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early changes following meniscectomy and conservative intervention strategies

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MECHANICAL AND PHYSIOLOGICAL FACTORS IN KNEE JOINT CONTACT MECHANICS

– EARLY CHANGES FOLLOWING MENISCECTOMY AND CONSERVATIVE INTERVENTION STRATEGIES

BY
CARSTEN M. MØLGAARD

DISSERTATION SUBMITTED 2015

AALBORG UNIVERSITY
DENMARK

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2. Villumsen M, Jorgensen MG, Andreasen J, Rathleff MS, Molgaard CM. Very low levels of physical activity in older patients during hospitalization at an acute geriatric ward - A prospective cohort study. J Aging Phys Act. 2014.
3. Rathleff MS, Molgaard CM, Fredberg U, et al. High-load strength training improves outcome in patients with plantar fasciitis: A randomized controlled trial with 12-month follow-up. Scand J Med Sci Sports. 2014.
4. Mølgaard CM, Kersting UG. The effect of shoe design and lateral wedges on knee load and neuromuscular control in healthy subjects during walking. Footwear Science. 2014;6(1):51-58.

5. Andreasen J, Molgaard CM, Christensen M, et al. Exercise therapy and custom-made insoles are effective in patients with excessive pronation and chronic foot pain--a randomized controlled trial. Foot (Edinb). 2013;23(1):22-28.

6. Skou ST, Rathleff MS, Moelgaard CM, Rasmussen S, Olesen JL. The influence of time-of-day variation and loading on the aponeurosis plantaris pedis: An ultrasonographic study. J Sports Med Phys Fitness. 2012;52(5):506-512.

7. Molgaard C, Rathleff MS, Simonsen O. Patellofemoral pain syndrome and its association with hip, ankle, and foot function in 16- to 18-year-old high school students: A single-blind case-control study. J Am Podiatr Med Assoc. 2011;101(3):215-222.

8. Rathleff MS, Moelgaard C, Lykkegaard Olesen J. Intra- and interobserver reliability of quantitative ultrasound measurement of the plantar fascia. J Clin Ultrasound. 2011;39(3):128-134.

9. Rathleff MS, Olesen CG, Moelgaard CM, Jensen K, Madeleine P, Olesen JL. Non-linear analysis of the structure of variability in midfoot kinematics. Gait Posture. 2010;31(3):385-390.

10. Molgaard C, Lundbye-Christensen S, Simonsen O. High prevalence of foot problems in the danish population: A survey of causes and associations. Foot (Edinb). 2010;20(1):7-11.

11. Nielsen RG, Rathleff MS, Moelgaard CM, et al. Video based analysis of dynamic midfoot function and its relationship with foot posture index scores. Gait Posture. 2010;31(1):126-130.

12. Nielsen RG, Rathleff M, Kersting UG, et al. The predictive value of the foot posture index on dynamic function. J Foot Ankle Res. 2008;1(Suppl 1):O37.

13. Simonsen OH, Revald P, Kjaer IL, Christensen M, Molgaard C, Lass P. Tibialis posterior tendon dysfunction. an often neglected cause of painful adult flatfoot. Ugeskr Laeger. 2006;168(39):3314-3316.

ENGLISH SUMMARY

Numerous biomechanical studies have provided evidence for a positive effect of laterally wedged insoles for reducing knee adduction moment in healthy controls as well as patients with knee osteoarthritis at the medial tibial and femoral condyles. The knee adduction moment has been recognized as a suitable biomechanical marker for progression of knee osteoarthritis. However, recent clinical trials have not been able to confirm the potential favourable impact. With the increasing prevalence of knee osteoarthritis and knee replacement surgery the demand for early conservative treatment modalities also increases.

This thesis aimed to evaluate the hypothesis that 1) shoe design has a strong influence on the effectiveness of lateral wedges to reduce knee adduction moment, 2) It is possible to reduce the knee adduction moment with lateral wedges in healthy subjects during experimental knee pain, 3) Patients who previously underwent medial arthroscopic partial meniscectomy walk with increased knee adduction moment 3-5 years post OP compared to healthy controls and 4) In patients with medial partial meniscectomy a lateral wedge can reduce knee adduction moment to a similar level as healthy controls during walking.

The results showed that shoe design and lateral wedges are equally important factors in knee adduction moment, but the shoe designs tested did not further improve or reduce the effect of lateral wedges. Secondly, experimental knee pain did not mediate the effect of lateral wedges and the impact of experimental knee pain has a larger impact on knee extension moment than knee adduction moment. Medial arthroscopic partial meniscectomy significantly increased the knee adduction moment 3-5 years postoperatively in an otherwise active group of patients when compared to a matched healthy group of people. Finally, lateral wedges can decrease knee adduction moment in APM patients, however not to the level of healthy matched controls.

In conclusion, although similar reductions in knee adduction moment can be achieved with different types of shoe design the difference between a neutral running shoe and oxford leather shoes are similar to the effect of lateral wedges. Pain did not seem to change the effect of lateral wedges independently. The knee adduction moment 3-5 years after a medial arthroscopic partial meniscectomy was at a similar level to what has been observed in patients with KOA knee osteoarthritis. Lateral wedged insoles and type of footwear should be considered part of the mechanical solution to the increased risk of progression of KOA in this patient group.

DANSK RESUME

Talrige biomekaniske undersøgelser har vist en positiv effekt af indlægssåler til reduktion af belastningen over knæet - mere specifik knæets adduktionsmoment. Det er vist både for raske mennekser og tilsvarende for patienter med knæ artrose i mediale ledkammer. Knæets adduktionsmoment er indtil videre den bedste biomekaniske markør for progression af knæartrose. De seneste kliniske forsøg har imidlertid ikke kunnet bekræfte samme positive virkninger. Forekomsten af af knæ artrose stiger ligesom antallet af operationer grund af dette, derfor er der nu et stort behov for gode konservative behandlingsmetoder tilligt i sygdomsforløbet.

Denne afhandling har til formål at teste hypoteserne: 1) sko design har en væsentlig indflydelse på effekten af laterale kiler for at reducere knæets adduktionsmoment, 2) Det er muligt at reducere knæ adduktion momentet med laterale kiler hos raske forsøgspersoner under eksperimentel knæsmerter, 3) Patienter, som har fået foretaget medial artroskopisk partiel meniskresektion har et øget adduktionsmoment 3-5 år postoperativt, sammenlignet med raske kontrolpersoner og 4) en lateral kile kan reducere knæets adduktionsmoment under gang hos denne patientgruppe til samme niveau som matchede raske forsøgspersoner.

Resultaterne viste, at forskellen mellem skotype og effekten af laterale kiler tilsvarende betydning i forhold til reduktion af knæet adduktionsmoment. Der var dog ikke nogen signifkant forskel på effekten af en lateral kile mellem de forskellige typer af sko. Eksperimentel induceret knæsmerte påvirkede ikke effekten af laterale kiler. Det var desuden kun knæets ekstensionmoment som tydeligt blev påvirket af inducerede knæsmerter. 3-5 år efter en medial artroskopisk partiel meniskresektion var knæets adduktionsmoment significant højere i en ellers aktiv gruppe af patienter sammenlignet med en matchet kontrolgruppe. En 10 graders laterale kiler knæets adduktionsmoment signikant, men dog ikke til tilsvarende niveau som hos en raske kontrolgruppe.

På trods af at der ikke var tydelig forskel på hvor effektivt kilerne fungerede i de forskellige skotyper, har valg af fodtøj en afgørende betydning for belastningen af knæet. Forskellen mellem en neutral løbesko og en almindelig lædersko, svarede til effekten af en 10 graders lateral kile. Smerter syntes ikke at ændre virkningen af laterale kiler uafhængigt. 3-5 år efter en medial artroskopisk partiel meniskresektion var knæets adduktionsmoment væsentligt højere end hos en tilsvarende kontrolgruppe. Laterale kiler og valg af fodtøj bør derfor inddrages som en del af den biomekaniske løsning på den øgede risiko for tidlig artrose hos patienter som får fjernet en del af menisken.

ACKNOWLEDGEMENTS

In 1954 Edwin Powell Hubble wrote in The Nature of Science: “Equipped with his five senses, man explores the universe around him and calls the adventure Science”. But the five senses are far from enough in the world of biomechanics and the technological advances have made the science of human movement overcome huge obstacles in the last decades.

Thanks to my supervisors professor Thomas Graven-Nielsen and professor Uwe Kersting at Center for Sensory-Motor Interaction, Aalborg University for continuous encouragement and support. A special thanks to my supervisor Dr. med Ole Simonsen at the Orthopaedic department Aalborg University Hospital who made this opportunity possible for me. I also wish to thank my colleagues at Aalborg University Hospital and University College North Denmark. Thanks to my colleagues at SMI, Jakob Svendsen and Sauro Elemeric Salomoni, who helped me through the challenges of Matlab. Without important funding from the Bevica Foundation, the orthopaedic department Aalborg University Hospital and Aalborg University this work would not have been possible.

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TABLE OF CONTENTS

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INTRODUCTION

The mechanical environment of the knee during walking can influence both the health and breakdown of articular cartilage of the knee. Walking is the most common activity of daily living and results in a cyclical, reproducible pattern of loading and as a result a close link to the maintenance of healthy knee cartilage is indicated. Likewise, the mechanics of walking can influence the initial breakdown of cartilage if the normal patterns of loading are changed due to injury or other conditions. In that case the normal balance between loading and the biological maintenance of healthy cartilage would be altered.

While it is generally accepted that there exists an optimal window for cartilage loading in order to postpone or avoid knee osteoarthritis (Andriacchi 2004) it remains unknown how various factors interact and influence the pathogenesis of osteoarthritis and the quest for biomarkers that can predict OA progression is on-going (Harkey 2015). It would obviously be extremely helpful to increase the knowledge about how these factors interact and how such knowledge can be transferred to a clinically context and used in a specific patient group at high risk of early knee osteoarthritis such as meniscectomized patients.

There are several reasons for looking into gait mechanics and a simple gait modification such as lateral wedged insoles. First, the prevalence of knee OA (KOA) is increasing with an increasing elderly population, increased prevalence of obesity, and also for a range of still unknown reasons. This challenges the existing expensive treatment strategy with joint replacement and stress the importance of inexpensive readily available treatment modalities which can be applied in the early stages of KOA. Second, biomechanical joint loading during walking is under strong suspicion of being a part of the pathogenesis behind KOA (Felson 2004; Sharma 2006). Finally, laterally wedges insoles are a possible model to modulate the mechanical loading in patients as well as healthy subjects and have been hypothesized to have a clinical meaningful effect. This has been challenged by a well conducted randomized clinical trial (Bennell 2011a).

Hence, laterally wedged insoles may act by decreasing joint load and alter movement strategies; e.g. different joint mechanics during walking in close interplay with the footwear worn. The experimental introduction of pain in otherwise healthy subjects may affect changes in the locomotion pattern observed with laterally wedges, which may be comparable to those observed in subjects suffering from clinical pain in e.g. knee OA patients. This may challenge an optimal mechanical loading in subjects with knee pain. The size of the loading window may depend on the degradation state of the joint and other mechanical and physiological factors. The studies included in the following thesis could therefore be considered as components contributing to the development of a more optimal use of biomechanical interventions such as lateral wedges and to clarify the potential effects in patients at high risk of early knee Osteoarthritis.

AIMS

Thus, the aim of this project is to 1) identify relationships between footwear and lateral wedged insoles in a healthy group, 2) to evaluate the mechanical and physiological factors of experimental pain when introducing a laterally wedged insoles to otherwise healthy subjects, and 3) to identify the acute effect of laterally wedged insoles on biomechanical markers in patients after a meniscectomy.

4. HYPOTHESIS

The following hypotheses were tested in three studies in order to achieve this:

Study I

1.1 Shoe design has a strong influence on the effectiveness of lateral wedges to reduce knee adduction moment.

Study II

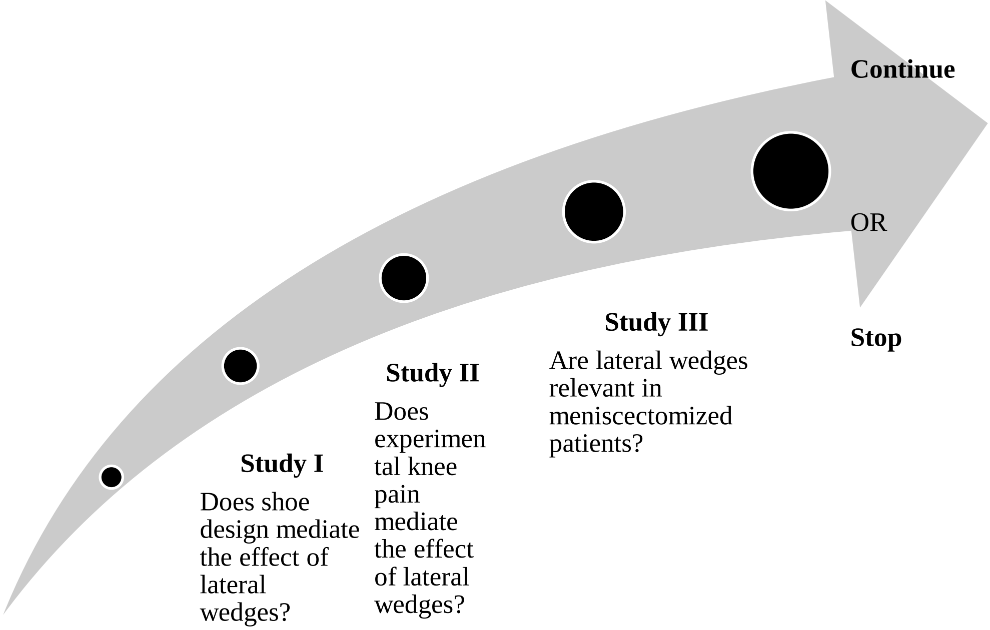
2.1 Laterally wedged insoles reduce knee adduction moment and this reduction is further increased by experimental knee pain during walking.

Study III

3.1 Patients within the first five years after medial APM have a significantly higher knee adduction moment during walking in comparison to healthy controls.

3.2 Lateral foot wedges will significantly decrease the knee adduction moment and impulse during walking with a similar effect in both meniscectomized patients and healthy age matched healthy controls.

Study I and II will expectantly provide answers to improve the effect of or understand the limitations of lateral wedges. As lateral wedges are worn together with a shoe the differences between shoes need clarification. Furthermore knee pain is the cardinal symptom of early knee OA and often the primary reason for choosing wedges as a treatment. As to the clinical importance of the lateral wedges, study III will demonstrate if the mechanical changes will eliminate differences in knee joint loading between healthy and meniscectomized patients during activities of daily living such as walking.



Study I

Does shoe design mediate the effect of lateral wedges?

Study II

Does experimental knee pain mediate the effect of lateral wedges?

Study III

Are lateral wedges relevant in meniscectomized patients?

When lateral wedges reduce biomechanical markers of knee joint loading – why then is the clinical effect not more convincing?

RISK FACTORS IN KNEE OSTEOARTHRITIS

Osteoarthritis (OA) is the most common form of arthritis. Several factors are associated with OA which include: Increasing age, female sex, obesity, and race, which may represent genetic or sociocultural influences. Abnormal loadings of the joints are also factors associated with OA (Neogi 2013). Old age, female gender, overweight and obesity, knee injury, repetitive use of joints, bone density, muscle weakness, and joint laxity all play roles in the development of joint OA, particularly in the weight-bearing joints. Modifying these factors may reduce the risk of OA and prevent subsequent pain and disability (Zhang & Jordan 2010b).

↑Age	↓Female	↑Obesity	Genetics	Race	Diet	↑Bone density
Susceptible individual						
			+		**→ Susceptible to KOA**	
Susceptible joint						
Injury	↑Activity	Occupation	Unequal Leg length	↑Subchondral bone	↓Strength	↑MalAlignment

Table 1. Potential risk factors for susceptibility to incidence and progression of osteoarthritis, varying degrees of evidence to support the association (Neogi 2013).

In the Framingham Osteoarthritis (FOA) cohort study, the age and body mass index BMI-adjusted prevalence of knee pain and symptomatic knee osteoarthritis approximately tripled in men and almost doubled in women over a 20-yr period. However, there was no substantial change in the age and BMI-adjusted prevalence of radiographic osteoarthritis over this same period. At the same time the age and BMI-adjusted prevalence of radiographic osteoarthritis among those +60 years or those with severe radiographic osteoarthritis (K/L ≥ 3) for both men and women were not increased (Nguyen 2011). Which naturally questions if the cause for KOA 20 years ago were something different than what it is today? Osteoarthritis today is considered a disease of the whole joint organ. Hence, the disease is no longer viewed as a passive, degenerative disorder alone but rather an active disease process with an imbalance between the repair and destruction of joint tissues driven primarily by mechanical factors (Figure 1). Mechanics may play a critical role in the initiation, progression, and successful treatment of OA (Wilson 2013).

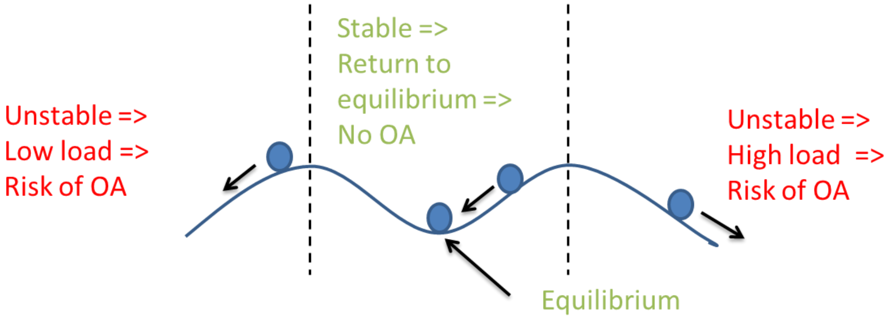


Figure 1. Illustration of equilibrium in the knee joint cartilage. The ball indicates the state of the cartilage.

WHY IS THE KNEE JOINT AT HIGHER RISK THAN THE ANKLE AND HIP?

The weight-bearing joints are particularly exposed to risk factors such as overweight, old age, female gender, knee injury, repetitive use of joints, bone density, muscle weakness, and joint laxity in the development of joint OA (W. Zhang 2010a). However the bi-condylar configuration of the knee makes it particularly susceptible to changes in the mechanical environment associated with injuries (e.g., meniscal tears), aging or menopause (Andriacchi 2004), since a greater abduction or adduction moment in a bicondylar joint will shift the net contact point and load toward one compartment. In contrast, the subtalar and talocrural joints of the ankle and hip of a healthy person have highly congruent articulating surfaces (Mundermann 2005).

The tibial plateau of the knee exhibits a concave surface on the medial side and a convex surface on the lateral side. This medial plateau concavity results in a greater conformity of the medial compartment (Figure 2) and thereby the contact location is more sensitive to rotation on the medial side than the lateral side (Andriacchi & Mundermann 2006b). The medial meniscus is also more prone to injuries than the lateral meniscus (Rath and Richmond, 2000). This is thought to be a result of the lower mobility of the medial meniscus and due to its attachment to the medial collateral ligament (Fithian 1990).

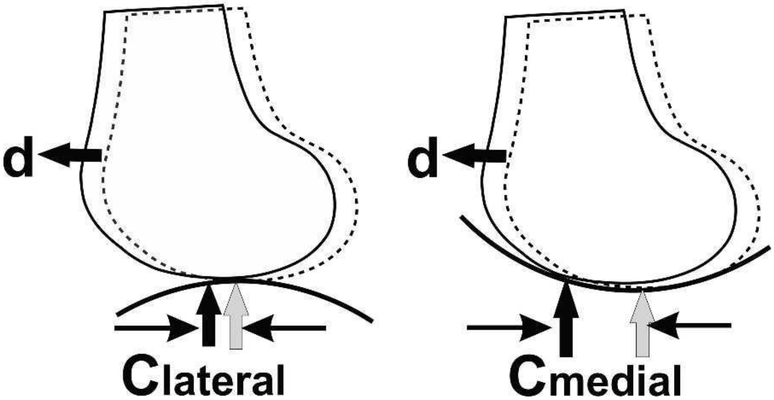


Figure 2. "*The medial compartment is more sensitive to kinematic changes at the knee because the greater conformity of the medial compartment relative to the lateral compartment will produce a larger shift in the medial tibiofemoral contact (C medial) than the lateral tibiofemoral contact (C lateral) for the same joint displacement (d)*" (Andriacchi 2006a)

The prevalence of symptomatic knee and hip OA in people above 30 are respectively 6% and 3% in the US (Felson & Zhang 1998), whereas the prevalence of ankle OA is approximately 1% (Barg 2013). From an observational study of 390 patients consulting an orthopaedic foot and ankle center, it was concluded that ankle OA developed secondary to previous traumas, primarily malleolar fractures, ankle ligament lesions, and tibial Pilon fractures. Furthermore, it was found that OA with no history of trauma or any kind of secondary or infectious OA, in the ankle is rare (Valderrabano 2009).

Joint moments can be described by a force couple, and applying a greater moment to a ball-and-socket joint or about the sole axis of rotation of a hinge joint does not necessarily increase contact forces as they depend on muscle co-contraction. Thus, a change in frontal plane joint moments at the hip may not be as critical as a similar change in the knee (Mundermann 2005).

In a longitudinal study of individuals (347 knees) with minimal baseline cartilage damage, the presence of high BMI, meniscal damage, synovitis or effusion, or any severe baseline MR-depicted lesions was strongly associated with an increased risk of fast cartilage loss at 30-month follow-up. Patients with similar risk factors may therefore be ideal subjects for preventative or treatment trials (Roemer 2009).

MENISCECTOMY - AN EARLY RISK FACTOR OF OSTEOARTHRITIS

In the general population, irrespective of the presence of OA, investigators have found a meniscal tear in about every third knee (Ding 2007). In Denmark more than 17000 arthroscopic operations were carried out in 2011 and the number has doubled over 10 years (Thorlund 2014) and now it ranks among the top ten most frequent surgical procedures in Denmark. Furthermore, every second meniscectomized patient shows radiographic features of knee OA 10-15 years after surgery (Englund 2003). Studies have shown that meniscal injuries in addition to other knee injuries are associated with a higher risk of KOA compared to knee injuries without concomitant meniscus tears (Oiestad 2009), and are in many ways similar to KOA in general (Doherty 1983; EnglundParadowski 2004; Englund 2004). The strong association of meniscal tears with a subsequent loss of knee cartilage, alteration in bone size, and prevalence of radiographic knee OA in subjects undiagnosed as having knee OA suggests that the presence of a meniscal tear is an early event in the disease process, and a strong predictor for osteoarthritis development (Englund & Lohmander 2004). The strongest prognostic factor associated with the development of osteoarthritic changes in patients who previously underwent open and arthroscopic meniscectomy was the amount of tissue removed when summarizing 32 clinical trials in a systematic review (Papalia 2011).

There is no consensus on classification of patients as degenerative or traumatic meniscal injury. Injuries can be subdivided based on injury mechanism (high or low energy injury) (Sihvonen 2013) or type of meniscal lesion eg. bucket handle or vertical tears often defined as traumatic (Englund 2003). Degenerative tears can be described as horizontal cleavages, flap tears or complex tears, which are often observed in middleaged and older population (Poehling 1990). These tears are primarily observed in the medial meniscus (Noble & Hamblen 1975) and are common also in asymptomatic individuals (Bhattacharyya 2003; Englund 2008).

The etiology however remains unclear and patients undergoing surgery for degenerative tears have worse long-term outcome after meniscectomy than patients with traumatic tears (Englund et al., 2003). The RRs for combined radiographic and symptomatic OA after degenerative and traumatic types of meniscal tear were 7.0 (95% confidence interval [95% CI] 2.1–23.5) and 2.7 (95% CI 0.9–7.7), respectively, compared with matched controls (Englund 2003). This indicates that the meniscal injury in it-self is only a part of the explanation for early KOA.

When considering the co-occurrence of KOA in 3026 individuals +50 years of age, no independent association between meniscal damage identified with MRi and the development of frequent knee symptoms were found (OR 1.05,95% CI 0.80–1.37). The authors concluded that any association between meniscal damage and the development of frequent knee pain seems to be present because both pain and meniscal damage are related to OA and not because of a direct link between the two (Englund 2007). Nevertheless several longitudinal studies associated partial or total removal of the meniscus with early onset of knee OA. In a 30-month follow-up study assessment included knee magnetic resonance imaging (MRI) and fluoroscopically positioned weight-bearing knee radiographs. Both changes in meniscal position and changes in articular cartilage score contributed substantially to narrowing of the joint space (Hunter 2006). The odds ratio for patellofemoral osteoarthritis also increase with meniscectomy: 2.6 (CI, 1.1 to 6.6) after medial meniscectomy and 5.3 (CI; 1.9 to 15.0) after lateral meniscectomy compared to controls (Englund & Lohmander 2004).

Cartilage in highly loaded areas mechanically adapt relative to underused areas in which signs of fibrillation can be observed in healthy knees in relatively young subjects (Bullough 2004). An average shift toward internal tibial rotation (Andriacchi & Dyrby 2005) has been shown following meniscectomy (Netravali 2010), which alters contact mechanics in the newly loaded regions and thereby produce local degenerative changes in the articular cartilage (Andriacchi 2004; Herzog 2004; Andriacchi 2006a; Chaudhari 2008).

Patients with an anterior cruciate ligament deficiency show a thinning of tibial cartilage that has been associated with specific kinematic changes (Andriacchi 2009). The response of healthy cartilage to load is consistent with the findings of theoretical studies suggesting that load can produce an adaptive response with thickening and enhanced mechanical properties (Smith 1995; Ikenoue 2003). Interestingly, higher bone density exists in the proximal medial tibia 12 years post-meniscectomy (Petersen 1996), and faster rates of cartilage volume loss in the 2 years post-meniscectomy compared to matched controls (Cicuttini 2002). These findings raise the underlying question as to whether larger adduction moments in meniscectomy subjects, contribute to changes in knee architecture and development of OA (Sturnieks 2008).

Furthermore, the effect of lateral wedges in patients at high risk of early osteoarthritis, such as patients with meniscal tears, remains unknown. A positive relationship between the presence and severity of medial meniscal lesions and a higher magnitude of the first peak knee adduction moment (KAM1) however has been demonstrated in a cross-sectional study (Davies-Tuck 2008). Reducing the mechanical load of the medial compartment in the knee may utilize more knowledge on the effect of early interventions in order to reduce symptoms and postpone total knee replacement.

EXTERNAL KNEE ADDUCTION MOMENT

In particular, it has been shown that the knee adduction moment during walking influences the distribution of forces between the medial and lateral compartments (Schipplein & Andriacchi 1991) of the knee, thus providing a useful measure to evaluate medial-to-lateral variations in cartilage thickness. The magnitude of the KAM1 during normal gait has been associated with the ratio of medial-to-lateral cartilage thickness in the common load-bearing regions of the knee during walking (Andriacchi 2004; Koo & Andriacchi 2007) and progression of knee osteoarthritis (Amin 2004; Miyazaki 2002). In particular, for healthy cartilage the relative thickness of the medial cartilage correlates with the magnitude of the KAM, suggesting that healthy cartilage adapts to higher repetitive loads during walking by an increased local or regional thickness. In contrast to healthy cartilage, a decreased thickness in the load-bearing regions of the medial compartment in KOA patients with a higher adduction moment (Andriacchi & Mundermann 2006b). Increased bone density of the proximal medial tibia has also been positively correlated with KAM in normal subjects (Hurwitz 1998) and KAM and particularly $KAM_{impulse}$ have been shown to predict cartilage volume loss (Bennell 2011). Most previous studies have compared the KAM1 (Baliunas 2002; Hurwitz 1998; Kaufman 2001), and a reduction in KAM1 is believed to decrease knee contact forces, leading to a reduction in joint degeneration and pain.

MECHANOTRANSDUCTION

The mechanisms by which mechanical stimulus such as KAM is converted to electrical or chemical signals in chondrocyte activity is regulated by a complex interplay between genetic, environmental, and biomechanical factors (Grodzinsky 2000). Growth factors, cytokines, and extracellular matrix composition are some of the factors that dictate the environment of these cells. Biomechanical factors are a result of mechanical loads distributed on chondrocytes and the extracellular matrix. These include tension, compression, shear, osmolarity, fluid pressure, and associated electrokinetic effects (Soltz & Ateshian 1998; Urban 2000). The local loads on cartilage and its substructures are dictated by the transmission and sharing of body level mechanical loads. Within a local region of the cartilage, tissue level loads are distributed differently among superficial and deep zones within the cartilage dictated by the differences in microstructural properties. The collagen fibre architecture in the extracellular matrix and the pericellular matrix combined with the chondrocyte shape and distribution provide the basis for cellular deformations and fiber loading. Most importantly the strength of the collagen architecture and the joint health are dependent on regular and adequate loading of the joint (Grodzinsky 2000; Helminen 2000).

KNEE PAIN AND GAIT BIOMECHANICS

In contrast to a general popular perception, pain is not necessarily a good indicator determining the extent of articular cartilage damage, although the risk of having symptomatic knee OA increase with the number of structural changes (Zhang 2010a). Pain, however is the main patient reported symptom, and pain-related treatment thus a priority. Knee pain mechanisms are nevertheless generally complex and attributed to several factors:

- Psychosocial pain component
- Peripheral or central sensitisation
- Referred pain
- Inflammation
- Subchondral bone
- “Osteophytes compression”
- Cartilage
- Ligament + capsule (Malalignment)
- Menisci
- Trigger points and/or muscle soreness

Several studies have shown that pain relief or induced pain may change knee loading during walking (Schnitzer 1993; Henriksen 2006; Briem 2009; Hurwitz 2000; Henriksen 2010). That indicates that pain may be considered as a protective mechanism by reduction of the medial knee loading. The prerequsities, however remains relative unknown and it is not fully understood if and how pain may best be controlled to slow down disease progression (Hurwitz 2000). As listed above a series of changes potentially occur with KOA, including joint deformities, instability, muscle weakness, reduced proprioception, inflammation and joint effusion (O'Reilly & Doherty 2003). When studying movement and motor control this may introduce unwanted variability. As example patients with joint effusion increase muscle activation of hamstrings and quadriceps together with increased knee flexion angles and decreased KE moment in mid-late stance during walking (Rutherford 2012). This makes it difficult to assess the isolated neuromuscular effects of pain in patient populations. Experimental techniques to induce pain in healthy subjects are thus advantageous in this respect (Henriksen 2010). The infrapatellar fat pad has a high proportion of nociceptive afferents (Bohnsack 2005) and stimulation of this structure induces anteromedial knee pain with a distribution similar to that of knee OA patients (Hodges 2009).

ALIGNMENT

Among 237 persons with primary KOA standing knee alignment of more than 5° (in either varus or valgus) in both knees has been associated with significantly greater functional deterioration during 18 months than having alignment of less than 5°, after adjusting for age, sex, body mass index, and pain. Pain increased 10 mm on a 100-mm visual analogue scale (VAS) with each 5° of malalignment and a similar result was observed with functional change in chair-stand rate after additionally accounting for pain (Sharma 2001).

While static knee alignment is correlated to the degree of KOA measured by KL-score (Sharma 2001; Tanamas 2009). Dynamic alignment (eg. walking) on the other hand is influenced by a combination of the static limb alignment and the dynamics of loading at the knee during human movement. The dynamic loading at the knee can be influenced by subconscious control of limb position such as foot placement (Lin 2001), active muscle contraction (Rutherford 2010), passive soft-tissue stability (Lewek 2004) and the velocity during gait. The loads generated during these dynamic activities are substantially higher than during static postures. Therefore, limb alignment based on static radiographic measurements provides one component to the complete analysis of the factors influencing loading at the knee joint. Dynamic malalignment that occurs during activities such as gait should be considered in evaluating the progression of disease processes as well as the selection of appropriate treatment modalities. However applying lateral wedges in healthy (Crenshaw 2000; Kakihana 2004) or in medial KOA patients (Butler 2007) did not change dynamic knee alignment. While varus malalignment increases medial compressive forces and is correlated with KAM measures, it has been observed that the $\text{KAM}_{\text{impulse}}$ is independently associated with changes in cartilage volume even after adjusting for knee malalignment (Bennell 2011). This accentuates the additional contribution of dynamic knee joint contact mechanics as a risk factor for disease progression.

LATERAL WEDGES

The latest recommendations from OARSI (McAlindon 2014) included biomechanical interventions (insoles and braces) as directed by an appropriate specialist. This conclusion was based on one systematic review and three recent RCTs that evaluated the effectiveness of knee braces, knee sleeves, and foot orthoses in conservative management of knee OA (Raja & Dewan 2011; Bennell 2011a; Erhart 2010; van Raaij 2010). Conflicting results were found in relation to lateral wedge insoles - one RCT indicated no symptomatic or structural benefits (Bennell 2011a) and a second asserting their appropriateness as a possible alternative to valgus bracing for conservative medial knee OA treatment (van Raaij 2010). A recent RCT found that variable-stiffness walking shoes reduced adduction movement and pain and improved function after 6 months, although this benefit was not statistically significant when compared to constant-stiffness footwear (Erhart 2010).

Lateral wedge insoles are aiming to reduce the load of the medial compartment as an alternative to changing gait patterns, knee bracing or surgical treatment. Reductions in peak moment are correlated with more lateral center of pressure, less varus malalignment, reduced knee-ground reaction force lever arm, less hip adduction and a more vertical frontal plane ground reaction force vector. Only reduction in knee-ground reaction force lever arm was nevertheless significantly predictive of pain reduction with lateral wedges (Hinman 2012). The changes in leverarm are not altered by changes in knee alignment (Barrios 2013; Maly 2002; Yasuda & Sasaki 1987).

Most studies have focused on the effect of lateral wedging of the foot on the KAM1. Moment reductions have been reported in healthy subjects fitted with a 5 to 10 degree lateral wedge (Crenshaw 2000; Kakihana 2004) and in individuals with medial knee OA (Kerrigan 2002; Maly 2002). When testing a 5° lateral wedge KAM1 was reduced -5.8% (Hinman 2012).

A smaller wedge (3°) was not significantly different from neutral in healthy subjects (Kakihana 2004). While a 10° wedge has been shown to be more effective than 5°, it may be less comfortable (Kerrigan 2002). Others found more than 40% of the subjects reporting worsening symptoms with the 16-mm-thick wedged insole compared to 8- and 12-mm-thick compressible wedged insoles (Toda 2004). Although, some subjects may greatly benefit from more aggressive reductions, the higher wedge has produced less consistent results across the population comparing 4 and 8 wedges. While a more moderate intervention may be more predictable, the small reduction from a 4° wedge may be insufficient, despite the uniformity of response (Fisher 2007).

The clinical evidence behind biomechanical interventions such as lateral wedgning has primarily been conducted in older people with KOA. Ogata et al. (Ogata 1997) suggested that laterally wedged insoles are most effective in patients with low-grade OA. Based on explorative subgroup analysis only half of patients with medial OA (Kellgren-Lawrence Grade 2) responded to the laterally wedged insole after 6 months in a RCT (van Raaij 2010). This underlines the need for further studies to better understand the possibilities at earlier stages of disease progression.

Two main areas are identified when aiming to understand the effect of lateral wedges. First the interaction between shoe design and wedges and second the effect of knee pain as a cardinal symptom of knee OA need to undergo further research.

METHODOLOGY

DESIGN

Study I: Cross-over study

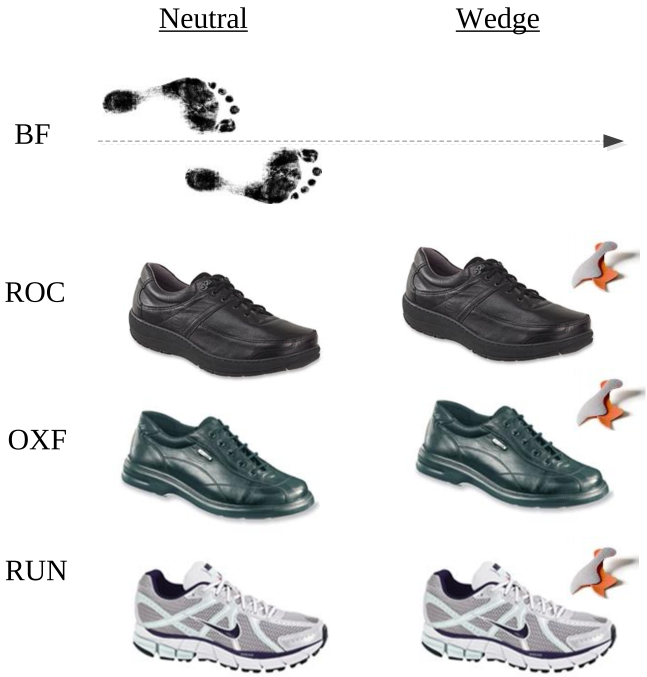
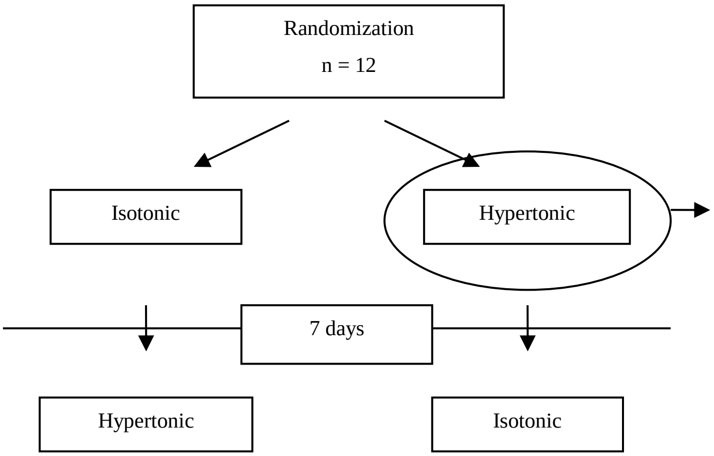


Figure 3. The four conditions tested. 1) Barefoot neutral 2) Leather shoe with a rocker. 3)“Oxford” type leather shoe 4) Nike Pegasus running shoe. A ten degree laterally wedged insole. Rehband, Technogel® - Pes Velour was applied in the three shoes tested (2-4).

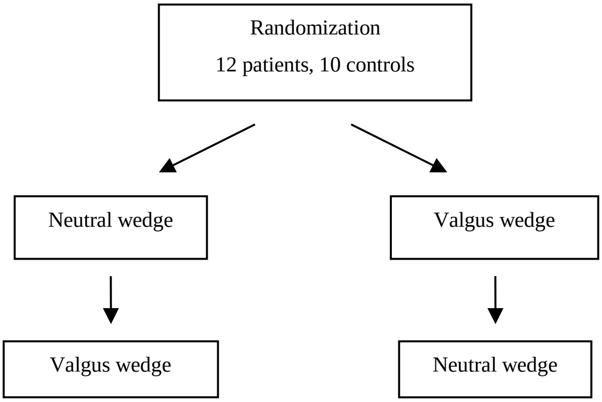
Study II: Cross-over study



<u>Control</u>
Series 1-2 (Neutral / Lateral wedge)
<u>1st Injection</u>
Series 3 (Neutral / Lateral wedge)
10 min break
<u>2nd Injection</u>
Series 4 (Neutral / Lateral wedge)
10 min break
<u>3rd Injection</u>
Series 5 (Neutral / Lateral wedge)
10 min break
<u>4th Injection</u>
Series 6 (Neutral / Lateral wedge)

Figure 4. Subject tested on two days separated by at least one week. During each test day, six series of walking trials were performed alternating between neutral and wedged shoes and the initial conditions randomized in a balanced design. A neutral running shoe (Nike Air Pegasus) was used both with and without a full length 10° laterally wedged insole.

Study III: Crossover and Case-control Study design.



Subjects were examined twice in one day randomly allocated to lateral or neutral wedged insoles in a standard running shoe (Nike Pegasus).

SUBJECTS

Study I: Thirteen healthy subjects (nine male) aged 18-60 years participated. Average height was 1.78 (1.73-1.83) m; bodyweight of 76.9 (71-83) kg; average walking speed of 1.5 (1.49-1.56) m/s; Knee injury and Osteoarthritis Outcome Scores (KOOS) (100=No problems) (Roos et al. 1998) were: Pain 97, Symptoms 97, ADL 99, Sport 96, and Quality of Life 91. All had a neutral knee alignment measured with a manual goniometer and neutral alignment defined as a valgus-varus angle between 175-185°(Sharma 2001). One subject had a supinated foot posture whereas the rest had a neutral foot posture (Redmond 2008).

Study II: Twelve healthy individuals with no current knee pain or history of trauma or knee surgery were included. Eight men and four women with an average age of 31.9 years (range: 22-50), height of 1.75 m (range: 1.57-1.96); body mass index (BMI): 24.0 (range: 20.2-28.6). None of the included subjects suffered from neurological, psychological, or cardiovascular diseases or had any pain during the week prior to participating. Knee injury and Osteoarthritis Outcome Scores (KOOS) (100=No problems) (Roos et al. 1998) were: Pain 100, Symptoms 95, ADL 100, Sport 97, and Quality of Life 96. All subjects, but one, had a neutral foot posture assessed using the Foot Posture Index (FPI-6) (Redmond et al. 2006).

Study III: Twelve male patients and ten age-matched healthy controls between 30-50 years were included. The patients had an APM of the posterior half of the medial meniscus between 3-5 years earlier (mean 41 months, CI: 34;49). Patients with previous knee ligament injury, misclassification by surgical code, severe cartilage changes defined as deep clefts or visible bone at APM and self-reported co-morbidities were excluded. Patients were recruited from the Orthopaedic Division North Denmark. Fifty potential candidates received a letter of invitation and one week later a phone call to secure the ex- and inclusion criteria. Healthy age-matched controls were free of injuries for a minimum of 6 months prior to commencement of the study and with no history of knee surgery. Controls were from the same geographic area and selection convenience sample. One subject had a pronated foot posture among patients and one had a supinated foot posture among healthy controls, whereas the rest had neutral foot posture (Redmond 2008).

SHOE DESIGN

Three types of footwear, a leather shoe with rocker (ROC -, Klaveness new rehab®), an Oxford-type shoe (OXF - Klaveness Thor®) and a neutral running shoe (RUN - Nike, Air Pegasus®) were tested. Normal barefoot walking was included as a reference (BaF).

Oxford leather shoe (OXF): Material: Nappa, Lining: Leather, Sole: flat polyurethane

Rocker (ROC): Material: Nappa, Lining: Perlon Velour, Sole: rocker polyurethane w/carbon

Running shoe (RUN): Nike Pegasus.

Lateral wedges

Heel wedges and two-thirds length laterally wedged insoles have not demonstrated a consistent reduction in the KAM (Baker 2007; Barrios 2009; Pham 2004). With an individual adjustment of the average degree of wedging necessary to produce the maximum amount of pain relief was 9.6° (SD=3.2) in patients with medial KOA (Butler 2007). When considering price, comfort accessibility against possible effectiveness, an of-the-self and full length 10° wedge was chosen as the best compromise (Figure 6. Rehband, Technogel® - Pes Velour).

Figure 5. Rehband, Technogel® - Pes Velour.

EXPERIMENTAL KNEE PAIN

Sensorimotor changes observed in response to experimental muscle pain can be challenging to interpret. An alternative model avoiding these constraints is a pain induction model based on injection of hypertonic saline into the infrapatellar fat pad. This structure is sensitive to mechanical stimulation (Dye 1998), has a high proportion of nociceptive afferents (Bohnsack 2005), and is a source of knee pain (Dye 2005) including some pain in KOA (Hill 2007). Furthermore, this technique induces anteromedial knee pain with a distribution equivalent to clinical knee pain (Bennell 2004). This experimental model has the potential to determine whether knee pain leads to sensorimotor changes that affects the effectiveness of lateral wedges.

Sterile hypertonic saline (5.8%, 0.25 ml) was injected into the right infrapatellar fat pad, medial to the patella tendon and proximal to the joint line. The injection was directed at 45° in a superolateral direction (Hodges 2009). Similar procedure with injection of isotonic saline (0.9%, 0.25 ml) was used as control condition. Immediately before each walking trial the pain intensity was verbally rated by the participant on an 11-point numerical rating scale (NRS) where 0 indicated ’no pain’ and 10 was equal to ’worst pain possible’ (Farrar 2001).

3D-GAITANALYSIS

Participants walked along the walkway at a self-selected pace measured by two photoelectric cells. Self-selected walking velocity was practiced until a comfortable speed was maintained within ± 5%. Trials not meeting these criteria were excluded. The instruction was to walk as relaxed or normal as possible with or without the wedged insoles. Requirements were to obtain the walking speed without adjusting step length, and to have the required walking speed while crossing the force platform incorporated in the walkway. Trials not meeting these criteria were excluded from the analysis.

Movement data were collected at 120 Hz using an 8-camera system (Qualisys Oqus 3+, Gotenburg, Sweden) and ground reaction force were recorded at 1200 Hz from two AMTI force platforms (AMTI OR6-5, Advanced Mechanical Technologies, Inc., MA, USA). Motion and force recordings were synchronized. Joint centers of the lower right limb were defined using 19-mm retroreflective markers placed bilaterally over the iliac crests, spina iliaca anterior superior, on the sacrum, greater trochanters, femoral condyles, malleoli, calcaneus, and the fifth and first metatarsal heads. Marker clusters made of rigid pre-shaped shells affixed with 4 markers were attached to the thigh and shank. Both shank and thigh shells were placed postero-laterally and secured with tape as tight as possible, but still comfortable for the subject (Manal 2000). All markers on the shoes were secured to the upper aspect with tape. Individual markers remained throughout all test conditions.

Peak knee adduction moment (KAM) has proven a valid proxy of knee loading (Zhao 2007) with excellent reliability ICC(2,1) 0.86 (95% CI: 0.73;0.96) (Birmingham 2007). We found similar results in a test-retest of twelve healthy subjects, ICC(2.1)= 0.90 (95% CI: 0.69:0.97). KAM-impulse may provide a more comprehensive information about medial knee joint loading, because it includes both the magnitude of load and the duration of stance (Kean 2012; Zhao 2007). Additionally both sagittal and frontal plane moments are of importance when considering the effect of biomechanical treatment modalities (Molgaard 2014). Likewise, the hip and ankle moments are necessary secondary variables to explain the mechanism behind a wedge-effect.

KAM1	Maximum Adduction Moment at the knee during first 50% of stance phase.
KAM2	Maximum Adduction Moment at the knee during second 50% of stance phase.
KEM	Peak external Knee Extension Moment
KFM	Peak external Knee Flexion Moment second 50% of stance phase.
AAM	Maximum Adduction (inversion) moment at the ankle during stance phase.
HAM1	Maximum Adduction Moment at the hip during first 50% of stance phase.
HAM2	Maximum Adduction Moment at the hip during second 50% of stance phase.
A2	Concentric burst of propulsive plantar flexor activity during preswing (pos. power).
K2	Concentric knee extensor activity during midstance (pos. power).
H2	Eccentric hip flexor activity during midstance (neg. power).
H3	Concentric activity in the hip flexors during preswing - "pull off" (pos. power).

Table 2. Definition and abbreviations for biomechanical markers during gait.

EMG

Surface electromyographic (EMG) signals were recorded using a bipolar configuration from six muscles of the right leg (vastus lateralis (VL) and medialis (VM), Biceps femoris - long head (BF), Semitendinosus (ST), Gastronemius lateralis (GL) and medialis (GM). Electrodes were placed according to SENIAM procedures and secured using Fixomull tape (Smith & Nephew). EMG signals were sampled at 2400 Hz using a wireless system (Noraxon Telemyo 2400, Arizona).

DATA ANALYSIS

Marker trajectories and force signals were low-pass filtered (Butterworth fourth order, zero phase lag) at 6 and 40 Hz, respectively. Kinematics were calculated using rigid body analysis and Euler angles based on the standing reference measurement. Joint moments were derived using inverse dynamics (Visual3D; C-Motion, Rockville, MD) and scaled to body weight (BW) and height (Ht). Stance was time normalized to 100% and averaged across trials for each participant and condition. Primary outcome measures were the 1st and 2nd peak KAM. Other joint moments of interest were early knee extension moment (KEM1) and late knee flexion moment (KFM2) as well as Ankle Adduction Moment (AAM) and hip joint moments in the frontal plane (HAM1 and 2). Additional variables extracted from the movement analysis were knee flexion at heel strike (HS) and knee flexion excursion, ankle, knee and hip joint moments in the frontal plane and the sagittal plane. Joint power was calculated for the concentric plantar flexor activity during pre-swing (A2), concentric knee extensor activity during midstance (K2), eccentric hip flexor activity during midstance (H2) and the concentric activity of the hip flexors during push off (pre-swing) (H3) (Winter 2009).

All EMG signals were band pass filtered at 15-400 Hz and moving RMS with 100-ms window. An amplitude analysis was carried out to study the changes in peak muscle activity and average EMG activity during stance phase.

Weight and height were measured for all subjects. Self-reported physical activity level was recorded with a validated questionnaire – The physical activity scale (Aadahl & Jorgensen 2003). This was used as a simple and valid alternative to measuring physical activity by diary in adult moderately active populations. The physical activity scale encompasses work, leisure time, and sports activity in one measure as a single measure of the total amount of physical activity on an average weekday. The activity is expressed in metabolic equivalents (METs), which allows for estimation of energy expenditure. Knee injury and Osteoarthritis Outcome Score (KOOS) (Roos 1998) were obtained. The static foot posture was evaluated using the

Foot posture index (Redmond 2006). Finally a clinical knee evaluation of knee laxity and effusion was completed in relation to the gait analysis.

STATISTICAL ANALYSIS

All data were visually inspected by QQplots and data are reported as mean and 95% confidence interval (CI). A statistical significance was accepted at $P < 0.05$ (two-tailed). Pearssons and Spearmans Correlation Coefficients were used to test for correlation between variables. All statistical analyses were performed using SPSS 20 (SPSS, Chicago,IL).

Repeated measures analysis of variance

Paper I: A repeated measures analysis of variance (rANOVA) was utilized to analyse the shoe-effect, wedge-effect and shoe*wedge interactions within subjects. When Mauchly’s Test of Sphericity indicated that the assumption of sphericity had been violated, a Greenhouse-Geisser correction was used.

Any significant shoe wedge interactions were broken down post hoc (Bonferroni) by exploration of the pairwise differences between the shoe conditions.

Paper II: A longitudinal data model was applied to assess multiple repeated-measures on the same subject. The primary analysis focused on the fixed effects rANOVA of wedge (neutral, wedge), test number (1st/2nd) and condition (control, isotonic, hypertonic) applying each factor as main factors in the model, including the corresponding interactions.

Paper III: The analysis focused on the rANOVA of Wedge (Neutral, Wedge) and group (Healthy/Patient), including the corresponding interaction (Wedge*Group).

RESULTS

STUDY I: DYNAMIC LOADING AND SHOE DESIGN

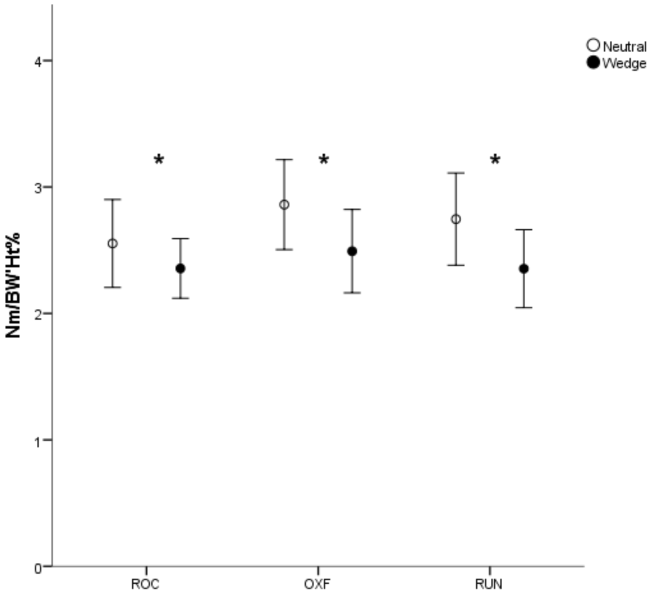


Figure 6. Differences in first peak knee adduction moment during walking at a self-selected speed. Three very different types of shoe design were tested: Shoe wither a rocker (ROC), typical oxford leather shoe (OXF) and a common neutral running shoe (RUN). * indicate significant wedge effect.

The observed reductions in KAM1 were significant with the laterally wedged insole for all three shoe types (Figure 7). The relative reductions for the ROC, OXF and the RUN shoe were 5.9% (CI: 0.9-12.7), 12.8 % (CI: 8.2-17.4) and 14.1 % (CI: 9.6-18.6), respectively.

The absolute reduction in the KAM1with lateral wedges were not significantly different among the shoes tested. Neutral condition with the ROC shoe produced the lowest KAM1, while the RUN neutral and the OXF neutral were 7.8% and 12.2% higher, respectively.

MUSCLE ACTIVITY AND SHOE DESIGN

		Absolute (Neutral)			Absolute (Difference)			Relative (Difference)		
Condition		Volt	95%CI		Volt	95%CI		(%)	95%CI	
ROC	VM	0.052	.028;	.076	-.0049	.0026;	-.0123	-5.7	1.9	;-13.3
	VL	0.062	.019;	.105	-.0059	.0023;	-.0141	-5.3	2.0	;-12.6
	ST	0.043	.030;	.056	.0015	.0053;	-.0022	5.2	14.1	;-3.7
	BF	0.072	.026;	.119	.0026	.0051;	-.0103	6.0	24.1	;-12.2
	GM	0.126	.092;	.159	.002	.0095;	-.0135	1.2	8.5	;-6.0
	GL	0.076	.057;	.095	.0016	.012;	-.0087	3.6	14.7	;-7.4
OXF	VM	0.050	.026;	.073	-.003	.0034;	-.0095	-2.5	9.1	;-14.2
	VL	0.060	.013;	.106	-.0067	.0066;	-.0201	-4.1	3.9	;-12
	ST	0.044	.032;	.056	-.0019	.0017;	-.0055	-3.2	6.2	;-12.7
	BF	0.076	.032;	.121	.0005	.0063;	-.0072	1.0	11.6	;-9.6
	GM	0.119	.095;	.144	-.0024	.0013;	-.0061	-1.7	1.0	;-4.5
	GL	0.072	.056;	.088	-.0029	.0009;	-.0066	-4.6	-0.2	;-9
RUN	VM	0.051	.028;	.075	-.0058	.0001;	-.0116	-7.9	0.7	;-16.4
	VL	0.053	.021;	.085	-.0024	.0023;	-.007	-2.7	2.8	;-8.2
	ST	0.043	.032;	.054	.002	.0067;	-.0026	4.7	14.4	;-5.1
	BF	0.074	.031;	.117	-.0055	.001;	-.012	-6.2	7.1	;-19.4
	GM	0.116	.094;	.139	.0001	.0067;	-.007	0.4	6.7	;-6.0
	GL	0.075	.054;	.097	.0015	.0053;	-.0083	0.5	7.5	;-6.5

Table 3. Comparison of Peak muscle activity during neutral (baseline) walking with a rocker, “Oxford” type and Nike shoes both with and without a 10 degree laterally wedged insole (rANOVA). VM = vatus Medialis, VL = Vastus lateralis, ST = Semi Tendinosus, BF = Biceps femoris, GM = Gastrocnemius medialis, GL = Gastrocnemius lateralis.

Relative small differences with lateral wedges and large variations were observed among subject with no clear significant trends. For all shoes a small non-significant reduction was observed in VM and VLwhen applying the lateral wedge.

The effects of lateral wedges were not significantly influenced by the shoe type in healthy subjects walking at a preferred walking speed. It is remarkable that shoe type and lateral wedges are equally important factors in reducing KAM. The positive effect from laterally wedged insoles resulted in minor changes during gait.

STUDY II – EXPERIMENTAL KNEE PAIN AND LATERAL WEDGE EFFECT

Figure 7. Peak pain score during four injections with hypertonic (HYP) and isotonic (ISO) saline.

The average pain level reported for the four series after hypertonic saline injections was 4.2 out of 10 (CI: 3.2–5.2) and 0.7 (CI: 0.2–1.2) with isotonic saline (Figure 8). Pain gradually declined and all participants were pain free 7 min (CI: 5–9) after hypertonic saline injections and 1 min (CI: 0–2) after isotonic injections (Figure 9). Pain was reported in the anterior inferior medial region combined with retropatellar pain.

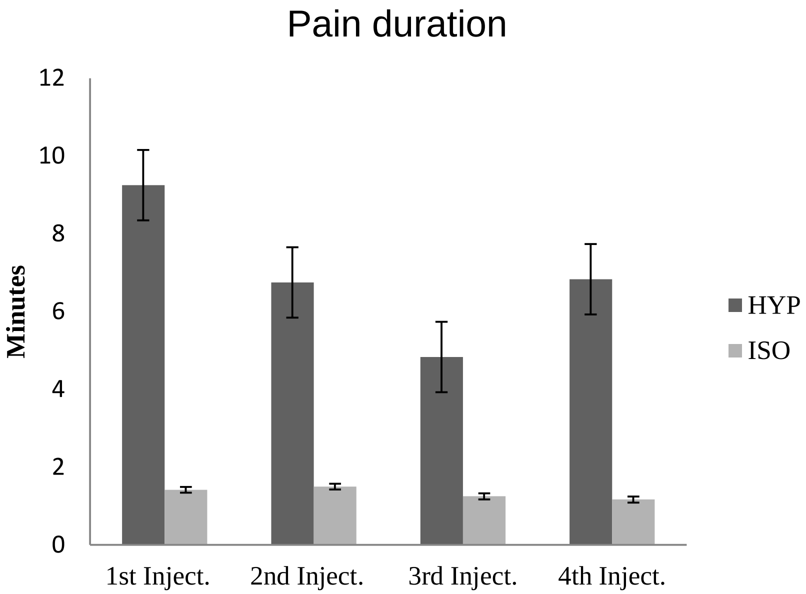


Figure 8. Pain duration in minutes with four injections with hypertonic (HYP) and isotonic (ISO) saline.

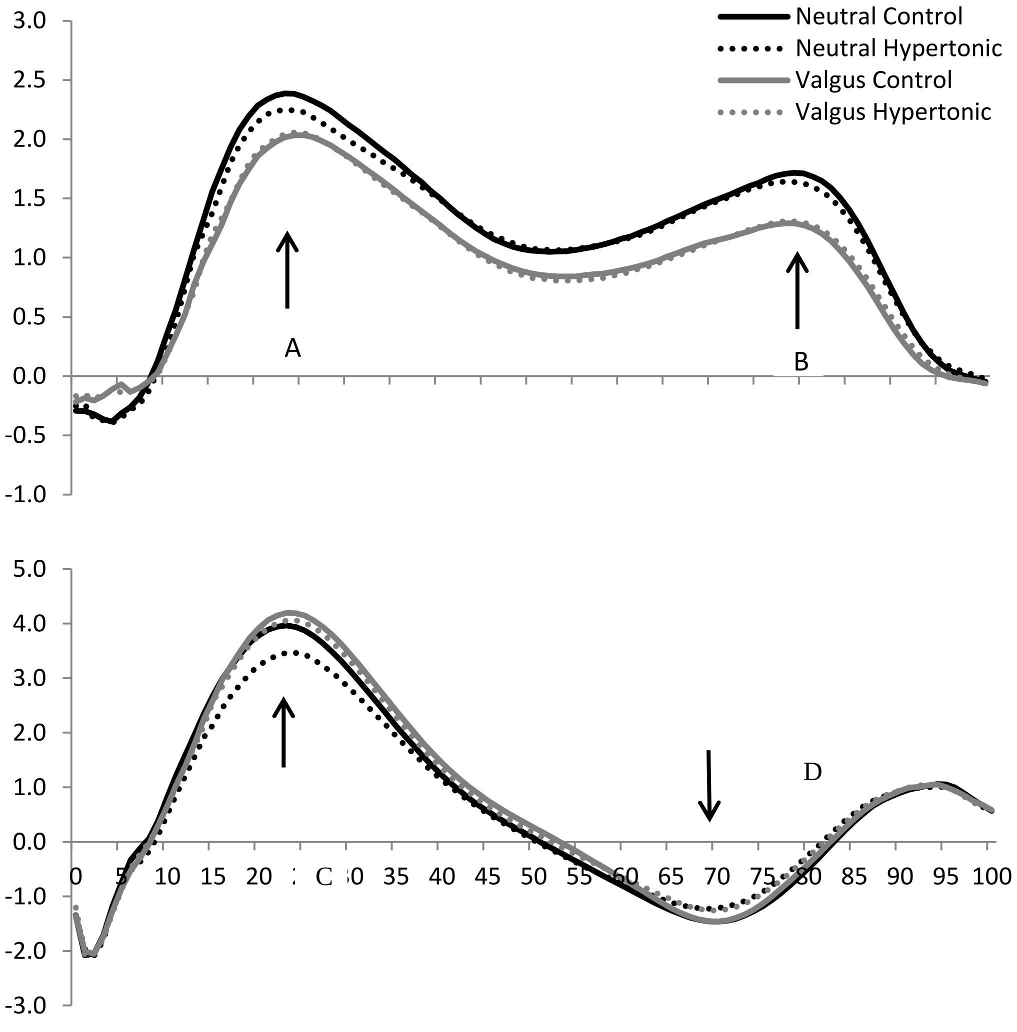


Figure 9. Average knee moments (Nm/BW*Ht) during stance phase of walking with neutral or valgus wedges during control or experimental knee pain. **Top**, Frontal plane moment: Positive values indicate net external adduction and negative values indicate net external abduction moment. **A** and **B** indicate the first and second peak external adduction moments, respectively. **Bottom**, Sagittal plane moment: Positive values indicate net internal extensor moment (quadriceps moment), and negative values indicate net internal flexor moment (hamstring and gastrocnemius). **C** and **D** indicate the peak internal extensor and flexor moments, respectively.

For both the KAM1 and KAM2 there was a significant wedge effect ($P < 0.001$; Fig. 9). The average wedge effect reduced KAM1 by 14% (CI: 9–19), and KAM2 by 13% (CI: 0–27). The condition effects (CTR/ISO/HYP) were non-significant for KAM1 ($P = 0.84$) and for KAM2 ($P = 0.87$). A small reduction with pain (HYP) was observed in KAM1 although this was not significant. The KAM1was remarkably unaffected by ISO and HYP when using the wedged insole (Figure 10). No significant effects with test number (P = 0.09) or any interaction effects were observed.

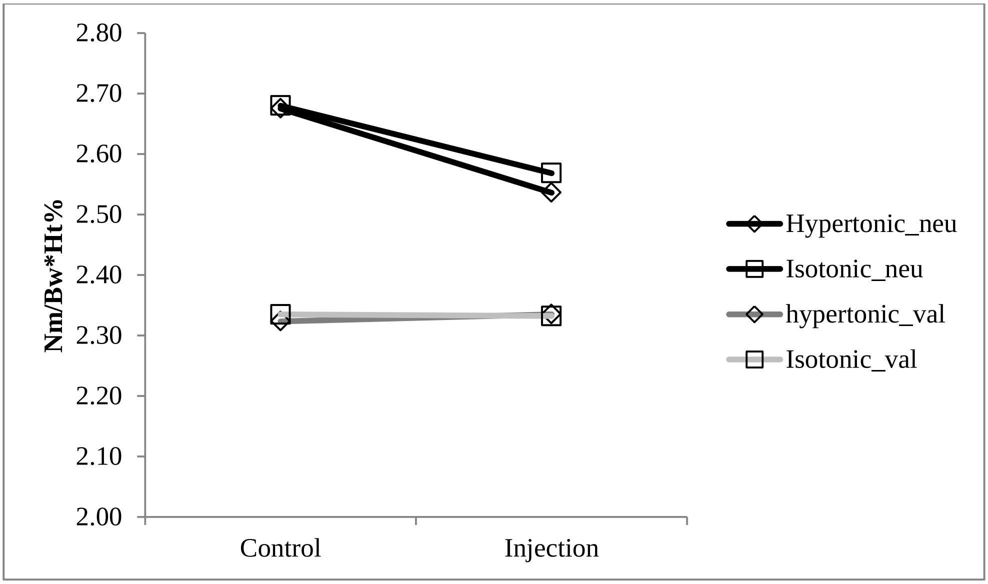


Figure 10. First peak Knee adduction moment (KAM1) during walking at a constant self-selected walking speed while experimental knee pain is induced with hypertonic saline. Control: No injection. Isotonic saline is a non-painful injection. Neu: neutral wedged insole compared to Val: 10° laterally wedged insole.

Experimental knee pain does not mediate the effect of lateral wedges on KAM in fact experimental knee pain has a larger influence on KEM than KAM. There was a trade-off between reduction in KAM and small increase in KEM when applying a 10° lateral wedge (Figure 9).

STUDY III – LATERAL WEDGES AND MENISCECTOMY

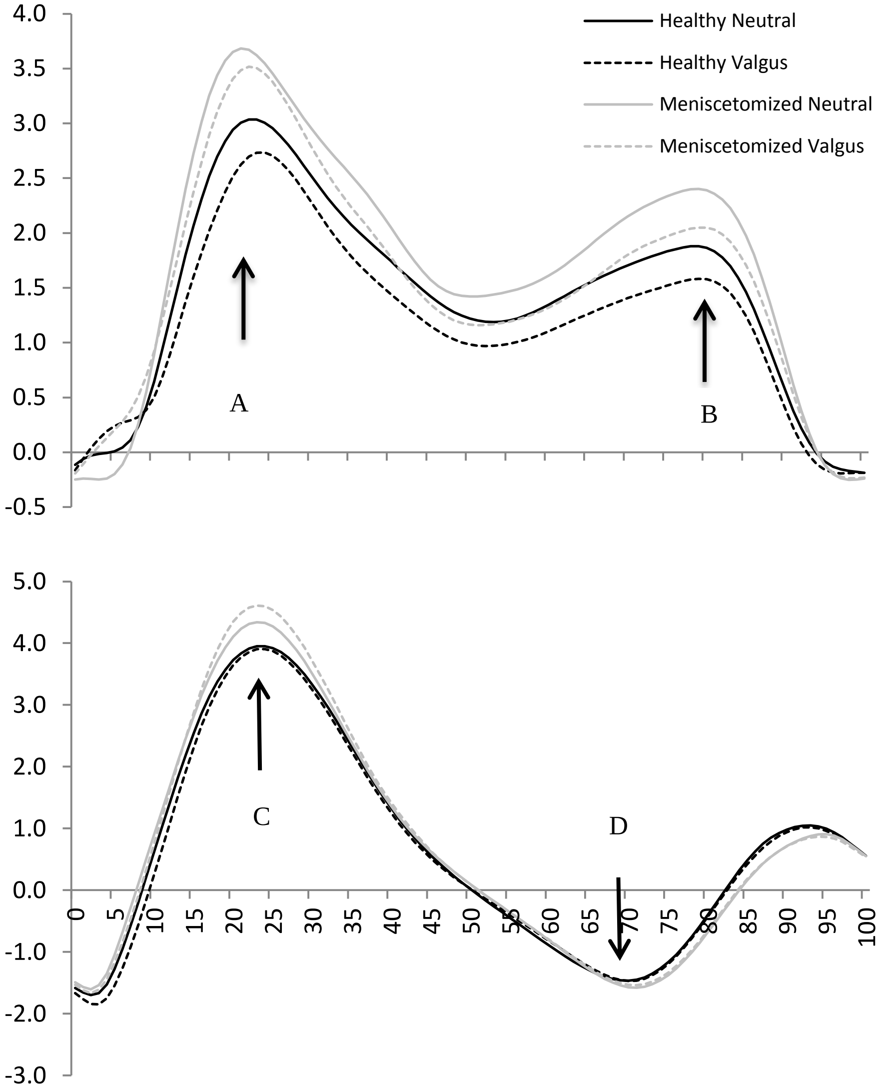


Figure 11. Average knee moments (Nm/BW*Ht) during stance phase of walking with neutral or valgus wedges during control or experimental knee pain. **Top**, Frontal plane moment: Positive values indicate net external adduction and negative values indicate abduction moment. A and B indicate the first and second peak adduction moments, respectively. **Bottom**, Sagittal plane moment: Positive values indicate extensor moment (quadriceps moment), and negative values indicate flexor moment (hamstring and gastrocnemius). C and D indicate the peak extensor and flexor moments, respectively.

A significant wedge-effect ($P<0.001$) was observed as a reduction in $KAM_{impulse}$, and the group difference was significant ($P=0.04$) with 21% higher impulse in the patient group (Figure 11). However, no wedge*group interaction effect ($P=0.72$) was observed. The lateral wedges reduced $KAM_{impulse}$ in the patient group, although not to the equivalent level as observed in healthy controls walking with a neutral wedge. The relative reductions in $KAM_{impulse}$ were 12% in the control group and 10% in APM group. Likewise, a significant wedge- ($P<0.01$) and group-effect ($P<0.01$) was observed in both KAM1 and KAM2. There were no differences in wedge-effect between the two groups, wedge*group interaction effect ($P>0.16$). The relative reductions in KAM1 were 10% in the control group and 5% in the APM group, whereas the relative reductions in KAM2 were 16% in the control group and 17% in the APM group.

It was possible for all 22 participants in study III to walk for one hour with a 10° lateral wedge at 5 km/h, although only three subjects reported no discomfort. The typical complaints were blisters, soreness at the medial side of the ankle, soreness at the 5th metatarsal and/or muscle soreness.

The knee adduction moment was increased 3-5 years postoperatively in an otherwise active group of patients when compared to a matched healthy group of people. Lateral wedges can result in decreased knee adduction moment in APM patients, however not to the level of healthy matched controls. A challenge related to comfort during walking was observed, as most subjects reported discomfort during gait with the laterally wedged insole.

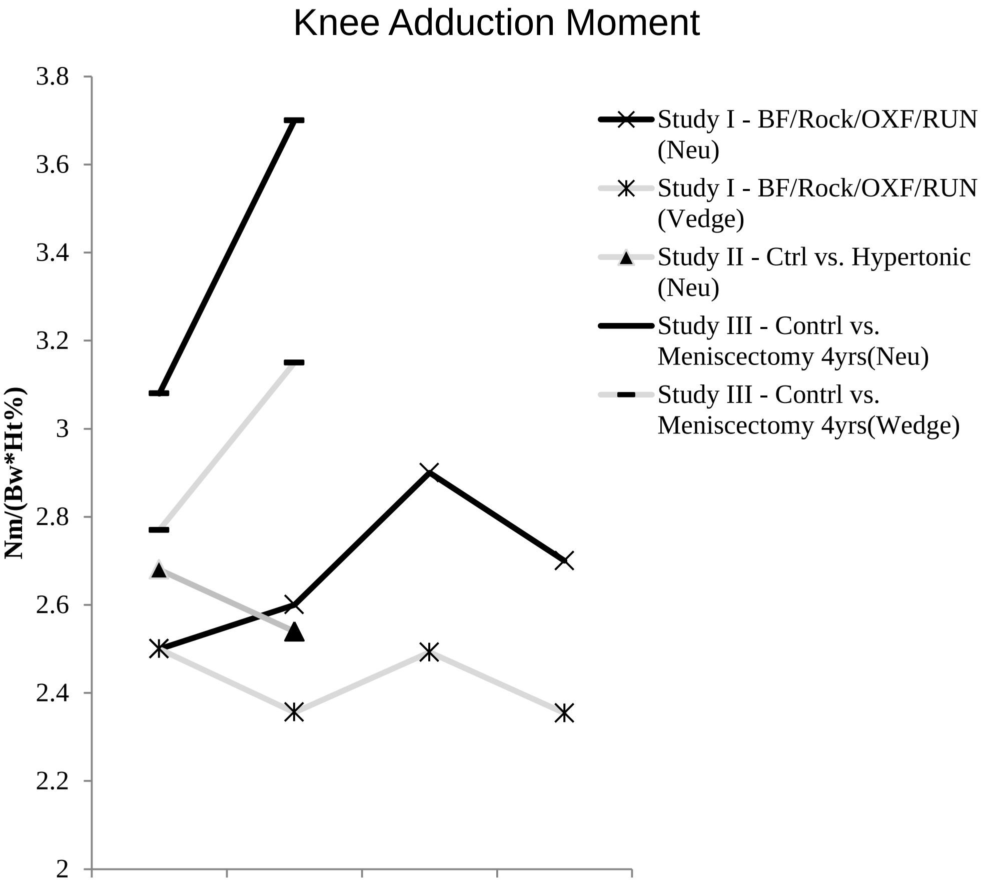


Figure 12. First peak knee adduction moment (KAM1) during across the studies presented in the theses. The results are not adjusted for walking speed, age or gender. Average walking speed in study: I) 5,5 km/t, II) 4,9 km/t and III) 5,2 km/t.

DISCUSSION

MAIN FINDINGS

Overall, the results from the three studies add important knowledge on biomechanical interventions when aiming to reduce the knee adduction moments with an underlying aim of decreasing the progression of knee osteoarthritis. More explicitly, results from study I showed that 100% of the participants reduced KAM1 with a ten degree laterally wedged insole with a relative reduction for ROC, OXF and the RUN shoe of 5.9% (CI: 0.9-12.7), 12.8 % (CI: 8.2-17.4) and 14.1 % (CI: 9.6-18.6), respectively. However the biggest difference among shoe designs tested was -14.3% (CI95%:-25.3;-3.1) between ROC and OXF, but the shoe type did not change the wedge-effect.

Experimental knee pain reduced KAM non-significantly and did not change the effect of lateral wedges in healthy subjects. Importantly, experimental knee pain primarily affected KEM. The results of study II are in accordance with the lack of clear causal relationship between KAM and pain also described by van Raaij et al. with 17% classified as responders to lateral wedging (van Raaij 2010). In study III, meniscectomized patients were characterized by increased KAM combined with a lower self-reported KOOS score 3-5 years after APM when compared to healthy controls. Lateral wedges decreased KAM in APM patients, however not to the level of healthy matched controls.

KNEE MECHANICS: FOOTWEAR AND INSOLES

Previous studies have reported a mean reduction in the peak KAM by approximately 6% with a 5° lateral wedge in people with knee OA (Butler 2007; Hinman 2008a; Hinman 2008b; Hinman 2012; Kakihana 2005; Kerrigan 2002; Kuroyanagi 2007; Shimada 2006). When using smaller lateral wedges less consistent effects have been demonstrated. Kakihana et al. showed in 18% of the investigated OA patients that walking with a lateral wedge of six degrees increased rather than decreased KAM (Kakihana 2005). In a study with 239 knee OA patients, Kerrigan et al. demonstrated 8.3% reduction in KAM1 with a 10° wedge with no insole (Kerrigan 2002), which is similar to the findings in study III with 5 and 10%, but somewhat less than the 14% observed in study I and II. A smaller wedge-effect in study III compared to study I and II was also seen in both meniscectomized patients and controls for AAM. The most important difference in study III was that subjects had been walking for one hour prior to gait analysis, which allowed for a longer time to get acustommized with the wedges. A previous study found that the acute wedge-effect did not change over a one month period (Hinman 2009).

Customized insoles may be needed for long term clinical use, wh_ich potentially also change the wedge effect. A combination of a customized wedge degree and medial arch support (Butler 2007; Skou 2013) or a lateral wedge with a customized medial arch support (Jones 2013) have been successful in increasing the level of comfort.

KNEE MECHANICS AND PAIN

The typical causal association assumption so far in clinical studies looking at lateral wedge-effect was based on interaction between reduction in KAM1 or $KAM_{impulse}$ and reduced knee pain. Based on the results from study II this assumption is challenged since experimental knee pain only slightly and non-significantly decrease KAM. Increase in KAM after reduction of pain is previously shown in patients (Schnitzer 1993; Henriksen 2006). Contrary to this, pain affects knee mechanics in the sagittal plane. Although, not significantly a small trade-off between KAM and KEM was observed when applying a lateral wedge changes (Figure 12). Pain reduction from neuromuscular strength training is well documented, but does not reduce KAM (Bennell 2014; Lim 2008). Subsequently, when neither experimental pain nor pain relive from exercise reduce KAM, it seems unlikely that pain reduction will follow from a reduction of KAM.

KNEE MECHANICS AFTER MENISCECTOMY

Early changes in knee joint mechanics during walking are often small and degradation of cartilage only expected to develop over years, which again challenges continued evidence based development of conservative treatment modalities. A change toward external tibial rotation has been observed clinically after partial medial meniscectomy, resulting in decreased strains in the posterior medial horn of the menisci and increased strains in the anterior medial horn (Netravali 2011). This may serve as a compensatory mechanism since medial posterior horn lesions are the most common injury. Applying a 10° lateral wedge insole during gait resulted in increased AAM, which counteract the external rotation of tibia as increased AAM (foot pronation) increase internal tibial rotation (Barton 2012). A shift in centrally loaded areas of the cartilage post-meniscectomy may initiate a direct damage to the cartilage matrix or indirectly by altering the hydration of the tissue. In peripheral regions, a reduced loading may facilitate subchondral vascular invasion, and endochondral ossification consistent with the central fibrillation and peripheral osteophyte formation seen in post-meniscectomy osteoarthritis (Song 2008).

Knee adduction/abduction and internal/external rotation angles were not reported in the present thesis, because it has been shown that their relative values during gait are of a similar magnitude to that of the measurement error associated with kinematic cross-talk and skin motion (Reinschmidt 1997; Ramsey & Wretenberg 1999; Piazza & Cavanagh 2000).

LATERALLY WEDGED INSOLE AND SURFACE EMG

Results from study I indicated that lateral wedges did not affect the neuromuscular control of the kneespanning muscles during walking at a self-selected walking speed. Neuromuscular control was also tested in nine patients waiting for open wedge osteotomy due to medial KOA during squat and lunge exercises +/- lateral wedges. In this group, a significant reduction in average BF activity was observed during squat (Mølgaard et al. Unpublished data). Which could be explained by a higher degree of joint laxity in KOA patients or that walking does not challenge the neuromuscular control sufficiently to observe an effect of lateral wedges. A reduced activity in ST and VM have also been observed during stair descending in meniscectomized patients 2-4 years after surgery (Thorlund 2011). This may represent a strategy to lower KAM and decreased medial knee joint compartment loading (Heiden 2009). Additionally, a recent study in eight healthy male subjects showed that both knee-spanning and non-knee-spanning muscles contributed to compartment forces. More importantly, the non-knee-spanning muscles compressed one compartment but unloaded the other, whereas the knee-spanning muscles compressed both compartments (Sritharan 2012). The combination of a relatively large lateral wedge (10°) and the lower muscle activity during walking lead to large variations among subjects and finally the importance of non-kneespanning muscles contribution to knee load should not be underestimated.

METHODOLOGICAL CONSIDERATIONS

SUBJECTS

When selecting the people most likely to have a biomechanical benefit from laterally wedged insoles, it would be relevant to look at people at high risk of Knee-only OA with either: 1)An increased mechanical load: Varus/valgus alignment, meniscectomy, cruciate ligament rupture, static/dynamic instability e.g. people walking with a lateral thrust, unicompartment KOA and candidate for tibiaosteotomy or 2) People with a decreased mechanical load tolerance as observed with: cruciate ligament rupture, partial meniscectomy, fractures of the tibial/femoral condyle, intraarticular bleeding, cartilage injuries, subchondral bone edema, increased subchondral bone stiffness. In study III a homogenic group of male patients was tested all at high risk of early KOA and both healthy controls and meniscectomized subjects all had a significant wedge-effect. This is an extremely important distinction, as both increase and decrease in KAM has been observed with smaller wedges (Kerrigan 2002) or in more heterogenic populations such as those tested in a clinical trial (Hinman 2008b).

STUDY DESIGN

Large variation in human movement is well known (Latash 2008) and should be considered when observing relative small groups of people moving in a laboratory for a relatively short period of time. It is however the most accurate and reliable way of approaching human movement patterns. When extrapolating the biomechanical results to general populations or larger randomized trials large variations have often resulted in small effect sizes, which is a challenge to the study design of larger clinical trials in this area.

While sound theoretical background and previous studies emphasize the likelihood of the causality, it is not possible to conclude that the findings in the present study were a result of APM surgery alone. The differences in load-related variables after APM may have existed prior to surgery and although not confirmed in studies, these mechanisms may even have contributed to the cartilage injury.

OUTCOMES

External knee load and EMG measures as accurate indicators of internal knee contact forces during gait were tested with instrumented prosthesis. When testing a wide range of different walking patterns caution should be exercised when inferring changes in knee contact forces based on observed changes in external knee load and EMG measures (Meyer 2013). No significant correlations were found between KAM1 and peak medial forces in a study by Zhao et al. (Zhao 2007). However, this was studied in a single subject with an instrumented knee implant and two other studies with the same subject reported different results. In a study from Walter et al. (Walter 2010) reductions of KAM1 did not correspond to reductions of the first medial force peak, whereas reductions of the second KAM peak correlated to the corresponding medial force peak. In the second study from Erhart et al. (Erhart

2010) reductions of the first KAM peak were correlated with reductions of the first medial force peak. A laterally wedged insole may therefore not guarantee a substantial reduction in medial contact forces in the knee joint although increased wedge angles tend to result in higher force reduction (Kutzner 2011). The differences in knee joint loading magnitudes between studies and laboratories may also be a result of differences in gait analysis protocols across the involved gait labs, for example, in the selection of reference frame convention for the calculation of the KAM (Schache 2007).

It has been shown, both in vivo and in vitro, that joint damage can be delivered with an impulsive mode either from a single osteochondral damage, or from small repetitive impulsive loads. When bone and cartilage sustain microscopic damage that accumulates, this also increase subchondral stiffening and the shear stresses deep in the overlying articular cartilage (Radin 1991).
Nine weeks of daily impulsive loading in rabbits showed histologically cartilage damage. Even when the 9 weeks of loading were followed by 6 months of normal activity, the impact loading initiated changes that progressed to total cartilage loss (Radin 1991). A more specific cyclic load simulating of normal gait has been applied to four sheep knees. Articular cartilage thickness and nominal strain were compared during 1h loading and 2.5h after loading was stopped measured with MRi. When comparing knee before and after meniscectomy the maximum strains after 1h of loading were about 55% in the intact knees and 72% in the meniscectomized knees. With meniscectomy, tibial articular cartilage in the central load bearing region remained deformed and dehydrated 2.5h after loading (Song 2008). While the results of animal studies indicate that short term overload and return to normal activities may lead to KOA, this cannot transferred directly to humans. While peak KAM1 has been identified as a strong predictor of KOA progression radiological (Miyazaki 2002), $KAM_{impulse}$ has been identified as the best predictor of decrease in cartilage volume measured with MRi (Bennell 2011). The altered knee joint biomechanics observed in APM patients may go some way to explain the more pathological morphology observed in the knee, since the results from study III

indicated both increased KAM1 and $KAM_{impulse}$ in patients compared to controls. More constant increase in weight loading gain of more than 5% also increased risk of cartilage degeneration (Bucknor 2015).

CONCLUSION

Shoe type does not compromise the efficacy of lateral wedges, although the design in it-self has a strong influence on knee adduction moment during walking (Study I). A change of footwear should always be the first step before applying laterally wedged insoles in patients.

It is possible to reduce the knee adduction moment by lateral wedges in healthy subjects during experimental knee pain (Study II). The biomechanical impact of experimental knee pain however is higher in the sagittal plane compared to the frontal plane. It may therefore be questioned if the rationales behind pain as primary outcome in randomized clinical trials investigating the effectiveness of laterally wedged insoles are misleading.

Lateral foot wedges will significantly result in decreased knee adduction moment and impulse in otherwise healthy and active APM patients, however not to the level of healthy matched controls. Despite efforts trying to preserve the meniscus during arthroscopic surgery a larger group of patients have part of their menisci resected, which is the subgroup tested in this thesis. Based on these results it would be required to first prove the effectiveness of interventions (wedge & footwear & walking technique) combined to bring the KAM to the normal level and then assess the clinical outcome in a prospective study. This has not been done yet.

PERSPECTIVES

- NEXT STEP WITH LATERAL WEDGES?

Laterally wedged insoles may have clinical potential when applied to the right subgroup of people, but shoe design or pain in it-self may introduce larger changes in mechanical loading and obscures clinicians estimate of knee loading. The scientific community has a challenge in the quest of finding a clinical treatment algorithm that leads to the optimal window of loading, with laterally wedged insoles specifically and the multiplicity of variables generally. Even though pain is the primary complaint with patients it should not be the primary outcome when testing biomechanical interventions aiming at more optimal loading of the cartilage which are not the direct the source of pain since the tissue are not containing nociceptive afferents and an extremely low chondrocyte turnover. Short term cartilage adaptation experiments looking at acute changes in cartilage volume (Song 2008; Subburaj 2012) in conjunction with long term clinical studies may have some prospects for the future. This question should be explored in future studies in combination with biomarkers on cartilage turnover (Niehoff 2010), phenotype diagnostics (Cotofana 2013), pharmacologic agents and stem cell therapy.

While still attainable it is not a simple task to adjust a patients loading pattern in a certain direction outside a 3D movement lab. More effective and still individually comfortable shoes and/or insoles are needed to achieve further effect of this type of treatment. However, in the clinical setup of today knee braces or orthopaedic surgery with the risk of complications are the existing and unpleasant alternatives. Most importantly biomechanical interventions such as laterally wedged insoles were never intended as a standalone treatment option, but a part of a multimodal treatment (McAlindon 2014). Other important treatments to consider prior to or combined with lateral wedges are: Weight loss, neuromuscular exercise (Ageberg 2010), reducing joint pain and stiffness, maintaining and improving joint mobility, educating patients about the nature of the disorder and its management.

LITERATURE LIST

Aadahl, M., & Jorgensen, T. (2003). Validation of a new self-report instrument for measuring physical activity. *Medicine and Science in Sports and Exercise, 35*(7), 1196-1202.

Ageberg, E., Link, A., & Roos, E. M. (2010). Feasibility of neuromuscular training in patients with severe hip or knee OA: The individualized goal-based NEMEX-TJR training program. *BMC Musculoskeletal Disorders, 11*, 126-2474-11-126.

Amin, S., Luepongsak, N., McGibbon, C. A., LaValley, M. P., Krebs, D. E., & Felson, D. T. (2004). Knee adduction moment and development of chronic knee pain in elders. *Arthritis and Rheumatism, 51*(3), 371-376.

Andriacchi, T. P., Briant, P. L., Bevill, S. L., & Koo, S. (2006a). Rotational changes at the knee after ACL injury cause cartilage thinning. *Clinical Orthopaedics and Related Research, 442*, 39-44.

Andriacchi, T. P., & Dyrby, C. O. (2005). Interactions between kinematics and loading during walking for the normal and ACL deficient knee. *Journal of Biomechanics, 38*(2), 293-298.

Andriacchi, T. P., Koo, S., & Scanlan, S. F. (2009). Gait mechanics influence healthy cartilage morphology and osteoarthritis of the knee. *The Journal of Bone and Joint Surgery.American Volume, 91 Suppl 1*, 95-101.

Andriacchi, T. P., & Mundermann, A. (2006b). The role of ambulatory mechanics in the initiation and progression of knee osteoarthritis. *Current Opinion in Rheumatology, 18*(5), 514-518.

Andriacchi, T. P., Mundermann, A., Smith, R. L., Alexander, E. J., Dyrby, C. O., & Koo, S. (2004). A framework for the in vivo pathomechanics of osteoarthritis at the knee. *Annals of Biomedical Engineering, 32*(3), 447-457.

Baker, K., Goggins, J., Xie, H., Szumowski, K., LaValley, M.et al. . (2007). A randomized crossover trial of a wedged insole for treatment of knee osteoarthritis. *Arthritis and Rheumatism, 56*(4), 1198-1203.

Baliunas, A. J., Hurwitz, D. E., Ryals, A. B., Karrar, A., Case, J. P.et al. . (2002). Increased knee joint loads during walking are present in subjects with knee osteoarthritis. *Osteoarthritis and Cartilage / OARS, Osteoarthritis Research Society, 10*(7), 573-579.

Barg, A., Pagenstert, G. I., Hugle, T., Gloyer, M., Wiewiorski, M.et al. . (2013). Ankle osteoarthritis: Etiology, diagnostics, and classification. *Foot and Ankle Clinics, 18*(3), 411-426.

Barrios, J. A., Butler, R. J., Crenshaw, J. R., Royer, T. D., & Davis, I. S. (2013). Mechanical effectiveness of lateral foot wedging in medial knee osteoarthritis after 1 year of wear. *Journal of Orthopaedic Research, 31*(5), 659-664.

Barrios, J. A., Davis, I. S., Higginson, J. S., & Royer, T. D. (2009). Lower extremity walking mechanics of young individuals with asymptomatic varus knee alignment. *Journal of Orthopaedic Research, 27*(11), 1414-1419.

Barton, C. J., Levinger, P., Crossley, K. M., Webster, K. E., & Menz, H. B. (2012). The relationship between rearfoot, tibial and hip kinematics in individuals with patellofemoral pain syndrome. *Clinical Biomechanics (Bristol, Avon), 27*(7), 702-705.

Bennell, K. L., Bowles, K. A., Payne, C., Cicuttini, F., Williamson, E.et al. . (2011a). Lateral wedge insoles for medial knee osteoarthritis: 12 month randomised controlled trial. *BMJ (Clinical Research Ed.), 342,* d2912.

Bennell, K. L., Bowles, K. A., Wang, Y., Cicuttini, F., Davies-Tuck, M., & Hinman, R. S. (2011). Higher dynamic medial knee load predicts greater cartilage loss over 12 months in medial knee osteoarthritis. *Annals of the Rheumatic Diseases, 70*(10), 1770-1774.

Bennell, K. L., Hinman, R. S., & Metcalf, B. R. (2004). Association of sensorimotor function with knee joint kinematics during locomotion in knee osteoarthritis. *American Journal of Physical Medicine & Rehabilitation / Association of Academic Physiatrists, 83*(6), 455-63; quiz 464-6, 491.

Bennell, K. L., Kyriakides, M., Metcalf, B., Egerton, T., Wrigley, T. V.et al. . (2014). Neuromuscular versus quadriceps strengthening exercise in patients with medial knee osteoarthritis and varus malalignment: A randomized controlled trial. *Arthritis & Rheumatology (Hoboken, N.J.), 66*(4), 950-959.

Bhattacharyya, T., Gale, D., Dewire, P., Totterman, S., Gale, M. E.et al. . (2003). The clinical importance of meniscal tears demonstrated by magnetic resonance imaging in osteoarthritis of the knee. *The Journal of Bone and Joint Surgery.American Volume, 85-A*(1), 4-9.

Birmingham, T. B., Hunt, M. A., Jones, I. C., Jenkyn, T. R., & Giffin, J. R. (2007). Test-retest reliability of the peak knee adduction moment during walking in patients with medial compartment knee osteoarthritis. *Arthritis and Rheumatism, 57*(6), 1012-1017.

Bohnsack, M., Meier, F., Walter, G. F., Hurschler, C., Schmolke, S.et al. . (2005). Distribution of substance-P nerves inside the infrapatellar fat pad and the adjacent synovial tissue: A neurohistological approach to anterior knee pain syndrome. *Archives of Orthopaedic and Trauma Surgery, 125*(9), 592-597.

Briem, K., Axe, M. J., & Snyder-Mackler, L. (2009). Medial knee joint loading increases in those who respond to hyaluronan injection for medial knee osteoarthritis. *Journal of Orthopaedic Research : Official Publication of the Orthopaedic Research Society, 27*(11), 1420-1425.

Bucknor, M. D., Nardo, L., Joseph, G. B., Alizai, H., Srikhum, W.et al. . (2015). Association of cartilage degeneration with four year weight gain - 3T MRI data from the osteoarthritis initiative. *Osteoarthritis and Cartilage / OARS, Osteoarthritis Research Society,*

Bullough, P. G. (2004). The role of joint architecture in the etiology of arthritis. *Osteoarthritis and Cartilage / OARS, Osteoarthritis Research Society, 12 Suppl A,* S2-9.

Butler, R. J., Marchesi, S., Royer, T., & Davis, I. S. (2007). The effect of a subject-specific amount of lateral wedge on knee mechanics in patients with medial knee osteoarthritis. *Journal of Orthopaedic Research : Official Publication of the Orthopaedic Research Society, 25*(9), 1121-1127.

Chaudhari, A. M., Briant, P. L., Bevill, S. L., Koo, S., & Andriacchi, T. P. (2008). Knee kinematics, cartilage morphology, and osteoarthritis after ACL injury. *Medicine and Science in Sports and Exercise, 40*(2), 215-222.

Cicuttini, F. M., Forbes, A., Yuanyuan, W., Rush, G., & Stuckey, S. L. (2002). Rate of knee cartilage loss after partial meniscectomy. *The Journal of Rheumatology, 29*(9), 1954-1956.

Cotofana, S., Wyman, B. T., Benichou, O., Dreher, D., Nevitt, M.et al. . (2013). Relationship between knee pain and the presence, location, size and phenotype of femorotibial denuded areas of subchondral bone as visualized by MRI. *Osteoarthritis and Cartilage / OARS, Osteoarthritis Research Society, 21*(9), 1214-1222.

Crenshaw, S. J., Pollo, F. E., & Calton, E. F. (2000). Effects of lateral-wedged insoles on kinetics at the knee. *Clinical Orthopaedics and Related Research, (375)*(375), 185-192.

Ding, C., Martel-Pelletier, J., Pelletier, J. P., Abram, F., Raynauld, J. P.et al. . (2007). Meniscal tear as an osteoarthritis risk factor in a largely non-osteoarthritic cohort: A cross-sectional study. *The Journal of Rheumatology, 34*(4), 776-784.

Doherty, M., Watt, I., & Dieppe, P. (1983). Influence of primary generalised osteoarthritis on development of secondary osteoarthritis. *Lancet, 2*(8340), 8-11.

Dye, S. F. (2005). The pathophysiology of patellofemoral pain: A tissue homeostasis perspective. *Clinical Orthopaedics and Related Research, (436)*(436), 100-110.

Dye, S. F., Vaupel, G. L., & Dye, C. C. (1998). Conscious neurosensory mapping of the internal structures of the human knee without intraarticular anesthesia. *The American Journal of Sports Medicine, 26*(6), 773-777.

Englund, M. (2004). Meniscal tear--a feature of osteoarthritis. *Acta Orthopaedica Scandinavica.Supplementum, 75*(312), 1-45, backcover.

Englund, M., Guermazi, A., Gale, D., Hunter, D. J., Aliabadi, P.et al. . (2008). Incidental meniscal findings on knee MRI in middle-aged and elderly persons. *The New England Journal of Medicine, 359*(11), 1108-1115.

Englund, M., & Lohmander, L. S. (2004). Risk factors for symptomatic knee osteoarthritis fifteen to twenty-two years after meniscectomy. *Arthritis and Rheumatism, 50*(9), 2811-2819.

Englund, M., Niu, J., Guermazi, A., Roemer, F. W., Hunter, D. J.et al. . (2007). Effect of meniscal damage on the development of frequent knee pain, aching, or stiffness. *Arthritis and Rheumatism, 56*(12), 4048-4054.

Englund, M., Paradowski, P. T., & Lohmander, L. S. (2004). Association of radiographic hand osteoarthritis with radiographic knee osteoarthritis after meniscectomy. *Arthritis and Rheumatism, 50*(2), 469-475.

Englund, M., Roos, E. M., & Lohmander, L. S. (2003). Impact of type of meniscal tear on radiographic and symptomatic knee osteoarthritis: A sixteen-year followup of meniscectomy with matched controls. *Arthritis and Rheumatism, 48*(0004-3591; 8), 2178-2187.

Erhart, J. C., Mundermann, A., Elspas, B., Giori, N. J., & Andriacchi, T. P. (2010). Changes in knee adduction moment, pain, and functionality with a variable-stiffness walking shoe after 6 months. *Journal of Orthopaedic Research : Official Publication of the Orthopaedic Research Society, 28*(7), 873-879.

Farrar, J. T., Young, J. P.,Jr, LaMoreaux, L., Werth, J. L., & Poole, R. M. (2001). Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain, 94*(2), 149-158.

Felson, D. T. (2004). Risk factors for osteoarthritis: Understanding joint vulnerability. *Clinical Orthopaedics and Related Research, (427 Suppl)*(427 Suppl), S16-21.

Felson, D. T., & Zhang, Y. (1998). An update on the epidemiology of knee and hip osteoarthritis with a view to prevention. *Arthritis and Rheumatism, 41*(8), 1343-1355.

Fisher, D. S., Dyrby, C. O., Mundermann, A., Morag, E., & Andriacchi, T. P. (2007). In healthy subjects without knee osteoarthritis, the peak knee adduction moment influences the acute effect of shoe interventions designed to reduce medial compartment knee load. *Journal of Orthopaedic Research : Official Publication of the Orthopaedic Research Society, 25*(4), 540-546.

Fithian, D. C., Kelly, M. A., & Mow, V. C. (1990). Material properties and structure-function relationships in the menisci. *Clinical Orthopaedics and Related Research, (252)*(252), 19-31.

Grodzinsky, A. J., Levenston, M. E., Jin, M., & Frank, E. H. (2000). Cartilage tissue remodeling in response to mechanical forces. *Annual Review of Biomedical Engineering, 2,* 691-713.

Harkey, M. S., Luc, B. A., Golightly, Y. M., Thomas, A. C., Driban, J. B.et al. . (2015). Osteoarthritis-related biomarkers following anterior cruciate ligament injury and reconstruction: A systematic review. *Osteoarthritis and Cartilage / OARS, Osteoarthritis Research Society, 23*(1), 1-12.

Heiden, T. L., Lloyd, D. G., & Ackland, T. R. (2009). Knee joint kinematics, kinetics and muscle co-contraction in knee osteoarthritis patient gait. *Clinical Biomechanics (Bristol, Avon), 24*(10), 833-841.

Helminen, H. J., Hyttinen, M. M., Lammi, M. J., Arokoski, J. P., Lapvetelainen, T.et al. . (2000). Regular joint loading in youth assists in the establishment and strengthening of the collagen network of articular cartilage and contributes to the prevention of osteoarthrosis later in life: A hypothesis. *Journal of Bone and Mineral Metabolism, 18*(5), 245-257.

Henriksen, M., Graven-Nielsen, T., Aaboe, J., Andriacchi, T. P., & Bliddal, H. (2010). Gait changes in patients with knee osteoarthritis are replicated by experimental knee pain. *Arthritis Care & Research, 62*(4), 501-509.

Henriksen, M., Simonsen, E. B., Alkjaer, T., Lund, H., Graven-Nielsen, T.et al. . (2006). Increased joint loads during walking--a consequence of pain relief in knee osteoarthritis. *The Knee, 13*(6), 445-450.

Herzog, W., Clark, A., & Longino, D. (2004). Joint mechanics in osteoarthritis. *Novartis Foundation Symposium, 260,* 79-95; discussion 95-9, 100-4, 277-9.

Hill, C. L., Hunter, D. J., Niu, J., Clancy, M., Guermazi, A.et al. . (2007). Synovitis detected on magnetic resonance imaging and its relation to pain and cartilage loss in knee osteoarthritis. *Annals of the Rheumatic Diseases, 66*(12), 1599-1603.

Hinman, R. S., Bowles, K. A., & Bennell, K. L. (2009). Laterally wedged insoles in knee osteoarthritis: Do biomechanical effects decline after one month of wear? *BMC Musculoskeletal Disorders, 10*, 146-2474-10-146.

Hinman, R. S., Bowles, K. A., Metcalf, B. B., Wrigley, T. V., & Bennell, K. L. (2012). Lateral wedge insoles for medial knee osteoarthritis: Effects on lower limb frontal plane biomechanics. *Clinical Biomechanics (Bristol, Avon), 27*(1), 27-33.

Hinman, R. S., Bowles, K. A., Payne, C., & Bennell, K. L. (2008a). Effect of length on laterally-wedged insoles in knee osteoarthritis. *Arthritis and Rheumatism, 59*(1), 144-147.

Hinman, R. S., Payne, C., Metcalf, B. R., Wrigley, T. V., & Bennell, K. L. (2008b). Lateral wedges in knee osteoarthritis: What are their immediate clinical and biomechanical effects and can these predict a three-month clinical outcome? *Arthritis and Rheumatism, 59*(3), 408-415.

Hodges, P. W., Mellor, R., Crossley, K., & Bennell, K. (2009). Pain induced by injection of hypertonic saline into the infrapatellar fat pad and effect on coordination of the quadriceps muscles. *Arthritis and Rheumatism, 61*(1), 70-77.

Hunter, D. J., Zhang, Y. Q., Tu, X., Lavalley, M., Niu, J. B.et al. . (2006). Change in joint space width: Hyaline articular cartilage loss or alteration in meniscus? *Arthritis and Rheumatism, 54*(8), 2488-2495.

Hurwitz, D. E., Ryals, A. R., Block, J. A., Sharma, L., Schnitzer, T. J., & Andriacchi, T. P. (2000). Knee pain and joint loading in subjects with osteoarthritis of the knee. *Journal of Orthopaedic Research : Official Publication of the Orthopaedic Research Society, 18*(4), 572-579.

Hurwitz, D. E., Sumner, D. R., Andriacchi, T. P., & Sugar, D. A. (1998). Dynamic knee loads during gait predict proximal tibial bone distribution. *Journal of Biomechanics, 31*(5), 423-430.

Ikenoue, T., Trindade, M. C., Lee, M. S., Lin, E. Y., Schurman, D. J.et al. . (2003). Mechanoregulation of human articular chondrocyte aggrecan and type II collagen expression by intermittent hydrostatic pressure in vitro. *Journal of Orthopaedic Research : Official Publication of the Orthopaedic Research Society, 21*(1), 110-116.

Jones, R. K., Zhang, M., Laxton, P., Findlow, A. H., & Liu, A. (2013). The biomechanical effects of a new design of lateral wedge insole on the knee and ankle during walking. *Human Movement Science, 32*(4), 596-604.

Kakihana, W., Akai, M., Yamasaki, N., Takashima, T., & Nakazawa, K. (2004). Changes of joint moments in the gait of normal subjects wearing laterally wedged insoles. *American Journal of Physical Medicine & Rehabilitation / Association of Academic Physiatrists, 83*(4), 273-278.

Kakihana, W., Torii, S., Akai, M., Nakazawa, K., Fukano, M., & Naito, K. (2005). Effect of a lateral wedge on joint moments during gait in subjects with recurrent ankle sprain. *American Journal of Physical Medicine & Rehabilitation / Association of Academic Physiatrists, 84*(11), 858-864.

Kaufman, K. R., Hughes, C., Morrey, B. F., Morrey, M., & An, K. N. (2001). Gait characteristics of patients with knee osteoarthritis. *Journal of Biomechanics, 34*(7), 907-915.

Kean, C. O., Hinman, R. S., Bowles, K. A., Cicuttini, F., Davies-Tuck, M., & Bennell, K. L. (2012). Comparison of peak knee adduction moment and knee adduction moment impulse in distinguishing between severities of knee osteoarthritis. *Clinical Biomechanics (Bristol, Avon), 27*(5), 520-523.

Kerrigan, D. C., Lelas, J. L., Goggins, J., Merriman, G. J., Kaplan, R. J., & Felson, D. T. (2002). Effectiveness of a lateral-wedge insole on knee varus torque in patients with knee osteoarthritis. *Archives of Physical Medicine and Rehabilitation, 83*(7), 889-893.

Koo, S., & Andriacchi, T. P. (2007). A comparison of the influence of global functional loads vs. local contact anatomy on articular cartilage thickness at the knee. *Journal of Biomechanics, 40*(0021-9290; 13), 2961-2966.

Kuroyanagi, Y., Nagura, T., Matsumoto, H., Otani, T., Suda, Y.et al. . (2007). The lateral wedged insole with subtalar strapping significantly reduces dynamic knee load in the medial compartment gait analysis on patients with medial knee osteoarthritis. *Osteoarthritis and Cartilage / OARS, Osteoarthritis Research Society, 15*(1063-4584; 8), 932-936.

Kutzner, I., Damm, P., Heinlein, B., Dymke, J., Graichen, F., & Bergmann, G. (2011). The effect of laterally wedged shoes on the loading of the medial knee compartment-in vivo measurements with instrumented knee implants. *Journal of Orthopaedic Research, 29*(12), 1910-1915.

Latash, M. L., Gorniak, S., & Zatsiorsky, V. M. (2008). Hierarchies of synergies in human movements. *Kinesiology (Zagreb, Croatia), 40*(1), 29-38.

Lewek, M. D., Rudolph, K. S., & Snyder-Mackler, L. (2004). Control of frontal plane knee laxity during gait in patients with medial compartment knee osteoarthritis. *Osteoarthritis and Cartilage / OARS, Osteoarthritis Research Society, 12*(9), 745-751.

Lim, B., Hinman, R. S., Wrigley, T. V., Sharma, L., & Bennell, K. L. (2008). Does knee malalignment mediate the effects of quadriceps strengthening on knee adduction moment, pain, and function in medial knee osteoarthritis? A randomized controlled trial. *Arthritis Care & Research, 59*(7), 943-951.

Lin, C. J., Lai, K. A., Chou, Y. L., & Ho, C. S. (2001). The effect of changing the foot progression angle on the knee adduction moment in normal teenagers. *Gait & Posture, 14*(2), 85-91.

Maly, M. R., Culham, E. G., & Costigan, P. A. (2002). Static and dynamic biomechanics of foot orthoses in people with medial compartment knee osteoarthritis. *Clin.Biomech.(Bristol., Avon.), 17*(8), 603-610.

Manal, K., McClay, I., Stanhope, S., Richards, J., & Galinat, B. (2000). Comparison of surface mounted markers and attachment methods in estimating tibial rotations during walking: An in vivo study. *Gait & Posture, 11*(1), 38-45.

McAlindon, T. E., Bannuru, R. R., Sullivan, M. C., Arden, N. K., Berenbaum, F.et al. . (2014). OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis and Cartilage / OARS, Osteoarthritis Research Society, 22*(3), 363-388.

Meyer, A. J., D'Lima, D. D., Besier, T. F., Lloyd, D. G., Colwell, C. W., & Fregly, B. J. (2013). Are external knee load and EMG measures accurate indicators of internal knee contact forces during gait? *Journal of Orthopaedic Research, 31*(6), 921-929.

Miyazaki, T., Wada, M., Kawahara, H., Sato, M., Baba, H., & Shimada, S. (2002). Dynamic load at baseline can predict radiographic disease progression in medial compartment knee osteoarthritis. *Annals of the Rheumatic Diseases, 61*(7), 617-622.

Molgaard, C. M., Graven-Nielsen, T., Simonsen, O., & Kersting, U. G. (2014). Potential interaction of experimental knee pain and laterally wedged insoles for knee off-loading during walking. *Clinical Biomechanics (Bristol, Avon), 29*(8), 848-854.

Mundermann, A., Dyrby, C. O., & Andriacchi, T. P. (2005). Secondary gait changes in patients with medial compartment knee osteoarthritis: Increased load at the ankle, knee, and hip during walking. *Arthritis and Rheumatism, 52*(9), 2835-2844.

Neogi, T. (2013). The epidemiology and impact of pain in osteoarthritis. *Osteoarthritis and Cartilage / OARS, Osteoarthritis Research Society, 21*(9), 1145-1153.

Netravali, N. A., Giori, N. J., & Andriacchi, T. P. (2010). Partial medial meniscectomy and rotational differences at the knee during walking. *Journal of Biomechanics, 43*(15), 2948-2953.

Netravali, N. A., Koo, S., Giori, N. J., & Andriacchi, T. P. (2011). The effect of kinematic and kinetic changes on meniscal strains during gait. *Journal of Biomechanical Engineering, 133*(1), 011006.

Nguyen, U. S., Zhang, Y., Zhu, Y., Niu, J., Zhang, B., & Felson, D. T. (2011). Increasing prevalence of knee pain and symptomatic knee osteoarthritis: Survey and cohort data. *Annals of Internal Medicine, 155*(11), 725-732.

Niehoff, A., Kersting, U. G., Helling, S., Dargel, J., Maurer, J.et al. . (2010). Different mechanical loading protocols influence serum cartilage oligomeric matrix protein levels in young healthy humans. *European Journal of Applied Physiology, 110*(3), 651-657.

Noble, J., & Hamblen, D. L. (1975). The pathology of the degenerate meniscus lesion. *The Journal of Bone and Joint Surgery.British Volume, 57*(2), 180-186.

Ogata, K., Yasunaga, M., & Nomiyama, H. (1997). The effect of wedged insoles on the thrust of osteoarthritic knees. *International Orthopaedics, 21*(5), 308-312.

Oiestad, B. E., Engebretsen, L., Storheim, K., & Risberg, M. A. (2009). Knee osteoarthritis after anterior cruciate ligament injury: A systematic review. *The American Journal of Sports Medicine, 37*(7), 1434-1443.

O'Reilly, S. C., & Doherty, M. (2003). Signs, symptoms and laboratory tests in osteoarthritis. In K. D. Brandt, M. Doherty & L. S. Lohmander (Eds.), *Osteoarthritis* (2nd ed., pp. 197-210). Oxford UK: Oxford University Press.

Papalia, R., Del Buono, A., Osti, L., Denaro, V., & Maffulli, N. (2011). Meniscectomy as a risk factor for knee osteoarthritis: A systematic review. *British Medical Bulletin,*

Petersen, M. M., Olsen, C., Lauritzen, J. B., Lund, B., & Hede, A. (1996). Late changes in bone mineral density of the proximal tibia following total or partial medial meniscectomy. A randomized study. *Journal of Orthopaedic Research : Official Publication of the Orthopaedic Research Society, 14*(1), 16-21.

Pham, T., Maillefert, J. F., Hudry, C., Kieffert, P., Bourgeois, P.et al. . (2004). Laterally elevated wedged insoles in the treatment of medial knee osteoarthritis. A two-year prospective randomized controlled study. *Osteoarthritis and Cartilage / OARS, Osteoarthritis Research Society, 12*(1), 46-55.

Piazza, S. J., & Cavanagh, P. R. (2000). Measurement of the screw-home motion of the knee is sensitive to errors in axis alignment. *Journal of Biomechanics, 33*(8), 1029-1034.

Poehling, G. G., Ruch, D. S., & Chabon, S. J. (1990). The landscape of meniscal injuries. *Clinics in Sports Medicine, 9*(3), 539-549.

Radin, E. L., Burr, D. B., Caterson, B., Fyhrie, D., Brown, T. D., & Boyd, R. D. (1991). Mechanical determinants of osteoarthrosis. *Seminars in Arthritis and Rheumatism, 21*(3 Suppl 2), 12-21.

Raja, K., & Dewan, N. (2011). Efficacy of knee braces and foot orthoses in conservative management of knee osteoarthritis: A systematic review. *American Journal of Physical Medicine & Rehabilitation / Association of Academic Physiatrists, 90*(3), 247-262.

Ramsey, D. K., & Wretenberg, P. F. (1999). Biomechanics of the knee: Methodological considerations in the in vivo kinematic analysis of the tibiofemoral and patellofemoral joint. *Clinical Biomechanics (Bristol, Avon), 14*(9), 595-611.

Redmond, A. C., Crane, Y. Z., & Menz, H. B. (2008). Normative values for the foot posture index. *Journal of Foot and Ankle Research, 1*(1), 6-1146-1-6.

Redmond, A. C., Crosbie, J., & Ouvrier, R. A. (2006). Development and validation of a novel rating system for scoring standing foot posture: The foot posture index. *Clinical Biomechanics (Bristol, Avon), 21*(1), 89-98.

Reinschmidt, C., van Den Bogert, A. J., Murphy, N., Lundberg, A., & Nigg, B. M. (1997). Tibiocalcaneal motion during running, measured with external and bone markers. *Clinical Biomechanics (Bristol, Avon), 12*(1), 8-16.

Roemer, F. W., Zhang, Y., Niu, J., Lynch, J. A., Crema, M. D.et al. . (2009). Tibiofemoral joint osteoarthritis: Risk factors for MR-depicted fast cartilage loss over a 30-month period in the multicenter osteoarthritis study. *Radiology, 252*(3), 772-780.

Roos, E. M., Roos, H. P., Lohmander, L. S., Ekdahl, C., & Beynnon, B. D. (1998). Knee injury and osteoarthritis outcome score (KOOS)--development of a self-administered outcome measure. *The Journal of Orthopaedic and Sports Physical Therapy, 28*(2), 88-96.

Rutherford, D. J., Hubley-Kozey, C. L., & Stanish, W. D. (2010). The neuromuscular demands of altering foot progression angle during gait in asymptomatic individuals and those with knee osteoarthritis. *Osteoarthritis and Cartilage / OARS, Osteoarthritis Research Society, 18*(5), 654-661.

Rutherford, D. J., Hubley-Kozey, C. L., & Stanish, W. D. (2012). Knee effusion affects knee mechanics and muscle activity during gait in individuals with knee osteoarthritis. *Osteoarthritis and Cartilage / OARS, Osteoarthritis Research Society, 20*(9), 974-981.

Schache, A. G., Baker, R., & Vaughan, C. L. (2007). Differences in lower limb transverse plane joint moments during gait when expressed in two alternative reference frames. *Journal of Biomechanics, 40*(1), 9-19.

Schipplein, O. D., & Andriacchi, T. P. (1991). Interaction between active and passive knee stabilizers during level walking. *Journal of Orthopaedic Research : Official Publication of the Orthopaedic Research Society, 9*(0736-0266; 1), 113-119.

Schnitzer, T. J., Popovich, J. M., Andersson, G. B., & Andriacchi, T. P. (1993). Effect of piroxicam on gait in patients with osteoarthritis of the knee. *Arthritis and Rheumatism, 36*(9), 1207-1213.

Sharma, L., Kapoor, D., & Issa, S. (2006). Epidemiology of osteoarthritis: An update. *Current Opinion in Rheumatology, 18*(2), 147-156.

Sharma, L., Song, J., Felson, D. T., Cahue, S., Shamiyeh, E., & Dunlop, D. D. (2001). The role of knee alignment in disease progression and functional decline in knee osteoarthritis. *JAMA : The Journal of the American Medical Association, 286*(0098-7484; 2), 188-195.

Shimada, S., Kobayashi, S., Wada, M., Uchida, K., Sasaki, S.et al. . (2006). Effects of disease severity on response to lateral wedged shoe insole for medial compartment knee osteoarthritis. *Archives of Physical Medicine and Rehabilitation, 87*(11), 1436-1441.

Sihvonen, R., Paavola, M., Malmivaara, A., Itala, A., Joukainen, A.et al. . (2013). Arthroscopic partial meniscectomy versus sham surgery for a degenerative meniscal tear. *The New England Journal of Medicine, 369*(26), 2515-2524.

Skou, S. T., Hojgaard, L., & Simonsen, O. H. (2013). Customized foot insoles have a positive effect on pain, function, and quality of life in patients with medial knee osteoarthritis. *Journal of the American Podiatric Medical Association, 103*(1), 50-55.

Smith, R. L., Donlon, B. S., Gupta, M. K., Mohtai, M., Das, P.et al. . (1995). Effects of fluid-induced shear on articular chondrocyte morphology and metabolism in vitro. *Journal of Orthopaedic Research : Official Publication of the Orthopaedic Research Society, 13*(6), 824-831.

Soltz, M. A., & Ateshian, G. A. (1998). Experimental verification and theoretical prediction of cartilage interstitial fluid pressurization at an impermeable contact interface in confined compression. *Journal of Biomechanics, 31*(10), 927-934.

Song, Y., Greve, J. M., Carter, D. R., & Giori, N. J. (2008). Meniscectomy alters the dynamic deformational behavior and cumulative strain of tibial articular cartilage in knee joints subjected to cyclic loads. *Osteoarthritis and Cartilage / OARS, Osteoarthritis Research Society, 16*(12), 1545-1554.

Sritharan, P., Lin, Y. C., & Pandy, M. G. (2012). Muscles that do not cross the knee contribute to the knee adduction moment and tibiofemoral compartment loading during gait. *Journal of Orthopaedic Research : Official Publication of the Orthopaedic Research Society, 30*(10), 1586-1595.

Sturnieks, D. L., Besier, T. F., Mills, P. M., Ackland, T. R., Maguire, K. F.et al. . (2008). Knee joint biomechanics following arthroscopic partial meniscectomy. *Journal of Orthopaedic Research : Official Publication of the Orthopaedic Research Society, 26*(8), 1075-1080.

Subburaj, K., Kumar, D., Souza, R. B., Alizai, H., Li, X.et al. . (2012). The acute effect of running on knee articular cartilage and meniscus magnetic resonance relaxation times in young healthy adults. *The American Journal of Sports Medicine, 40*(9), 2134-2141.

Tanamas, S., Hanna, F. S., Cicuttini, F. M., Wluka, A. E., Berry, P., & Urquhart, D. M. (2009). Does knee malalignment increase the risk of development and progression of knee osteoarthritis? A systematic review. *Arthritis and Rheumatism, 61*(4), 459-467.

Thorlund, J. B., Hare, K. B., & Lohmander, L. S. (2014). Large increase in arthroscopic meniscus surgery in the middle-aged and older population in denmark from 2000 to 2011. *Acta Orthopaedica, 85*(3), 287-292.

Thorlund, J. B., Roos, E. M., & Aagaard, P. (2011). Neuromuscular function during stair descent in meniscectomized patients and controls. *Medicine and Science in Sports and Exercise, 43*(7), 1272-1279.

Toda, Y., Tsukimura, N., & Kato, A. (2004). The effects of different elevations of laterally wedged insoles with subtalar strapping on medial compartment osteoarthritis of the knee. *Archives of Physical Medicine and Rehabilitation, 85*(4), 673-677.

Urban, J. P. (2000). Present perspectives on cartilage and chondrocyte mechanobiology. *Biorheology, 37*(1-2), 185-190.

Valderrabano, V., Horisberger, M., Russell, I., Dougall, H., & Hintermann, B. (2009). Etiology of ankle osteoarthritis. *Clinical Orthopaedics and Related Research, 467*(7), 1800-1806.

van Raaij, T. M., Reijman, M., Brouwer, R. W., Bierma-Zeinstra, S. M., & Verhaar, J. A. (2010). Medial knee osteoarthritis treated by insoles or braces: A randomized trial. *Clinical Orthopaedics and Related Research, 468*(7), 1926-1932.

Walter, J. P., D'Lima, D. D., Colwell, C. W.,Jr, & Fregly, B. J. (2010). Decreased knee adduction moment does not guarantee decreased medial contact force during gait. *Journal of Orthopaedic Research : Official Publication of the Orthopaedic Research Society, 28*(10), 1348-1354.

Wilson, D. R., McWalter, E. J., & Johnston, J. D. (2013). The measurement of joint mechanics and their role in osteoarthritis genesis and progression. *Rheumatic Diseases Clinics of North America, 39*(1), 21-44.

Winter, D. A. (2009). *Biomechanics and motor control of human movement* Hoboken, N.J. : John Wiley.

Yasuda, K., & Sasaki, T. (1987). The mechanics of treatment of the osteoarthritic knee with a wedged insole. *Clinical Orthopaedics and Related Research, (215)*(215), 162-172.

Zhang, W., Doherty, M., Peat, G., Bierma-Zeinstra, M. A., Arden, N. K.et al. . (2010a). EULAR evidence-based recommendations for the diagnosis of knee osteoarthritis. *Annals of the Rheumatic Diseases, 69*(3), 483-489.

Zhang, Y., & Jordan, J. M. (2010b). Epidemiology of osteoarthritis. *Clinics in Geriatric Medicine, 26*(3), 355-369.

Zhao, D., Banks, S. A., Mitchell, K. H., D'Lima, D. D., Colwell, C. W.,Jr, & Fregly, B. J. (2007). Correlation between the knee adduction torque and medial contact force for a variety of gait patterns. *Journal of Orthopaedic Research : Official Publication of the Orthopaedic Research Society, 25*(6), 789-797.

SUMMARY

Numerous biomechanical studies have provided evidence that laterally wedged insoles reduce the knee adduction moment during walking in healthy controls as well as patients with knee osteoarthritis potentially reducing the contact stress of medial tibial and femoral condyles. The knee adduction moment has been recognized as a suitable biomechanical marker for progression of knee osteoarthritis. However, recent clinical trials have not been able to confirm this potentially favourable effect. With the increasing prevalence of knee osteoarthritis and knee replacement surgery the demand for early conservative treatment modalities also increases.

The aim of this thesis was to 1) identify relationships between footwear and laterally wedged insoles in a healthy group, 2) to evaluate the mechanical and physiological factors of experimental pain when introducing a laterally wedged insoles to otherwise healthy subjects, and 3) to identify the acute effect of laterally wedged insoles on biomechanical markers in patients after an medial arthroscopic partial meniscectomy.

The results showed that shoe design and lateral wedges are equally important factors for changing the knee adduction moment, but the shoe designs tested did however not further improve or reduce the effect of lateral wedges. Second, experimental knee pain did not mediate the effect of lateral wedges in fact experimental knee pain has a larger impact on knee extension moment than knee adduction moment. Medial arthroscopic partial meniscectomy significantly increased the knee adduction moment 3-5 years postoperatively in an otherwise active group of patients when compared to a matched healthy group of people. Finally, lateral wedges can decrease knee adduction moment in medial arthroscopic partial meniscectomy patients, however not to the level of healthy matched controls.

In conclusion, although similar reductions can be achieved by choice of shoe design the difference between a neutral running shoe and Oxford leather shoes are similar in magnitude compared to the effect of lateral wedges in any type of shoe. Experimental pain does not seem to change the effect of lateral wedges independently. The knee adduction moment in patients 3-5 years after a medial arthroscopic partial meniscectomy was at a similar level to what is observed with advanced knee osteoarthritis. Therefore, laterally wedged insoles should be considered part of the mechanical solution to the increased risk of progression of knee osteoarthritis in this patient group.

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