to Baseline

Patient	Muscular Strength	Baseline	Endpoint	Change
1	Knee Extension Torque (Nm)	161	174	13
	Knee Flexion Torque (Nm)	105	110	5
2	Knee Extension Torque (Nm)	80	86	6
	Knee Flexion Torque (Nm)	40	48	8
3	Knee Extension Torque (Nm)	177	152	-26
	Knee Flexion Torque (Nm)	67	82	15
4	Knee Extension Torque (Nm)	116	131	15
	Knee Flexion Torque (Nm)	57	79	22
5	Knee Extension Torque (Nm)	182	159	-23
	Knee Flexion Torque (Nm)	80	96	16
6	Knee Extension Torque (Nm)	85	207	**121***
	Knee Flexion Torque (Nm)	43	125	82
7	Knee Extension Torque (Nm)	94	120	26
	Knee Flexion Torque (Nm)	36	80	44
8	Knee Extension Torque (Nm)	231	174	**-56***
	Knee Flexion Torque (Nm)	117	129	12

Values in bold exceeded the Minimum Detectable Change.

Table A.7: Changes in the Peak Knee Adduction Moment and the Adduction Impulse for each Individual Patient Comparing Endpoint to Baseline

Patient	Knee Adduction Moment	Baseline	Endpoint	Change
1	Peak (Nm)	41.7	11.3	-30.4
	Peak (%BW*Ht)	2.17	0.60	**-1.57¥**
	Impulse (Nms)	19.2	4.3	-14.9
2	Peak (Nm)	38.2	40.4	2.2
	Peak (%BW*Ht)	3.01	3.29	0.28
	Impulse (Nms)	20.4	18.8	-1.6
3	Peak (Nm)	73.6	44.5	-29.1
	Peak (%BW*Ht)	4.03	2.55	**-1.49¥**
	Impulse (Nms)	36.7	17.4	-19.2
4	Peak (Nm)	42.7	12.4	-30.3
	Peak (%BW*Ht)	2.83	0.83	**-2.00¥**
	Impulse (Nms)	18.1	5.3	-12.8
5	Peak (Nm)	60.4	30.4	-30.1
	Peak (%BW*Ht)	3.72	1.98	**-1.74¥**
	Impulse (Nms)	23.3	12.6	-10.7
6	Peak (Nm)	39.0	20.3	-18.7
	Peak (%BW*Ht)	2.07	1.16	**-0.92♯**
	Impulse (Nms)	25.3	8.7	-16.6
7	Peak (Nm)	50.5	23.7	-26.9
	Peak (%BW*Ht)	2.72	1.35	**-1.38¥**
	Impulse (Nms)	23.8	10.3	-13.4
8	Peak (Nm)	75.1	20.1	-55.0
	Peak (%BW*Ht)	3.68	1.11	**-2.57¥**
	Impulse (Nms)	33.5	7.8	-25.7

Peak knee adduction moment data were also presented relative to percent body weight times height (%BW*Ht) in order to report Minimum Detectable Change for each individual.

Values in bold exceeded the Minimum Detectable Change.

¥Minimum Detectable Change surpassed at 95% confidence interval.

♯Minimum Detectable Change surpassed the 90% Confidence interval.

Table A.8: Changes in the Knee Injury and Osteoarthritis Outcome Scores for each Individual Patient Comparing Baseline to Endpoint

Patient	KOOS	Baseline	Endpoint	Change
1	Pain	69	86	**17***
	Symptoms	61	79	**18***
	ADLs	75	99	**24***
	Sport&Rec	35	55	**20***
	Quality of Life	38	75	**37***
2	Pain	36	67	**31***
	Symptoms	39	54	**15***
	ADLs	47	81	**34***
	Sport&Rec	25	40	**15***
	Quality of Life	25	50	**25***
3	Pain	36	100	**64***
	Symptoms	50	64	**14***
	ADLs	42	94	**52**
	Sport&Rec	10	85	**75***
	Quality of Life	31	94	**63***
4	Pain	47	64	**17***
	Symptoms	35	61	**26***
	ADLs	50	82	**32***
	Sport&Rec	40	55	**15***
	Quality of Life	25	50	**25***
5	Pain	81	100	**19***
	Symptoms	64	71	7
	ADLs	96	100	4
	Sport&Rec	40	100	**60***
	Quality of Life	69	94	**25***
6	Pain	11	75	**64***
	Symptoms	0	57	**57***
	ADLs	8	84	**76***
	Sport&Rec	0	50	**50***
	Quality of Life	6	44	**38***
7	Pain	44	78	**34***
	Symptoms	39	54	**15***
	ADLs	57	74	**17***
	Sport&Rec	10	40	**30***
	Quality of Life	31	56	**25***
8	Pain	53	61	8
	Symptoms	64	50	**-14***
	ADLs	64	81	**17***
	Sport&Rec	15	20	5
	Quality of Life	25	13	**-12***

Values in bold exceeded the Minimal Clinically Important Difference

Tables Demonstrating Changes for all outcomes for each Individual Patient During the Pre-operative MPT

Table A.9: Changes in Body Composition for each Individual Patient During the Pre-operative Multi-modal Physiotherapy Intervention (MPT)

Patient	Body Composition	Pre MPT	Post MPT	Change
1	Fat mass(kg)	37.8	32.0	**-5.8¥**
	Percent Fat(%)	36.1	31.6	**-4.5¥**
	Lean Mass(kg)	66.8	69.1	**2.3¥**
2	Fat mass(kg)	36.3	32.4	**-3.9¥**
	Percent Fat(%)	45.3	42.0	**-3.3¥**
	Lean Mass(kg)	43.8	44.6	0.8
3	Fat mass(kg)	23.0	19.3	**-3.7¥**
	Percent Fat(%)	22.7	19.6	**-3.1¥**
	Lean Mass(kg)	78.3	79.3	**1.0§**
4	Fat mass(kg)	31.4	27.2	**-4.2¥**
	Percent Fat(%)	34.1	30.2	**-3.9¥**
	Lean Mass(kg)	60.7	62.9	**2.2¥**
5	Fat mass(kg)	25.6	21.4	**-4.2¥**
	Percent Fat(%)	27.6	24.5	**-3.1¥**
	Lean Mass(kg)	67.1	66.0	**-1.1§**
6	Fat mass(kg)	38.0	30.3	**-7.7¥**
	Percent Fat(%)	35.3	29.8	**-5.5¥**
	Lean Mass(kg)	69.5	71.6	**2.1¥**
7	Fat mass(kg)	39.5	33.6	**-5.9¥**
	Percent Fat(%)	36.6	33.3	**-3.3¥**
	Lean Mass(kg)	68.6	67.3	**-1.3€**
8	Fat mass(kg)	37.1	28.6	**-8.5¥**
	Percent Fat(%)	32.2	27.5	**-4.7¥**
	Lean Mass(kg)	77.9	75.5	**-2.4¥**

Values in bold exceeded the Minimum Detectable Change
¥ Minimum Detectable Change surpassed at 95%CI.
€ Minimum Detectable Change surpassed at 85%CI.
§ Minimum Detectable Change surpassed at 75%CI

Table A.10: Changes in Isokinetic Knee Extension and Flexion for each Individual Patient During the Pre-operative Multi-modal Physiotherapy Intervention

Patient	Muscular Strength	Pre MPT	Post MPT	Change
1	Knee Extension Torque (Nm)	161	156	-5
	Knee Flexion Torque (Nm)	105	104	-1
2	Knee Extension Torque (Nm)	80	96	16
	Knee Flexion Torque (Nm)	40	49	9
3	Knee Extension Torque (Nm)	177	206	29
	Knee Flexion Torque (Nm)	67	100	33
4	Knee Extension Torque (Nm)	116	141	25
	Knee Flexion Torque (Nm)	57	67	10
5	Knee Extension Torque (Nm)	182	179	-3
	Knee Flexion Torque (Nm)	80	97	17
6	Knee Extension Torque (Nm)	85	186	**101***
	Knee Flexion Torque (Nm)	43	123	80
7	Knee Extension Torque (Nm)	94	136	**42***
	Knee Flexion Torque (Nm)	36	82	46
8	Knee Extension Torque (Nm)	231	266	**35***
	Knee Flexion Torque (Nm)	117	128	11

Values in bold exceeded the Minimum Detectable Change

Table A.11: Changes in the Peak Knee Adduction Moment and Adduction Impulse During the Pre-operative Multi-modal Physiotherapy Intervention (MPT)

Patient	Knee Adduction Moment	Pre MPT	Post MPT	Change
1	Peak (Nm)	41.7	52.4	10.7
	Peak (%BW*Ht)	2.17	2.83	**0.66**∞
	Impulse(Nms)	19.2	24.0	4.8
2	Peak (Nm)	38.2	46.8	8.6
	Peak (%BW*Ht)	3.01	3.85	**0.84**¥
	Impulse(Nms)	20.4	23.5	3.1
3	Peak (Nm)	73.6	68.3	-5.3
	Peak (%BW*Ht)	4.03	3.84	-0.19
	Impulse(Nms)	36.7	32.2	-4.5
4	Peak (Nm)	42.7	38.6	-4.1
	Peak (%BW*Ht)	2.83	2.61	-0.22
	Impulse(Nms)	18.1	16.8	-1.3
5	Peak (Nm)	60.4	52.7	-7.7
	Peak (%BW*Ht)	3.72	3.44	-0.28
	Impulse(Nms)	23.3	22.8	-0.5
6	Peak (Nm)	39.0	42.6	3.6
	Peak (%BW*Ht)	2.07	2.39	0.32
	Impulse(Nms)	25.3	22.1	-3.2
7	Peak (Nm)	50.5	52.0	1.5
	Peak (%BW*Ht)	2.72	2.98	0.26
	Impulse(Nms)	23.8	23.3	-0.5
8	Peak (Nm)	75.1	81.7	6.6
	Peak (%BW*Ht)	3.68	4.37	**0.69**∞
	Impulse(Nms)	33.5	33.7	0.2

Peak knee adduction moment data were also presented relative to percent body weight times height (%BW*Ht) in order to report minimal detectable change for each individual
Values in bold exceed the Minimum Detectable Change
¥Minimum Detectable Change surpassed at 90% confidence interval
∞Minimum Detectable Change surpassed the 80% confidence interval

Table A.12: Changes in Knee Injury and Osteoarthritis Outcome Scores for each Individual Patient During the Pre-operative Multi-modal Physiotherapy Intervention (MPT)

Patient	KOOS	Pre MPT	Post MPT	Change
1	Pain	69	66	-3
	Symptoms	61	71	**10***
	ADLs	75	79	4
	Sport&Rec	35	15	**-20***
	Quality of Life	38	50	**12***
2	Pain	36	66	**30***
	Symptoms	39	54	**15***
	ADLs	47	81	**34***
	Sport&Rec	25	75	**50***
	Quality of Life	25	44	**19***
3	Pain	36	30	-6
	Symptoms	50	29	**-21***
	ADLs	42	32	**-10***
	Sport&Rec	10	5	-5
	Quality of Life	31	13	**-18***
4	Pain	47	47	0
	Symptoms	35	36	1
	ADLs	50	60	**10***
	Sport&Rec	40	40	0
	Quality of Life	25	19	-6
5	Pain	81	88	7
	Symptoms	64	79	**15***
	ADLs	96	94	-2
	Sport&Rec	40	55	**15***
	Quality of Life	69	69	0
6	Pain	11	36	**25***
	Symptoms	0	18	**18***
	ADLs	8	50	**42***
	Sport&Rec	0	0	0
	Quality of Life	6	13	7
7	Pain	44	55	**11***
	Symptoms	39	50	**11***
	ADLs	57	66	9
	Sport&Rec	10	20	**10***
	Quality of Life	31	31	0
8	Pain	53	58	5
	Symptoms	64	71	7
	ADLs	64	72	8
	Sport&Rec	15	30	**15***
	Quality of Life	25	25	0

Values in bold exceed the Minimal Clinically Important Difference

Tables Demonstrating Changes in all Outcomes after HTO

Table A.13: Changes in Body Composition in each Individual Patient Six Months after Medial Opening Wedge HTO

Patient	Body Composition	Pre HTO	Post HTO	Change
1	Fat mass(kg)	32.0	34.1	**2.1**¥
	Percent Fat(%)	31.6	33	**1.4**€
	Lean Mass(kg)	69.1	69.3	0.2
2	Fat mass(kg)	32.4	35.3	**2.9**¥
	Percent Fat(%)	42.0	46	**4.0**¥
	Lean Mass(kg)	44.6	41.4	**-3.2**¥
3	Fat mass(kg)	19.3	19.1	-0.2
	Percent Fat(%)	19.6	19.2	-0.4
	Lean Mass(kg)	79.3	80.4	**1.1**∞
4	Fat mass(kg)	27.2	34.8	**7.6**¥
	Percent Fat(%)	30.2	37.2	**7.0**¥
	Lean Mass(kg)	62.9	58.6	**-4.3**¥
5	Fat mass(kg)	21.4	24	**2.6**¥
	Percent Fat(%)	24.5	26.3	**1.8**¥
	Lean Mass(kg)	66.0	67.1	**1.1**∞
6	Fat mass(kg)	30.3	32.1	**1.8**♯
	Percent Fat(%)	29.8	30.5	0.7
	Lean Mass(kg)	71.6	73	**1.4**♯
7	Fat mass(kg)	33.6	35.7	**2.1**¥
	Percent Fat(%)	33.3	34.2	0.9
	Lean Mass(kg)	67.3	68.7	**1.4**♯
8	Fat mass(kg)	28.6	33.7	**5.1**¥
	Percent Fat(%)	27.5	31.9	**4.4**¥
	Lean Mass(kg)	75.5	72.1	**-3.4**¥

Values in bold exceed the Minimum Detectable Change
¥ Minimum Detectable Change surpassed at 95% confidence interval
♯ Minimum Detectable Change surpassed at 90% confidence interval
€ Minimum Detectable Change surpassed at 85% confidence interval
∞Minimum Detectable Change surpassed at 80% confidence interval

Table A.14: Changes in Isokinetic Knee Extension and Flexion for each Individual Patient Six Months after Medial Opening Wedge HTO

Patient	Muscular Strength	Pre HTO	Post HTO	Change
1	Knee Extension Torque (Nm)	156	98	**-58***
	Knee Flexion Torque (Nm)	104	84	-20
2	Knee Extension Torque (Nm)	96	86	-10
	Knee Flexion Torque (Nm)	49	41	-8
3	Knee Extension Torque (Nm)	206	133	**-73***
	Knee Flexion Torque (Nm)	100	79	-21
4	Knee Extension Torque (Nm)	141	124	-17
	Knee Flexion Torque (Nm)	67	75	8
5	Knee Extension Torque (Nm)	179	178	-1
	Knee Flexion Torque (Nm)	97	80	-17
6	Knee Extension Torque (Nm)	186	173	-13
	Knee Flexion Torque (Nm)	123	130	7
7	Knee Extension Torque (Nm)	136	109	-27
	Knee Flexion Torque (Nm)	82	61	-21
8	Knee Extension Torque (Nm)	266	133	**-133***
	Knee Flexion Torque (Nm)	128	119	-9

Values in bold exceeded the Minimum Detectable Change

Table A.15: Change in the Peak Knee Adduction Moment and Adduction Impulse Six Months after Medial Opening Wedge HTO

Patient	Knee Adduction Moment	Pre HTO	Post HTO	Change
1	Peak (Nm)	52.4	8.1	-44.3
	Peak (%BW*Ht)	2.83	0.43	**-2.40¥**
	Impulse(Nms)	24.0	2.1	-21.9
2	Peak (Nm)	46.8	20.7	-26.1
	Peak (%BW*Ht)	3.85	1.80	**-2.05¥**
	Impulse(Nms)	23.5	8.8	-14.7
3	Peak (Nm)	68.3	46.3	-22
	Peak (%BW*Ht)	3.84	2.58	**-1.26¥**
	Impulse(Nms)	32.2	16.9	-15.3
4	Peak (Nm)	38.6	17.8	-20.8
	Peak (%BW*Ht)	2.61	1.18	**-1.43¥**
	Impulse(Nms)	16.8	8.6	-8.2
5	Peak (Nm)	52.7	30.6	-22.1
	Peak (%BW*Ht)	3.44	1.93	**-1.51¥**
	Impulse(Nms)	22.8	10.3	-12.5
6	Peak (Nm)	42.6	25.5	-17.1
	Peak (%BW*Ht)	2.39	1.38	**-1.01¥**
	Impulse(Nms)	22.1	13.9	-8.2
7	Peak (Nm)	52.0	-16.3♮	-68.3
	Peak (%BW*Ht)	2.98	-0.92♮	**-3.90¥**
	Impulse(Nms)	23.3	0♭	-23.3
8	Peak (Nm)	81.7	28.6	-53.1
	Peak (%BW*Ht)	4.37	1.47	**-2.90¥**
	Impulse(Nms)	33.7	11.8	-21.9

Peak knee adduction moment data were also presented relative to percent body weight times height (%BW*Ht) in order to report Minimum Detectable Change for each individual

¥ Minimum Detectable Change surpassed the 95% confidence interval.

♮ Patient demonstrated an abduction moment during gait analysis

♭ Patient did not demonstrate an adduction impulse

Table A.16: Changes in Mechanical Axis Angle Six Months after Medial Opening Wedge HTO

Patient	MAA(°)Pre HTO	MAA(°)Post HTO	Change(°)
1	-5	4.9	9.9
2	-8.3	2	10.3
3	-7.8	-1.3	6.5
4	-7.8	-0.8	7
5	-6.2	-2.1	4.1
6	-6.2	1.8	8
7	-5.9	4.2	10.1
8	-8.4	4.2	12.6

MAA=Mechanical Axis Angle, °=Degrees

Table A.17: Changes in the Knee Injury and Osteoarthritis Outcome Scores Six Months after Medial Opening Wedge HTO

Patient	KOOS	Pre HTO	Post HTO	Change
1	Pain	66	64	-2
	Symptoms	71	61	**-10***
	ADLs	79	81	2
	Sport&Rec	15	25	**10***
	Quality of Life	50	63	**13***
2	Pain	66	67	1
	Symptoms	54	61	7
	ADLs	81	78	-3
	Sport&Rec	75	50	**-25***
	Quality of Life	44	50	6
3	Pain	30	92	**62***
	Symptoms	29	86	**57***
	ADLs	32	87	**55***
	Sport&Rec	5	90	**85***
	Quality of Life	13	56	**43***
4	Pain	47	69	**22***
	Symptoms	36	46	**10***
	ADLs	60	74	**14***
	Sport&Rec	40	40	0
	Quality of Life	19	31	**12***
5	Pain	88	97	9
	Symptoms	79	96	**17***
	ADLs	94	100	6
	Sport&Rec	55	100	**45***
	Quality of Life	69	100	**31***
6	Pain	36	67	**31***
	Symptoms	18	64	**46***
	ADLs	50	74	**24***
	Sport&Rec	0	45	**45***
	Quality of Life	13	44	**31***
7	Pain	55	69	**14***
	Symptoms	50	75	**25***
	ADLs	66	81	**15***
	Sport&Rec	20	25	5
	Quality of Life	31	44	**13***
8	Pain	58	42	**-16***
	Symptoms	71	29	**-42***
	ADLs	72	56	**-16***
	Sport&Rec	30	0	**-30***
	Quality of Life	25	0	**-25***

Values in bold exceed the Minimal Clinically Important Difference

Tables Demonstrating Changes in all Outcomes for each Individual Patient after the Post-operative MPT intervention

Table A.18: Changes in Body Composition for each Individual Patient During the Post-operative Multi-modal Physiotherapy Intervention (MPT)

Patient		Pre MPT	Post MPT	Change
1	Fat mass(kg)	37.1	33.5	**-3.6¥**
	Percent Fat(%)	34.8	32.8	**-2.0¥**
	Lean Mass(kg)	69.4	68.5	-0.9
2	Fat mass(kg)	42.8	37.8	**-5.0¥**
	Percent Fat(%)	53	48.7	**-4.3¥**
	Lean Mass(kg)	38	39.8	**1.8¥**
3	Fat mass(kg)	25.1	18	**-7.1¥**
	Percent Fat(%)	25.2	18.6	**-6.6¥**
	Lean Mass(kg)	74.5	78.5	**4.0¥**
4	Fat mass(kg)	34.8	29.7	**-5.1¥**
	Percent Fat(%)	37.2	32.9	**-4.3¥**
	Lean Mass(kg)	58.6	60.6	**2.0¥**
5	Fat mass(kg)	24	20.8	**-3.2¥**
	Percent Fat(%)	26.3	23.9	**-2.4¥**
	Lean Mass(kg)	67.1	66.2	-0.9
6	Fat mass(kg)	32.1	29.3	**-2.8¥**
	Percent Fat(%)	30.5	29.2	**-1.3∞**
	Lean Mass(kg)	73	71.1	**-1.9¥**
7	Fat mass(kg)	35.7	35.6	-0.1
	Percent Fat(%)	34.2	35.0	0.8
	Lean Mass(kg)	68.7	66.2	**-2.5¥**
8	Fat mass(kg)	33.7	28.2	**-5.5¥**
	Percent Fat(%)	31.9	27.9	**-4.0¥**
	Lean Mass(kg)	72.1	73.0	0.9

Values in bold exceed the Minimum Detectable Change
¥ Minimum Detectable Change surpassed at 95% confidence interval
∞Minimum Detectable Change surpassed at 80% confidence interval

Table A.19: Changes in Isokinetic Knee Extension and Flexion for each Individual Patient During the Post-operative Physiotherapy Intervention (MPT)

Patient	Muscular Strength	Pre MPT	Post MPT	Change
1	Knee Extension Torque (Nm)	176	174	-2
	Knee Flexion Torque (Nm)	124	110	-14
2	Knee Extension Torque (Nm)	79	86	7
	Knee Flexion Torque (Nm)	41	48	7
3	Knee Extension Torque (Nm)	133	152	19
	Knee Flexion Torque (Nm)	82	82	0
4	Knee Extension Torque (Nm)	124	131	7
	Knee Flexion Torque (Nm)	75	79	4
5	Knee Extension Torque (Nm)	178	159	-19
	Knee Flexion Torque (Nm)	80	96	16
6	Knee Extension Torque (Nm)	173	207	**34***
	Knee Flexion Torque (Nm)	130	125	-5
7	Knee Extension Torque (Nm)	109	120	11
	Knee Flexion Torque (Nm)	61	80	19
8	Knee Extension Torque (Nm)	133	174	**41***
	Knee Flexion Torque (Nm)	119	129	10

Values in bold exceed the Minimum Detectable Change

Table A.20: Changes in the Peak Knee Adduction Moment and Adduction Impulse During the Post-operative Multi-modal Physiotherapy Intervention (MPT)

Patient	Knee Adduction Moment	Pre MPT	Post MPT	Change
1	Peak (Nm)	8.1	11.3	3.2
	Peak (%BW*Ht)	0.43	0.60	0.17
	Impulse (Nms)	2.1	4.3	2.2
2	Peak (Nm)	20.7	40.4	19.7
	Peak (%BW*Ht)	1.47	3.29	**1.82¥**
	Impulse (Nms)	8.8	18.8	10
3	Peak (Nm)	46.3	44.5	-1.8
	Peak (%BW*Ht)	2.60	2.55	-0.05
	Impulse (Nms)	16.9	17.4	0.5
4	Peak (Nm)	17.8	12.4	-5.4
	Peak (%BW*Ht)	1.18	0.83	-0.35
	Impulse (Nms)	8.6	5.3	-3.3
5	Peak (Nm)	30.6	30.4	-0.2
	Peak (%BW*Ht)	1.93	1.98	0.05
	Impulse (Nms)	10.3	12.6	2.3
6	Peak (Nm)	25.5	20.3	-5.2
	Peak (%BW*Ht)	1.38	1.16	-0.22
	Impulse (Nms)	13.9	8.7	-5.2
7	Peak (Nm)♮	-16.3	23.7♮	40.0
	Peak (%BW*Ht)♮	-0.92	1.35♮	**2.27¥**
	Impulse (Nms)♭	0	10.3♭	10.3
8	Peak (Nm)	28.6	20.1	-8.5
	Peak (%BW*Ht)	1.47	1.11	-0.36
	Impulse (Nms)	11.8	7.8	-4

Peak knee adduction moment data were also presented relative to percent body weight times height (%BW*Ht) in order to report minimal detectable change for each individual. Values in bold exceeded the Minimum Detectable Change

¥ Minimum Detectable Change surpassed the 95% confidence interval.

♮ Patient demonstrated an abduction moment during gait analysis

♭ Patient did not demonstrate an adduction impulse

Table A.21: Changes in the Knee Injury and Osteoarthrtis Outcome Scores for each Individual Patient During the Post-operative Multi-modal Physiotherapy Intervention (MPT)

Patient	KOOS	Pre MPT	Post MPT	Change
1	Pain	92	86	-6
	Symptoms	82	79	-3
	ADLs	97	99	2
	Sport&Rec	60	55	-5
	Quality of Life	94	75	**-19***
2	Pain	55	67	**12***
	Symptoms	46	54	8
	ADLs	65	81	**16***
	Sport&Rec	40	40	0
	Quality of Life	31	50	**19***
3	Pain	81	100	**19***
	Symptoms	86	64	**-22***
	ADLs	93	94	1
	Sport&Rec	75	85	**10***
	Quality of Life	63	94	**31***
4	Pain	69	64	-5
	Symptoms	46	61	**15***
	ADLs	74	82	8
	Sport&Rec	40	55	**15***
	Quality of Life	31	50	**19***
5	Pain	97	100	3
	Symptoms	96	71	**-25***
	ADLs	100	100	0
	Sport&Rec	100	100	0
	Quality of Life	100	94	-6
6	Pain	67	75	8
	Symptoms	64	57	-7
	ADLs	74	84	**10***
	Sport&Rec	45	50	5
	Quality of Life	44	44	0
7	Pain	69	78	9
	Symptoms	75	54	**-21***
	ADLs	81	74	-7
	Sport&Rec	25	40	**15***
	Quality of Life	44	56	**12***
8	Pain	42	61	**19***
	Symptoms	29	50	**21***
	ADLs	56	81	**25***
	Sport&Rec	0	20	**20***
	Quality of Life	0	13	**13***

Values in bold exceeded the Minimal Clinically Important Difference

APPENDIX B: Ethics Approval Forms

Western Research

Research Ethics

Use of Human Participants - Ethics Approval Notice

Principal Investigator: Dr. Trevor Birmingham
File Number:1187
Review Level: Delegated
Approved Local Adult Participants:900
Approved Local Minor Participants:0
Protocol Title: Medial Opening Wedge High Tibial Osteotomy for the Treatment of Knee Osteoarthritis: Evaluation of Dynamic Joint Loads and Health-Related Quality of Life - 09812E
Department & Institution: Health Sciences\Physical Therapy,Western University
Sponsor: Canadian Institutes of Health Research

Ethics Approval Date: March 26, 2013 **Expiry Date:**April 30, 2017
Documents Reviewed & Approved & Documents Received for Information:

Document Name	Comments	Version Date
Revised Letter of Information & Consent		
Revised Western University Protocol		

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced revision(s) or amendment(s) on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the University of Western Ontario Updated Approval Request Form.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

The Chair of the HSREB is Dr. Joseph Gilbert. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

[redacted]

Ethics Officer to Contact for Further Information

Janice Sutherland (jsutherl@uwo.ca)	Grace Kelly (grace.kelly@uwo.ca)	Shantel Walcott (swalcot@uwo.ca)

This is an official document. Please retain the original in your files.

Office of Research Ethics

The University of Western Ontario
Room 4180 Support Services Building, London, ON, Canada N6A 5C1
Telephone: (519) 661-3036 Fax: (519) 850-2466 Email: ethics@uwo.ca
Website: www.uwo.ca/research/ethics

Use of Human Subjects - Ethics Approval Notice

Principal Investigator: Dr. T.B. Birmingham
Review Number: 12498E **Revision Number:** 1
Review Date: July 31, 2008 **Review Level:** Expedited
Protocol Title: Pre-Operative Muscle Strengthening for Patients undergoing High Tibial Osteotomy
Department and Institution: Physical Therapy, University of Western Ontario
Sponsor:
Ethics Approval Date: July 31, 2008 **Expiry Date:** August 31, 2010
Documents Reviewed and Approved: Revised Study End Date
Documents Received for Information:

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced revision(s) or amendment(s) on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the UWO Updated Approval Request Form.

During the course of the research, no deviations from, or changes to, the protocol or consent form may be initiated without prior written approval from the HSREB except when necessary to eliminate immediate hazards to the subject or when the change(s) involve only logistical or administrative aspects of the study (e.g. change of monitor, telephone number). Expedited review of minor change(s) in ongoing studies will be considered. Subjects must receive a copy of the signed information/consent documentation.

Investigators must promptly also report to the HSREB:

a) changes increasing the risk to the participant(s) and/or affecting significantly the conduct of the study;
b) all adverse and unexpected experiences or events that are both serious and unexpected;
c) new information that may adversely affect the safety of the subjects or the conduct of the study.

If these changes/adverse events require a change to the information/consent documentation, and/or recruitment advertisement, the newly revised information/consent documentation, and/or advertisement, must be submitted to this office for approval.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

[redacted]

Chair of HSREB: Dr. Paul G. Harding

Ethics Officer to Contact for Further Information			
☐ Janice Sutherland (jsutherl@uwo.ca)	☐ Elizabeth Wambolt (ewambolt@uwo.ca)	☐ Grace Kelly (grace.kelly@uwo.ca)	☑ Denise Grafton (dgrafton@uwo.ca)

This is an official document. Please retain the original in your files.

cc: ORE File
LHRI

Curriculum Vitae

Angelo Boulougouris B.Kin(Hons)., M.A., MSc(PT)., PhD(cand)., Sport Cert.

EDUCATION

The University of Western Ontario, London, Ontario
2007-Present
Ph.D. in Health and Rehabilitation Sciences (Physiotherapy)
Dissertation: "Mitigating Risk Factors for Disease Progression in Patients with Varus Gonarthrosis"

McMaster University, Hamilton, Ontario
2002-2004
M.Sc. Physiotherapy
Clinical Degree in Physiotherapy

The University of Western Ontario, London, Ontario
1998-2000
M.A. Kinesiology
Thesis: Disengaging the negative priming process in location tasks

The University of Western Ontario, London, Ontario
1994-1998
B.A.(Hons). Kinesiology with second area of concentration in Psychology

TEACHING EXPERIENCE

The University of Western Ontario, London, Ontario
2013
Instructor – Physical Therapy in Physical Therapy Clinics I

The University of Western Ontario, London, Ontario
2007-2011
Teaching Assistant – Instructor for Graduate Physical Therapy Program: "Regional Assessment" and "Treatment of Regional Conditions".

The University of Western Ontario, London, Ontario
2007-2008
Lecturer – Graduate Physiotherapy "Principles in Sport Physiotherapy"

The University of Western Ontario, London, Ontario
2008-Present
Lecturer – Undergraduate Health Sciences "Orthopaedic Conditions in Health"

The University of Western Ontario, London, Ontario
2005
Lecturer *– Undergraduate Kinesiology "Athletic Injuries"*

McMaster University, Hamilton, Ontario
2006
Clinical Instructor – Graduate Physiotherapy "Manual assessment and treatment"

The University of Western Ontario, London, Ontario
1999-2000
Teaching Assistant – Undergraduate Health Sciences "Health and Wellness"
Tutorial instructor for Dr. Don Morrow and Dr. Jennifer Irwin

CLINICAL WORK EXPERIENCE

Fowler Kennedy Sport Medicine Clinic
2005-Present
Clinical Physiotherapist
Clinical assessment and treatment of orthopaedic disorders

CBI
2004-2005
Clinical Physiotherapist
Clinical assessment, treatment and functional return to work evaluation of orthopaedic disorders

York Central Hospital Cardiac Rehabilitation Program
2000-2002
Clinical Kinesiologist
Program instructor for patients with various cardiac conditions

RELATED EXPERIENCE

Charge Therapist
2006
Gus Macker 3-on-3 Basketball Tournament
Lead therapist for main tent medical coverage of weekend basketball tournament

Charge Therapist
2006
London Marathon
Lead therapist Forest City Road Race organizing volunteer and course medical coverage

Team Physiotherapist
2005
Women's Varsity Field Hockey Team, The University of Western Ontario

Fanshawe College Sport Physiotherapist
2005-2006
On-site Physiotherapist for various varsity sports and tournaments

AWARDS AND ACHIEVEMENTS

- Nan Philliipson Award for excellence in teaching
  2011
- Sport Physiotherapy Canada, David Magee Award
  2007
- Sport Certificate, Physiotherapy Canada
  2007
- Sport Physiotherapy Fellowship, Fowler-Kennedy Sports Medicine Clinic
  2005-2006

PROFESSIONAL DEVELOPMENT

- Acupuncture Foundation Canada Institute
  - Level 2A/3A upper and lower needling techniques
- Orthopedic Division Manual Therapy
  - Level 3 upper extremity manual assessment and treatment
  - Level 2 upper and lower extremity manual assessment and treatment
- Shirley Sahrmann: Treatment of movement system impairment syndromes
- McKenzie Part A: Mechanical diagnosis and therapy for low back pain

MEMBERSHIPS

- Canadian Physiotherapy Association
- Sport Physiotherapy Canada
- Orthopeadic Division of the Canadian Physiotherapy Association