University of Porto

Faculty of Sport

The effects of application of lateral wedge insoles on medial osteoarthritis of the knee

Dissertation submitted in fulfilment of the requirements for the degree of Doctor in Physiotherapy by the Faculty of Sport of the University of Porto, under the Law 74/2006 from March 24th.

Thesis prepared under the supervision of:

Professor Doutor Paulo Jorge Roriz (supervisor)
Institute University of Maia, Maia, Portugal

Professor Doutor Leandro José Rodrigues Machado (co-supervisor)
Faculty of Sport, University of Porto, Portugal

Vitor Manuel Fontes Ferreira

Porto, 2020

Ferreira, V. (2020). The effects of application of lateral wedge insoles on medial osteoarthritis of the knee. Doctorate dissertation in Physiotherapy, presented at the Faculty of Sport, University of Porto.

KEYWORDS: INSOLES; EXTERNAL KNEE ADDUCTION MOMENT; BIOMECHANICS; GAIT; PHYSICAL FUNCTION.

Acknowledgments

I would like to acknowledge several people without whom this thesis would not have been possible:

My supervisor, Professor Paulo Roriz, for his continuous support throughout the project, for giving me the energy and motivation, his expertise in scientific aspects and encouragement for scientific production.

My co-supervisor, Professor Leandro Machado, for sharing his knowledge on human biomechanics.

All patients who participated in the developed studies, essential in the course of this process, my thanks!

The Faculty of Sport of the University of Porto. It has been a privilege to use their research facilities, namely resources available at the Porto Biomechanics Laboratory (LABIOMEP).

I owe a special thanks to Eng. Pedro Fonseca, particularly, for his help in preparing the data collection.

My parents, António and Fernanda, for the sacrifice they made to get me here. I'm in debt to you.

To my remaining family, my sister Eunice, my brothers in law Ana, Mónica, Nuno, Ricardo, Tiago, my nephews Diogo, David, Santiago, Sofia, Rodrigo, and my father in law Diamantino. Thank you! I will never forget your friendship and constant support!

My children, Gonçalo and Nuno. You are undoubtedly my main motivation for never giving up.

Finally, I would like to give special thanks to my life partner, Rita, for providing me everything I needed to complete this journey.

List of publications

Publications in Peer-Reviewed Journals

Ferreira, V., Simões, R., Gonçalves, R.S., Machado, L., Roriz, P.. The optimal degree of lateral wedge insoles for reducing knee joint load: a systematic review and meta-analysis. Arch Physiother 9, 18 (2019). doi:10.1186/s40945-019-0068-1.

Ferreira, V., Machado, L., Roriz, P.. The effects on lower limbs kinematics of different lateral wedge insoles. Journal of Mechanical Engineering and Biomechanics, Vol. 4, Issue 4, Page 77-82, (2020).

Ferreira, V., Machado, L., Vilaça, A., Xará-Leite, F., Roriz, P.. Biomechanics performance in 30-s chair stand test in patients with medial knee osteoarthritis. Int. J. Human Factors and Ergonomics, Vol. 6, No. 4, (2019).

Ferreira, V., Machado, L., Vilaça, A., Xará-Leite, F., Roriz, P.. Biomechanical changes on patients with knee osteoarthritis due to slight variations on lateral wedge insoles (Submitted for publication).

Ferreira, V., Machado, L., Vilaça, A., Xará-Leite, F., Roriz, P.. Tailored lateral wedge insoles in medial knee osteoarthritis: 12 weeks randomised controlled trial (Submitted for publication).

Abstracts in Conference Proceedings

Ferreira, V., Machado, L., Roriz, P.. The biomechanical effects of lateral wedge insoles with different heights on the knee: a preliminary study. Abstract book of the 7th Portuguese Congress of Biomechanics, 10-11 February (2017). Guimarães, Portugal.

Ferreira, V., Machado, L., Roriz, P.. Análise da Repetibilidade do Momento Externo de Adução do Joelho Durante a Marcha. Abstract book of the X

Congresso Nacional Fisioterapeutas, 10-12 November (2017). pp 44. Aveiro, Portugal.

Ferreira, V., Machado, L., Roriz, P.. Efeitos Imediatos da Aplicação de Palmilhas em Cunha Lateral na Estática do Joelho. Abstract book of the X Congresso Nacional Fisioterapeutas, 10-12 November (2017). pp 80. Aveiro, Portugal.

Ferreira, V., Machado, L., Vilaça, A., Xará-Leite, F., Roriz, P.. Test–retest reliability of physical function tests in patients with knee osteoarthritis. Journal Motricidade; Volume 15; nº S1; pp 45, Sup. 2019 http://dx.doi.org/10.6063/motricidade.16967.

Ferreira, V., Machado, L., Vilaça, A., Xará-Leite, F., Roriz, P.. Center of pressure alterations with the application of lateral wedge insoles. Journal Motricidade; Volume 15; nº S1; pp 61, Sup. 2019 http://dx.doi.org/10.6063/motricidade.16967.

Ferreira, V., Machado, L., Vilaça, A., Xará-Leite, F., Roriz, P.. Spatiotemporal parameters of gait in patients with knee osteoarthritis. In Proceedings Health and Well-Being Intervention International Congress, 31 of May – 1 June (2019). Journal Work (In press). Viseu, Portugal.

Table of Contents

List of figures

List of tables

Resumo

As palmilhas com cunha lateral parecem melhorar o momento externo de adução do joelho, em indivíduos com osteoartrose medial do joelho. Esta tese procurou estudar as alterações biomecânicas e a eficácia do uso deste tipo de palmilhas. Foram realizados cinco estudos. Três estudos (estudo II, IV e V), procuraram entender os efeitos deste tipo de palmilhas na biomecânica e nos resultados clínicos. Vinte e três participantes saudáveis (estudo II) e trinta e oito participantes com osteoartrose medial do joelho foram recrutados (estudo III, IV e V). Foi usado um sistema tridimensional de captura de movimento juntamente com plataformas de força para a recolha dos dados. Uma revisão sistemática com meta-análise (estudo I) sugere que uma cunha mais elevada (> 9 graus) não é mais eficaz do que uma cunha mais baixa (≤ 9 graus). Um estudo distinto (estudo III), que analisou o desempenho dos participantes no teste de 30 segundos sentar-levantar, verificou que estes, não apresentavam diferenças biomecânicas significativas durante o teste, entre o joelho mais e menos doloroso. Foram testadas seis palmilhas com cunha lateral, com pequenas variações na angulação (2 graus). Verificou-se que estas induzem efeitos imediatos, de forma incremental, no plano frontal do pé e joelho (estudo II e IV). Por outro lado, o uso continuado de palmilhas personalizadas pela análise biomecânica, durante 12 semanas, não se mostrou eficaz em melhorar os resultados biomecânicos e clínicos, exceto nos sintomas, quando comparado com uma palmilha neutra (estudo V). O uso contínuo desse tipo de dispositivo carece de evidência mais robusta que apoie o seu uso em indivíduos com osteoartrose medial do joelho.

Palavras-chave: PALMILHAS; MOMENTO EXTERNO ADUÇÃO JOELHO; BIOMECÂNICA; MARCHA; FUNÇÃO FÍSICA.

Abstract

The lateral wedge insoles seem to improve the external moment of knee adduction in individuals with medial knee osteoarthritis. This thesis sought to study the biomechanical changes and the effectiveness of using this type of insoles. Five studies were carried out. Three studies (study II, IV and V), sought to understand the effects of this type of insoles on biomechanics and clinical results. Twenty-three healthy participants (study II) and thirty-eight participants with medial knee osteoarthritis were recruited (study III, IV and V). A three-dimensional motion capture system was used together with force platforms for data collection. A systematic review with meta-analysis (study I) suggests that higher wedges (> 9 degrees) are not more effective than lower wedges (≤ 9 degrees). A distinct study (study III), which analysed the participants' performance in the 30-second chair stand test, found that they did not present significant biomechanical differences during the test, between the most and least painful knee. Six lateral wedge insoles with slight variations (2 degrees) were tested. It was found that they induce immediate effects incrementally in the frontal plane of the foot and knee (study II and IV). On the other hand, the continuous use of personalized insoles by biomechanical analysis, for 12 weeks, was not effective in improving biomechanical and clinical outcomes, except in symptoms, when compared with a neutral insole (study V). The continuous use of this type of device needs more robust evidence to support its use in individuals with medial knee osteoarthritis.

Key words: INSOLES; EXTERNAL KNEE ADDUCTION MOMENT; BIOMECHANICS; GAIT; PHYSICAL FUNCTION

List of abbreviations and symbols

12-step SCT	12-step Stair Climb Test
30s-CST	30 second Chair Stand Test
40m FPWT	40 meters Fast Paced Walk Test
ADL	Activities of daily living
CAST	Calibrated anatomical system technique
CI	Confidence interval
CoP	Center of pressure
EKAM	External knee adduction moment
GRF	Ground reaction force
ICC	Intraclass correlation coefficient
K/L scale	Kellgren and Lawrence grading scale
KAAI	Knee adduction angular impulse
KOOS	Knee injury Osteoarthritis Outcome Score
LABIOMEP	Porto Biomechanics Laboratory
MDC	Minimal detectable change
MCID	Minimal clinically important difference
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
QoL	Quality of life
SD	Standard deviation
SEM	Standard error of measurement
SMD	Standardized mean difference
VAS	Visual analogue scale
BMI	Body Mass Index
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

Chapter 1 – Thesis organisation

1.1 Rationale of the Thesis

Even though lateral wedge insoles are a generally accepted treatment modality for patients with knee osteoarthritis (OA), there are some research issues to explore, such as the effects of lateral wedge insoles in knee OA. This Thesis is focused on it and has been organized into five chapters. In **Chapter I** a general description of the organization of the thesis is defined, the main research question is posed, and the objectives are defined. **Chapter II** provided an introduction to knee OA and addresses the main clinical and biomechanical topics of the pathology. **Chapter III** is composed of five original studies, were developed the research problems to address the main research question of this Thesis. An integrated discussion of the main findings and overall limitations follows in **Chapter IV**. Finally, **Chapter V** outlines the main conclusions and implications for future research and clinical practice emanating from the studies which make up this Thesis. **Figure 1** provides a graphic presentation with the rationale of this Thesis.

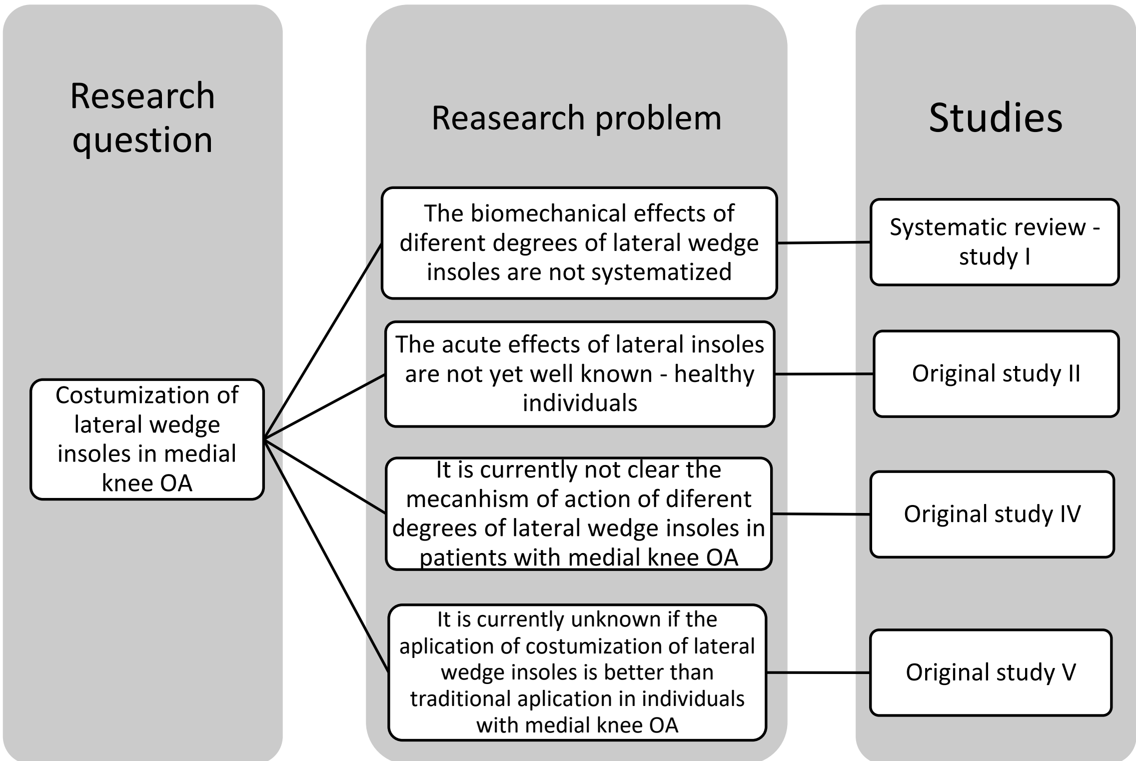


Figure 1. Graphic presentation explaining the rationale of this Thesis.

The main research question of this Thesis is developed in **Chapter III** and is linked to the customization of the application of lateral wedge insoles in individuals with knee OA. In theory, a prescription for insoles that considers biomechanical differences between individuals seems to be a valid approach for a more effective treatment. In the field of research of lateral wedge insoles, the critical issue for this customization will be the amount of the wedging degree. To summarize the existing evidence about the biomechanical effects of insoles with different angulations on medial knee OA the state-of-art is described in **Study I** by means of systematic review with meta-analysis. As the literature review suggested that the application of lateral wedge insoles is typically the same for all individuals, regardless of biomechanical aspects, a study was conducted in healthy individuals to understand the acute effects of different insoles (**Study II**). It gives an insight on the kinematics of lateral wedge insoles with slight differences (2 degrees) between them. Studying these effects in healthy individuals allows to eliminate potential adaptations caused by the pathology.

Understanding the mechanisms of action of insoles is an interesting challenge. **Study IV** is also a contribution for that purpose trying to understand more deeply the effects of slight variations on lateral wedge insoles in the biomechanics on the foot in patients with medial knee OA. Still within this research question, **Study V** sought to develop the main research problem of this thesis. To this end, individuals with medial knee OA were recruited to use voluntarily, lateral wedge insoles adjusted to knee biomechanics over a period of 12 weeks. The customization was done by the analysis of individual biomechanical acute effects, selecting for each participant the lower degree of wedge that promoted a reduction on the first peak of EKAM. Finally, and because in the treatment of patients with medial knee OA it is necessary to take into consideration not only the biomechanical features but also the clinical aspects, some complementary studies have been carried out which allowed to better understand other issues raised with the development of this thesis. **Study III** explores the biomechanics performance in the 30 second Chair Stand Test (30s-CST) in patients with medial knee OA. That study tried to appreciate the challenges that the test in question posed to patients with medial knee OA and

the strategies used in its execution. Other minor research problems are presented in the **Appendices** section and sought to respond to the challenges that arose during the course of writing this Thesis.

Chapter 2 – Introduction

2.1 Osteoarthritis

The existence of osteoarthritis (OA) in man appears to be quite old. OA was found in the ‘‘Java man’’, one of our earliest known ancestors (500,000 years ago) (Talbott, 1964). Nowadays, OA is the most common form of arthritis and is one of the leading causes of disability in older adults (Jordan et al., 2003). The likelihood of developing osteoarthritis increases with age. It is also known that a majority of individuals over the age of 65 have radiographic and/or clinical evidence of OA (Goldring & Goldring, 2007). Epidemiological studies have revealed that there are both endogenous and exogenous risk factors for OA. The main factors associated with OA were obesity (Body Mass Index (BMI) >30), previous knee trauma, female gender, mechanical causes and aging (Blagojevic, Jinks, Jeffery, & Jordan, 2010; Grotle, Hagen, Natvig, Dahl, & Kvien, 2008; Silverwood et al., 2015). With the continued aging of the population and rising obesity rates, the prevalence of OA is estimated to increase 40% by 2025 (Woolf & Pfleger, 2003).

OA is characterized by degeneration of articular cartilage, limited intraarticular inflammation with synovitis, and changes in peri-articular and subchondral bone (Goldring & Goldring, 2007). Among the various structures making up the knee joint, the hyaline cartilage is the structure in which the disease begins and the target of the injurious stimulus that cause OA. Hyaline cartilage consists of 95% of extracellular matrix and the dynamic equilibrium between the continual, ongoing formation and breakdown of the cartilaginous matrix is regulated by an interplay of anabolic influences (e.g., insulin-like growth factors I and II) and catabolic influences (e.g., interleukin-1, tumor necrosis factor alpha, and proteinases) (Michael, Schluter-Brust, & Eysel, 2010). The causes of cartilage degeneration are still not well understood. Mechanical and enzymatic factors are thought to impair chondrocyte function and to damage the matrix (Michael et al., 2010). Chondrocytes can respond to direct biomechanical perturbation by upregulating synthetic activity or by increasing the production of inflammatory cytokines initiating an inflammatory process, often with chronic characteristics (Goldring & Goldring, 2007). An abnormal mechanical stress

applied to a joint can be converted into activated intracellular signals at the joint cells by mechanoreceptors located at the surface of joint cells (Berenbaum, 2013). These signals, may eventually, lead to the overexpression of inflammatory mediators when a certain threshold is reached. Likewise, the capacity of the chondrocyte to remodel and repair the cartilage extracellular matrix diminishes with age and this has been attributed, primarily, to a decrease in the anabolic capacity of these cells (Aigner, Haag, Martin, & Buckwalter, 2007). In addition to the potentially adverse effects of synovial inflammation on chondrocyte function, the synovial inflammatory products may also contribute to the symptoms of pain, which is one of the most common complaints of patients (Vos et al., 2012). These synovial products may be measured in the synovial fluid of patients with OA and may include inflammatory cytokines, chemokines, or other inflammatory mediators (Goldring & Otero, 2011). Although the normal joint may respond predictably to painful stimuli, there is often a poor correlation between apparent joint disease and perceived pain in chronic OA (Goldring & Goldring, 2007). This persistence of knee pain will have to be attributed more to synovial inflammation than to other structures such as cartilage as it is avascular and aneural (Scanzello & Goldring, 2012). Although they are not a source of pain, chondrocytes are decidedly responsive to mechanical stress (Goldring & Otero, 2011).

Of all the joints of the body, the hip and the knee are the most affected by arthritis. Similarly, they are also among the most prevalent global diseases having a greater number of years lived with disability (Vos et al., 2012). It is estimated that during a one-year period 25% of people over 55 years have a persistent episode of knee pain for at least one month (Peat, McCarney, & Croft, 2001; Turkiewicz et al., 2014) and it is more common in women than in men (Felson, 2006). At these ages, in addition to the persistent presence of pain, knee OA is associated with mild to moderate functional disability that affects about 10% of patients (Peat et al., 2001; Turkiewicz et al., 2014). In daily life the most common affected activities are climbing stairs, getting out of a chair and walking (Dobson et al., 2013). During walking, knee joint loading is associated with discomfort and has a substantial negative influence gait cycle. Changes on the gait pattern when

compared to controls have been reported frequently in individuals suffering from knee OA (Debi et al., 2009).

2.2 Gait biomechanics

Since most or almost all OA is caused partly by mechanically induced injury to joint tissues, alterations in gait biomechanics are particularly interesting to explain the progression of the disease (Felson, 2013). Mechanically, the entire lower extremity acts as an integrated kinetic chain; hence altered loading patterns at one level may have a profound impact on other levels (Block & Shakoor, 2010). The widely used indirect method to assess dynamic joint loading is laboratory gait analysis, which is non-invasive and highly reproducible (Andriacchi & Alexander, 2000). When walking the forces that cross the knee are not equally transmitted between the medial and lateral compartments. There is a predominance of forces in the medial compartment of the knee during the stance phase (Zhao et al., 2007). Understanding knee joint moments can support the knowledge of disease progression and provides a valid indication of the knee joint loads during walking (Birmingham, Hunt, Jones, Jenkyn, & Giffin, 2007; Hunt & Bennell, 2011).

The external knee adduction moment (EKAM) has become an important variable of interest in the study of knee joint loads in OA and it is related to the distribution of forces between the medial and lateral compartments. The EKAM is calculated as the product between the ground reaction force (GRF), generated by the foot-ground interaction and the perpendicular distance of this force vector, measured in the frontal plane from the knee center of rotation, also known as the lever arm of the GRF vector (Farrokhi, Voycheck, Tashman, & Fitzgerald, 2013). In a lower limb with neutral alignment, the GRF vector, during the stance phase of walking, commonly passes medial to the knee joint’s center of rotation, consequently creating an EKAM (**Figure 2**).

By passing medially to the knee joint center, the force vector creates an adduction moment that is thought to increase the medial compartment load (Kutzner, Trepczynski, Heller, & Bergmann, 2013). Subsequently, the higher the

EKAM the higher the knee adduction and its varus position, increasing OA severity (Foroughi, Smith, & Vanwanseele, 2009). This unequal distribution of forces may be the reason why the medial compartment in OA has a higher prevalence relative to the lateral compartment, particularly in men (Wise et al., 2012). Therefore, the EKAM is 50% greater in OA patients compared to a matched group (Kumar, Manal, & Rudolph, 2013).

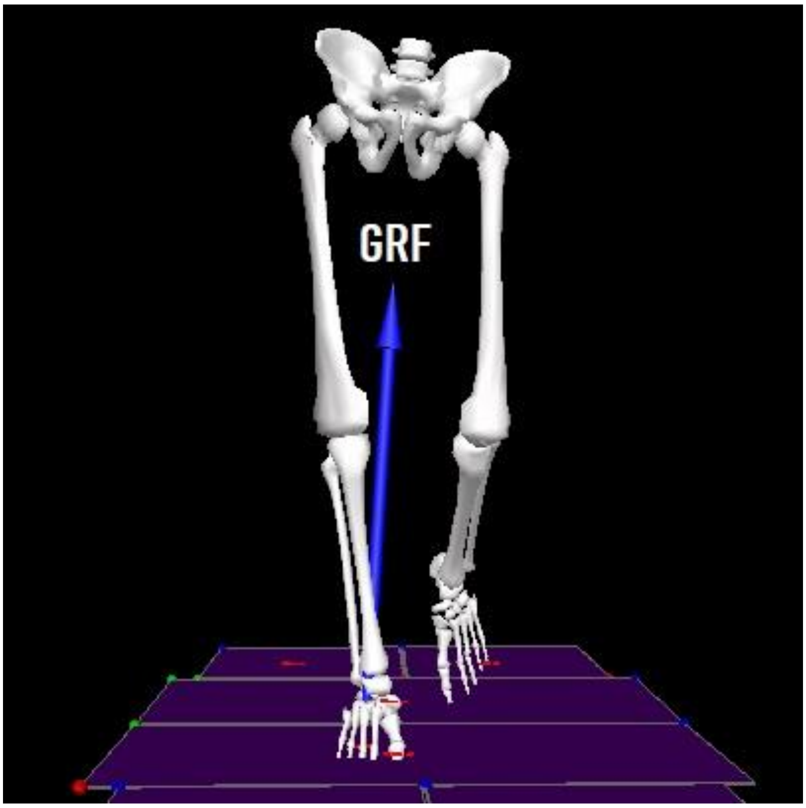


Figure 2. The GRF passing medial to knee center of rotation creates an EKAM that concentrates compressive forces on the medial tibiofemoral compartment (courtesy from Porto Biomechanics Laboratory - LABIOMEP).

Through the stance phase, the EKAM has classically two peaks: the first peak occurs during the load-acceptance phase of gait (15%–30% of the stance phase) and the second peak occurring in late stance (70%–80% of the stance phase) (Kutzner et al., 2013) (**Figure 3**). The first peak, which is also the higher, has a high correlation with radiographic disease severity (Kutzner et al., 2013). In the study of Miyazaki et al. (2002) was observed that the risk of progression of

knee OA increased 6.5 times with a 1% increase in the first peak of EKAM (Miyazaki et al., 2002). This biomechanical parameter showed an excellent reproducibility between two gait analysis sessions in patients with medial knee OA, with an intraclass correlation coefficient (ICC) of 0.86 (95% confidence interval (CI) 0.73; 0.96) (Birmingham et al., 2007).

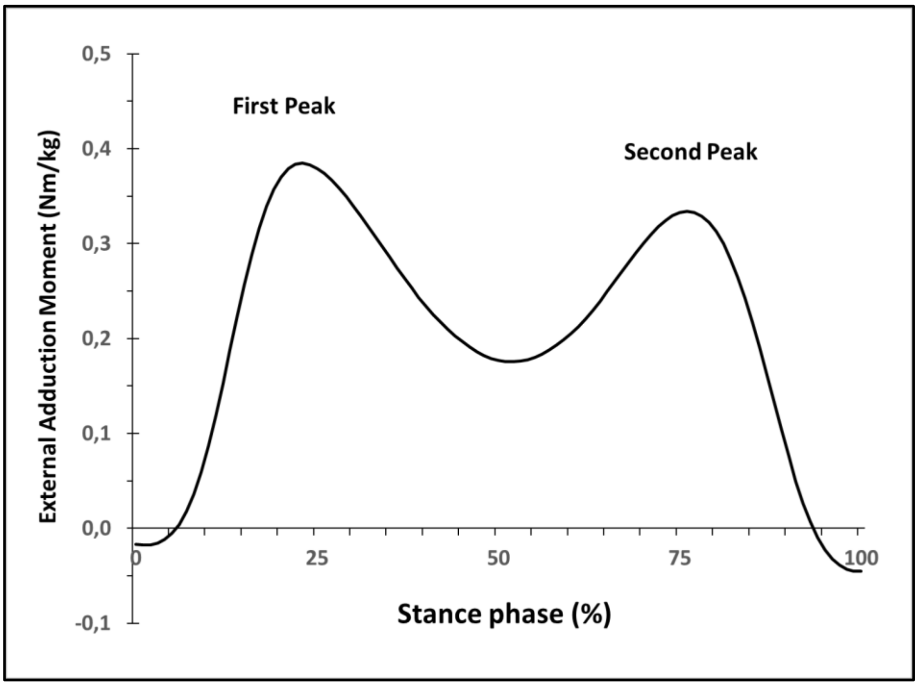


Figure 3. Schematic representation of the waveform of EKAM during the stance phase of gait. The EKAM exhibits 2 peaks: first peak of EKAM and second peak of EKAM.

The first peak of EKAM has become a primary measure in several studies to evaluate the effectiveness of several interventions with a common goal: reducing the EKAM (Kang, Lee, & Zhang, 2014; Shull et al., 2013; Simic, Hinman, Wrigley, Bennell, & Hunt, 2011; Simic, Wrigley, Hinman, Hunt, & Bennell, 2013). Current clinical approaches for reducing the EKAM are primarily designed around the premise that GRF and its frontal plane lever arm are independent variables that can be manipulated through different interventions (Farrokhi et al., 2013). Therefore, strategies that could either limit the influence of the patient's body mass on the magnitude of GRF (eg, using a cane) (Kemp, Crossley, Wrigley, Metcalf, & Hinman, 2008) or decrease the acceleration of the patient's center of mass (eg, by reducing gait speed) (Mundermann, Dyrby, Hurwitz, Sharma, &

Andriacchi, 2004) could be effectively used to decrease the EKAM. Additionally, strategies to decrease the length EKAM lever arm in the frontal plane, through lower-limb realignment could also reduce the EKAM magnitude. Moving the GRF vector closer to the knee center of rotation by moving the center of pressure laterally through lateral wedge insoles could be effective in reducing the EKAM by shortening its frontal plane lever arm (Butler, Marchesi, Royer, & Davis, 2007; Lewinson et al., 2014).

2.3 Malalignment of the knee

Malalignment (valgus or varus) of the knee is assumed to correlate with unicompartmental OA of the knee (Janakiramanan et al., 2008). However, it is still unknown whether malalignment precedes the development of radiographic OA, whether malalignment is a result of OA, or (probably more likely) whether the relationship between malalignment and OA is bidirectional (Brouwer et al., 2007). Although, this malalignment of the knee leads to an increase in the imbalance of forces between the two articular compartments, putting more pressure on already fragile tissues. Knee static alignment is usually assessed with a single anteroposterior radiograph. The gold standard for assessment is the weight-bearing full-leg radiograph, which allows the mechanical axis of the lower limb to be determined, with the angle formed with the hip, knee and ankle joint centers in the frontal plane (Zampogna et al., 2015).

In a previous study, varus and valgus malalignment of the knee have been shown to increase the risk of knee OA progression (Brouwer et al., 2007). The varus alignment increases the risk of medial OA progression while valgus alignment increases the risk of lateral OA progression (Sharma et al., 2001). Likewise, having malalignment of more than 5º (in either directions) and in both knees was associated with significantly greater functional deterioration (Sharma et al., 2001). On the other hand, varum alignment presents a higher risk of knee osteoarthritis incidence (Sharma et al., 2010). This increased risk was especially seen in overweight and obese individuals (Brouwer et al., 2007). In theory,

augmented knee varus can lead to acute increase of medial compartment load during the stance phase of gait and possibly accelerate structural damage. Results of previous studies showed knees with an observed varus malalignment with a greater first peak of EKAM (Hunt, Schache, Hinman, & Crossley, 2011; Williams & Isom, 2012). Results of previous studies suggested that interventions aimed at reducing dynamic malalignment might be effective in reducing medial compartment loading and establishing normal medio-lateral load sharing patterns (Kumar et al., 2013). Because the presence of static and dynamic malalignment is a likely cause of knee pain, treatment strategies for this type of phenotypes are necessary (Iijima et al., 2015).

2.4 Measurement of treatment outcomes

Measurement of treatment outcomes and change in health status, pain and physical function over time is a critical component of research and clinical practice for people with knee OA (Dobson et al., 2012). In recent years some measures have been developed for the assessment of symptoms and physical disability for patients with knee OA. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and the Knee injury Osteoarthritis Outcome Score (KOOS) are among the most used in scientific research.

KOOS is a tool based on the WOMAC (Bellamy, Buchanan, Goldsmith, Campbell, & Stitt, 1988) and includes additional items (Roos, Roos, & Lohmander, 1999). It has the advantage of being easily used to assess short and long-term consequences of primary OA and injuries of several knee structures that could lead to the development of secondary OA (Roos & Lohmander, 2003). In a review of the literature, KOOS was considered the most appropriate to assess health problems related with the knee joint, because of better reliability, validity and responsiveness (Garratt, Brealey, Gillespie, & Team, 2004). KOOS allows to assess health status in five dimensions: pain (9 items), other symptoms (7 items), function in daily living (ADL) (17 items), function in sport and recreation

(5 items), and knee-related quality of life (QoL) (4 items) (Roos, Roos, Lohmander, Ekdahl, & Beynnon, 1998).

Since pain is one of the most frequent symptoms in OA, the Visual Analogue Scale (VAS) is also commonly used in clinical trials as primary or secondary outcome. The VAS is a simple tool that assesses intensity of pain with a 100 mm long straight line, marked at each end with labels which anchor the scale (Williamson & Hoggart, 2005). Patients are asked to place a mark on the line at a point representing the severity of their pain with the extremes being “no pain at all” (0 mm) and “worst imaginable pain” (100 mm) (Hawker, Mian, Kendzerska, & French, 2011). The clinical interpretation of VAS has important limitations. Some authors have defined “optimal” cut points for pain classification, however it is not unanimously accepted (Hirschfeld & Zernikow, 2013). Particularly by the “ceiling and floor” effect (Reed & Van Nostran, 2014). Nevertheless, the most widely accepted interpretation boils down to a higher score corresponding to more intense pain (Hawker et al., 2011). The variability and imprecision inherent in VAS confounds extrapolation of findings from differing researches when applied to a global patient population (Reed & Van Nostran, 2014). Thus, a previous study has provided strong evidence that the VAS does not behave linearly and as a consequence should not be used as a primary measure or for power calculations (Kersten, White, & Tennant, 2014).

The degree of physical function impairment can be assessed using several tests. The minimal core set tests recommended by the Osteoarthritis Research Society International (OARSI) for people diagnosed with knee OA are: the 30 second Chair Stand Test (30s-CST); the Stair Climb Test (SCT) and 40 meters Fast Paced Walk Test (40m FPWT) (Dobson et al., 2013). A sit-to-stand movement, which is defined as a movement of standing up from a chair to an upright posture, is one of the most demanding daily activities in mechanical terms (Yoshioka, Nagano, Hay, & Fukashiro, 2009). The 30s-CST is an important functional evaluation clinical test for OA patients because it measures indirectly lower body strength and the corresponding performance in this important task of daily living (Nakatani, Nadamoto, Mimura, & Itoh, 2002). A previous study showed

that these patients in the 30s-CST had reduced energy absorption in the knee extensors, reduced knee extensor efficiency, and made greater use of physiological energy (Anan et al., 2015). However, further research in the analysis of this task is important in order to better understand the motor strategies used, that allow the development of new approaches in rehabilitation therapies to minimize the impact of the disease on the quality of life of these patients (**Figure 4**).

Figure 4. An example of a patient performing the 30 second Chair Stand Test (30s-CST).

2.5 Management of knee osteoarthritis

There is no cure for OA, and the first step for the non-surgical management of knee OA is conservative, predominantly focused on pain relief, minimizing functional disability, and limiting progression of structural joint changes (London, Miller, & Block, 2011). With various surgical and nonsurgical modalities of treatment being available, the course of treatment of a patient with knee OA largely depends on the disease severity. Pain is the major clinical symptom and a key determinant for seeking medical care. In this sense, the prescription of anti-inflammatory and analgesic medications, intra-articular hyaluronic acid and steroid injections, and arthroscopic lavage and debridement are often applied on a progressive ladder. However, these measures often fail, and their long-term

efficacy is poor (Davis & MacKay, 2013). Nevertheless, persistent use of analgesics and anti-inflammatories may even encourage a greater mechanical load because they mask the pain increasing the likelihood of accelerating disease progression (Henriksen et al., 2006). As the disease slowly progresses, cause moderate-to-severe pain and/or disability and total knee arthroplasty represents the end-stage treatment. There is a definitive treatment gap for the patients who are unresponsive to conservative care yet refuses to undergo or is not an appropriate candidate for invasive surgical procedures. This treatment gap, defined as the time from unsuccessful exhaustion of conservative treatment to surgical intervention, isn't a short period. In fact, it represents an extended period of years and often decades in which the patient experiences debilitating pain, reduced quality of life, and a significant financial problem. These typical treatment period can extend up to 20 years (London et al., 2011). Thus, there is great need for a safe and cost-effective treatment option for patients with moderate to severe OA that could enjoy high patient acceptance.

Treatments which correct the pathomechanics have long lasting favorable effects on pain and joint function compared with treatments that suppress inflammation which have only temporary effects (Felson, 2013). OARSI in a guideline update for the management of knee OA recommend the use of biomechanical interventions like braces, orthoses and lateral wedged insoles (McAlindon et al., 2014). Lateral wedges insoles are orthotic devices placed within the shoes intended to reduce significantly the biomechanical risk factors associated with knee OA (Arnold, Wong, Jones, Hill, & Thewlis, 2016). Because the elevation in the lateral region of the wedge (**Figure 5**), the main mechanism of action seems to be a reduction of the EKAM (Butler et al., 2007; Hinman, Payne, Metcalf, Wrigley, & Bennell, 2008; Kerrigan et al., 2002). These mechanical interventions might have the potential to decelerate the progression of OA over time redistributing the forces across articular surface in a more equitable manner. In a previous study of Jones et al., the application of a valgus knee brace and lateral wedged insoles significantly increased walking speed, reduced the first EKAM peak to 12%, and reduced the knee adduction angular impulse (KAAI) to 16% (Jones et al., 2013). Both treatments reduced the knee

loading, but lateral wedge insoles appear to have a greater effect, particularly with the level of acceptance by patients. A computer modeling simulation (Shelburne, Torry, Steadman, & Pandy, 2008) found for every 2.5% reduction in EKAM produced by lateral wedge insoles, a reduction of 1% of the knee medial compartment load. Also, a 3D finite element model demonstrated that 5 or 10 degrees lateral wedged insoles, significant decreases von Mises stress and contact force in the knee medial compartment comparing to 0 degree insoles (Liu & Zhang, 2013).

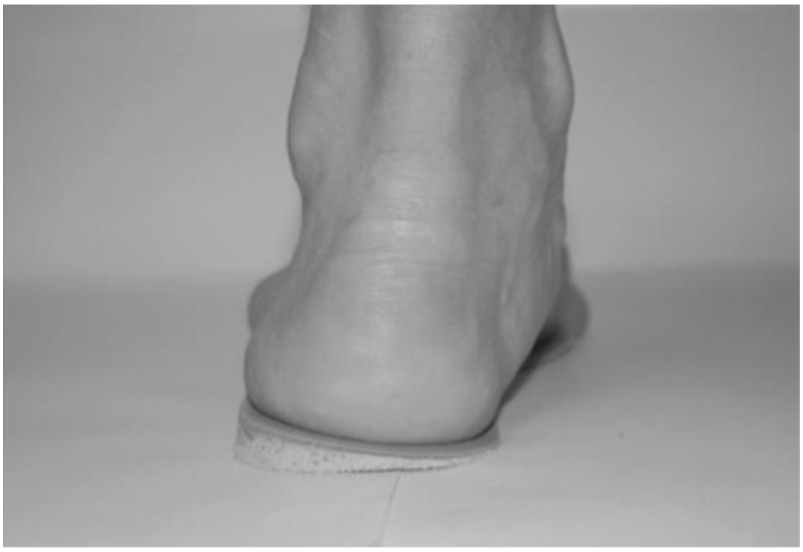


Figure 5. An example of a lateral wedge insole with 4-degree angle used in the present study.

Past research has demonstrated that lateral wedge insoles with different angulations decrease the EKAM in patients with medial knee OA (Baker et al., 2007; Butler et al., 2007; Hinman, Bowles, Metcalf, Wrigley, & Bennell, 2012; Hinman et al., 2008). However, individual's response to lateral wedge insoles seems to be quite variable. Some patients show an increase in EKAM (Hinman et al., 2012) and others show irrelevant changes in clinical measures like pain or physical function (Bennell et al., 2011). A previous meta-analysis suggests no significant change in pain in individuals with knee OA that have used lateral wedge insoles compared to neutral insoles (Parkes et al., 2013). Other meta-analysis did not show significant results in the biomechanical parameters (Arnold et al., 2016; Xing et al., 2017). The modest effect on reduction of EKAM and the

unsatisfactory effects in pain or physical function could be related to the variability in the degree of lateral wedge insoles used by the participants. The prescription of angulation in previous studies ranges from 4 (Fantini Pagani, Hinrichs, & Bruggemann, 2012) to 15 degrees (Barrios, Crenshaw, Royer, & Davis, 2009). However, most studies used the typical 5 or 6 degree wedging for all participants (Duivenvoorden et al., 2014; Hinman, Bowles, & Bennell, 2009; Jones, Chapman, Forsythe, Parkes, & Felson, 2014; Kakihana, Akai, Yamasaki, Takashima, & Nakazawa, 2004). This lack of customization to the individual's biomechanics may be a critical issue for an improvement in the knee OA with the use of lateral wedge insoles (Penny, Geere, & Smith, 2013). On the other hand, a link between biomechanics and clinical findings is an emerging issue. To the best of our knowledge, there are no known studies seeking to understand the application of tailored insoles based on biomechanical acute effects. Therefore, more research is needed to understand the effects of lateral wedge insoles based on biomechanical customization in patients with knee OA.

References

Aigner, T., Haag, J., Martin, J., & Buckwalter, J. (2007). Osteoarthritis: aging of matrix and cells--going for a remedy. *Curr Drug Targets, 8*(2), 325-331. doi:10.2174/138945007779940070

Anan, M., Shinkoda, K., Suzuki, K., Yagi, M., Ibara, T., & Kito, N. (2015). Do patients with knee osteoarthritis perform sit-to-stand motion efficiently? *Gait Posture, 41*(2), 488-492. doi:10.1016/j.gaitpost.2014.11.015

Andriacchi, T. P., & Alexander, E. J. (2000). Studies of human locomotion: past, present and future. *J Biomech, 33*(10), 1217-1224.

Arnold, J. B., Wong, D. X., Jones, R. K., Hill, C. L., & Thewlis, D. (2016). Lateral Wedge Insoles for Reducing Biomechanical Risk Factors for Medial Knee Osteoarthritis Progression: A Systematic Review and Meta-Analysis. *Arthritis Care Res (Hoboken), 68*(7), 936-951. doi:10.1002/acr.22797

Baker, K., Goggins, J., Xie, H., Szumowski, K., LaValley, M., Hunter, D. J., & Felson, D. T. (2007). A randomized crossover trial of a wedged insole for treatment of knee osteoarthritis. *Arthritis Rheum, 56*(4), 1198-1203. doi:10.1002/art.22516

Barrios, J. A., Crenshaw, J. R., Royer, T. D., & Davis, I. S. (2009). Walking shoes and laterally wedged orthoses in the clinical management of medial tibiofemoral osteoarthritis: a one-year prospective controlled trial. *Knee, 16*(2), 136-142. doi:10.1016/j.knee.2008.10.002

Bellamy, N., Buchanan, W. W., Goldsmith, C. H., Campbell, J., & Stitt, L. W. (1988). Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol, 15*(12), 1833-1840.

Bennell, K. L., Bowles, K. A., Payne, C., Cicuttini, F., Williamson, E., Forbes, A., . . . Hinman, R. S. (2011). Lateral wedge insoles for medial knee osteoarthritis: 12 month randomised controlled trial. *BMJ, 342*, d2912. doi:10.1136/bmj.d2912

Berenbaum, F. (2013). Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). *Osteoarthritis Cartilage, 21*(1), 16-21. doi:10.1016/j.joca.2012.11.012

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 Rheum, 57*(6), 1012-1017. doi:10.1002/art.22899

Blagojevic, M., Jinks, C., Jeffery, A., & Jordan, K. P. (2010). Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. *Osteoarthritis Cartilage, 18*(1), 24-33. doi:10.1016/j.joca.2009.08.010

Block, J. A., & Shakoor, N. (2010). Lower limb osteoarthritis: biomechanical alterations and implications for therapy. *Curr Opin Rheumatol, 22*(5), 544-550. doi:10.1097/BOR.0b013e32833bd81f

Brouwer, G. M., van Tol, A. W., Bergink, A. P., Belo, J. N., Bernsen, R. M., Reijman, M., . . . Bierma-Zeinstra, S. M. (2007). Association between valgus and varus alignment and the development and progression of radiographic osteoarthritis of the knee. *Arthritis Rheum, 56*(4), 1204-1211. doi:10.1002/art.22515

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. *J Orthop Res, 25*(9), 1121-1127. doi:10.1002/jor.20423

Davis, A. M., & MacKay, C. (2013). Osteoarthritis year in review: outcome of rehabilitation. *Osteoarthritis Cartilage, 21*(10), 1414-1424. doi:10.1016/j.joca.2013.08.013

Debi, R., Mor, A., Segal, O., Segal, G., Debbi, E., Agar, G., . . . Elbaz, A. (2009). Differences in gait patterns, pain, function and quality of life between males and females with knee osteoarthritis: a clinical trial. *BMC Musculoskelet Disord, 10*, 127. doi:10.1186/1471-2474-10-127

Dobson, F., Hinman, R. S., Hall, M., Terwee, C. B., Roos, E. M., & Bennell, K. L. (2012). Measurement properties of performance-based measures to assess physical function in hip and knee osteoarthritis: a systematic review. *Osteoarthritis Cartilage, 20*(12), 1548-1562. doi:10.1016/j.joca.2012.08.015

Dobson, F., Hinman, R. S., Roos, E. M., Abbott, J. H., Stratford, P., Davis, A. M., . . . Bennell, K. L. (2013). OARSI recommended performance-based tests to assess physical function in people diagnosed with hip or knee osteoarthritis. *Osteoarthritis Cartilage, 21*(8), 1042-1052. doi:10.1016/j.joca.2013.05.002

Duivenvoorden, T., van Raaij, T. M., Horemans, H. L., Brouwer, R. W., Bos, P. K., Bierma-Zeinstra, S. M., . . . Reijman, M. (2014). Do Laterally Wedged Insoles or Valgus Braces Unload the Medial Compartment of the Knee in Patients With Osteoarthritis? *Clin Orthop Relat Res*, 1-10. doi:10.1007/s11999-014-3947-5

Fantini Pagani, C. H., Hinrichs, M., & Bruggemann, G. P. (2012). Kinetic and kinematic changes with the use of valgus knee brace and lateral wedge insoles in patients with medial knee osteoarthritis. *J Orthop Res, 30*(7), 1125-1132. doi:10.1002/jor.22032

Farrokhi, S., Voycheck, C. A., Tashman, S., & Fitzgerald, G. K. (2013). A biomechanical perspective on physical therapy management of knee osteoarthritis. *J Orthop Sports Phys Ther, 43*(9), 600-619. doi:10.2519/jospt.2013.4121

Felson, D. T. (2006). Clinical practice. Osteoarthritis of the knee. *N Engl J Med, 354*(8), 841-848. doi:10.1056/NEJMcp051726

Felson, D. T. (2013). Osteoarthritis as a disease of mechanics. *Osteoarthritis Cartilage, 21*(1), 10-15. doi:10.1016/j.joca.2012.09.012

Foroughi, N., Smith, R., & Vanwanseele, B. (2009). The association of external knee adduction moment with biomechanical variables in osteoarthritis: a systematic review. *Knee, 16*(5), 303-309. doi:10.1016/j.knee.2008.12.007

Garratt, A. M., Brealey, S., Gillespie, W. J., & Team, D. T. (2004). Patient-assessed health instruments for the knee: a structured review. *Rheumatology (Oxford), 43*(11), 1414-1423. doi:10.1093/rheumatology/keh362

Goldring, M. B., & Goldring, S. R. (2007). Osteoarthritis. *J Cell Physiol, 213*(3), 626-634. doi:10.1002/jcp.21258

Goldring, M. B., & Otero, M. (2011). Inflammation in osteoarthritis. *Curr Opin Rheumatol, 23*(5), 471-478. doi:10.1097/BOR.0b013e328349c2b1

Grotle, M., Hagen, K. B., Natvig, B., Dahl, F. A., & Kvien, T. K. (2008). Obesity and osteoarthritis in knee, hip and/or hand: an epidemiological study in the general population with 10 years follow-up. *BMC Musculoskelet Disord, 9*, 132. doi:10.1186/1471-2474-9-132

Hawker, G. A., Mian, S., Kendzerska, T., & French, M. (2011). Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). *Arthritis Care Res (Hoboken), 63 Suppl 11*, S240-252. doi:10.1002/acr.20543

Henriksen, M., Simonsen, E. B., Alkjaer, T., Lund, H., Graven-Nielsen, T., Danneskiold-Samsoe, B., & Bliddal, H. (2006). Increased joint loads during walking--a consequence of pain relief in knee osteoarthritis. *Knee, 13*(6), 445-450. doi:10.1016/j.knee.2006.08.005

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 Musculoskelet Disord, 10*, 146. doi:10.1186/1471-2474-10-146

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. *Clin Biomech (Bristol, Avon), 27*(1), 27-33. doi:10.1016/j.clinbiomech.2011.07.010

Hinman, R. S., Payne, C., Metcalf, B. R., Wrigley, T. V., & Bennell, K. L. (2008). Lateral wedges in knee osteoarthritis: what are their immediate clinical and biomechanical effects and can these predict a three-month clinical outcome? *Arthritis Rheum, 59*(3), 408-415. doi:10.1002/art.23326

Hirschfeld, G., & Zernikow, B. (2013). Variability of "optimal" cut points for mild, moderate, and severe pain: neglected problems when comparing groups. *Pain, 154*(1), 154-159. doi:10.1016/j.pain.2012.10.008

Hunt, M. A., & Bennell, K. L. (2011). Predicting dynamic knee joint load with clinical measures in people with medial knee osteoarthritis. *Knee, 18*(4), 231-234. doi:10.1016/j.knee.2010.05.014

Hunt, M. A., Schache, A. G., Hinman, R. S., & Crossley, K. M. (2011). Varus thrust in medial knee osteoarthritis: quantification and effects of different gait-related interventions using a single case study. *Arthritis Care Res (Hoboken), 63*(2), 293-297. doi:10.1002/acr.20341

Iijima, H., Fukutani, N., Aoyama, T., Fukumoto, T., Uritani, D., Kaneda, E., . . . Matsuda, S. (2015). Clinical Phenotype Classifications Based on Static Varus Alignment and Varus Thrust in Japanese Patients With Medial Knee Osteoarthritis. *Arthritis Rheumatol, 67*(9), 2354-2362. doi:10.1002/art.39224

Janakiramanan, N., Teichtahl, A. J., Wluka, A. E., Ding, C., Jones, G., Davis, S. R., & Cicuttini, F. M. (2008). Static knee alignment is associated with the risk of unicompartmental knee cartilage defects. *J Orthop Res, 26*(2), 225-230. doi:10.1002/jor.20465

Jones, R. K., Chapman, G. J., Forsythe, L., Parkes, M. J., & Felson, D. T. (2014). The relationship between reductions in knee loading and immediate pain response whilst wearing lateral wedged insoles in knee osteoarthritis. *J Orthop Res, 32*(9), 1147-1154. doi:10.1002/jor.22666

Jones, R. K., Nester, C. J., Richards, J. D., Kim, W. Y., Johnson, D. S., Jari, S., . . . Tyson, S. F. (2013). A comparison of the biomechanical effects of valgus knee braces and lateral wedged insoles in patients with knee osteoarthritis. *Gait Posture, 37*(3), 368-372. doi:10.1016/j.gaitpost.2012.08.002

Jordan, K. M., Arden, N. K., Doherty, M., Bannwarth, B., Bijlsma, J. W., Dieppe, P., . . . Standing Committee for International Clinical Studies Including Therapeutic Trials, E. (2003). EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Ann Rheum Dis, 62*(12), 1145-1155. doi:10.1136/ard.2003.011742

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. *Am J Phys Med Rehabil, 83*(4), 273-278.

Kang, S. H., Lee, S. J., & Zhang, L. Q. (2014). Real-time tracking of knee adduction moment in patients with knee osteoarthritis. *J Neurosci Methods, 231*(0), 9-17. doi:10.1016/j.jneumeth.2013.12.001

Kemp, G., Crossley, K. M., Wrigley, T. V., Metcalf, B. R., & Hinman, R. S. (2008). Reducing joint loading in medial knee osteoarthritis: shoes and canes. *Arthritis Rheum, 59*(5), 609-614. doi:10.1002/art.23578

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. *Arch Phys Med Rehabil, 83*(7), 889-893. doi:http://dx.doi.org/10.1053/apmr.2002.33225

Kersten, P., White, P. J., & Tennant, A. (2014). Is the pain visual analogue scale linear and responsive to change? An exploration using Rasch analysis. *PLoS ONE, 9*(6), e99485. doi:10.1371/journal.pone.0099485

Kumar, D., Manal, K. T., & Rudolph, K. S. (2013). Knee joint loading during gait in healthy controls and individuals with knee osteoarthritis. *Osteoarthritis Cartilage, 21*(2), 298-305. doi:10.1016/j.joca.2012.11.008

Kutzner, I., Trepczynski, A., Heller, M. O., & Bergmann, G. (2013). Knee adduction moment and medial contact force--facts about their correlation during gait. *PLoS ONE, 8*(12), e81036. doi:10.1371/journal.pone.0081036

Lewinson, R. T., Collins, K. H., Vallerand, I. A., Wiley, J. P., Woodhouse, L. J., Reimer, R. A., . . . Stefanyshyn, D. J. (2014). Reduced knee joint loading with lateral and medial wedge insoles for management of knee osteoarthritis: a protocol for a randomized controlled trial. *BMC Musculoskelet Disord, 15*, 405. doi:10.1186/1471-2474-15-405

Liu, X., & Zhang, M. (2013). Redistribution of knee stress using laterally wedged insole intervention: Finite element analysis of knee-ankle-foot complex. *Clin Biomech, 28*(1), 61-67. doi:10.1016/j.clinbiomech.2012.10.004

London, N. J., Miller, L. E., & Block, J. E. (2011). Clinical and economic consequences of the treatment gap in knee osteoarthritis management. *Med Hypotheses, 76*(6), 887-892. doi:10.1016/j.mehy.2011.02.044

McAlindon, T. E., Bannuru, R. R., Sullivan, M. C., Arden, N. K., Berenbaum, F., Bierma-Zeinstra, S. M., . . . Underwood, M. (2014). OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis Cartilage, 22*(3), 363-388. doi:10.1016/j.joca.2014.01.003

Michael, J. W., Schluter-Brust, K. U., & Eysel, P. (2010). The epidemiology, etiology, diagnosis, and treatment of osteoarthritis of the knee. *Dtsch Arztebl Int, 107*(9), 152-162. doi:10.3238/arztebl.2010.0152

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. doi:DOI 10.1136/ard.61.7.617

Mundermann, A., Dyrby, C. O., Hurwitz, D. E., Sharma, L., & Andriacchi, T. P. (2004). Potential strategies to reduce medial compartment loading in patients with knee osteoarthritis of varying severity: reduced walking speed. *Arthritis Rheum, 50*(4), 1172-1178. doi:10.1002/art.20132

Nakatani, T., Nadamoto, M., Mimura, K.-I., & Itoh, M. (2002). Validation of a 30-sec chair-stand test for evaluating lower extremity muscle strength in Japanese elderly adults. *Taiikugaku kenkyu (Japan Journal of Physical Education, Health and Sport Sciences), 47*(5), 451-461. doi:10.5432/jjpehss.KJ00003390725

Parkes, M. J., Maricar, N., Lunt, M., LaValley, M. P., Jones, R. K., Segal, N. A., . . . Felson, D. T. (2013). Lateral wedge insoles as a conservative treatment for pain in patients with medial knee osteoarthritis: a meta-analysis. *JAMA, 310*(7), 722-730. doi:10.1001/jama.2013.243229

Peat, G., McCarney, R., & Croft, P. (2001). Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. *Annals of the Rheumatic Diseases, 60*(2), 91-97. doi:Doi 10.1136/Ard.60.2.91

Penny, P., Geere, J., & Smith, T. O. (2013). A systematic review investigating the efficacy of laterally wedged insoles for medial knee osteoarthritis. *Rheumatol Int, 33*(10), 2529-2538. doi:10.1007/s00296-013-2760-x

Reed, M. D., & Van Nostran, W. (2014). Assessing pain intensity with the visual analog scale: a plea for uniformity. *J Clin Pharmacol, 54*(3), 241-244. doi:10.1002/jcph.250

Roos, E. M., & Lohmander, L. S. (2003). The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. *Health Qual Life Outcomes, 1*, 64. doi:10.1186/1477-7525-1-64

Roos, E. M., Roos, H. P., & Lohmander, L. S. (1999). WOMAC Osteoarthritis Index--additional dimensions for use in subjects with post-traumatic osteoarthritis of the knee. Western Ontario and MacMaster Universities. *Osteoarthritis Cartilage, 7*(2), 216-221. doi:10.1053/joca.1998.0153

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. *J Orthop Sports Phys Ther, 28*(2), 88-96. doi:10.2519/jospt.1998.28.2.88

Scanzello, C. R., & Goldring, S. R. (2012). The role of synovitis in osteoarthritis pathogenesis. *Bone, 51*(2), 249-257. doi:10.1016/j.bone.2012.02.012

Sharma, L., Song, J., Dunlop, D., Felson, D., Lewis, C. E., Segal, N., . . . Nevitt, M. (2010). Varus and valgus alignment and incident and progressive knee osteoarthritis. *Ann Rheum Dis, 69*(11), 1940-1945. doi:10.1136/ard.2010.129742

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, 286*(2), 188-195. doi:10.1001/jama.286.2.188

Shelburne, K. B., Torry, M. R., Steadman, J. R., & Pandy, M. G. (2008). Effects of foot orthoses and valgus bracing on the knee adduction moment and medial joint load during gait. *Clinical Biomechanics, 23*(6), 814-821. doi:DOI 10.1016/j.clinbiomech.2008.02.005

Shull, P. B., Silder, A., Shultz, R., Dragoo, J. L., Besier, T. F., Delp, S. L., & Cutkosky, M. R. (2013). Six-week gait retraining program reduces knee adduction moment, reduces pain, and improves function for individuals with medial compartment knee osteoarthritis. *J Orthop Res, 31*(7), 1020-1025. doi:10.1002/jor.22340

Silverwood, V., Blagojevic-Bucknall, M., Jinks, C., Jordan, J. L., Protheroe, J., & Jordan, K. P. (2015). Current evidence on risk factors for knee osteoarthritis in older adults: a systematic review and meta-analysis. *Osteoarthritis Cartilage, 23*(4), 507-515. doi:10.1016/j.joca.2014.11.019

Simic, M., Hinman, R. S., Wrigley, T. V., Bennell, K. L., & Hunt, M. A. (2011). Gait modification strategies for altering medial knee joint load: a systematic review. *Arthritis Care Res (Hoboken), 63*(3), 405-426. doi:10.1002/acr.20380

Simic, M., Wrigley, T. V., Hinman, R. S., Hunt, M. A., & Bennell, K. L. (2013). Altering foot progression angle in people with medial knee osteoarthritis: the effects of varying toe-in and toe-out angles are mediated by pain and malalignment. *Osteoarthritis Cartilage, 21*(9), 1272-1280. doi:10.1016/j.joca.2013.06.001

Talbott, J. H. (1964). A Short History of the Gout and the Rheumatic Diseases. *JAMA, 189*(8), 647-647. doi:10.1001/jama.1964.03070080053027

Turkiewicz, A., Gerhardsson de Verdier, M., Engstrom, G., Nilsson, P. M., Mellstrom, C., Lohmander, L. S., & Englund, M. (2014). Prevalence of knee pain and knee OA in southern Sweden and the proportion that seeks medical care. *Rheumatology (Oxford)*. doi:10.1093/rheumatology/keu409

Vos, T., Flaxman, A. D., Naghavi, M., Lozano, R., Michaud, C., Ezzati, M., . . . Murray, C. J. L. (2012). Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *The Lancet, 380*(9859), 2163-2196. doi:10.1016/s0140-6736(12)61729-2

Williams, D. S., & Isom, W. (2012). Decreased frontal plane hip joint moments in runners with excessive varus excursion at the knee. *J Appl Biomech, 28*(2), 120-126.

Williamson, A., & Hoggart, B. (2005). Pain: a review of three commonly used pain rating scales. *J Clin Nurs, 14*(7), 798-804. doi:10.1111/j.1365-2702.2005.01121.x

Wise, B. L., Niu, J., Yang, M., Lane, N. E., Harvey, W., Felson, D. T., . . . Multicenter Osteoarthritis, G. (2012). Patterns of compartment involvement in tibiofemoral osteoarthritis in men and women and in whites and African Americans. *Arthritis Care Res (Hoboken), 64*(6), 847-852. doi:10.1002/acr.21606

Woolf, A. D., & Pfleger, B. (2003). Burden of major musculoskeletal conditions. *Bull World Health Organ, 81*(9), 646-656.

Xing, F., Lu, B., Kuang, M. J., Wang, Y., Zhao, Y. L., Zhao, J., . . . Ma, X. L. (2017). A systematic review and meta-analysis into the effect of lateral wedge arch support insoles for reducing knee joint load in patients with medial knee osteoarthritis. *Medicine (Baltimore), 96*(24), e7168. doi:10.1097/MD.0000000000007168

Yoshioka, S., Nagano, A., Hay, D. C., & Fukashiro, S. (2009). Biomechanical analysis of the relation between movement time and joint moment development during a sit-to-stand task. *Biomed Eng Online, 8*, 27. doi:10.1186/1475-925X-8-27

Zampogna, B., Vasta, S., Amendola, A., Uribe-Echevarria Marbach, B., Gao, Y., Papalia, R., & Denaro, V. (2015). Assessing Lower Limb Alignment: Comparison of Standard Knee Xray vs Long Leg View. *Iowa Orthop J, 35*, 49-54.

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. *J Orthop Res, 25*(6), 789-797. doi:10.1002/jor.20379

Chapter 3 - Original studies

Study I: The optimal degree of lateral wedge insoles for reducing knee joint load: A systematic review and meta-analysis

Authors:

Vitor Ferreira, Rita Simões, Rui Soles Gonçalves, Leandro Machado, Paulo Roriz

Journal:

Archives of Physiotherapy

Arch Physiother 9, 18 (2019). doi:10.1186/s40945-019-0068-1

ABSTRACT

Background: Lateral wedge insoles are traditionally used to reduce the adduction moment that crosses the knee during walking in people with medial knee osteoarthritis. However, the best degree to reduce knee joint load is not yet well established.

Methods: Electronic databases were searched from their inception until May 2017. Included studies reported on the immediate biomechanical effects of different degrees of lateral wedge insoles during walking in people with knee osteoarthritis. The main measures of interest relating to the biomechanics were the first and second peak of external knee adduction moment and knee adduction angular impulse. For the comparison of the biomechanical effects of different degrees of insoles, the studies were divided in three subgroups: insoles with a degree higher than 0° and equal to or lower than 5°; insoles higher than 5° and equal to or lower than 9°; and insoles higher than 9°. Eligible studies were pooled using random-effects meta-analysis.

Results: Fifteen studies with a total of 415 participants met all eligibility criteria and were included in the final review and meta-analysis. The overall effect suggests that lateral wedge insoles resulted in a statistically significant reduction in the first peak (standardized mean difference [SMD] –0.25; 95% confidence interval [CI] –0.36, –0.13; P <0.001), second peak (SMD –0.26 [95% CI –0.48, –0.04]; P = 0.02) and knee adduction angular impulse (SMD –0.17 [95% CI –0.31, –0.03]; P =0.02). The test of subgroups found no statistically significant differences.

Conclusion: Systematic review and meta-analysis suggests that lateral wedge insoles cause an overall slight reduction in the biomechanical parameters. Higher degrees do not show higher reductions than lower degrees. Prior analysis of biomechanical parameters may be a valid option for selecting the optimal angle of wedge that best fits in knee osteoarthritis patients with the lowest possible degree.

Keywords: Lateral wedge insoles; external knee adduction moment; osteoarthritis; knee; meta-analysis

BACKGROUND

Knee osteoarthritis (OA) is one of the most common forms of arthritis and is a leading cause of disability in older adults (Jordan et al., 2003; Peat, McCarney, & Croft, 2001). Joint loads during walking are implicated in the pathogenesis of knee OA (Bennell et al., 2010). The ground reaction force (GRF) vector and the corresponding position vector, relative to the knee joint center, contribute to quantify the knee joint reaction force and illustrate better how load is distributed

across the knee compartments. In fact, the external knee adduction moment (EKAM), mainly used in the study of knee OA, is obtained from the cross product between the frontal plane components of the previous vectors. During walking, the forces across the knee are not transmitted equally between the medial and lateral compartments (Zhao et al., 2007). The medial compartment has a higher load prevalence in subjects with tibiofemoral OA relative to the lateral compartment, especially in men (Wise et al., 2012). A reduction in the EKAM leads to a change in medial-to-lateral distribution and a relative lowering of the internal forces in the medial compartment (Schipplein & Andriacchi, 1991).

Yasuda and Sasaki, in the 1980s, originally described the potential of lateral wedged insoles to manage medial knee OA (Sasaki & Yasuda, 1987). Lateral wedge insoles are placed inside shoes and shift the point of application of the GRF toward the outside of the foot (laterally), reducing the moment arm (i.e., the position vector that is normal to the GRF vector) during walking (Hinman, Bowles, Metcalf, Wrigley, & Bennell, 2012). Therefore, the magnitude of the EKAM is also reduced, leading not only to a redistribution of knee load but also to a reduction of the load at the medial compartment (Kerrigan et al., 2002; Liu & Zhang, 2013). However, a current meta-analysis demonstrated that lateral wedge insoles caused small reductions in the EKAM and knee adduction angular impulse (KAAI) during walking, which could be ineffective in people with medial knee OA (Arnold, Wong, Jones, Hill, & Thewlis, 2016). Moreover, it is estimated that at least 20% of the individuals using lateral wedge insoles could even increase EKAM during gait (Chapman, Parkes, Forsythe, Felson, & Jones, 2015; Hinman et al., 2012; Jones, Chapman, Forsythe, Parkes, & Felson, 2014; Kakihana, Akai, Nakazawa, Naito, & Torii, 2007; Lewinson et al., 2016). Nevertheless, it is reasonable to argue that some factors may have affected the previous outcomes, such as the type of insole and the wedge degree. Several variations of the insole have been described, ranging from a wedge only on the heel (Hinman, Bowles, Payne, & Bennell, 2008; Maillefert et al., 2001; Pham et al., 2004) to one on the whole foot (Butler, Marchesi, Royer, & Davis, 2007; Hinman, Bowles, & Bennell, 2009; Hunt et al., 2017) and with (Abdallah & Radwan, 2011; Jones et al., 2013; Nakajima et al., 2009) or without arch support (Baker et al., 2007; Dessery, Belzile, Turmel, &

Corbeil, 2016; Duivenvoorden et al., 2015). On the other hand, most of the studies have been performed using the same wedge degree for all individuals, typically a 5 or 6 wedge degree (Duivenvoorden et al., 2014; Hinman et al., 2009; Jones et al., 2014; Kakihana, Akai, Yamasaki, Takashima, & Nakazawa, 2004). This lack of customization of insoles has been proposed as a relevant research question in an Arnold's Editorial Journal article, “One size fits all, some or none?” (Arnold, 2016). Certainly, it is a question that needs more research.

To our knowledge, no systematic review pursues an understanding of the effects of the amount of wedge insole angulation on biomechanical factors associated with medial knee OA. Reviews have sought to distinguish the effects on biomechanics, but only on the global effect of several types of angulations (Arnold et al., 2016) or on the influence of an arch support in the wedge insoles (Xing et al., 2017). Therefore, the main objective of the present review was to determine the biomechanical effects of lateral wedge insoles of different angles in people with knee OA and attempt to understand whether any angulation is more effective in improving biomechanical parameters in patients with knee OA.

METHODS

A systematic literature search was conducted, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) group statement (Liberati et al., 2009). The study protocol is registered in PROSPERO (International prospective register of systematic reviews), with registration number CRD42017070785 (http://www.crd.york.ac.uk/prospero/).

The Population, Intervention, Comparison, and Outcome (PICO) framework was used to define the search strategy (Schardt, Adams, Owens, Keitz, & Fontelo, 2007): P (population) individuals diagnosed with knee osteoarthritis; I (intervention) that used lateral wedge insoles; C (comparison) who wore neutral insoles or their own shoes; O (outcome) first peak EKAM, second peak EKAM and KAAI when available

Combinations of keywords and specific subject headings related to knee osteoarthritis, external knee adduction moment, biomechanics kinetics and kinematics, and interventions to reduce dynamic loading of the knee were employed. Boolean operators “OR” and “AND” were used to combine search terms. No restrictions were set for the searches with respect to language or publication year. Two investigators (VF, RS) developed the search strategy (**Table 1**) and completed the systematic search. Medline/PubMed, CINAHL, and Scopus were searched from their inception through May 31, 2017. Syntax was adjusted appropriately for use in multiple databases. Keywords were identical for all searches. Keywords Medical Subject Headings (MeSH) proofed and non-MeSH proofed were used to increase the chances of finding the intended studies.

Table 1. Example of MEDLINE search strategy

Search	Query
1	knee
2	arthritis OR arthrosis OR osteoarthr*
3	1 AND 2
4	biomechanic* OR kinematics* OR kinetics*
5	3 AND 4
6	adduction moment
7	ekam* OR kam* OR varus moment* OR knee varus*
8	6 OR 7
9	lateral* OR wedge* OR insole*
10	5 AND 8
11	9 AND 10

Eligibility criteria

The articles from those databases were collected, and duplicates were removed and cross-checked between the researchers to ensure agreement. Two authors (VF, RS) reviewed the titles and abstracts of all articles for eligibility based on the criteria list. When in doubt, full-text articles were reviewed. Disagreements were resolved by discussion until consensus was reached.

Studies to be included in this review must have been peer-reviewed studies that examined the acute biomechanical effects of laterally wedged insoles in patients with medial compartment knee OA, published as full text. There were no restrictions on design and severity of knee OA. Studies must have investigated a lateral wedged insole, defined as an in-shoe orthotic device with a degree of inclination toward the lateral border of the foot. No restrictions were made regarding the features of insoles (i.e., length: heel or full length) or presence of concurrent arch support in the device. Only baseline data inferring the immediate effects of lateral wedge insoles were used. Studies must have included a comparison condition that could be the insole removed or neutral insole (without any degree). If studies included the two control conditions (neutral insole or insole removed), only the data from neutral insole were analyzed. If an article analyzed customization intervention, but did not provide individual results, the article was excluded. Systematic and narrative reviews were eligible for the purposes of a manual reference list, searching only to identify any studies missed in the primary search. Studies were excluded if they did not include patients with osteoarthritis or osteoarthrosis, and if they were abstracts, case reports, editorials, conference proceedings papers, study protocols or unpublished papers, or without full access.

Data extraction

From the full articles that formed the results of this systematic review, the principal author extracted data of the characteristics of the individual trials and all outcomes into spreadsheets. A second author (RS) checked the data for accuracy. The main data extracted was the study design, number of patients, patient characteristics, type of insole, degree of lateral wedge, control condition, biomechanical outcome measures, statistical information, and funding sources. Primary outcome variables of interest extracted included features of the external knee adduction moment: the first peak EKAM, second peak EKAM, and KAAI.

Assessment of risk of bias in included studies

The risk-of-bias assessment was completed by one author (VF) and checked by a second author (RS), using the Cochrane Risk of Bias assessment tool (Higgins et al., 2011). Each article was graded (unclear, low, or high risk of bias) based on selection bias (random sequence generation and allocation concealment), detection bias (blinding of outcome assessment), blinding of participants and personnel (performance bias), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other bias. In case of disagreements, a common consensus was established and a third author (PR) was consulted if consensus could not be reached after consulting the guidelines of the software used.

Data analysis

Statistical information, including descriptive (means, medians, standard deviations [SDs], change scores) and inferential (P values, confidence interval [CI]) information, was extracted and cross-checked by two authors (VF, RS). For the meta-analysis, standardized mean differences (SMDs) were calculated as the mean difference in EKAM change produced by the degree of the insole and the control (neutral insole or without insole), divided by the pooled standard deviation of the measurement. Hence, a negative effect size indicated a beneficial effect for the insole group. Effect sizes were interpreted as 0.2 (small), 0.5 (medium), and 0.8 (large) (Lipsey & Wilson, 2001). Meta-analysis was performed in Review Manager (RevMan) software (version 5.3, Cochrane Collaboration), using the inverse variance method (Borenstein, Hedges, Higgins, & Rothstein, 2010), where the contribution of effect sizes from individual studies was weighted on sample size. For studies not reporting enough data, and where the authors could not provide data, they were calculated from other available data when possible (e.g., from 95% CI or *P* values from *t*-tests). It was decided to use a random-effects model, a priori, to estimate the pooled effect of intervention more conservatively.

Heterogeneity was assessed using a χ^2 test (Q value), its corresponding degrees of freedom, and p value. The extent of heterogeneity was analyzed using Higgins' I^2 value (expressed as %) (Higgins & Thompson, 2002). Heterogeneity determined the percentage of total variation across studies that is due to heterogeneity rather than to chance and examines the null hypothesis that all studies are evaluating the same effect (Higgins, Thompson, Deeks, & Altman, 2003). For the interpretation of heterogeneity, the values of 25%, 50%, and 75% were followed, which represent low, moderate, and high heterogeneity, respectively (Higgins et al., 2003). The risk of small-study effects was assessed using the Egger's regression test (Higgins et al., 2011) and, if present, adjustment was planned using a trim-and-fill method (Duval & Tweedie, 2000) with STATA software (version 12, StataCorp).

RESULTS

Study selection and characteristics

A total of 597 records were identified, and 399 were screened on title and abstract. After assessing eligibility against the criteria, 26 studies were retained for full-text review. Fifteen studies, with a total of 415 participants, met all eligibility criteria and were included in the final review and meta-analysis (**Figure 6**).

Table 2 summarizes the characteristics of the included studies and participants. Seven studies had small samples sizes (n <20) (Dessery et al., 2016; Fantini Pagani, Hinrichs, & Bruggemann, 2012; Hinman, Bowles, et al., 2008; Kakihana et al., 2005; Kerrigan et al., 2002; Lewinson et al., 2016; Maly, Culham, & Costigan, 2002). Most studies included participants aged over 45 years. The mean age was about the sixties. The principal criterion to classify OA severity was the Kellgren and Lawrence (K/L) scale (Kellgren & Lawrence, 1957). Seven studies included only participants with grade 2 or 3 on the K/L scale (Abdallah & Radwan, 2011; Dessery et al., 2016; Fantini Pagani et al., 2012; Hatfield et al., 2016; Hinman et al., 2009; Hinman et al., 2012; Hinman, Bowles, et al., 2008; Jones et al., 2014).

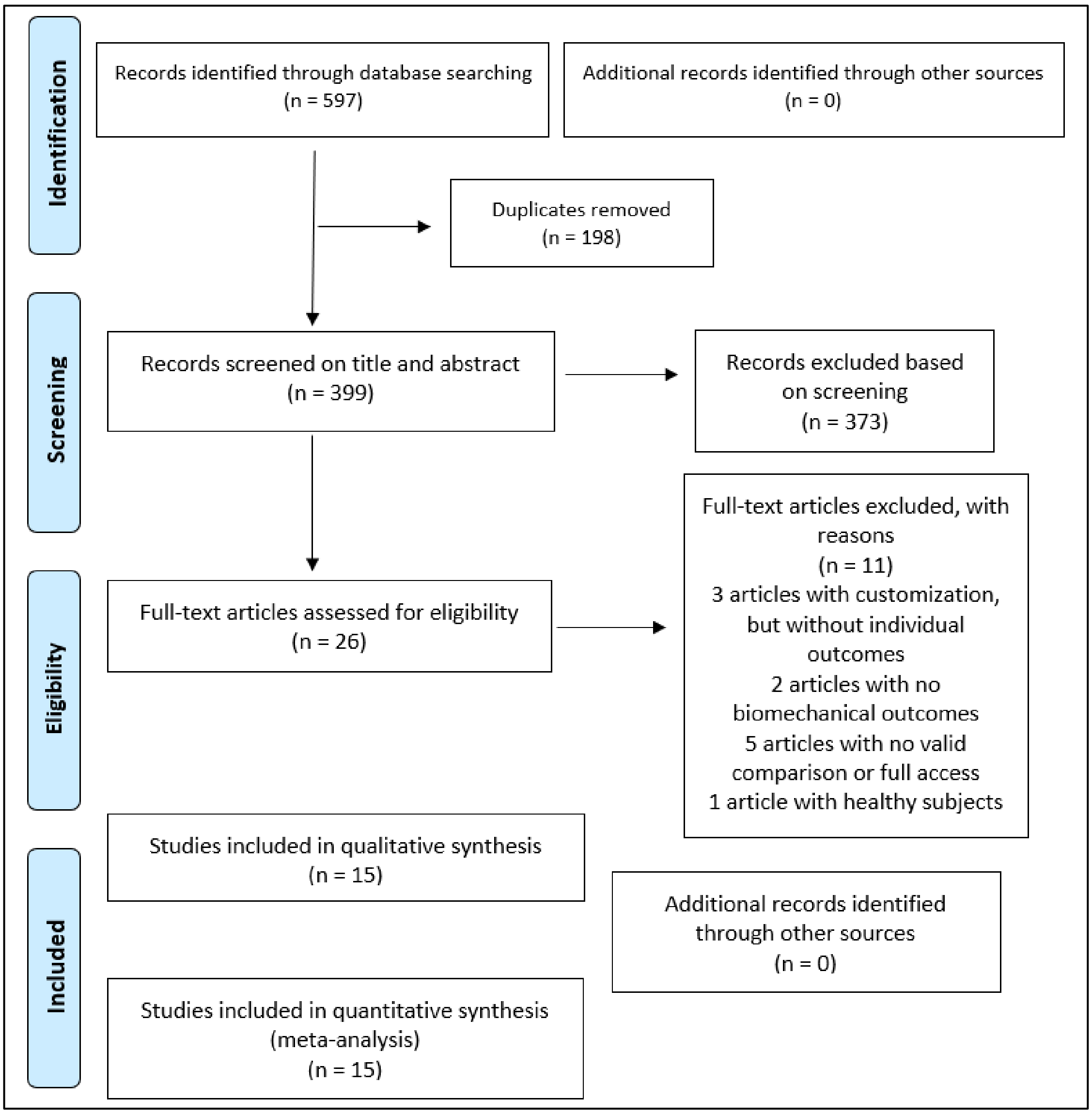


Figure 6. PRISMA flow diagram of the study selection process.

One study used an intervention with an insole of 4 degrees (Fantini Pagani et al., 2012), eight studies used an intervention with an insole of 5 degrees (Hatfield et al., 2016; Hinman et al., 2009; Hinman et al., 2012; Hinman, Bowles, et al., 2008; Hinman, Payne, Metcalf, Wrigley, & Bennell, 2008; Jones et al., 2014; Kerrigan et al., 2002; Maly et al., 2002), five studies used an insole of 6 degrees (Abdallah & Radwan, 2011; Dessery et al., 2016; Duivenvoorden et al., 2015; Kakihana et al., 2005; Lewinson et al., 2016; Shimada et al., 2006), two studies with an insole of 10 degrees (Dessery et al., 2016; Kerrigan et al., 2002), and one study used

an insole of 11 degrees (Abdallah & Radwan, 2011). A neutral insole was the comparison condition in four studies (Abdallah & Radwan, 2011; Dessery et al., 2016; Kakihana et al., 2005; Kerrigan et al., 2002); nine studies used participants' shoes (Duivenvoorden et al., 2015; Fantini Pagani et al., 2012; Hinman et al., 2009; Hinman et al., 2012; Hinman, Bowles, et al., 2008; Hinman, Payne, et al., 2008; Lewinson et al., 2016; Maly et al., 2002; Shimada et al., 2006), and two used control shoes (Hatfield et al., 2016; Jones et al., 2014). For the comparison of the biomechanical effects of different degrees of insoles, the studies were divided into three subgroups: comparison of interventions with insoles with a degree higher than 0° and equal to or lower than 5° (insole ≤5°); comparison of interventions with insoles higher than 5° and equal to or lower than 9° (insole >5° and ≤9°); and comparisons of interventions with insoles higher than 9° (insole >9°). These intervals were chosen because they have been the most studied in the literature.

Risk of bias

Inter-rater agreement for each item of the methodological quality assessment was moderate to high (k = 0.72 to 0.91). In 71% of trials, the random sequence generation had adequate or unclear risk of bias. Adequate allocation concealment was observed as low risk of bias in 19%, unclear in 52%, and high risk of bias in 29% of the included trials. Most of the studies were not blinded to the participants, personnel, or the outcome assessment, but the review authors' judgement remained that the outcome was not likely to be influenced by lack of blinding because, in this type of evaluation, the data processing was carried out later.

Therefore, the performance and the detection bias were considered 100% adequate. Incomplete outcome data were presented in 5% of the trials, and selective reporting was observed as low risk of bias in 86% of the trials (**see Additional file 1 and 2**).

Table 2. Characteristics of included studies (n=15).

Authors (year)	n	Sex, M:F	Age (y)	Varus alignment (°)	K/L Grade severity (n)				Funding Source
					1	2	3	4	
Kerrigam et al. (2002)	15	8:7	69.7±7.6	n/r	0	0	10	5	Supported by the Ellison Foundation and by the US Public Health Service.
Maly et al. (2002)	12	9:3	60±9.39	6.67±4.2	n/r	n/r	n/r	n/r	Drummond Foundation and the Natural Sciences and Engineering Research Council of Canada.
Kakihana et al. (2005)	13	n/r	63.3±5.6	2.5±3.9	n/r	n/r	n/r	n/r	Not stated
Shimada et al. (2006)	23	6:17	67.0±8.7	6.2±4.4	11	11	13	11	Not stated
Hinman et al. (2008a)	40	16:24	64.7±9.4	5.5°	3	10	11	16	University Grants and the Arthritis Foundation of Australia.
Hinman et al. (2008b)	13	6:7	59.7±6.2	1.9°±2.9	0	7	6	0	National Health and Medical Research Council of Australia
Hinman et al. (2009)	20	8:12	63.5±9.4	n/r	0	8	12	0	National Health & Medical Research Council of Australia and the ANZ Charitable Trusts
Abdallah and Radwan (2011)	21	0:21	54.1±7.4	176–180°	0	n/r	n/r	0	Not stated
Hinman et al. (Hinman et al., 2012)	73	28:45	63.3±8.4	0.9° valgus	0	41	32	0	National Health & Medical Research Council of Australia
Pagani et al. (2012)	10	2:8	57.5±7.1	2.1°±1.2	0	6	4	0	Institute of Biomechanics of the German Sport University Cologne.
Jones et al. (2014)	70	43:27	60.3±9.6	n/r	0	17	25	0	Arthritis Research UK and National Institute for Health Research Biomedical Research Unit Funding Scheme.
Duivenvoorden et al. (2015)	42	14:28	54.0±7.0	n/r	15	8	18	1	Not stated
Hatfield et al. (2016)	26	4:22	64.0±8.0	n/r	0	16	10	0	Pedorthic Foundation of Canada. Canadian Institutes of Health Research the Natural Sciences and Engineering Research Council of Canada, and the Michael Smith Foundation for Health Research
Dessery et al. (2016)	18	8:10	54.5±8.6	4.5°±2.8	0	15	3	0	Fonds de Recherche du Québec – Nature et Technologies. Natural Sciences and Engineering Research Council of Canada. Ergoresearch Inc
Lewinson et al. (2016)	19	6:13	59.9±7.4	n/r	5	2	3	9	Canadian Institutes of Health Research. Alberta Innovates Health Solutions. Killam Trusts. New Balance Athletic Shoe Inc

Values are indicated as mean ± SD unless indicated otherwise; M : F = male : female; (y) years; K/L = Kellgren/Lawrence; n/r – not reported

Meta-analysis

The **first peak EKAM** was the major outcome reported in the studies. All 15 studies stated the first peak EKAM. Because some studies made multiple comparisons with different features of the insole, such as the arch support or the length of the wedge, a total of 21 comparisons were included in the meta-analysis for the first peak EKAM (see **Table 3**). The overall effect suggests that lateral wedge insoles resulted in a statistically significant reduction in the first peak EKAM (n = 578, SMD –0.25 [95% CI –0.36, –0.13], P <0.001), with a low level of statistical heterogeneity (x^2 = 5.44, P = 1.00, I^2 0%) (Figure 7). The comparison for subgroups did not show a statistically significant difference (x^2 = 0.31, P = 0.85, I^2 0%). Two subgroups presented statistically significant reductions: insole ≤5° (SMD –0.22 [95% CI –0.37, –0.08], P =0.002) and insole >5° and ≤9° (SMD –0.29 [95% CI –0.53, –0.05], P = 0.02). However, the subgroup insole >9° showed no statistically significant reduction (SMD –0.30 [95% CI –0.68, 0.08], P = 0.12). The Egger's regression test for funnel plot asymmetry was positive (β = –0.75, standard error (SE) 0.33, P = 0.034), indicating weak evidence of publication bias for the first peak EKAM (**see Additional file 3**). When using the trim and fill method, no trimming was performed, and the data remained unchanged. Only six studies reported the **second peak EKAM** (Dessery et al., 2016; Fantini Pagani et al., 2012; Hinman et al., 2009; Hinman, Bowles, et al., 2008; Hinman, Payne, et al., 2008; Kerrigan et al., 2002). A total of nine comparisons were included in the data synthesis (**Table 3**). Six comparisons were for insoles ≤5°. The overall effect suggests that lateral wedge insoles resulted in a statistically significant reduction in the second peak EKAM (n = 162, SMD –0.26 [95% CI –0.48, –0.04], P = 0.02), with a low level of statistical heterogeneity (x^2 = 0.39, P = 1.00, I^2 0%) (Figure 8). None of the subgroups showed a statistically significant reduction of the overall effect, with pooled effect similar between them when compared with the control condition: insole ≤5° (SMD –0.24 [95% CI –0.50, 0.03], P = 0.08); insole >5° and ≤9° (SMD –0.27 [95% CI –0.92, 0.39], P = 0.43); and insole >9° (SMD –0.32 [95% CI –0.80, 0.17], P = 0.2).

Table 3. Comparisons of interventions of included studies.

Authors (year)	Unit of measure	Comparisons		SMD (95% CI)
		Intervention	Control	
First peak EKAM				
Kerrigam et al. (2002)a	Nm/Kg*m	5° insole	5° Control insole (3.2mm)	-0.17 [-0.88, 0.55]
Kerrigam et al. (2002)b	Nm/Kg*m	10° insole	10° Control insole (6.4mm)	-0.37 [-1.09, 0.36]
Maly et al. (2002)	Nm/Kg	5°insole	Participant shoes	-0.08 [-0.88, 0.72]
Kakihana et al. (2005)	Nm/Kg	6° insole	Neutral insole	-0.97 [-1.79, -0.15]
Shimada et al. (2006)	Nm/Kg	6° insole	Participant shoes	-0.20 [-0.78, 0.38]
Hinman et al.) (2008a	%BW*Ht	5° insole	Participant shoes	-0.21 [-0.65, 0.23]
Hinman et al. (2008b)a	%BW*Ht	5° full-length wedges	Participant shoes	-0.54 [-1.33, 0.24]
Hinman et al. (2008b)b	%BW*Ht	5° rearfoot wedges	Participant shoes	-0.33 [-1.10, 0.45]
Hinman et al. (2009)	%BW*Ht	5° insole	Participant shoes	-0.33 [-1.10, 0.45]
Abdallah and Radwan (2011)a	Nm/Kg	6° insole	Neutral insole	-0.18 [-0.79, 0.42]
Abdallah and Radwan (2011)b	Nm/Kg	11° insole	Neutral insole	-0.32 [-0.93, 0.29]
Hinman et al. (2012)	%BW*Ht	5° insole	Participant shoes	-0.29 [-0.61, 0.04]
Pagani et al. (2012)	Nm/Kg	4° insole	Participant shoes	-0.20 [-1.08, 0.67]
Jones et al. (2014)a	Nm/Kg	5° insole with arch support	Control shoes	-0.16 [-0.49, 0.17]
Jones et al. (2014)b	Nm/Kg	5° insole without arch support	Control shoes	-0.17 [-0.50, 0.17]
Duivenvoorden et al. (2015)	Nm/kg	6° insole	Participant shoes	-0.12 [-0.55, 0.31]
Hatfield et al. (2016)a	Nm/kg	5° insole with arch support	Control shoes	-0.19 [-0.74, 0.35]
Hatfield et al. (2016)b	Nm/kg	5° insole without arch support	Control shoes	-0.25 [-0.80, 0.29]
Dessery et al. (2016)a	%BW*Ht	6° insole with arch support	Control insole	-0.42 [-1.08, 0.24]
Dessery et al. (2016)b	%BW*Ht	10° insole with arch support	Control insole	-0.23 [-0.88, 0.43]
Lewinson et al. (2016)	Nm	6° insole	Participant shoes	-0.38 [-1.03, 0.26]
Second peak EKAM				
Kerrigam et al. (2002)a	Nm/Kg*m	5° insole	5° Control insole (3.2mm)	-0.17 [-0.89, 0.55]
Kerrigam et al. (2002)b	Nm/Kg*m	10° insole	10° Control insole (6.4mm)	-0.30 [-1.02, 0.42]
Hinman et al. (2008a)	%BW*Ht	5° insole	Participant shoes	-0.31 [-0.75, 0.13]
Hinman et al. (2008b)a	%BW*Ht	5° full-length wedges	Participant shoes	-0.34 [-1.12, 0.43]
Hinman et al. (2008b)b	%BW*Ht	5° rearfoot wedges	Participant shoes	-0.17 [-0.94, 0.60]
Hinman et al. (2009)	%BW*Ht	5° insole	Participant shoes	-0.16 [-0.78, 0.46]
Pagani et al. (2012)	Nm/Kg	4° insole	Participant shoes	-0.18 [-1.06, 0.70]
Dessery et al. (2016)a	%BW*Ht	6° insole with arch support	Control insole	-0.27 [-0.92, 0.39]
Dessery et al. (2016)b	%BW*Ht	10° insole with arch support	Control insole	-0.33 [-0.99, 0.33]
Knee adduction angular impulse				
Hinman et al. (2009)	%BW*Ht	5° insole	Participant shoes	-0.14 [-0.76, 0.48]
Hinman et al. (2012)	%BW*Ht	5° insole	Participant shoes	-0.21 [-0.54, 0.11]
Pagani et al. (2012)	Nm/Kg	4° insole	Participant shoes	-0.15 [-1.03, 0.73]
Jones et al. (2014)a	Nm/Kg	5° insole with arch support	Control shoes	-0.14 [-0.47, 0.19]
Jones et al. (2014)b	Nm/Kg	5° insole without arch support	Control shoes	-0.19 [-0.52, 0.15]
Duivenvoorden et al. (2015)	Nm/kg	6° insole	Participant shoes	-0.02 [-0.45, 0.40]
Hatfield et al. (2016)a	Nm/kg	5° insole with arch support	Control shoes	-0.12 [-0.66, 0.43]
Hatfield et al. (2016)b	Nm/kg	5° insole without arch support	Control shoes	-0.12 [-0.66, 0.43]
Dessery et al. (2016)a	%BW*Ht	6° insole with arch support	Control insole	-0.34 [-1.00, 0.32]
Dessery et al. (2016)b	%BW*Ht	10° insole with arch support	Control insole	-0.34 [-1.00, 0.32]
Lewinson et al. (2016)	Nms	6° insole	Participant shoes	-0.23 [-0.87, 0.41]

SMD: standardized mean differences; Nm/kg: Newton-meter / kilogram; %BW*Ht: % body weight x height; mm: millimeter

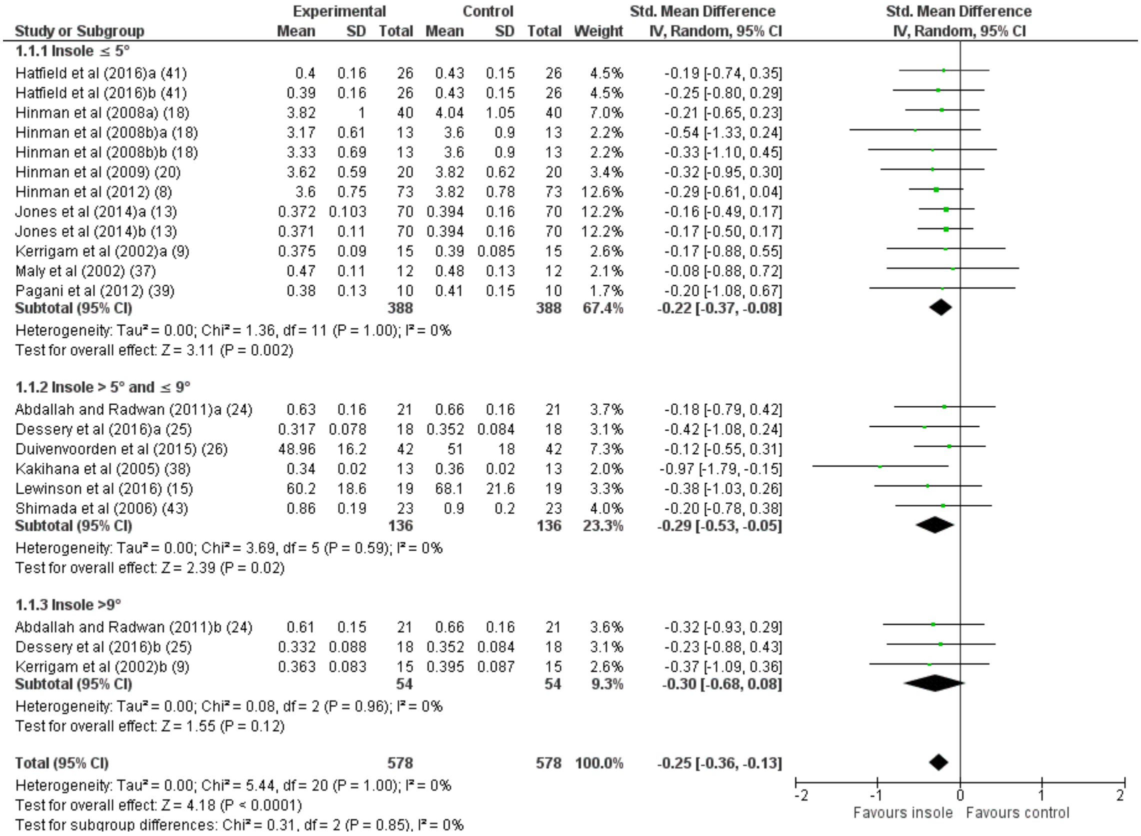


Figure 7. Forest plot of comparison: first peak external knee adduction moment (EKAM)

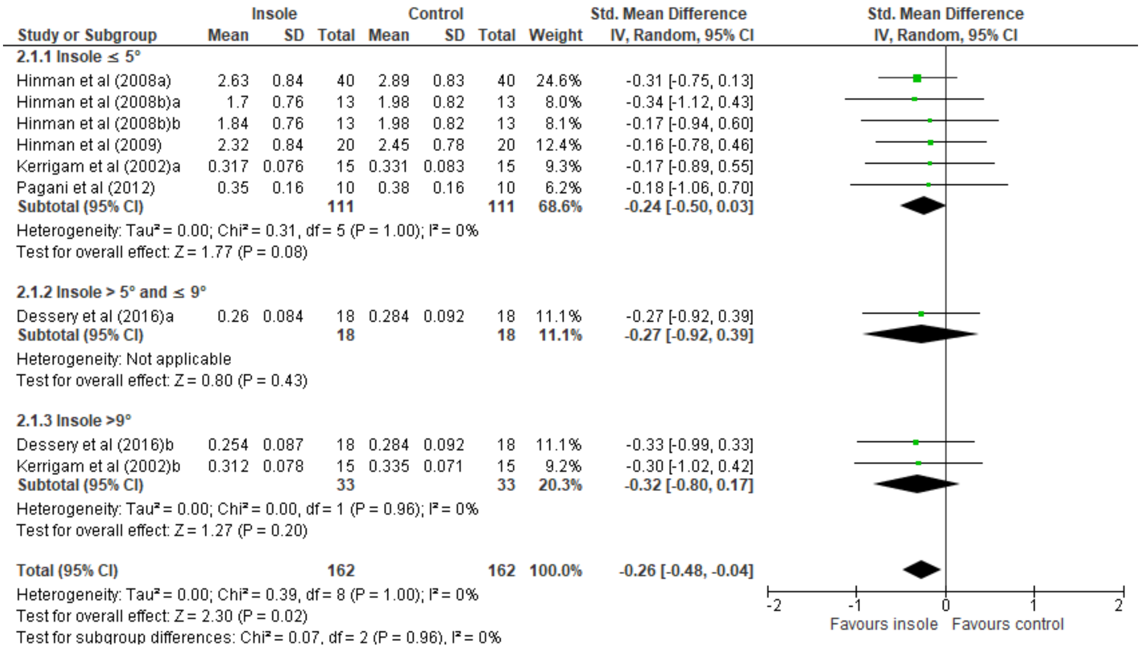


Figure 8. Forest plot of comparison: second peak external knee adduction moment (EKAM)

Egger's regression test for funnel plot asymmetry was not statistically significant, indicating weak evidence of publication bias for the second peak EKAM ($\beta = 0.40$, SE 0.36, P = 0.306) (**see Additional file 4**).

The **KAAI** was considered in the study of biomechanical risks in past years and was reported in eight studies (Dessery et al., 2016; Duivenvoorden et al., 2015; Fantini Pagani et al., 2012; Hatfield et al., 2016; Hinman et al., 2009; Hinman et al., 2012; Jones et al., 2014; Lewinson et al., 2016). A total of 11 comparisons were included in the data synthesis (**Table 3**). The overall pooled estimate indicated that a statistically significant reduction in the KAAI favors lateral wedge insoles (n = 392, SMD –0.17 [95% CI –0.31, –0.03], *P* = 0.02) with a low level of statistical heterogeneity (x^2 = 1.19, *P* = 1.00, I^2 0%) (Figure 9). Subgroup comparisons yielded different pooled effects (x^2 = 0.29, *P* = 0.86, I^2 0%). The insole ≤5° showed association with KAAI compared to the control condition (SMD –0.17 [95% CI –0.33, –0.00], *P* =0.04). The subgroups insole >5° and ≤9° (SMD –0.15 [95% CI –0.46, 0.17], *P* =0.36) and insole >9° (SMD –0.34 [95% CI –1.00, 0.32], *P* = 0.31) showed no associations with KAAI compared to the control condition. The Egger publication bias plot for funnel plot asymmetry was not statistically significant, indicating weak evidence of publication bias for the KAAI (β = –0.21, SE 0.34, P = 0.559) (**see Additional file 5**).

DISCUSSION

The main objective of this review was to determine the biomechanical effects of different angles of lateral wedge insoles in people with knee OA and understand if different amounts of angulations induce different responses. This meta-analysis confirms that lateral wedge insoles cause an immediate reduction on knee load in conservative treatment for people with medial knee OA. Biomechanical parameters related to the medial knee load, including first peak EKAM, second peak EKAM, and KAAI were reduced with the use of a lateral wedge insole, apart from the amount of the degree. To the best of our knowledge, no previous reviews evaluated the effect of different angulations on biomechanical parameters.

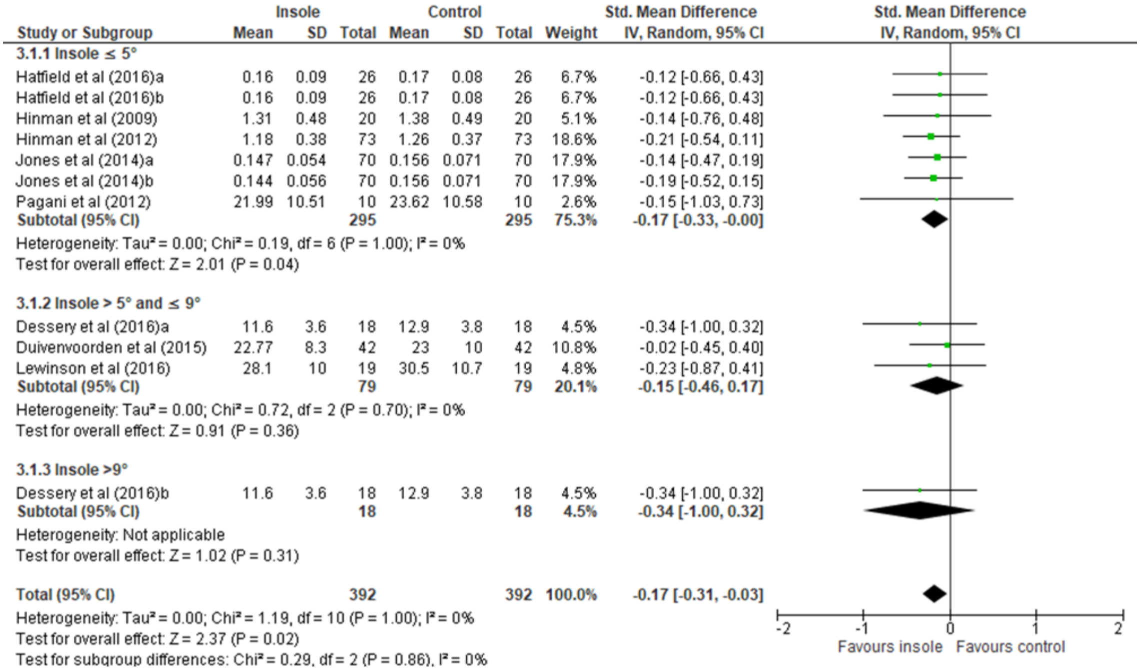


Figure 9. Forest plot of comparison: Knee adduction angular impulse (KAAI).

The latest meta-analysis (Arnold et al., 2016; Xing et al., 2017) regarding these issues did not focus on the effects of different angulations on reducing knee load in people with OA. In the review by Arnold et al. (Arnold et al., 2016), the authors explore the overall effects of lateral wedge insoles on biomechanical risk factors and, in the subgroups analysis, studied the immediate effects among the application of lateral wedge insoles, neutral insoles, or shoes without insoles. In an up-to-date meta-analysis, Xing et al. (Xing et al., 2017) also studied the immediate effects of lateral wedge insoles, but in the subgroups analysis the authors studied the influence of arch supports on lateral wedge insoles compared to control shoes or neutral insoles. In these two meta-analyses, a small SMD was verified in the reduction of the first and second peak of EKAM and in KAAI. For the first peak EKAM, was found an SMD = –0.19 ([95% CI –0.23, –0.15], P <0.001) in the meta-analysis of Arnold et al. (Arnold et al., 2016), an SMD = –0.22 ([95% CI –0.37, –0.07], P = 0.001) in the meta-analysis of Xing et al. (Xing et al., 2017), and in the present meta-analysis a very similar SMD = –0.25 ([95% CI –0.36, –0.13], P <0.001). With regard to the second peak EKAM, was found an SMD = –0.25 ([95% CI –0.31, –0.18], P <0.001) in the meta-analysis of Arnold

et al. (Arnold et al., 2016), an SMD = –0.26 ([95% CI –0.47, –0.06], P = 0.01) in the meta-analysis of Xing et al. (Xing et al., 2017), and in the present meta-analysis an analogous value of SMD = –0.26 ([95% CI –0.48, –0.04], P = 0.02). Likewise, for the KAAI, was found an SMD = –0.14 ([95% CI –0.21, –0.07], P <0.001) in the meta-analysis of Arnold et al. (Arnold et al., 2016), an SMD = –0.21 ([95% CI –0.39, –0.02], P = 0.01) in the meta-analysis of Xing et al. (Xing et al., 2017), and in the present meta-analysis a similar value of SMD = –0.17 ([95% CI –0.31, –0.03], P = 0.02). All three meta-analysis support an immediate effect on the reduction of the adductor moment applied at the knee with the use of lateral wedge insoles. This positive effect may be independent of the presence of a lateral arch support (Xing et al., 2017), and the presence of a neutral insole as a comparator may not be totally inert (Arnold et al., 2016). Also, as present in this meta-analysis, the effect of a higher wedge degree does not seem to be very relevant compared to lower-angle insoles. In the same way, it should not be forgotten that insoles, particularly the ones with higher degrees, are associated with some discomfort with prolonged use (Tipnis, Anloague, Laubach, & Barrios, 2014).

The main objective of this review was to understand whether the amount of the angulation of the wedge influenced the EKAM and KAAI in patients with medial knee OA. It was our hypothesis that larger angulations would lead to a higher effect. However, the effect size of insoles with wedges ≤5° (SMD = –0.22) and the effect size of insoles with wedges >9° (SMD = –0.30) are very similar for the first peak and for the second peak EKAM. For KAAI, because was retrieved only one study (n = 18) (Dessery et al., 2016) that studied insoles with a wedge greater than 9°, it is not possible to form any conclusion. An emerging problem that would require further analysis is related to the correct adjustment of the insoles to each patient. Apparently, there is no research investigating an optimal dose–response concerning the degree of lateral wedge insoles for each patient based on biomechanical factors. From our knowledge, only one study attempted to examine the effect of incrementally increasing lateral wedge amounts on EKAM (Tipnis et al., 2014). However, a key limitation of that study was that the participants were healthy and young. The authors tested seven inclinations of

lateral wedging (0°, 2°, 4°, 6°, 8°, 10°, 12°). Yet, it is curious that with an insole angled at 2°, the average reduction was surprisingly 6.4% in the first peak EKAM and 5.1% in the KAAI, values that are similar when compared to studies with participants with medial knee OA, where insoles with angles of 5° and 6° are typically applied (Duivenvoorden et al., 2015; Hinman et al., 2012; Jones et al., 2014). Some studies have attempted to apply lateral wedge insoles in a customization way but based on other indicators such as subjective comfort, pain relief, or static pedometer evaluation (Barrios, Butler, Crenshaw, Royer, & Davis, 2013; Butler, Barrios, Royer, & Davis, 2009; Butler et al., 2007; Maillefert et al., 2001; Moyer et al., 2013). Their conclusions seem more promising than traditional applications based only on one degree for all individuals. In the study by Barrios et al. (Barrios et al., 2013), the authors observed an increased EKAM over time (1 year) in the control group but not in the intervention group and, within the intervention group, the mechanical effectiveness of the lateral wedging did not decrease over time.

However, the extent of these effects remains ambiguous, with some authors suggesting that the effect size of the decrease in load on the medial compartment observed with lateral wedge insoles is too small to be clinically relevant such as reducing pain or symptoms (Baker et al., 2007; Bennell et al., 2011; Lewinson et al., 2016). On the other hand, other authors (Farrokhi, Voycheck, Tashman, & Fitzgerald, 2013; Jones et al., 2013) suggest that minor changes in knee load may have a positive effect on patients' symptoms given the number of steps taken per day (about 6500) (Bennell et al., 2011). An interesting question that has not yet been answered is whether a difference of 1 or 2 degrees in the wedge could have an impact on the biomechanical parameters and, in particular, on the patient's complaints over a long time, especially when referring to a chronic and evolutive disease with a great impact on patients' health-related quality of life (Picavet & Hoeymans, 2004). We know that the biomechanical response to insoles by patients with similar characteristics presents a considerable variability.

Some limitations can be addressed to the present review, primarily the heterogeneity between the study designs and the participants. Most of the studies were single-group crossover and, from our judgment, presented an unclear or

high risk of bias in the selection bias (random sequence generation and allocation concealment). These could be a problem because, in past years, the literature sought to identify different knee OA phenotypes (Iijima et al., 2015; van der Esch et al., 2015). The selection of participants based on biomechanical criteria included in randomized controlled trials should be the way forward, based on the prescription of biomechanical response. Another limitation is the different methodologies used in the studies to calculate EKAM. It is not clear enough in some studies how EKAM was calculated in the procedures, which may limit the comparison between studies. On the other hand, the different setup of placement of the passive markers can make comparison of the results difficult in an area that is so sensitive to small differences. Possible differences in sample size or differences in different gender elements can also be seen as a limitation in the comparison of results.

Setting the optimal angulation for each patient can contribute to improve outcomes in these patients. The results of this study may contribute to a better definition of individual angulation. Future studies should focus on optimizing the angulation of the insole and personalizing the intervention.

CONCLUSION

This systematic review with meta-analysis suggests that lateral wedge insoles have a small effect on reducing the forces that cross the medial knee in people with medial knee OA, regardless of the angulation applied.

The path of customization of the interventions may be the right path, and the support of clinical biomechanics may play an important role in therapeutic decisions. The analysis of biomechanical parameters may be a beneficial option for the application of lateral wedge insoles for individuals with knee OA. The optimal degree should be obtained from individual fitting with the lowest possible angle that causes an important reduction of biomechanical risks.

Given the clear biomechanical benefits, further research is needed to investigate targeted use of lateral wedge insoles in biomechanical phenotypes over a longer time to determine conclusively the effects of lateral wedge insoles.

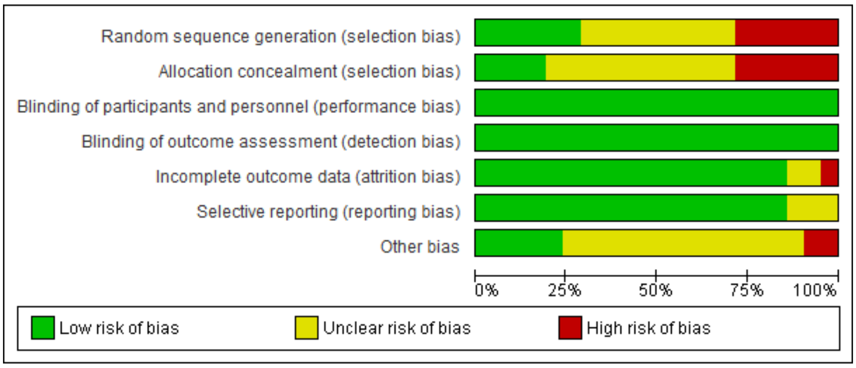
Abbreviations

CI: Confidence interval; EKAM: external knee adduction moment; GRF: Ground reaction force; K/L: Kellgren & Lawrence scale; KAAI: Knee adduction angular impulse; OA: Osteoarthritis; SD: Standard deviations; SMD: Standardized mean differences

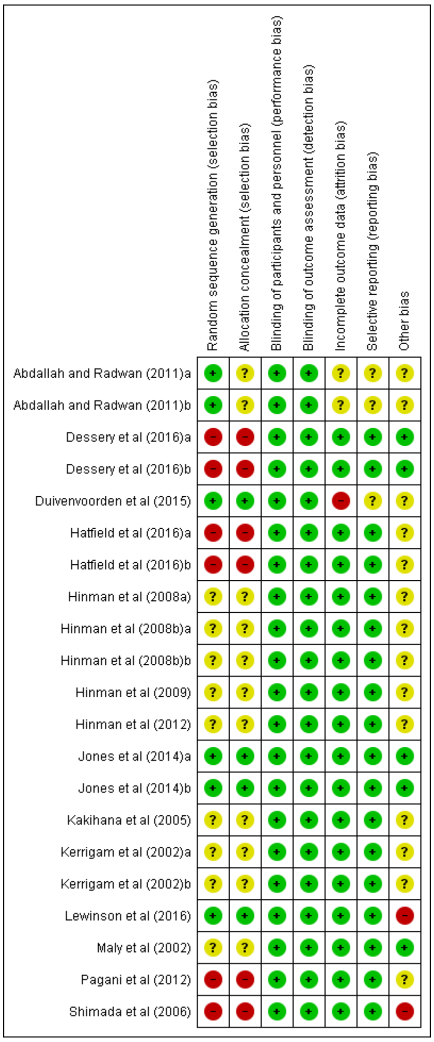
Authors' contributions

Majority of presented data was gathered by VF as part of her PhD thesis. PR and LM functioned as project mentors. Data collection parameters were defined by VF and RS. RSG reviewed and analyzed the data with particular attention. All authors read and approved the final manuscript.

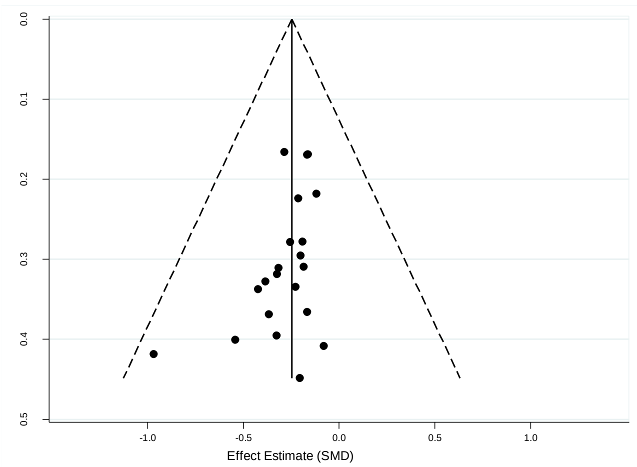
Supplementary information



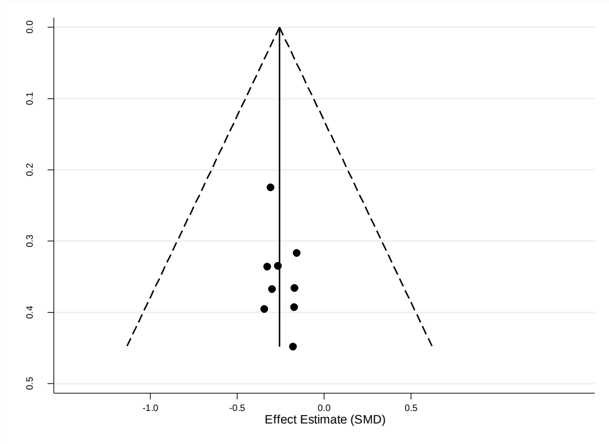
Additional file 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



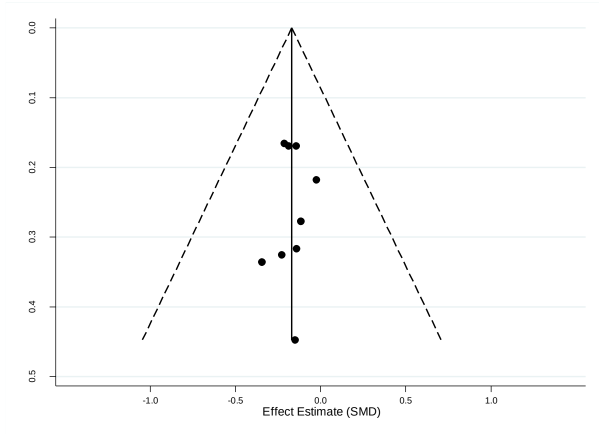
Additional file 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study: (+) – Low risk; (?) – Unclear risk; (-) – high risk.



Additional file 3. Funnel plot of comparison: first peak EKAM



Additional file 4. Funnel plot of comparison: second peak EKAM



Additional file 5. Funnel plot of comparison: knee adduction angular impulse (KAAI)

References

Abdallah, A. A., & Radwan, A. Y. (2011). Biomechanical changes accompanying unilateral and bilateral use of laterally wedged insoles with medial arch supports in patients with medial knee osteoarthritis. *Clin Biomech, 26*(7), 783-789. doi:10.1016/j.clinbiomech.2011.03.013

Arnold, J. B. (2016). Lateral wedge insoles for people with medial knee osteoarthritis: one size fits all, some or none? *Osteoarthritis Cartilage, 24*(2), 193-195. doi:10.1016/j.joca.2015.09.016

Arnold, J. B., Wong, D. X., Jones, R. K., Hill, C. L., & Thewlis, D. (2016). Lateral Wedge Insoles for Reducing Biomechanical Risk Factors for Medial Knee Osteoarthritis Progression: A Systematic Review and Meta-Analysis. *Arthritis Care Res (Hoboken), 68*(7), 936-951. doi:10.1002/acr.22797

Baker, K., Goggins, J., Xie, H., Szumowski, K., LaValley, M., Hunter, D. J., & Felson, D. T. (2007). A randomized crossover trial of a wedged insole for treatment of knee osteoarthritis. *Arthritis Rheum, 56*(4), 1198-1203. doi:10.1002/art.22516

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. *J Orthop Res, 31*(5), 659-664. doi:10.1002/jor.22252

Bennell, K. L., Bowles, K. A., Payne, C., Cicuttini, F., Williamson, E., Forbes, A., . . . Hinman, R. S. (2011). Lateral wedge insoles for medial knee osteoarthritis: 12 month randomised controlled trial. *BMJ, 342*, d2912. doi:10.1136/bmj.d2912

Bennell, K. L., Creaby, M. W., Wrigley, T. V., Bowles, K. A., Hinman, R. S., Cicuttini, F., & Hunter, D. J. (2010). Bone marrow lesions are related to dynamic knee loading in medial knee osteoarthritis. *Ann Rheum Dis, 69*(6), 1151-1154. doi:10.1136/ard.2009.118182

Borenstein, M., Hedges, L. V., Higgins, J. P., & Rothstein, H. R. (2010). A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synth Methods, 1*(2), 97-111. doi:10.1002/jrsm.12

Butler, R. J., Barrios, J. A., Royer, T., & Davis, I. S. (2009). Effect of laterally wedged foot orthoses on rearfoot and hip mechanics in patients with medial knee osteoarthritis. *Prosthet Orthot Int, 33*(2), 107-116. doi:10.1080/03093640802613237

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. *J Orthop Res, 25*(9), 1121-1127. doi:10.1002/jor.20423

Chapman, G. J., Parkes, M. J., Forsythe, L., Felson, D. T., & Jones, R. K. (2015). Ankle motion influences the external knee adduction moment and may predict who will respond to lateral wedge insoles?: an ancillary analysis from the SILK trial. *Osteoarthritis Cartilage, 23*(8), 1316-1322. doi:10.1016/j.joca.2015.02.164

Dessery, Y., Belzile, E., Turmel, S., & Corbeil, P. (2016). Effects of foot orthoses with medial arch support and lateral wedge on knee adduction moment in patients with medial knee osteoarthritis. *Prosthet Orthot Int*. doi:10.1177/0309364616661254

Duivenvoorden, T., van Raaij, T. M., Horemans, H. L., Brouwer, R. W., Bos, P. K., Bierma-Zeinstra, S. M., . . . Reijman, M. (2014). Do Laterally Wedged Insoles or Valgus Braces Unload the Medial Compartment of the Knee in Patients With Osteoarthritis? *Clin Orthop Relat Res*, 1-10. doi:10.1007/s11999-014-3947-5

Duivenvoorden, T., van Raaij, T. M., Horemans, H. L., Brouwer, R. W., Bos, P. K., Bierma-Zeinstra, S. M., . . . Reijman, M. (2015). Do laterally wedged insoles or valgus braces unload the medial compartment of the knee in patients with osteoarthritis? *Clin Orthop Relat Res, 473*(1), 265-274. doi:10.1007/s11999-014-3947-5

Duval, S., & Tweedie, R. (2000). Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics, 56*(2), 455-463.

Fantini Pagani, C. H., Hinrichs, M., & Bruggemann, G. P. (2012). Kinetic and kinematic changes with the use of valgus knee brace and lateral wedge insoles in patients with medial knee osteoarthritis. *J Orthop Res, 30*(7), 1125-1132. doi:10.1002/jor.22032

Farrokhi, S., Voycheck, C. A., Tashman, S., & Fitzgerald, G. K. (2013). A biomechanical perspective on physical therapy management of knee osteoarthritis. *J Orthop Sports Phys Ther, 43*(9), 600-619. doi:10.2519/jospt.2013.4121

Hatfield, G. L., Cochrane, C. K., Takacs, J., Krowchuk, N. M., Chang, R., Hinman, R. S., & Hunt, M. A. (2016). Knee and ankle biomechanics with lateral wedges with and without a custom arch support in those with medial knee osteoarthritis and flat feet. *J Orthop Res, 34*(9), 1597-1605. doi:10.1002/jor.23174

Higgins, J. P., Altman, D. G., Gotzsche, P. C., Juni, P., Moher, D., Oxman, A. D., . . . Cochrane Statistical Methods, G. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ, 343*, d5928. doi:10.1136/bmj.d5928

Higgins, J. P., & Thompson, S. G. (2002). Quantifying heterogeneity in a meta-analysis. *Stat Med, 21*(11), 1539-1558. doi:10.1002/sim.1186

Higgins, J. P., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *BMJ, 327*(7414), 557-560. doi:10.1136/bmj.327.7414.557

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 Musculoskelet Disord, 10*, 146. doi:10.1186/1471-2474-10-146

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. *Clin Biomech (Bristol, Avon), 27*(1), 27-33. doi:10.1016/j.clinbiomech.2011.07.010

Hinman, R. S., Bowles, K. A., Payne, C., & Bennell, K. L. (2008). Effect of length on laterally-wedged insoles in knee osteoarthritis. *Arthritis Rheum, 59*(1), 144-147. doi:10.1002/art.23249

Hinman, R. S., Payne, C., Metcalf, B. R., Wrigley, T. V., & Bennell, K. L. (2008). Lateral wedges in knee osteoarthritis: what are their immediate clinical and biomechanical effects and can these predict a three-month clinical outcome? *Arthritis Rheum, 59*(3), 408-415. doi:10.1002/art.23326

Hunt, M. A., Takacs, J., Krowchuk, N. M., Hatfield, G. L., Hinman, R. S., & Chang, R. (2017). Lateral wedges with and without custom arch support for people with medial knee osteoarthritis and pronated feet: an exploratory randomized crossover study. *J Foot Ankle Res, 10*, 20. doi:10.1186/s13047-017-0201-x

Iijima, H., Fukutani, N., Aoyama, T., Fukumoto, T., Uritani, D., Kaneda, E., . . . Matsuda, S. (2015). Clinical Phenotype Classifications Based on Static Varus Alignment and Varus Thrust in Japanese Patients With Medial Knee Osteoarthritis. *Arthritis Rheumatol, 67*(9), 2354-2362. doi:10.1002/art.39224

Jones, R. K., Chapman, G. J., Findlow, A. H., Forsythe, L., Parkes, M. J., Sultan, J., & Felson, D. T. (2013). A new approach to prevention of knee osteoarthritis: reducing medial load in the contralateral knee. *J Rheumatol, 40*(3), 309-315. doi:10.3899/jrheum.120589

Jones, R. K., Chapman, G. J., Forsythe, L., Parkes, M. J., & Felson, D. T. (2014). The relationship between reductions in knee loading and immediate pain response whilst wearing lateral wedged insoles in knee osteoarthritis. *J Orthop Res, 32*(9), 1147-1154. doi:10.1002/jor.22666

Jordan, K. M., Arden, N. K., Doherty, M., Bannwarth, B., Bijlsma, J. W., Dieppe, P., . . . Standing Committee for International Clinical Studies Including Therapeutic Trials, E. (2003). EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Ann Rheum Dis, 62*(12), 1145-1155. doi:10.1136/ard.2003.011742

Kakihana, W., Akai, M., Nakazawa, K., Naito, K., & Torii, S. (2007). Inconsistent knee varus moment reduction caused by a lateral wedge in knee osteoarthritis. *Am J Phys Med Rehabil, 86*(6), 446-454. doi:10.1097/PHM.0b013e31805bfff5

Kakihana, W., Akai, M., Nakazawa, K., Takashima, T., Naito, K., & Torii, S. (2005). Effects of laterally wedged insoles on knee and subtalar joint moments. *Arch Phys Med Rehabil, 86*(7), 1465-1471. doi:https://doi.org/10.1016/j.apmr.2004.09.033

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. *Am J Phys Med Rehabil, 83*(4), 273-278.

Kellgren, J. H., & Lawrence, J. S. (1957). Radiological assessment of osteo-arthrosis. *Ann Rheum Dis, 16*(4), 494-502.

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. *Arch Phys Med Rehabil, 83*(7), 889-893. doi:http://dx.doi.org/10.1053/apmr.2002.33225

Lewinson, R. T., Vallerand, I. A., Collins, K. H., Wiley, J. P., Lun, V. M. Y., Patel, C., . . . Stefanyshyn, D. J. (2016). Reduced knee adduction moments for management of knee osteoarthritis:: A three month phase I/II randomized controlled trial. *Gait Posture, 50*, 60-68. doi:10.1016/j.gaitpost.2016.08.027

Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gotzsche, P. C., Ioannidis, J. P., . . . Moher, D. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med, 151*(4), W65-94.

Lipsey, M. W., & Wilson, D. B. (2001). *Practical meta-analysis*: SAGE Publications, Inc.

Liu, X., & Zhang, M. (2013). Redistribution of knee stress using laterally wedged insole intervention: Finite element analysis of knee-ankle-foot complex. *Clin Biomech, 28*(1), 61-67. doi:10.1016/j.clinbiomech.2012.10.004

Maillefert, J. F., Hudry, C., Baron, G., Kieffert, P., Bourgeois, P., Lechevalier, D., . . . Dougados, M. (2001). Laterally elevated wedged insoles in the treatment of medial knee osteoarthritis: a prospective randomized controlled study. *Osteoarthritis Cartilage, 9*(8), 738-745. doi:10.1053/joca.2001.0470

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. doi:https://doi.org/10.1016/S0268-0033(02)00073-6

Moyer, R. F., Birmingham, T. B., Dombroski, C. E., Walsh, R. F., Leitch, K. M., Jenkyn, T. R., & Giffin, J. R. (2013). Combined effects of a valgus knee brace and lateral wedge foot orthotic on the external knee adduction moment in patients with varus gonarthrosis. *Arch Phys Med Rehabil, 94*(1), 103-112. doi:10.1016/j.apmr.2012.09.004

Nakajima, K., Kakihana, W., Nakagawa, T., Mitomi, H., Hikita, A., Suzuki, R., . . . Fukui, N. (2009). Addition of an arch support improves the biomechanical effect of a laterally wedged insole. *Gait Posture, 29*(2), 208-213. doi:10.1016/j.gaitpost.2008.08.007

Peat, G., McCarney, R., & Croft, P. (2001). Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. *Annals of the Rheumatic Diseases, 60*(2), 91-97. doi:Doi 10.1136/Ard.60.2.91

Pham, T., Maillefert, J. F., Hudry, C., Kieffert, P., Bourgeois, P., Lechevalier, D., & Dougados, M. (2004). Laterally elevated wedged insoles in the treatment of medial knee osteoarthritis11This work was supported in part by the 'Programme Hospitalier de Recherche Clinique' (AOM 97 184) of the French Health Ministry. *Osteoarthritis and Cartilage, 12*(1), 46-55. doi:10.1016/j.joca.2003.08.011

Picavet, H. S., & Hoeymans, N. (2004). Health related quality of life in multiple musculoskeletal diseases: SF-36 and EQ-5D in the DMC3 study. *Ann Rheum Dis, 63*(6), 723-729. doi:10.1136/ard.2003.010769

Sasaki, T., & Yasuda, K. (1987). Clinical evaluation of the treatment of osteoarthritic knees using a newly designed wedged insole. *Clin Orthop Relat Res*(221), 181-187.

Schardt, C., Adams, M. B., Owens, T., Keitz, S., & Fontelo, P. (2007). Utilization of the PICO framework to improve searching PubMed for clinical questions. *BMC Med Inform Decis Mak, 7*, 16. doi:10.1186/1472-6947-7-16

Schipplein, O. D., & Andriacchi, T. P. (1991). Interaction between active and passive knee stabilizers during level walking. *J Orthop Res, 9*(1), 113-119. doi:10.1002/jor.1100090114

Shimada, S., Kobayashi, S., Wada, M., Uchida, K., Sasaki, S., Kawahara, H., . . . Baba, H. (2006). Effects of disease severity on response to lateral wedged shoe insole for medial compartment knee osteoarthritis. *Arch Phys Med Rehabil, 87*(11), 1436-1441. doi:10.1016/j.apmr.2006.08.018

Tipnis, R. A., Anloague, P. A., Laubach, L. L., & Barrios, J. A. (2014). The dose-response relationship between lateral foot wedging and the reduction of knee adduction moment. *Clin Biomech (Bristol, Avon), 29*(9), 984-989. doi:10.1016/j.clinbiomech.2014.08.016

van der Esch, M., Knoop, J., van der Leeden, M., Roorda, L. D., Lems, W. F., Knol, D. L., & Dekker, J. (2015). Clinical phenotypes in patients with knee osteoarthritis: a study in the Amsterdam osteoarthritis cohort. *Osteoarthritis Cartilage, 23*(4), 544-549. doi:10.1016/j.joca.2015.01.006

Wise, B. L., Niu, J., Yang, M., Lane, N. E., Harvey, W., Felson, D. T., . . . Multicenter Osteoarthritis, G. (2012). Patterns of compartment involvement in tibiofemoral osteoarthritis in men and women and in whites and African Americans. *Arthritis Care Res (Hoboken), 64*(6), 847-852. doi:10.1002/acr.21606

Xing, F., Lu, B., Kuang, M. J., Wang, Y., Zhao, Y. L., Zhao, J., . . . Ma, X. L. (2017). A systematic review and meta-analysis into the effect of lateral wedge arch support insoles for reducing knee joint load in patients with medial knee osteoarthritis. *Medicine (Baltimore), 96*(24), e7168. doi:10.1097/MD.0000000000007168

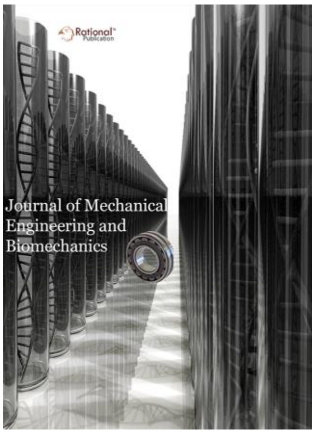
Zhao, D., Banks, S. A., Mitchell, K. H., D'Lima, D. D., Colwell, C. W., Jr., & Fregly, B. J. (2007). Correlation between the knee adduction torque and medial contact force for a variety of gait patterns. *J Orthop Res, 25*(6), 789-797. doi:10.1002/jor.20379

Study II: The effects on lower limbs kinematics of different lateral wedge insoles

Authors:

Vitor Ferreira, Leandro Machado, Paulo Roriz

Journal:



Journal of Mechanical Engineering and Biomechanics, Vol. 4, Issue 4, Page 77-82, (2020). https://doi.org/10.24243/JMEB/4.4.233

ABSTRACT: Lateral wedge insoles are typically used in patients with knee osteoarthritis. Several types and amounts of lateral wedge insoles have already been studied. However, the biomechanical response to lateral wedge insoles in the lower limb´s is not well known. Therefore, the aim of this study was to assess the immediate effects of lateral wedge insoles on lower limb's kinematics in healthy population. Twenty-three healthy volunteers (15 males), with age of 21.0 ± 5.13 years, weight of 65.8 ± 8.7 kg, and height 170 ± 5.13 cm were recruited. A motion analysis system with eleven cameras and two force platforms was used for three-dimensional kinematic and kinetic analysis. Six different amounts of wedges were tested: 0° (control condition), 2°, 4°, 6°, 8° and 10 degrees in a randomized order. Participants walked at their self-selected speed and performed at least five valid trials in each of the experimental conditions. Peak values for the lower limb joint angles were computed for each set of each participant. No significant changes ($p > 0.05$) were found in the three planes for the experimental conditions, except for the ankle joint in the frontal plane. A significant difference was found with the 10-degree insole in the eversion movement of the ankle at the first peak of external knee adduction moment. In the knee a significant difference ($p < 0.05$) was confirmed with insoles greater than 6-degrees for the first peak of external knee adduction moment. The increase in eversion of the ankle was the main kinematic change to lateral wedge insoles in the lower limbs. Other indicators should be studied, particularly using kinetic analysis to better understand the mechanism of action of lateral wedge insoles.

Keywords: Kinematics, lateral wedge insoles, gait, peak angles

1. Introduction

Human motion analysis is the systematic study of human motion through instrumentation for measuring body movements (Lu & Chang, 2012). In healthy population looks to be important in order to assess the influence caused by different interventions and provides the critical information needed to understand the role of diseases and to design therapeutic interventions (Favre & Jolles, 2016). Lateral wedge insoles are regularly used to correct altered gait pattern (Hinman, Bowles, & Bennell, 2009). Originally, lateral wedges insoles have been proposed to improve mechanical alignment of the lower limb (Sasaki & Yasuda, 1987; Yasuda & Sasaki, 1987). Subsequent studies have failed to demonstrate a significant change in static lower limb alignment (Maly, Culham, & Costigan, 2002). Yasuda and Sasaki, in the 1980s, described the potential of lateral wedged insoles to manage medial knee osteoarthritis (OA) (Sasaki & Yasuda, 1987). The

mechanism of action proposed undertook a reduction of external knee adduction moment (EKAM) (Kim, Richards, Jones, & Hegab, 2004). The EKAM is a biomechanical parameter used to indirectly measure the distribution of internal forces in the knee during walking (Schipplein & Andriacchi, 1991) because local mechanical environment plays an important role in the pathogenesis of the connective tissues (Felson, 2013). Excessive knee load is a significant risk factor for progressive structural degradation particular on medial tibiofemoral compartment (Felson & Radin, 1994; Miyazaki et al., 2002). Another risk factor that contributes to the evolution of medial knee OA is the static varus alignment due to increased load in the medial compartment (Tanamas et al., 2009).

The exact amount of wedging required to induce a biomechanical response with clinical significance is not well known. To our knowledge, only one study sought to understand the immediate biomechanical effects with different angulations (Tipnis, Anloague, Laubach, & Barrios, 2014). Was tested seven inclinations of lateral wedging (0°, 2°, 4°, 6°, 8°, 10° and 12 degrees) and was found a clear reduction on first peak EKAM in all experimental conditions compared the 0° insole. In that study the acute effects on foot was not analysed, only the effects on main kinetic and kinematic biomechanical parameters of the knee were studied. The authors of that study concluded that insoles with angulations between 4º to 6º presented the best biomechanical effects without compromising comfort with their use. In this area of study, several biomechanical parameters, types, shapes and amounts of wedges have been studied. In a recent study, the application of different forms of wedge showed diverse variations in range of movement and in the peak moments of the ankle, knee and hip joints (Soares, de Castro, Mendes, & Machado, 2014). However, only one type of wedge (in lateral front of the foot) showed a statistically significant difference from control insole. While many studies have shown evidence on the reduction of EKAM with the application of the lateral wedge insoles (Radzimski, Mündermann, & Sole, 2012), the analysis of the individual percentual change in the peak EKAM shows an interesting individual variability. About 20% of individuals failing to respond to the application of the insoles (Hinman, Bowles, Metcalf, Wrigley, & Bennell, 2012). The mechanism of action is thought to pass thought the lateral

displacement of center of pressure (CoP) under the foot which creates a displacement in the mechanical axis of the limb (Hinman et al., 2012). Shifting the CoP will cause a reduction of the external knee adduction moment arm to decrease, reducing the torque caused by the ground reaction forces. This in turn will lead to a better distribution of forces in the compartments of the knees.

Studies on the clinical benefits are still inconclusive which indicates that the biomechanical response may depend on variables that confound the effects of insoles (Kluge, Krinner, Lochmann, & Eskofier, 2017). Therefore, it will be necessary to continue studying the biomechanical effects of lateral wedge insoles to understand better the effects on lower limbs kinematics and to provide basic data allowing the identification of the main changes when insoles were applied. This study will allow to analyse better the acute effects of the lateral wedge insoles in particular on the foot and consequently to know better the causative mechanism of the insoles. The systematic increases of small angulations of the wedges could allow to observe changes in the kinematics of a more consistent form. The results of our study can contribute to the interpretation of the changes in lower limbs induced by the application of lateral wedge insoles. Thus, the aim of this study was to investigate the immediate effects of lateral wedge insoles on lower limbs kinematics in healthy population. Furthermore, we hypothesized that changes in the mechanical position of the foot during the stance phase may be one of the main causes of the EKAM reduction.

2. Methods and materials

2.1 Participants

Twenty-three healthy volunteers (15 males, with mean age of 21.0 ± 5.13, weight of 65.8 ± 8.7 kg, and height 170 ± 5.13 cm) were recruited. The inclusion criteria for the subjects included healthy young adults, aged 18 – 40 years, with a knee morphology in varus and without any symptoms or neuromuscular disorders. The presence of a varus morphology was validated by an experienced physiotherapist. No previous history of ankle, knee or hip pain was acceptable. This study was conducted in accordance with the principles of the Declaration of

Helsinki and was approved by the Ethics Committee of the Faculty of Sports of the University of Porto. All participants freely gave their written consent to participate after a verbal and written explanation of the study.

2.2 Equipment and data collect

Eleven cameras three-dimensional motion analysis (Qualisys, Gothenburg, Sweden) sampling at 200 Hz synchronized with four force platforms (Bertec, Columbus, USA) sampling at 1000 Hz, were used to collect the kinematic and kinetic data from participants walking along a 10-meter walkway. The Calibrated Anatomical System Technique (CAST) (Cappozzo, Catani, Croce, & Leardini, 1995) was employed to determine the movement of the segments during the walking trials. Reflective markers were attached on the principal bony prominences bilaterally on the subject's lower limbs and pelvis. Respectively in anterior superior iliac spine, posterior superior iliac spine, greater trochanter, medial condyles, lateral condyles, fibula head, tibial tubercle, lateral malleolus and medial malleolus. The markers at locations of calcaneus, 1st, 2nd and 5th metatarsal heads were glued on the shoes and the feet were assumed to be a rigid body. Four rigid clusters were placed bilaterally on anterior-lateral aspect of the leg and thigh. All the markers remained attached during the entire data collection. A static calibration of the markers was performed before walking trials. Participants were not given any walking instructions other than to walk at their self-selected speed and performed at least five valid trials in each of the experimental condition in a randomized order. A successful trial was defined as a trial in which the participant walked naturally landing the whole foot on the force plate. A several of walking trials were performed between conditions to allow the subjects to adapt to the new insole. Six experimental conditions were tested: a control condition (shoes with a 0° insole), and lateral wedge insoles with 2°, 4°, 6°, 8° and 10 degrees. The insoles were full-length costume made with a pronating wedge posterior long (Capron Podologie, France; Ref.: 8004F). An inclinometer was used to confirm the inclination of the insoles. Individuals used

their own shoes (flat shoes) and the insoles were worn bilaterally but only the data from the right side is presented.

2.3 Data Analysis

Post-processing calculation of the kinematic and kinetic time series data was conducted using Visual3D software (Version 6.00.12, C-Motion, Rockville, USA). Data were filtered (6 Hz) using a Butterworth 4th order filter. Lower limb joint angles (using a X-Y-Z Euler rotation sequence equivalent to the joint coordinate system) and joint moments (determined through inverse dynamics) were computed and expressed relatively to the proximal segment. Peak values for lower limb joint angles were computed for each set for each participant. The EKAM was expressed with respect to the tibial reference frame. The kinematic data were expressed in degrees (°) and were time normalized to 100% of the stance phase. The group mean kinematics were exported to SPSS 24.0 (IBM, Chicago, IL) and processed using a single factor, repeated measures analysis of variance. Post hoc pairwise comparisons were used to determine differences between experimental conditions to the baseline condition (0° insole). All tests were performed at the 95% confidence interval ($p < 0.05$) with a Bonferroni correction to adjust for the multiple pairwise comparisons.

3 Results

Lower limb's kinematic waveforms in several planes were presented in **Figure 10**. No significative changes were found in the three planes, except in ankle joint at the frontal plane. For the knee, hip and pelvis joints, no significant changes were found with the incremental application of the lateral wedge insoles. The overall effect shows a gradual increase with the increasing of the wedge insoles in the eversion movement of the ankle. The peak eversion angle at first peak EKAM improved almost two degrees with the 10-degree insole.

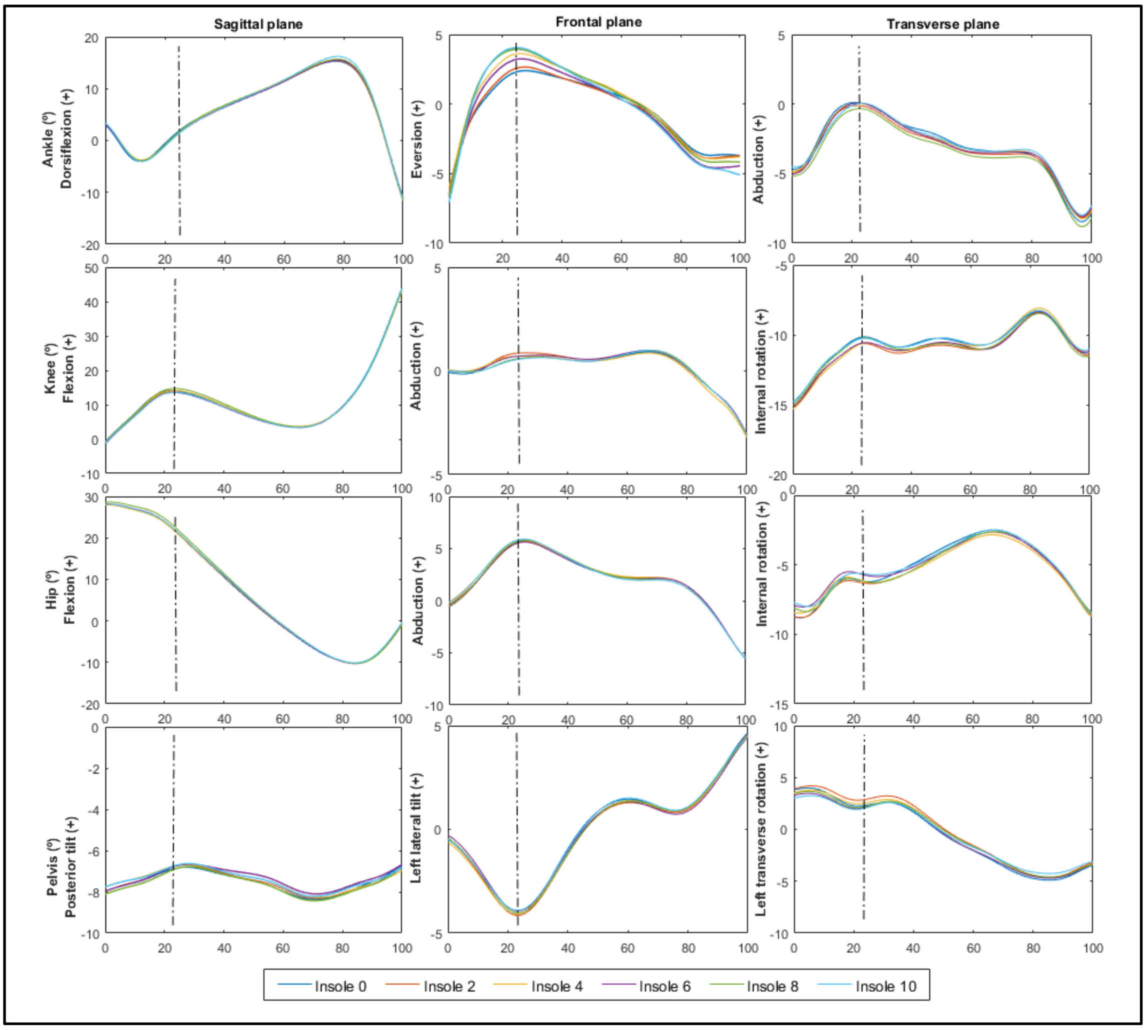


Figure 10. Ankle, knee, hip and pelvis kinematics waveforms during the stance phase. Each colour line represents the mean of different wedge insole. Vertical dashed lined represents the timing of first peak at external knee adduction moment.

Table 4 shows biomechanical parameters studied. Significative changes ($p = 0.027$) was found with the 10-degree insole for the ankle eversion when the first peak of EKAM occurs. When we tried to confirm the reduction in the first peak of the EKAM with the insoles used, was found a statistical difference ($p < 0.05$) with lateral wedge insoles greater than 6-degrees. Compare to the control condition, was found a reduction of 3% of EKAM with the 6-degree insole, a reduction of 6% with the 8-degree insole and 11% with the 10-degree insole.

Table 4. Biomechanical parameters in the six conditions with corresponding statistical findings.

	0° Insole	2° Insole	4° Insole	6° Insole	8° Insole	10° Insole
Peak eversion ankle angle (°)	2.98 (±2.71)	3.19 (±2.78)	4.04 (±3.33)	3.66 (±2.68)	4.40 (±3.65)	4.37 (±4.24)
p-values		*1.000*	*1.000*	*1.000*	*0.239*	*0.418*
Ankle eversion angle at 1st peak EKAM (°)	1.94 (±3.40)	2.32 (±3.34)	3.37 (±3.68)	2.89 (±3.07)	3.78 (±9.96)	3.93 (±4.44)
p-values		*1.000*	*0.551*	*0.699*	*0.050*	***0.027***
1st peak EKAM (Nm/Kg)	0.398 (±0.127)	0.401 (±0.127)	0.386 (±0.128)	0.377 (±0.131)	0.373 (±0.133)	0.355 (±0.133)
p-values		*1.000*	*0.219*	***0.020***	***0.007***	***0.000***

Values reported as mean (SD). *P* value different from the 0° condition; (bold indicates significance).

4 Discussion

This is the first study to evaluate the immediate effects of the incremental application of insoles with minimal differences on biomechanics of the foot. Previous studies investigating the effects of lateral wedge insoles focus only on the knee or used only one or two lateral wedges insoles. Our study considered six lateral wedge insoles with an incremental difference of two degrees between them. The overall effect of the lateral wedge insoles results in an increase on the range of motion in the frontal plane on the foot. There was an increase in eversion movement with higher wedges, and in particular there was a significant increase in eversion at first peak EKAM. The ankle is among the first joints in the lower extremity to be influenced by the wedged insoles (Butler, Barrios, Royer, & Davis, 2009) and the lack of significant changes in range of movement on the foot, in particular at peak eversion is inconsistent with the previous literature (Chapman, Parkes, Forsythe, Felson, & Jones, 2015; Hinman et al., 2012; Tipnis et al., 2014). An explanation for this may be related with the format of the wedge used in our study. In our study, was used a lateral wedge that fills the outer half of the heel and in previous studies were used wedges that filled the entire heel. This difference in the format of the wedge may decrease the tendency for a greater

foot eversion. However, the changes found at the first peak EKAM were consistent with previous studies. Despite the different form of the wedge statistically significant values were found in the first peak EKAM. In our study, the use of a 10-degree wedge when compared to the control condition showed an increase of eversion of about 2 degrees. Result similar to a previous study where the authors found an increase of about one degree of eversion during the first peak EKAM (Chapman et al., 2015). In addition to the type of wedge used, another explanation for this apparent inconsistency may be the footwear used. In our study participants used their own footwear, with understandable differences in configuration of arch support. The presence of the arch support on the shoes could modify the biomechanics of the foot. Nevertheless, a current study (Hatfield et al., 2016) showed that was no significative differences between insoles with and without arch support in the knee reducing first peak EKAM. Although, in the same study it was possible to observe that the lateral wedge with arch support showed differences in the peak ankle eversion and ankle eversion moment compare to lateral wedge without arch support. Another factor that could change the range of motion of the joint may be the walking speed. A current study has shown that range of movement of ankle eversion increased with higher speeds (Kluge et al., 2017). Thus, differences in the footwear and the natural variability of the walking speed may be explanations for these contradictory results in range of movement of ankle eversion.

When we try to understand if the alterations found in kinematics also have effects on the reduction of the first peak EKAM, findings from our study strengthens the evidence, regardless of the form of wedge, that lateral wedge insoles significantly reduce the first peak EKAM. Even in healthy individuals these was statistically significant with lateral wedge insoles greater than 6 degrees and was consistent with numerous studies, particularly in people with knee OA (Hatfield et al., 2016; Hinman et al., 2012; Hinman, Payne, Metcalf, Wrigley, & Bennell, 2008; Jones, Chapman, Forsythe, Parkes, & Felson, 2014). In the study of Tipnis et al (Tipnis et al., 2014), the difference between the 10-degree insole and the control insole at the first peak EKAM was 0.041 Nm/Kg. In ours, a similar value of 0.043 Nm/Kg. When we compared the 6-degree insole with the control

insole a similar result was found. In our study, the change to the control condition was 0.021 Nm/Kg, while in the Tipnis et al. study was 0.034 Nm/Kg. These similar values allow estimate that a 6-degree insole may have an acute effect of EKAM reduction among 0.020 to 0.030 N/Kg, in healthy individuals. Likewise, we can estimate that the 10-degree insole may have an acute effect at the first peak EKAM around 0.040 Nm/Kg. Another interesting aspect was that an increase of almost 1º degree (1.94º to 2.89º) is enough to produce a significative reduction at first peak EKAM. That is, small differences in kinetics translate into important changes in kinetics. However, this small change in the kinematics of the foot did not translate into changes in other joints of the lower limbs.

This experimental study conducted on healthy individuals had some limitations. First, because our study involved healthy participants, we can only draw conclusions about the effects of lateral wedge insoles without the consideration of potential disease-related limitations. Second, the morphology of the foot was not considered for the study. A previous study (Sawada et al., 2016) suggest that foot alignment has different effects in kinematics when wearing lateral wedge insoles. In particular, an individual with a normal foot is more likely to respond to lateral wedge insoles. In future studies will be a characteristic to be taken into account. Thirds, we seek to investigate only the immediate effects. In future studies it will be important to understand if the effects are similar in long-term studies.

5 Conclusions

Our findings demonstrated that lateral wedge insoles seem to promote a greater peak eversion on the foot, specific at first peak EKAM. Other parameters should be studied, particularly kinetic analysis to understand better the mechanism of action of lateral wedge insoles and the effects in the reduction of the first peak EKAM.

References

Butler, R. J., Barrios, J. A., Royer, T., & Davis, I. S. (2009). Effect of laterally wedged foot orthoses on rearfoot and hip mechanics in patients with medial knee osteoarthritis. *Prosthet Orthot Int, 33*(2), 107-116. doi:10.1080/03093640802613237

Cappozzo, A., Catani, F., Croce, U. D., & Leardini, A. (1995). Position and orientation in space of bones during movement: anatomical frame definition and determination. *Clin Biomech (Bristol, Avon), 10*(4), 171-178. doi:10.1016/0268-0033(95)91394-T

Chapman, G. J., Parkes, M. J., Forsythe, L., Felson, D. T., & Jones, R. K. (2015). Ankle motion influences the external knee adduction moment and may predict who will respond to lateral wedge insoles?: an ancillary analysis from the SILK trial. *Osteoarthritis Cartilage, 23*(8), 1316-1322. doi:10.1016/j.joca.2015.02.164

Favre, J., & Jolles, B. M. (2016). Gait analysis of patients with knee osteoarthritis highlights a pathological mechanical pathway and provides a basis for therapeutic interventions. *EFORT Open Rev, 1*(10), 368-374. doi:10.1302/2058-5241.1.000051

Felson, D. T. (2013). Osteoarthritis as a disease of mechanics. *Osteoarthritis Cartilage, 21*(1), 10-15. doi:10.1016/j.joca.2012.09.012

Felson, D. T., & Radin, E. L. (1994). What causes knee osteoarthrosis: are different compartments susceptible to different risk factors? *J Rheumatol, 21*(2), 181-183.

Hatfield, G. L., Cochrane, C. K., Takacs, J., Krowchuk, N. M., Chang, R., Hinman, R. S., & Hunt, M. A. (2016). Knee and ankle biomechanics with lateral wedges with and without a custom arch support in those with medial knee osteoarthritis and flat feet. *J Orthop Res, 34*(9), 1597-1605. doi:10.1002/jor.23174

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 Musculoskelet Disord, 10*, 146. doi:10.1186/1471-2474-10-146

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. *Clin Biomech (Bristol, Avon), 27*(1), 27-33. doi:10.1016/j.clinbiomech.2011.07.010

Hinman, R. S., Payne, C., Metcalf, B. R., Wrigley, T. V., & Bennell, K. L. (2008). Lateral wedges in knee osteoarthritis: what are their immediate clinical and biomechanical effects and can these predict a three-month clinical outcome? *Arthritis Rheum, 59*(3), 408-415. doi:10.1002/art.23326

Jones, R. K., Chapman, G. J., Forsythe, L., Parkes, M. J., & Felson, D. T. (2014). The relationship between reductions in knee loading and immediate pain response whilst wearing lateral wedged insoles in knee osteoarthritis. *J Orthop Res, 32*(9), 1147-1154. doi:10.1002/jor.22666

Kim, W. Y., Richards, J., Jones, R. K., & Hegab, A. (2004). A new biomechanical model for the functional assessment of knee osteoarthritis. *Knee, 11*(3), 225-231. doi:10.1016/S0968-0160(03)00068-1

Kluge, F., Krinner, S., Lochmann, M., & Eskofier, B. M. (2017). Speed dependent effects of laterally wedged insoles on gait biomechanics in healthy subjects. *Gait Posture, 55*, 145-149. doi:10.1016/j.gaitpost.2017.04.012

Lu, T. W., & Chang, C. F. (2012). Biomechanics of human movement and its clinical applications. *Kaohsiung J Med Sci, 28*(2 Suppl), S13-25. doi:10.1016/j.kjms.2011.08.004

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. doi:https://doi.org/10.1016/S0268-0033(02)00073-6

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. doi:DOI 10.1136/ard.61.7.617

Radzimski, A. O., Mündermann, A., & Sole, G. (2012). Effect of footwear on the external knee adduction moment — A systematic review. *The Knee, 19*(3), 163-175. doi:10.1016/j.knee.2011.05.013

Sasaki, T., & Yasuda, K. (1987). Clinical evaluation of the treatment of osteoarthritic knees using a newly designed wedged insole. *Clin Orthop Relat Res*(221), 181-187.

Sawada, T., Tokuda, K., Tanimoto, K., Iwamoto, Y., Ogata, Y., Anan, M., . . . Shinkoda, K. (2016). Foot alignments influence the effect of knee adduction moment with lateral wedge insoles during gait. *Gait Posture, 49*, 451-456. doi:10.1016/j.gaitpost.2016.08.011

Schipplein, O. D., & Andriacchi, T. P. (1991). Interaction between active and passive knee stabilizers during level walking. *J Orthop Res, 9*(1), 113-119. doi:10.1002/jor.1100090114

Soares, D. P., de Castro, M. P., Mendes, E., & Machado, L. (2014). Influence of wedges on lower limbs' kinematics and net joint moments during healthy elderly gait using principal component analysis. *Human Movement Science, 38*, 319-330. doi:10.1016/j.humov.2014.09.007

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 Rheum, 61*(4), 459-467. doi:10.1002/art.24336

Tipnis, R. A., Anloague, P. A., Laubach, L. L., & Barrios, J. A. (2014). The dose-response relationship between lateral foot wedging and the reduction of knee adduction moment. *Clin Biomech (Bristol, Avon), 29*(9), 984-989. doi:10.1016/j.clinbiomech.2014.08.016

Yasuda, K., & Sasaki, T. (1987). The mechanics of treatment of the osteoarthritic knee with a wedged insole. *Clin Orthop Relat Res*(215), 162-172.

Study III: Biomechanics performance in 30-s chair stand test in patients with medial knee osteoarthritis

Authors:

Vitor Ferreira, Leandro Machado, Adélio Vilaça, Francisco Xará-Leite, Paulo Roriz

Journal:

Int. J. Human Factors and Ergonomics, Vol. 6, No. 4 (2019). https://doi.org/10.1504/IJHFE.2019.105359

ABSTRACT: Knee osteoarthritis (OA) is characterized by weakness and knee joint pain which may affect the performance in some activities of daily life like sit-to-stand. The aim of this study was to evaluate the strategies used by patients with knee OA when performing the 30-second chair stand test (30s-CST), and its association with their well-being. Twenty-one patients with knee OA were recruited. A 3D motion analysis system and two force plates were used to capture the kinematics and kinetics during the 30s-CST. The sit-to-stand and the stand-to-sit phases of the test were analysed independently. Significant differences were found ($p < 0.05$) between the first three and the last three repetitions in the 30s-CST for knee joint moment and power. No significant differences have been found between the most painful knee and the contralateral knee. The correlations found between the subscales of the Knee injury and Osteoarthritis Outcome Score (KOOS) and biomechanical parameters were significant ($p < 0.05$). Patients with the best score in KOOS subscales also showed better performance in the 30s-CST. Assistive technologies that maximize biomechanical strategies could be a valuable contribution to improve the well-being of these patients.

Keywords: sit-to-stand; power; joint moment; knee; KOOS; VAS; motion analysis; performance; well-being.

1. Introduction

Osteoarthritis (OA) is one of the world's leading causes of impairment of mobility in the elderly population and is defined by structural alterations of subchondral bone and articular cartilage in joint spaces (Felson, 2006). Typically, OA affects weight-bearing joints, such as the knee, leading to severe alterations in their biomechanics and affecting most of the daily life activities (Vincent, Conrad, Fregly, & Vincent, 2012). Knee OA is characterized by weakness in the quadriceps femoris muscle and knee joint pain compromising the well-being of these patients (Palmieri-Smith, Thomas, Karvonen-Gutierrez, & Sowers, 2010). Knee flexion and extension actions with weight bearing are particularly difficult for those suffering from OA. The degree of physical function impairment can be assessed using several protocols. The Osteoarthritis Research Society International (OARSI) recommends the 30-second chair stand test (30s-CST). It is one of the minimal core set of performance-based measures of physical function for people diagnosed with knee OA (Dobson et al., 2013). Basically, the test comprises a sit-to-stand and a stand-to-sit task repeated for 30 seconds

(Turcot, Armand, Fritschy, Hoffmeyer, & Suva, 2012). Because it can assess the lower body function and correlates with isometric strength it is one of the most used functional tests (Macfarlane, Chou, Cheng, & Chi, 2006). The 30s-CST, is similar to other tests, such as the 5-stands test and the timed up and go test (TUG) and is able to differentiate between subjects with different frailty levels (Millor, Lecumberri, Gomez, Martinez-Ramirez, & Izquierdo, 2013). Nevertheless, the 30s-CST also enables to assess the effect of fatigue, due its duration and, consequently, the repetitions involved (Roldan-Jimenez, Bennett, & Cuesta-Vargas, 2015).

The biomechanics of the 30s-CST has been studied in different populations (Anan et al., 2015; Boonstra, Schwering, De Waal Malefijt, & Verdonschot, 2010). For instance, the sit-to-stand task requires a peak joint moment greater than the observed in stair climbing or walking tasks (Rodosky, Andriacchi, & Andersson, 1989). The duration of the sit-to-stand task is, generally, lower in young populations than it is in the elderly (Papa & Cappozzo, 2000). Patients with unilateral knee OA also put 10% more of their weight on the contralateral side (Turcot et al., 2012). Likewise, patients with knee OA seem to have significant reduced energy absorption in the knee extensors (Anan et al., 2015) and significant higher ground reaction force integrals for both legs (Duffell, Gulati, Southgate, & McGregor, 2013). On the other hand, patients with knee OA, increase the contralateral shift of the Center of Mass (CoM) as a strategy to unload the affected knee and reduce pain (Naili, Brostrom, Gutierrez-Farewik, & Schwartz, 2018). The height of the chair seat, use of armrests, and foot position are understandable determinants for the quality of movement execution (Al Amer, Sabbahi, Alrowayeh, Bryan, & Olson, 2018; Janssen, Bussmann, & Stam, 2002). The analyses of the 30s-CST biomechanics could be useful for guiding clinical decision making and to develop new technologies that help patients in performing this task.

Although the decrease in movement quality during the execution of the various repetitions of the test is foreseeable, to our knowledge no other study has attempted to understand the biomechanical changes during the execution of the test, particularly between the first and the last repetitions. Better understanding

of these changes and their association with symptoms is a key issue in adapting rehabilitation protocols to this specific group of patients. Therefore, the aim of this study was to evaluate the strategies used by patients with moderate medial knee OA when performing the 30s-CST, and their relationship with symptomatology and function.

2. Methods

2.1 Subjects

Twenty-one patients (7 men; mean age 62 ± 7.9 years; weight 76.0 ± 11.7 kg, height 1.60 ± 0.01 m and body mass index 29.8 ± 5.4 kg/m^2) with symptomatic medial knee OA were recruited from local hospital orthopaedic services to participate in this study. Clinical and radiological inclusion criteria followed those established by the American College of Rheumatology (Altman et al., 1986): medial knee pain; morning stiffness greater than 30 minutes and/or crepitus during motion. Additionally, only patients with grade 2 and 3 on the Kellgren–Lawrence grading scale (Kellgren & Lawrence, 1957) were included. The exclusion criteria defined were the presence of a joint prosthesis or an history of lower limb, neurological or orthopaedic disorders other than the presence of knee OA, that could affect the patient gait or balance. Written informed consents were obtained from all subjects. The study was approved by hospital and university ethics committees.

2.2 Pain and functional level assessment

Symptoms are essential for measuring the quality of life and well-being of patients. Symptomatology and function were measured by the Visual Analogue Scale (VAS) and the Knee injury Osteoarthritis Outcome Score (KOOS) previously validated for Portuguese population (Goncalves, Cabri, Pinheiro, & Ferreira, 2009). The VAS is a valid tool for measuring pain at one point in time (Kersten, White, & Tennant, 2014) with the extremes being “no pain at all” (0 mm) and “worst imaginable pain” (100 mm). The KOOS is a measure that allows to

assess patients with knee injuries and OA in five dimensions: pain (9 items), other symptoms (7 items), function in daily living (ADL) (17 items), function in sport and recreation (5 items), and knee-related quality of life (QoL) (4 items) (Roos, Roos, Lohmander, Ekdahl, & Beynnon, 1998). Standardized answer options are provided, and each question is rated on a scale from 0 to 4. A normalized score (100 indicating no symptoms and 0 indicating extreme symptoms) is then calculated for each subscale. The format is user-friendly, and the questionnaire takes about 10 minutes to complete (de Groot, Favejee, Reijman, Verhaar, & Terwee, 2008). For a better understanding of the data, the knee that was referred to as the most painful in the VAS was designated as painful knee and the knee referred to as the least painful or without pain in the VAS was designated as non-painful knee.

2.3 Instrumentation

A 3D motion analysis system (Qualisys Oqus, Gothenburg, Sweden) equipped with 11-cameras was used to capture the lower body kinematics during the 30s-CST. Reflective markers were placed on the pelvis and on both lower limbs according to the Calibrated Anatomical System Technique (CAST) protocol (Cappozzo, Catani, Croce, & Leardini, 1995). A total of 42 reflective markers were placed at the following anatomical landmarks: the anterior superior iliac spines, the posterior superior iliac spines, the greater trochanters, the medial condyles, the lateral condyles, the fibula head, the tibial tubercle, the lateral malleolus and the medial malleolus. The feet were assumed as rigid bodies and the corresponding markers, namely, the calcaneus, 1^{st}, 2^{nd} and 5^{th} metatarsal heads were glued on the shoes. Four rigid clusters were placed bilaterally on the anterior-lateral aspect of the leg and thigh. All the markers remained attached during the entire data collection. A static calibration of the markers was performed before walking trials. Two force plates (Bertec, Columbus, USA) embedded in the floor were used to capture the ground reaction forces for each foot. The motion and force plate data were synchronized and sampled at 200 and 1000 Hz, respectively.

2.4 30-second chair stand test assessment

All the subjects were evaluated in a standardized position and with the same chair. The subjects sat on an armless chair with the knees at 90º and the arms crossed in the chest. The feet were allowed to be placed in a comfortable position. Starting from the seated position, the subjects stands completely up so hips and knees were fully extended. Then they sit completely so the bottom fully touches the seat (Jones, Rikli, & Beam, 1999). Each subject completed the maximal repetitions at self-speed during the 30-second. Some repetitions were performed prior to the test by all participants in order to be familiarized with the task.

2.5 Data analysis

The 30s-CST was divided in two phases, the ‘stand-up’ and ‘sit-down’, from the movement of sit-to-stand and stand-to-sit respectively (Millor et al., 2013). The stand-up position was defined as the maximum extension of the knee and the sit-down position was defined as the maximum flexion of the knee. These instants were identified by an algorithm from the information of the reflective markers of the knee in the sagittal plane. The first three and the last three repetitions from sit-to-stand and stand-to-sit were used for data analysis. The mean of each the three repetitions was used to further analysis. Only data from sagittal plane was analysed.

Joint angles, joint moments and joint power were calculated using Visual3D (Version 6.00.12, C-Motion, Rockville, USA). All raw data were smoothed using a fourth-order Butterworth lowpass digital filter of 6 Hz. The peak joint moments and power were normalized for body weight (Nm/kg and W/kg respectively). Joint angles were referred to the orientation of a segment relative to the local segment and express in degrees (º). The peak angle of extension and flexion of the knee was calculated. Joint moments were resolved by proximal coordinate system, and the peak values calculated for the phase of sit-to-stand and stand-to-sit. Joint power was resolved to the proximal segment and also calculated for the two phases. A positive power indicates the muscles of the knee joint are generating

mechanical energy, and a negative power suggests they are absorbing energy (Winter, 2009).

All values are presented as mean and standard deviation (±). The T-test for independent samples was used to analyse the difference between the knees (painful or non-painful) and biomechanical parameters. The Person's correlation was calculated to evaluate the associations between clinical (i.e., pain, function) and biomechanical parameters. Tests were completed with SPSS 25.0 (IBM, Chicago, IL). The 95% confidence interval ($p < 0.05$) was adopted.

3. Results

The patients performed on average 12.2 (± 2.3) repetitions during the 30s-CST test, with a minimum of 8 and a maximum of 17 repetitions.

The results of KOOS subscales profile are shown in **Figure 11**. The participants reported a better outcome in the subscale symptoms (55.8 ± 16.0) and a worse outcome in the subscale knee related QoL (37.7 ± 16.2).

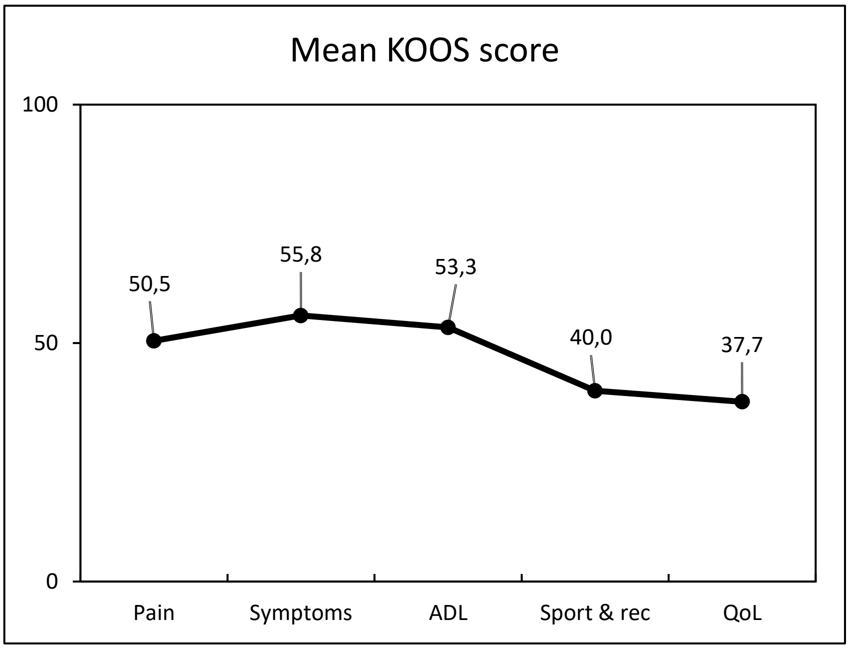


Figure 11. KOOS profile. Mean scores at subscales: ADL (function in daily living); QoL (quality of life); Sport & rec (function in sport and recreation).

Table 5 presents the values of biomechanical parameters of the first and the last three repetitions in the 30s-CST test. No differences (p > 0.05) have been found in the stand-to-sit phase between the first three and the last three repetitions for joint moment and joint power, either for the painful or non-painful knee. In the sit-to-stand phase, statistical differences (p < 0.05) were found for joint moment and power, either for the painful knee and the non-painful knee. In the painful knee, the patients performed an extension moment of 0.610 Nm/kg in the first three repetitions in relation to 0.567 Nm/kg in the last three repetitions (p = 0.000).

Table 5. Mean, standard deviation (SD) and *p* value of biomechanical parameters of the first three (Moment 1) and the last three (Moment 2) repetitions, calculated from the sit-to-stand and stand-to-sit phases for patients with knee OA.

	Sit-to-Stand			**Stand-to-Sit**		
	Mean	SD	*p*	Mean	SD	*p*
Pain Knee Moment 1 (Nm/kg)	0.610	0.255	0.000*	0.490	0.271	0.053
Pain Knee Moment 2 (Nm/kg)	0.567	0.253		0.465	0.265	
Mean Pain Knee (Nm/kg)	0.588	0.253		0.477	0.266	
No Pain Knee Moment 1 (Nm/kg)	0.574	0.255	0.019*	0.444	0.241	0.785
No Pain Knee Moment 2 (Nm/kg)	0.540	0.231		0.440	0.219	
Mean No Pain Knee Moment (Nm/kg)	0.557	0.241		0.442	0.228	
Pain Knee Power 1 (W/kg)	0.963	0.537	0.005*	-0.689	0.418	0.999
Pain Knee Power 2 (W/kg)	0.852	0.445		-0.689	0.421	
Mean Pain Knee Power (W/kg)	0.907	0.486		-0.689	0.414	
No Pain Knee Power 1 (W/kg)	0.862	0.452	0.035*	-0.630	0.393	0.173
No Pain Knee Power 2 (W/kg)	0.790	0.396		-0.668	0.395	
Mean No Pain Knee Power (W/kg)	0.826	0.419		-0.649	0.389	
Pain Knee Extension Angle 1 (º)	5.033	6.892	0.104			
Pain Knee Extension Angle 2 (º)	5.810	7.036				
Mean Pain Knee Extension Angle (º)	5.422	6.886				
No Pain Knee Extension Angle 1 (º)	5.491	6.398	0.260			
No Pain Knee Extension Angle 2 (º)	6.757	7.859				
Mean No Pain Knee Extension Angle (º)	6.124	6.715				

* Significant at the 0.05 level (2-tailed).

In the non-painful knee, the patients performed an extension moment of 0.574 Nm/kg in the first three repetitions in comparation to 0.540 Nm/kg in the last three repetitions ($p = 0.019$). No differences were found ($p > 0.05$) between the most painful knee and non-painful knee in both phases. As expected, the extension moment in both knees employed to performing the sit-to-stand phase was significantly higher ($p < 0.05$) than the knee flexion moment performed in the stand-to-sit phase. The power produced to extend the knees was also higher ($p < 0.05$) in the sit-to-stand phase than in the stand-to-sit phase.

Table 6 shows the correlations between sit-to-stand and stand-to-sit biomechanical parameters and clinical measurements. Several significant correlations ($p < 0.05$) were found between clinical measures and biomechanical parameters. For the painful knee in the sit-to-stand phase, positive significant correlations were found between the moment produced and the subscales KOOS pain ($r = 0.600$; $p = 0.004$), KOOS symptoms ($r = 0.461$; $p = 0.035$) and KOOS ADL ($r = 0.606$; $p = 0.004$). Also, positive and significant between power and the subscales KOOS pain ($r = 0.608$; $p = 0.003$), KOOS symptoms ($r = 0.434$; $p = 0.049$), KOOS ADL ($r = 0.655$; $p = 0.001$) and KOOS QoL ($r = 0.536$; $p = 0.012$). A positive and significant correlation was also found at the maximum knee extension angle at the end of the sit-to-stand phase and the intensity of pain in the VAS ($r = 0.449$; $p = 0.041$). Still, in the non-painful knee, a negative and significant correlation was found between the maximum knee extension angle and the subscale KOOS symptoms ($r = -0.449$; $p = 0.045$), KOOS sports ($r = -0.642$; $p = 0.002$) and a positive significant correlation with the pain intensity in VAS ($r = 0.449$; $p = 0.041$). No significant correlations were found for the non-painful knee between joint moment and power and clinical measures.

For the stand-to-sit phase in the painful knee, significant and positive correlations were found between the flexion moment and the subscales KOOS pain ($r = 0.631$; $p = 0.002$), KOOS symptoms ($r = 0.466$; $p = 0.033$) and KOOS ADL ($r = 0.602$; $p = 0.004$). Joint power in the painful knee, was significantly and negatively correlated with the subscales KOOS pain ($r = -0.584$; $p = 0.005$), KOOS ADL ($r = -0.588$; $p = 0.005$) and KOOS QoL ($r = -0.509$; $p = 0.018$); and significantly and positively correlated with pain intensity in the VAS ($r = 0.484$; $p = 0.026$). There

were also no significant correlations between the clinical measures and the non-painful knee.

Table 6. Correlations between biomechanical parameters, KOOS subscales and Visual Analogue Scale (VAS) in sit-to-stand and stand-to-sit phases.

Sit-to-Stand

	Pain Knee Moment	No Pain Knee Moment	Pain Knee Power	No Pain Knee Power	Pain Knee Angle	No Pain Knee Angle
KOOS Pain	0.600**	0.096	0.608**	0.179	0.024	-0.285
KOOS Symptom	0.461*	0.057	0.434*	0.110	-0.144	-0.441*
KOOS ADL	0.606**	0.134	0.655**	0.264	-0.148	-0.370
KOOS Sports	-0.011	-0.228	0.127	-0.066	-0.397	-0.642**
KOOS QoL	0.415	0.130	0.536*	0.274	-0.283	-0.422*
VAS	-0.212	-0.140	-0.428	-0.281	0.449*	0.544*

Stand-to-Sit

	Pain Knee Moment	No Pain Knee Moment	Pain Knee Power	No Pain Knee Power
KOOS Pain	0.631**	0.067	-0.584**	-0.115
KOOS Symptom	0.466*	0.098	-0.387	-0.119
KOOS ADL	0.602**	0.137	-0.588**	-0.247
KOOS Sports	0.044	-0.288	-0.153	0.154
KOOS QoL	0.393	0.046	-0.509*	-0.190
VAS	-0.250	-0.115	0.484*	0.311

* Correlation is significant at the 0.05 level (2-tailed); ** Correlation is significant at the 0.01 level (2-tailed).

4. Discussion

This study was conducted to evaluate biomechanical strategies in the 30s-CST in patients with medial knee OA. The findings showed that there is a clear reduction in the ability to produce extension moment and power between the first and last three repetitions in the test. The stand-to-sit phase is not affected by the repetition’s during the execution of the test. Also, there are several associations between clinical measures and the most painful knee. There were no associations between the clinical measures and the non-painful knee, except at the maximum extension angle.

One possible explanation for the results found may be due to the “unloading” strategy used by the patients. Avoiding the load on the most affected knee seems to reduce pain. On the other hand, the presence of pain and or other symptoms may change the quality of movement. This strategy can be seen as a compensatory mechanism and has already been observed in patients with moderate OA in other studies (Bouchouras, Patsika, Hatzitaki, & Kellis, 2015; Patsika, Kellis, & Amiridis, 2011; Sagawa et al., 2017). Bouchouras et al. (Bouchouras et al., 2015) found that women with moderate knee OA, rise from the chair using greater knee muscle co-contraction. Also, they use earlier and greater activation of the hamstrings that results in reduced range of motion but without compromising overall task duration. Patsika et al. (Patsika et al., 2011) found that women with OA performed the movement sit-to-stand with less efficient use of the knee extensor muscles (less force per unit of EMG) and, also with a higher hamstrings antagonist co-activation. Sagawa et al. (Sagawa et al., 2017) found that in individuals with grade 3 or 4 on the Kellgren & Lawrence scale (Kellgren & Lawrence, 1957) showed different sit-to-stand trunk strategies when compared with controls. The use of these compensatory strategies could explain the participants strategy, in the present study, to produce more force in the most painful knee in the two phases of the test. Nevertheless, our results do not match those of Turcot et al (Turcot et al., 2012), where an overload at the contralateral limb was found. Nevertheless, that study was performed in patients with advanced osteoarthritis (grade 4 in Kellgren & Lawrence scale). In this study, patients were recruited in a moderate stage (grade 2 or 3 in Kellgren & Lawrence scale), which may justify this difference in the results.

Significant differences were expected between the first three and the last three repetitions, due to tiredness or even pain. We found a difference of about 7% between the first and the last repetitions in the extension moment in both knees, 11.5% difference in knee joint power produced at the most painful knee and 8.3% difference in power at the less painful knee. These results were observed in the sit-to-stand motion. In the stand-to-sit motion, we observed a reduction of about 5% at the flexion moment and almost no change in the non-painful knee. In the power produced, we observed a negative value with no change in the painful

knee and an increase in the power for the non-painful knee. These results between the two phases can be seen as an additional strategy to compensate the pain and/or symptoms when the number of repetitions increases. This is particularly relevant in a challenging move such as lifting the body from a sitting position. The use of devices that allow to minimize the progression of the disease and the consequent biomechanical changes in the execution of functional tasks will be an advantage for these patients. On the other hand, the development of assisted technologies that allow maximizing biomechanical behaviors will be an important contribution to the well-being of these patients particularly in advanced disease stages. Technologies that enable the sit-to-stand movement may translate into functional improvements and promote better well-being for these patients. A more specific approach to these issues reinforces the need for further studies on the biomechanical analysis of the movement studied. Another important aspect that results from the data analysis, is related to the challenge that the test itself imposed on the patients. The 30s-CST test seems to be challenging enough for these patients and meets the OARSI recommendations (Dobson et al., 2013).

Significant differences and associations were found between different subscales of KOOS, VAS and biomechanical parameters (**Table 2**). Patients with best score in KOOS subscales showed better performance in 30s-CST. Although KOOS has good measurement properties (Collins et al., 2016; Dobson et al., 2012), it is still not used commonly. Compared with a similar measure, the WOMAC Osteoarthritis Index (Bellamy, Buchanan, Goldsmith, Campbell, & Stitt, 1988), the major difference is related to the focus that questionnaire gives to the long-term consequences (Roos & Lohmander, 2003). To our knowledge this is the first study that pursues to make an association between clinical measures and KOOS subscales in the two phases of 30s-CST. As expected, the performance of the 30s-CST test is closely related to a better condition in the KOOS subscales, particularly with the subscales pain, symptoms, and ADL. In a similar study, Turcot et al. (Turcot et al., 2012) found a weak association of WOMAC subscales with the extension moment (r = -0.09 to r = -0.26). However, the assessment of the motion was not carried out in the same way, and the authors only study the

sit-to-stand phase. In that study, the movement was performed only four times and the beginning and ending of movement was identified by the movement of the trunk. Another substantial issue that may influenced the results is the detail that only patients with grade 4 in Kellgren–Lawrence grading scale participated in that study. These patients developed a peak extension moment of 0.510 Nm/kg while in our study they developed a peak extension moment of 0.610 Nm/kg.

This study has some limitations. The test's repeatability was not analysed, which would be important to understand if the outcomes would be similar between different test sessions. Another limitation is related to the fact that we did not use a match control group and patients with a medical diagnosis of the other two levels of the Kellgren–Lawrence grading scale. This analysis would be important in future studies to allow understanding modifications in the strategies used by patients with different levels of disease and macheted with control patients. The fact that we have not assessed the muscle function of the lower limbs can also be seen as a limitation. It will be important in future studies the assessment of muscle strength and motor control and relate them with the biomechanical parameters.

5. Conclusions

In this study, patients in the first repetitions of the 30s-CST performed better compared to the last ones. Interestingly, they showed better results in the most painful knee. The stand-to-sit phase was not affected by the repetition’s during the execution of the test.

Patients with higher scores in KOOS subscales (ADL and QoL) exhibited higher capacity to produce power and force in the most painful knee.

Assistive technologies that allow to improve the quality of these movement could be a valuable contribution to improve the well-being of patients with knee OA.

References

Al Amer, H. S., Sabbahi, M. A., Alrowayeh, H. N., Bryan, W. J., & Olson, S. L. (2018). Electromyographic activity of quadriceps muscle during sit-to-stand in patients with unilateral knee osteoarthritis. *BMC Res Notes, 11*(1), 356. doi:10.1186/s13104-018-3464-9

Altman, R., Asch, E., Bloch, D., Bole, G., Borenstein, D., Brandt, K., . . . et al. (1986). Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis Rheum, 29*(8), 1039-1049.

Anan, M., Shinkoda, K., Suzuki, K., Yagi, M., Ibara, T., & Kito, N. (2015). Do patients with knee osteoarthritis perform sit-to-stand motion efficiently? *Gait Posture, 41*(2), 488-492. doi:10.1016/j.gaitpost.2014.11.015

Bellamy, N., Buchanan, W. W., Goldsmith, C. H., Campbell, J., & Stitt, L. W. (1988). Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol, 15*(12), 1833-1840.

Boonstra, M. C., Schwering, P. J., De Waal Malefijt, M. C., & Verdonschot, N. (2010). Sit-to-stand movement as a performance-based measure for patients with total knee arthroplasty. *Phys Ther, 90*(2), 149-156. doi:10.2522/ptj.20090119

Bouchouras, G., Patsika, G., Hatzitaki, V., & Kellis, E. (2015). Kinematics and knee muscle activation during sit-to-stand movement in women with knee osteoarthritis. *Clin Biomech (Bristol, Avon), 30*(6), 599-607. doi:10.1016/j.clinbiomech.2015.03.025

Cappozzo, A., Catani, F., Croce, U. D., & Leardini, A. (1995). Position and orientation in space of bones during movement: anatomical frame definition and determination. *Clin Biomech (Bristol, Avon), 10*(4), 171-178. doi:10.1016/0268-0033(95)91394-T

Collins, N. J., Prinsen, C. A., Christensen, R., Bartels, E. M., Terwee, C. B., & Roos, E. M. (2016). Knee Injury and Osteoarthritis Outcome Score (KOOS): systematic review and meta-analysis of measurement properties. *Osteoarthritis Cartilage, 24*(8), 1317-1329. doi:10.1016/j.joca.2016.03.010

de Groot, I. B., Favejee, M. M., Reijman, M., Verhaar, J. A., & Terwee, C. B. (2008). The Dutch version of the Knee Injury and Osteoarthritis Outcome Score: a validation study. *Health Qual Life Outcomes, 6*, 16. doi:10.1186/1477-7525-6-16

Dobson, F., Hinman, R. S., Hall, M., Terwee, C. B., Roos, E. M., & Bennell, K. L. (2012). Measurement properties of performance-based measures to assess physical function in hip and knee osteoarthritis: a systematic review. *Osteoarthritis Cartilage, 20*(12), 1548-1562. doi:10.1016/j.joca.2012.08.015

Dobson, F., Hinman, R. S., Roos, E. M., Abbott, J. H., Stratford, P., Davis, A. M., . . . Bennell, K. L. (2013). OARSI recommended performance-based tests to assess physical function in people diagnosed with hip or knee osteoarthritis. *Osteoarthritis Cartilage, 21*(8), 1042-1052. doi:10.1016/j.joca.2013.05.002

Duffell, L. D., Gulati, V., Southgate, D. F., & McGregor, A. H. (2013). Measuring body weight distribution during sit-to-stand in patients with early knee osteoarthritis. *Gait Posture, 38*(4), 745-750. doi:10.1016/j.gaitpost.2013.03.015

Felson, D. T. (2006). Clinical practice. Osteoarthritis of the knee. *N Engl J Med, 354*(8), 841-848. doi:10.1056/NEJMcp051726

Goncalves, R. S., Cabri, J., Pinheiro, J. P., & Ferreira, P. L. (2009). Cross-cultural adaptation and validation of the Portuguese version of the Knee injury and Osteoarthritis Outcome Score (KOOS). *Osteoarthritis Cartilage, 17*(9), 1156-1162. doi:10.1016/j.joca.2009.01.009

Janssen, W. G., Bussmann, H. B., & Stam, H. J. (2002). Determinants of the sit-to-stand movement: a review. *Phys Ther, 82*(9), 866-879.

Jones, C. J., Rikli, R. E., & Beam, W. C. (1999). A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. *Res Q Exerc Sport, 70*(2), 113-119. doi:10.1080/02701367.1999.10608028

Kellgren, J. H., & Lawrence, J. S. (1957). Radiological assessment of osteo-arthrosis. *Ann Rheum Dis, 16*(4), 494-502.

Kersten, P., White, P. J., & Tennant, A. (2014). Is the pain visual analogue scale linear and responsive to change? An exploration using Rasch analysis. *PLoS ONE, 9*(6), e99485. doi:10.1371/journal.pone.0099485

Macfarlane, D. J., Chou, K. L., Cheng, Y. H., & Chi, I. (2006). Validity and normative data for thirty-second chair stand test in elderly community-dwelling Hong Kong Chinese. *Am J Hum Biol, 18*(3), 418-421. doi:10.1002/ajhb.20503

Millor, N., Lecumberri, P., Gomez, M., Martinez-Ramirez, A., & Izquierdo, M. (2013). An evaluation of the 30-s chair stand test in older adults: frailty detection based on kinematic parameters from a single inertial unit. *J Neuroeng Rehabil, 10*(1), 86. doi:10.1186/1743-0003-10-86

Naili, J. E., Brostrom, E. W., Gutierrez-Farewik, E. M., & Schwartz, M. H. (2018). The centre of mass trajectory is a sensitive and responsive measure of functional compensations in individuals with knee osteoarthritis performing the five times sit-to-stand test. *Gait Posture, 62*, 140-145. doi:10.1016/j.gaitpost.2018.03.016

Palmieri-Smith, R. M., Thomas, A. C., Karvonen-Gutierrez, C., & Sowers, M. F. (2010). Isometric quadriceps strength in women with mild, moderate, and severe knee osteoarthritis. *Am J Phys Med Rehabil, 89*(7), 541-548. doi:10.1097/PHM.0b013e3181ddd5c3

Papa, E., & Cappozzo, A. (2000). Sit-to-stand motor strategies investigated in able-bodied young and elderly subjects. *J Biomech, 33*(9), 1113-1122.

Patsika, G., Kellis, E., & Amiridis, I. G. (2011). Neuromuscular efficiency during sit to stand movement in women with knee osteoarthritis. *J Electromyogr Kinesiol, 21*(5), 689-694. doi:10.1016/j.jelekin.2011.05.006

Rodosky, M. W., Andriacchi, T. P., & Andersson, G. B. (1989). The influence of chair height on lower limb mechanics during rising. *J Orthop Res, 7*(2), 266-271. doi:10.1002/jor.1100070215

Roldan-Jimenez, C., Bennett, P., & Cuesta-Vargas, A. I. (2015). Muscular Activity and Fatigue in Lower-Limb and Trunk Muscles during Different Sit-To-Stand Tests. *PLoS ONE, 10*(10), e0141675. doi:10.1371/journal.pone.0141675

Roos, E. M., & Lohmander, L. S. (2003). The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. *Health Qual Life Outcomes, 1*, 64. doi:10.1186/1477-7525-1-64

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. *J Orthop Sports Phys Ther, 28*(2), 88-96. doi:10.2519/jospt.1998.28.2.88

Sagawa, Y., Bonnefoy-Mazure, A., Armand, S., Lubbeke, A., Hoffmeyer, P., Suva, D., & Turcot, K. (2017). Variable compensation during the sit-to-stand task among individuals with severe knee osteoarthritis. *Ann Phys Rehabil Med, 60*(5), 312-318. doi:10.1016/j.rehab.2017.03.007

Turcot, K., Armand, S., Fritschy, D., Hoffmeyer, P., & Suva, D. (2012). Sit-to-stand alterations in advanced knee osteoarthritis. *Gait Posture, 36*(1), 68-72. doi:10.1016/j.gaitpost.2012.01.005

Vincent, K. R., Conrad, B. P., Fregly, B. J., & Vincent, H. K. (2012). The pathophysiology of osteoarthritis: a mechanical perspective on the knee joint. *PM R, 4*(5 Suppl), S3-9. doi:10.1016/j.pmrj.2012.01.020

Winter, D. A. (2009). *Biomechanics and Motor Control of Human Movement*.

Study IV: Biomechanical changes on patients with knee osteoarthritis due to slight variations on lateral wedge insoles

Authors:

Vitor Ferreira, Leandro Machado, Adélio Vilaça, Francisco Xará-Leite, Paulo Roriz

Journal:

(Submitted for publication)

ABSTRACT

Background: Knee osteoarthritis is a world leading disease, a cause of chronic pain and limited activity. Lateral wedge insoles are typically prescribed to minimize the effects of the disease. Biomechanically they seem to reduce the external knee adduction moment during the stance phase of gait, particularly its first peak, relieving the load on the medial tibiofemoral compartment and pain symptoms. The amount of wedging required to induce a biomechanical response with clinical significance is still controversial.

Research question: What is the immediate biomechanical response to different amounts of wedging in patients with medial knee osteoarthritis?

Methods: Thirty-eight volunteers with symptomatic medial knee osteoarthritis were recruited. A 3D motion capture system comprising twelve cameras and five force platforms was used to capture walking data along a 10-meter walkway. Each participant was tested for six different amounts of lateral wedge insoles (0, 2, 4, 6, 8 and 10-degrees) in a randomized order.

Results: The application of insoles resulted on an incremental reduction of the first peak of external knee adduction moment under all experimental conditions compared to the control condition. It was observed a significant increase in peak ankle eversion and in ankle eversion at the first peak of external knee adduction moment with insoles higher than 8-degrees. The peak ankle eversion moment increased with insoles greater than 6-degrees ($p < 0.05$). No changes were observed in center of pressure.

Significance: Slight variations on lateral wedge insoles induced adaptations in incremental way only in frontal plane suggesting that it is these adaptations that trigger the changes in knee adduction moment. The shift of center of pressure seems to have no influence on the mechanism for reducing knee adduction moment. Apparently, insoles with angles greater than 2 degrees can induce significant changes in the knee.

Keywords: Gait; lateral wedge insoles; external knee adduction moment; osteoarthritis

1. Introduction

Osteoarthritis (OA) is a world leading disease associated with significant morbidity and a cause of chronic pain and limited activity, particularly in the elderly population. Despite the relief of pain being a major and immediate aim, it is also important to minimise the risk of disease progression over time. A mechanical factor, such as the excessive load on the knee, seems to explain

almost all of the knee OA, making the strategies to minimize it a major issue (Felson, 2013). Thus, biomechanical interventions are among the recommended treatments for the management of the disease over time (McAlindon et al., 2014). Lateral wedges insoles are orthotic devices placed within the shoes intended to reduce significantly the biomechanical risk factors associated with knee OA (Arnold, Wong, Jones, Hill, & Thewlis, 2016). Their main mechanism of action seems to be a reduction of the external knee adduction moment (EKAM) (Butler, Marchesi, Royer, & Davis, 2007; Hinman, Payne, Metcalf, Wrigley, & Bennell, 2008; Kerrigan et al., 2002). The EKAM is a biomechanical parameter that quantifies the ground reaction force (GRF) contribution to rotation of the lower leg around the knee. Increasing values of EKAM may be caused by, and also contribute to, a more pronounced knee varus alignment, making the load on the medial compartment of the knee to increase (Schipplein & Andriacchi, 1991). Through the stance phase of walking, the EKAM exhibits two peaks: one at early stance, the other at late stance. The first peak seems to be highly correlated with the medial tibiofemoral contact force reaching 50% higher values than normal in OA patients (Kumar, Manal, & Rudolph, 2013). Moreover, higher first peak values of EKAM have been associated with more intensity and occurrence of pain (Kito et al., 2010).

The amount of wedging required to induce a biomechanical response with clinical significance is an important research question since the effects on the clinical condition are still controversial (Bennell et al., 2011; Zhang, Wang, & Zhang, 2018). Different amounts of lateral wedging have been suggested, such as 4 (Fantini Pagani, Hinrichs, & Bruggemann, 2012), 5 (Kerrigan et al., 2002), 6 (Kakihana et al., 2005), 10 (Dessery, Belzile, Turmel, & Corbeil, 2016) or 11 degrees (Abdallah & Radwan, 2011). So far, it is not yet possible to reach consensus on the prescribed amount of wedging. Typically, on clinical setting, the application of lateral wedge insoles is the same for all patients making the amount of wedging depend on clinical experience than evidence-based approach. To the best of our knowledge, only one study sought to understand the biomechanical effects of more than wedging angles (Tipnis, Anloague, Laubach, & Barrios, 2014). The six lateral wedging angles tested (2°, 4°, 6°, 8°, 10° and 12

degrees) suggested a clear reduction on first peak of EKAM, compared to the control condition (0 degrees). However, the previous study presented a key limitation since the individuals tested were all healthy.

The reason to justify customized interventions seems to rely on the fact that there are non-responders to the application of lateral wedge insoles (Hinman, Bowles, Metcalf, Wrigley, & Bennell, 2012; Lewinson, Vallerand, et al., 2016). In this way, it could be of clinical importance to define different phenotypes that respond to treatment (Deveza et al., 2017) and have a more comprehensive biomechanical understanding of the mechanisms of action of lateral wedge insoles. For example, it has been suggested that lateral wedges insoles may shift laterally the center of pressure (CoP) of the GRF [10]. Other studies also suggested that the reduction of the lever arm of EKAM is the main mechanism in load-reducing effect [11]. However, to date, the association between the amount of lateral wedging and changes in biomechanical parameters remains unclear. For example, understanding how small changes in the angle of lateral wedge insoles affect biomechanical parameters could be an important contribute to justify their customization and improve clinical prescription. Therefore, the aim of the present study was to assess the acute effects of incremental changes in lateral wedge insoles on the ankle and knee biomechanics.

2. Methods

2.1. Participants

Thirty-eight volunteers (15 males and 23 females; mean age of 61.6 ± 8.4 years; weight of 75.8 ± 12.8 kg; height of 1.61 ± 0.09 m and body mass index (BMI) of 29.3 ± 5.1 kg/m^2) with symptomatic medial knee OA were recruited in local hospitals. The clinical and radiological inclusion criteria followed those established by the American College of Rheumatology (Altman et al., 1986): medial knee pain; radiographic osteophyte in the medial joint space of the knee; and at least one of the following items, morning stiffness lasting more than 30 minutes or crepitus during motion. Other specific inclusion criteria were: age

between 45 and 80 years old; grade 2 and 3 on the Kellgren–Lawrence grading scale (Kellgren & Lawrence, 1957) and mechanical axis angle indicating varus alignment of the knee. The exclusion criteria included: joint prosthesis; patients with symptomatic evidence of lateral compartment; patellofemoral OA; knee surgery within the past six months; systemic arthritic conditions; corticosteroid injection within the previous six weeks; a BMI lower than 35 (due to the difficulty on accurate motion capture markers placement) and any other condition that could impar assessment of gait or balance. All participants freely gave their written consent to participate after a verbal and written explanation of the study. The study was conducted in accordance with the Declaration of Helsinki and was approved by hospital and university ethics committees.

2.2. Equipment and data acquisition

A motion capture three-dimensional system (Qualisys, Gothenburg, Sweden), comprising twelve optical cameras (Oqus) sampling at 200 Hz, and five force platforms (Bertec, Columbus, USA) sampling at 1000 Hz, was used to acquire walking kinematic and kinetic data along a 10 m walkway. The Calibrated Anatomical System Technique (CAST) was used (Cappozzo, Catani, Croce, & Leardini, 1995). Reflective markers were placed on subject's bony landmarks, bilaterally, in order to reconstruct the position and orientation of the lower limbs and pelvis. The bony landmarks used for the pelvis, thigh and shank were the anterior superior iliac spine, posterior superior iliac spine, greater trochanter, medial condyles, lateral condyles, fibula head, tibial tubercle, lateral malleolus and medial malleolus. The feet were considered rigid bodies and reconstructed with markers attached to the shoes and the locations of the calcaneus, 1st, 2nd and 5th metatarsal heads. Additionally, four rigid clusters were placed bilaterally on the anterior-lateral aspect of the thigh and shank. All the markers remained attached to the subject during data collection. A static calibration was performed before walking trials. Participants were not given any other instructions than walking at their self-selected pace, until they have performed at least 6 valid trials on each of the experimental conditions. A valid trial was set when the subject

walked naturally and the whole foot contacted the force plate surface without going beyond its contours. Six experimental conditions were tested in a randomized order: a control condition (shoes with a 0-degree insole), and lateral wedge insoles with 2, 4, 6, 8 and 10-degrees. The insoles were full-length costume made with a pronating wedge (**Figure 12**). An inclinometer was used to confirm the degree of wedging of the insoles. Participants used their own shoes (flat shoes) to decrease relevant biomechanical changes with the use of unusual shoes (Lewinson, Worobets, & Stefanyshyn, 2016). The insoles were worn bilaterally but only the data for the most painful knee is presented.

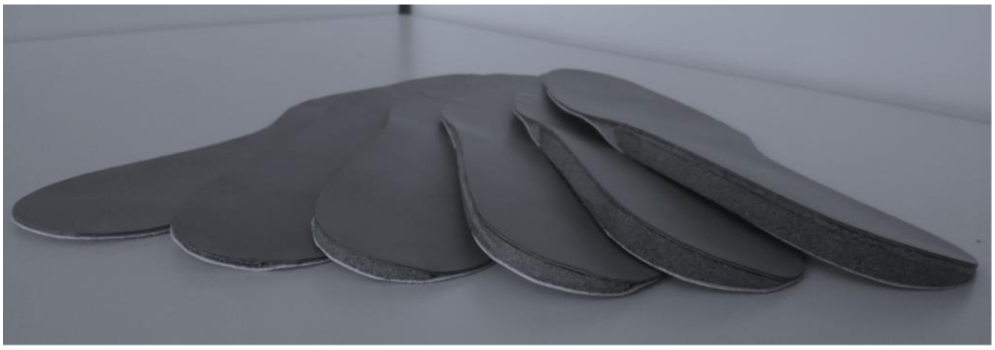


Figure 12. The 6 experimental insoles used in the study

2.3. Data Analysis

Data were previously treated with the Qualisys Track Manager software (Qualisys, Gothenburg, Sweden) to identify, edit and process markers trajectories. Post-processing calculation of the kinematic and kinetic time series data was conducted using Visual3D software (C-Motion, Rockville, USA). Data were filtered using a Butterworth 4th order filter (6 Hz). Lower limb joint angles (using a X-Y-Z Euler rotation sequence equivalent to the joint coordinate system) and joint moments (determined through inverse dynamics) were computed and expressed relatively to the proximal segment. Peak values for lower limb joint angles and joint moments of force, as well as time-distance parameters were computed for each set and for each participant. The EKAM was expressed with

respect to the tibial reference frame. The first and second peaks were identified from each of the EKAM waveforms. The kinematic joint data were expressed in degrees (°). The kinetic data were normalized to body mass (BM) (Nm/kg). The knee adduction angular impulse (KAAI) was calculated by integrating the EKAM signal for the stance phase (in % BM x Time). The kinematic and kinetic data were normalized in time to 100% for the stance phase. Power (W/kg) was computed in the segment coordinate system. A positive power output suggests concentric muscle action (power generation) while a negative power output indicates eccentric muscle activity (power absorption). The displacement of the CoP was defined as the distance of the CoP from the line of the foot (calcaneus to the midpoint between first and fifth metatarsals) and was calculated at the first peak of EKAM. CoP was normalized to the length (distance between proximal and distal ends of the segment) and width (distal radius) of the foot. A negative value indicates the CoP is at the medial side of the line of the foot and a positive value at the lateral side. Time to first peak of EKAM was calculated from the initial contact of the foot (beginning of the stance phase).

The mean values of kinematics and kinetics data were exported to SPSS 25.0 (IBM, Chicago, USA) and processed using a single factor, repeated measures analysis of variance. Post hoc pairwise comparisons were used to determine differences between experimental conditions to the control condition (0-degree insole). All tests were performed at the 95% confidence interval ($p < 0.05$) with a Bonferroni correction to adjust for the multiple pairwise comparisons.

3. Results

3.1. Walking speed

The mean walking speed was 1.15 (± 0.17) m/s with the 0-degree insole. There were no significant differences in walking speed between insoles (**Table 7**). The time to reach the first peak of EKAM was slightly higher with higher angulations and statistically significant with insoles greater than 6-degrees ($p < 0.05$).

Table 7. Biomechanical parameters at the knee and ankle in the six conditions with corresponding statistical findings (bold indicates significance).

	0° Insole	2° Insole	4° Insole	6° Insole	8° Insole	10° Insole
Peak ankle eversion (°)	4.37 (±3.14)	4.53 (±3.07)	4.79 (±3.02)	5.07 (±2.88)	5.52 (±3.00)	5.51 (±3.13)
p-values		*1.000*	*1.000*	*0.105*	***.001***	***.009***
Ankle eversion at 1st peak EKAM (°)	3.80 (±3.05)	3.93 (±3.04)	4.28 (±3.02)	4.56 (±2.95)	5.03 (±3.10)	4.94 (±3.33)
p-values		*1.000*	*1.000*	*.087*	***.000***	***.018***
Peak ankle eversion moment (Nm/kg)	0.052 (±0.039)	0.061 (±0.038)	0.066 (±0.040)	0.074 (±0.044)	0.080 (±0.039)	0.087 (±0.044)
p-values		*.197*	*.696*	***.043***	***.000***	***.000***
Ankle eversion moment at 1st peak EKAM (Nm/kg)	0.020 (±0.065)	0.032 (±0.062)	0.041 (±0.058)	0.050 (±0.062)	0.058 (±0.056)	0.060 (±0.067)
p-values		*.104*	***.000***	***.000***	***.000***	***.000***
Peak ankle power absorption (frontal plane) (W/kg)	-0.097 (±0.055)	-0.113 (±0.064)	-0.109 (±0.062)	-0.114 (±0.069)	-0.122 (±0.064)	-0.138 (±0.072)
p-values		*.173*	*.0357*	*.222*	***.004***	***.000***
Ankle power absorption at 1st peak EKAM (frontal plane) (W/kg)	-0.001 (±0.013)	0.000 (±0.013)	-0.001 (±0.014)	0.001 (±0.016)	0.001 (±0.014)	-0.002 (±0.021)
p-values		*1.000*	*1.000*	*1.000*	*1.000*	*1.000*
1st Peak EKAM (Nm/kg)	0.452 (±0.183)	0.428 (±0.181)	0.421 (±0.182)	0.424 (±0.189)	0.410 (±0.183)	0.402 (±0.182)
p-values		***.005***	***.000***	***.000***	***.000***	***.000***
2nd Peak EKAM (Nm/kg)	*0.384 (±0.161)*	0.378 (±0.195)	0.372 (±0.185)	0.377 (±0.189)	0.366 (±0.197)	0.371 (±0.187)
p-values		*1.000*	*1.000*	*1.000*	*1.000*	*1.000*
KAAI (Nm/kg^{x}s)	*0.196 (±0.104)*	0.188 (±0.107)	0.183 (±0.097)	0.185 (±0.100)	0.177 (±0.097)	0.177 (±0.100)
p-values		*.531*	*.109*	*.077*	***.001***	***0.000***
Time to 1st peak EKAM (ms)	0.184 (±0.058)	0.194 (±0.061)	0.195 (±0.063)	0.199 (±0.065)	0.197 (±0.062)	0.202 (±0.064)
p-values		*.060*	*.115*	***0.037***	***0.001***	***0.000***
CoP M/L at 1st peak EKAM (mm)	5.70 (±10.38)	6.70 (±9.31)	6.79 (±9.01)	6.84 (±9.84)	6.99 (±9.28)	6.74 (±11.08)
p-values		*1.000*	*.955*	*.781*	*1.000*	*1.000*
Speed (m/s)	1.145 (0.169)	1.136 (0.147)	1.138 (0.150)	1.142 (0.155)	1.147 (0.166)	1.136 (0.128)
		1.000	*1.000*	*1.000*	*1.000*	*1.000*

Values reported as mean (SD); *p* value different from the 0° condition.

3.2. Ankle biomechanical parameters

A significant increase in peak ankle eversion and ankle eversion at first peak of EKAM was observed for insoles equal to and higher than 8-degrees, compared to the control insole (**Table 7**). The peak ankle eversion moment increased significantly for insoles equal to and higher than 6-degrees ($p < 0.05$). The ankle eversion moment at first peak of EKAM increased significantly for insoles equal to and higher than 4-degrees ($p < 0.001$). Insoles higher than 8-degrees showed a significant increase in peak ankle power absorption. This peak occurred before the first peak of EKAM, immediately following the initial contact of the stance phase (**Figure 13**). In the first peak of EKAM, there was a balance between power production and absorption (in frontal plane) with non-incremental effects due to the insoles ($p > 0.05$). No differences were observed in the CoP at first peak of EKAM for all the experimental conditions.

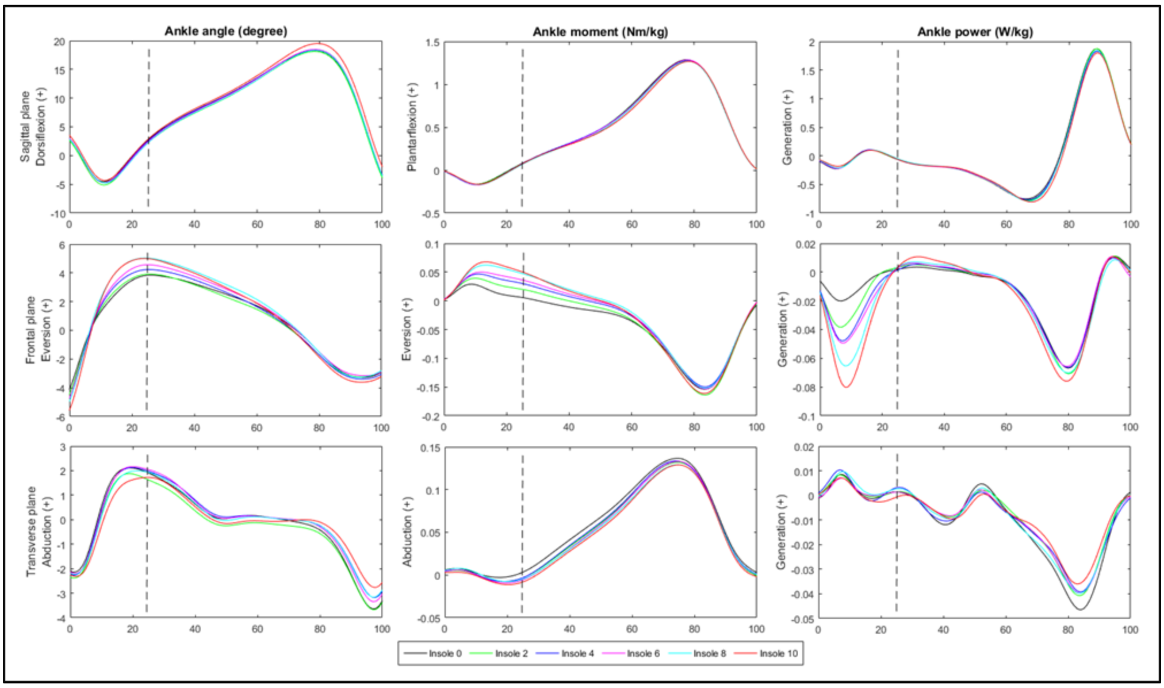


Figure 13. Ankle angles, moments, and power waveforms during the stance phase in the sagittal, frontal, and transverse plane. Each colour line represents the mean of different wedge insole. Vertical dashed lined represents the timing of first peak EKAM.

3.3. Knee biomechanical parameters

The application of insoles showed an incremental reduction of the first peak of EKAM under all experimental conditions (**Table 7**). With the 2-degree insole there was a reduction of 0.024 Nm/kg and with the 10-degree insole a reduction of 0.050 Nm/kg. There were no changes in the second peak of EKAM. There was a significant decrease in KAAI with insoles higher than 8-degrees ($p < 0.001$). No differences were observed in knee power except for the transverse plane with a significant decrease by insoles higher than 8-degrees.

4. Discussion

Any kind of treatment contributing to improve the wellbeing of patients with knee OA is a huge challenge. To the best of our knowledge, this is the first study that assesses the acute effects of small increments on lateral wedge insoles on the biomechanics on the ankle and knee in patients with knee OA. Previous studies attempted to study the effects of lateral wedge insoles focused only on the knee or used no more than one or two lateral wedges insoles. Present study considered six lateral wedge insoles with a difference of 2-degrees between them. Because long term use of footwear has been shown to result in anatomical and functional changes (Franklin, Grey, Heneghan, Bowen, & Li, 2015), it is also expected that the use of this type of insoles to produce similar effects.

Overall the participants presented significant changes in ankle range of movement particularly in peak eversion as also reported from the literature (Hinman et al., 2012; Tipnis et al., 2014). Ankle eversion increased with wedging angle being significant for 8-degree ($p = 0.001$) and 10-degree ($p = 0.009$) insoles (**Table 7**). The ankle angle during the first peak of EKAM also increased with the higher wedges, being significant with 8-degree ($p = 0.000$) and 10-degree ($p = 0.018$) insoles. Regarding to the eversion moment, there was also a significant increase ($p > 0.05$) for higher wedges, particularly during the first peak of EKAM and for insoles equal or greater than 4-degrees.

Findings from our study showed immediate effects at peak ankle power absorption as a biomechanical response in frontal plane to wearing lateral wedge insoles. In normal gait, the heel touches down in the initial contact phase with a slight inversion and in the loading response, the foot changes to eversion and pronation (Ludwig, Kelm, & Frohlich, 2016). These movements are controlled with a strictness neuromuscular control of tibialis anterior and peroneus longus muscles (Santilli et al., 2005). The presence of lateral wedge insole may modify the neuromuscular control during the stance phase, particularly, at the loading response. Future research should also analyse the influence of insoles on muscle motor control by means of electromyography.

No differences were found in CoP at first peak of EKAM. The lateral shift in CoP is considered by some studies a major mechanism responsible for reduction in the EKAM with the application of lateral wedge insoles (Hinman et al., 2012). However, in present study there was no significant change in the CoP at first peak of EKAM despite a significant reduction in the first peak of EKAM. These results are similar to those observed in a recent study (Kluge, Krinner, Lochmann, & Eskofier, 2017), with healthy individuals, for which the effect of different speeds along with the use of wedge insoles was analysed. Likewise, in present study no significant changes were found in gait speed for different insoles (**Table 7**).

If we look at **Figure 13**, the peak of the eversion angle occurs before the first peak of EKAM, such as the peak of eversion moment. It is also possible to observe an incremental power absorption mechanism just before the first peak of EKAM. These adaptations in incremental way only in frontal plane suggest that this type of insoles have no impact on other anatomical planes of motion. On the other hand, it may mean that it is these adaptations in frontal plane biomechanics that trigger the changes in EKAM.

When we try to understand the acute effects on the knee, the knee kinematics did not change along different insoles conditions. Nevertheless, a significant reduction in the first peak of EKAM, compared to the normal condition, was observed for all insoles. Findings from present study reinforce the evidence that lateral wedge insoles reduce significantly the first peak of EKAM. These was

consistent with several studies (Hinman et al., 2012; Hinman et al., 2008). However, in our study it is significant even with the smallest angle implemented (2-degree insole). These results are in line with other studies suggesting that any slight change under the foot induces adaptations in the upper segments or even in the opposite limb (Ma, Lee, Chen, & Aruin, 2016). In future studies this will be an interesting research field considering that high angulations under the foot usually cause more discomfort in its use (Tipnis et al., 2014). No other differences were found in major biomechanical parameters studied in the knee. Nevertheless, in other indicators considered significant changes are perceptible. Regarding the KAAI, we noticed a significant decrease with the 8-degree and 10-degree insoles and is also consistent with previous studies (Hinman et al., 2012). The time to reach the first peak of EKAM was extended with higher insoles. This value is significant with insoles equal to and higher than 6-degrees and is about 8.2% higher than control insole (**Table 7**). This can be explained by the increased ankle eversion movement caused by the incremental increase of the insoles, which carries a slight delay to the peak of the EKAM. When we verify the knee waveforms, no significant changes in angles, moments or power beyond the frontal plane are perceptible (**Figure 14**).

The present study has some limitations. Firstly, the morphology of the feet was not considered. A previous study (Sawada et al., 2016) suggested that foot alignment has different effects in kinematics when wearing lateral wedge insoles. Particularly, an individual with a normal foot is more likely to respond to lateral wedge insoles. In future studies it will be a characteristic to be considered. Secondly, a rigid foot model was adopted. Possible, the use of multisegmented foot models can better understand the influence of the foot in reducing the EKAM. Finally, we pursue to investigate only the immediate effects. Only a clinical trial with a long-term period can give us in future studies answers to personalize the intervention of lateral wedge insoles with the help of biomechanics.

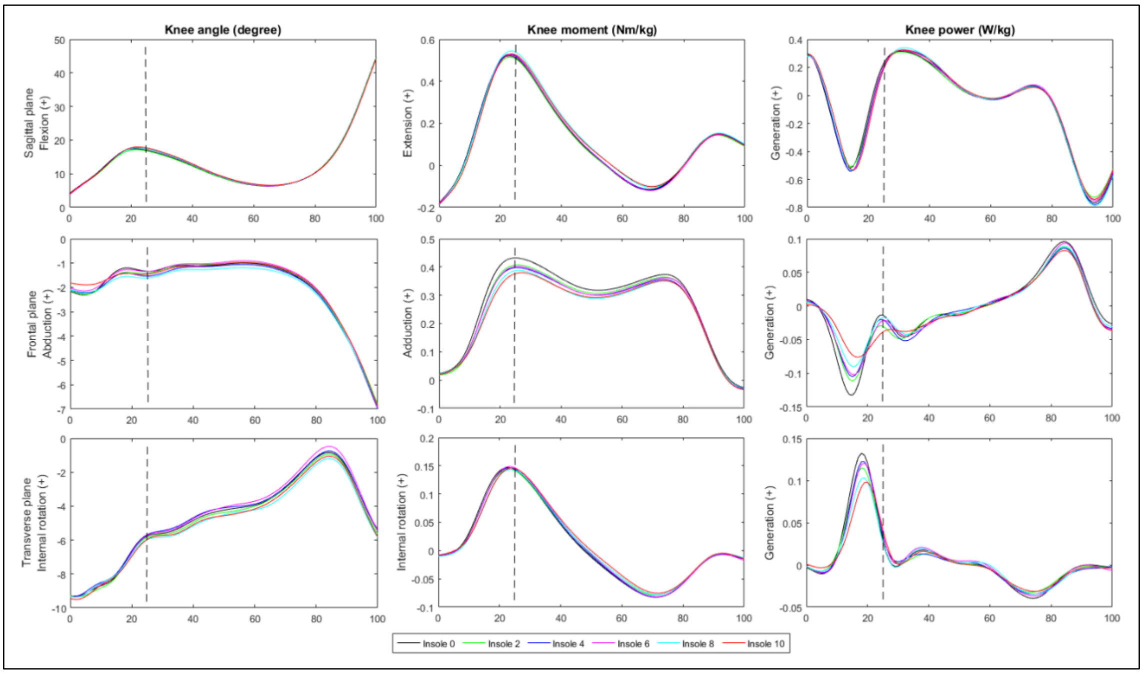


Figure 14. Knee angles, moments and power waveforms during the stance phase in the sagittal, frontal, and transverse plane. Each colour line represents the mean of different wedge insole. Vertical dashed lined represents the timing of first peak EKAM.

Conclusion

Slight variations on lateral wedge insoles induced adaptations in incremental way only in frontal plane suggesting that it is these adaptations that trigger the changes in EKAM. Increase ankle eversion in the foot during the stance phase seems to be the primary mechanism of action of lateral wedge insoles. The shift of CoP appears to have no influence on the mechanism responsible for reducing first peak of EKAM. On the face of it, even small changes under the foot induces significant changes in the knee joint. The findings of this study may allow further research on a better prescription of lateral wedge insoles.

References

Abdallah, A. A., & Radwan, A. Y. (2011). Biomechanical changes accompanying unilateral and bilateral use of laterally wedged insoles with medial arch supports in patients with medial knee osteoarthritis. *Clin Biomech, 26*(7), 783-789. doi:10.1016/j.clinbiomech.2011.03.013

Altman, R., Asch, E., Bloch, D., Bole, G., Borenstein, D., Brandt, K., . . . et al. (1986). Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee.

Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis Rheum, 29*(8), 1039-1049.

Arnold, J. B., Wong, D. X., Jones, R. K., Hill, C. L., & Thewlis, D. (2016). Lateral Wedge Insoles for Reducing Biomechanical Risk Factors for Medial Knee Osteoarthritis Progression: A Systematic Review and Meta-Analysis. *Arthritis Care Res (Hoboken), 68*(7), 936-951. doi:10.1002/acr.22797

Bennell, K. L., Bowles, K. A., Payne, C., Cicuttini, F., Williamson, E., Forbes, A., . . . Hinman, R. S. (2011). Lateral wedge insoles for medial knee osteoarthritis: 12 month randomised controlled trial. *BMJ, 342*, d2912. doi:10.1136/bmj.d2912

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. *J Orthop Res, 25*(9), 1121-1127. doi:10.1002/jor.20423

Cappozzo, A., Catani, F., Croce, U. D., & Leardini, A. (1995). Position and orientation in space of bones during movement: anatomical frame definition and determination. *Clin Biomech (Bristol, Avon), 10*(4), 171-178. doi:10.1016/0268-0033(95)91394-T

Dessery, Y., Belzile, E., Turmel, S., & Corbeil, P. (2016). Effects of foot orthoses with medial arch support and lateral wedge on knee adduction moment in patients with medial knee osteoarthritis. *Prosthet Orthot Int*. doi:10.1177/0309364616661254

Deveza, L. A., Melo, L., Yamato, T. P., Mills, K., Ravi, V., & Hunter, D. J. (2017). Knee osteoarthritis phenotypes and their relevance for outcomes: a systematic review. *Osteoarthritis Cartilage, 25*(12), 1926-1941. doi:10.1016/j.joca.2017.08.009

Fantini Pagani, C. H., Hinrichs, M., & Bruggemann, G. P. (2012). Kinetic and kinematic changes with the use of valgus knee brace and lateral wedge insoles in patients with medial knee osteoarthritis. *J Orthop Res, 30*(7), 1125-1132. doi:10.1002/jor.22032

Felson, D. T. (2013). Osteoarthritis as a disease of mechanics. *Osteoarthritis Cartilage, 21*(1), 10-15. doi:10.1016/j.joca.2012.09.012

Franklin, S., Grey, M. J., Heneghan, N., Bowen, L., & Li, F. X. (2015). Barefoot vs common footwear: A systematic review of the kinematic, kinetic and muscle activity differences during walking. *Gait Posture, 42*(3), 230-239. doi:10.1016/j.gaitpost.2015.05.019

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. *Clin Biomech (Bristol, Avon), 27*(1), 27-33. doi:10.1016/j.clinbiomech.2011.07.010

Hinman, R. S., Payne, C., Metcalf, B. R., Wrigley, T. V., & Bennell, K. L. (2008). Lateral wedges in knee osteoarthritis: what are their immediate clinical and biomechanical effects and can these predict a three-month clinical outcome? *Arthritis Rheum, 59*(3), 408-415. doi:10.1002/art.23326

Kakihana, W., Akai, M., Nakazawa, K., Takashima, T., Naito, K., & Torii, S. (2005). Effects of laterally wedged insoles on knee and subtalar joint moments. *Arch Phys Med Rehabil, 86*(7), 1465-1471. doi:https://doi.org/10.1016/j.apmr.2004.09.033

Kellgren, J. H., & Lawrence, J. S. (1957). Radiological assessment of osteo-arthrosis. *Ann Rheum Dis, 16*(4), 494-502.

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. *Arch Phys Med Rehabil, 83*(7), 889-893. doi:http://dx.doi.org/10.1053/apmr.2002.33225

Kito, N., Shinkoda, K., Yamasaki, T., Kanemura, N., Anan, M., Okanishi, N., . . . Moriyama, H. (2010). Contribution of knee adduction moment impulse to pain and disability in Japanese women with medial knee osteoarthritis. *Clin Biomech (Bristol, Avon), 25*(9), 914-919. doi:10.1016/j.clinbiomech.2010.06.008

Kluge, F., Krinner, S., Lochmann, M., & Eskofier, B. M. (2017). Speed dependent effects of laterally wedged insoles on gait biomechanics in healthy subjects. *Gait Posture, 55*, 145-149. doi:10.1016/j.gaitpost.2017.04.012

Kumar, D., Manal, K. T., & Rudolph, K. S. (2013). Knee joint loading during gait in healthy controls and individuals with knee osteoarthritis. *Osteoarthritis Cartilage, 21*(2), 298-305. doi:10.1016/j.joca.2012.11.008

Lewinson, R. T., Vallerand, I. A., Collins, K. H., Wiley, J. P., Lun, V. M. Y., Patel, C., . . . Stefanyshyn, D. J. (2016). Reduced knee adduction moments for management of knee osteoarthritis:: A three month phase I/II randomized controlled trial. *Gait Posture, 50*, 60-68. doi:10.1016/j.gaitpost.2016.08.027

Lewinson, R. T., Worobets, J. T., & Stefanyshyn, D. J. (2016). Control conditions for footwear insole and orthotic research. *Gait Posture, 48*, 99-105. doi:10.1016/j.gaitpost.2016.04.012

Ludwig, O., Kelm, J., & Frohlich, M. (2016). The influence of insoles with a peroneal pressure point on the electromyographic activity of tibialis anterior and peroneus longus during gait. *J Foot Ankle Res, 9*(1), 33. doi:10.1186/s13047-016-0162-5

Ma, C. C., Lee, Y. J., Chen, B., & Aruin, A. S. (2016). Immediate and short-term effects of wearing a single textured insole on symmetry of stance and gait in healthy adults. *Gait Posture, 49*, 190-195. doi:10.1016/j.gaitpost.2016.07.010

McAlindon, T. E., Bannuru, R. R., Sullivan, M. C., Arden, N. K., Berenbaum, F., Bierma-Zeinstra, S. M., . . . Underwood, M. (2014). OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis Cartilage, 22*(3), 363-388. doi:10.1016/j.joca.2014.01.003

Santilli, V., Frascarelli, M. A., Paoloni, M., Frascarelli, F., Camerota, F., De Natale, L., & De Santis, F. (2005). Peroneus longus muscle activation pattern during gait cycle in athletes affected by functional ankle instability: a surface electromyographic study. *Am J Sports Med, 33*(8), 1183-1187. doi:10.1177/0363546504274147

Sawada, T., Tokuda, K., Tanimoto, K., Iwamoto, Y., Ogata, Y., Anan, M., . . . Shinkoda, K. (2016). Foot alignments influence the effect of knee adduction moment with lateral wedge insoles during gait. *Gait Posture, 49*, 451-456. doi:10.1016/j.gaitpost.2016.08.011

Schipplein, O. D., & Andriacchi, T. P. (1991). Interaction between active and passive knee stabilizers during level walking. *J Orthop Res, 9*(1), 113-119. doi:10.1002/jor.1100090114

Tipnis, R. A., Anloague, P. A., Laubach, L. L., & Barrios, J. A. (2014). The dose-response relationship between lateral foot wedging and the reduction of knee adduction moment. *Clin Biomech (Bristol, Avon), 29*(9), 984-989. doi:10.1016/j.clinbiomech.2014.08.016

Zhang, J., Wang, Q., & Zhang, C. (2018). Ineffectiveness of lateral-wedge insoles on the improvement of pain and function for medial knee osteoarthritis: a meta-analysis of controlled randomized trials. *Archives of orthopaedic and trauma surgery, 138*(10), 1453-1462. doi:10.1007/s00402-018-3004-z

Study V: Effects of tailored lateral wedge insoles on medial knee osteoarthritis: 12-week randomised controlled trial

Authors:

Vitor Ferreira, Leandro Machado, Adélio Vilaça, Francisco Xará-Leite, Paulo Roriz

Journal:

(Submitted for publication)

ABSTRACT

Background: Previous clinical trials have not confirmed if patients suffering from knee osteoarthritis will benefit from the use of adjusted lateral wedge insoles

Objective: To assess the effects of adjusted lateral wedge insoles on knee osteoarthritis symptoms and gait biomechanical parameters and physical function tests (30 second sit-to-stand test, 40-m fast paced walk test and the 12-step stair-climb test).

Methods: A 12-weeks randomized controlled trial was performed. The study included thirty-eight individuals which were divided into two groups. A control group (N = 18) using neutral insoles and an experimental group (N = 20) using adjusted lateral wedge insoles of 2°, 4°, 6°, 8° or 10-degrees. After a biomechanical analysis an adjusted angle insole was selected by a minimal reduction of 5% of first peak of EKAM.

Results: Of the 121 potential participants, 83 (68.6%) were ineligible or did not wish to participate. In total 38 participants (20 in lateral wedge insoles group, and 18 in control insoles group) completed all initial test and 31 completed the trial. Change in pain intensity (−12.5 mm, [95% confidence interval −29.4 to 4.4]), biomechanical parameters, KOOS and physical performance tests over 3-months was not significantly between the lateral wedge insole and control group, except for the subscale KOOS other symptoms (13.8 points, [95% confidence interval 5.6 to 22.0]).

Conclusion: Continued use of insoles was not more effective in reducing EKAM and pain intensity or to improve status in KOOS and physical function than neutral insole. Only a significant improvement was observed in subscale KOOS other symptoms. However, the effects were small and without clinical significance.

Trial registration: ISRCTN13577116

Keywords: Gait analysis; knee; osteoarthritis; lateral wedge insoles; KOOS; physical function

1. Introduction

Knee Osteoarthritis (OA) is one of the most common form of arthritis (Lawrence et al., 2008). As no cure exists and the typical knee OA treatment gap extends up to 20 years (London, Miller, & Block, 2011), there is great need for a safe and cost-effective treatment option that enjoys high patient acceptance. Osteoarthritis Research Society International (OARSI) recommend the use of biomechanical

interventions like braces, orthoses and lateral wedged insoles (McAlindon et al., 2014). These mechanical interventions, which aim to reduce the external knee adduction moment (EKAM), might have the potential to decelerate the progression of OA over time. The EKAM is a biomechanical parameter used to indirectly measure the distribution of internal forces in the knee during walking (Schipplein & Andriacchi, 1991). Reducing the first peak of EKAM has become a common goal in many studies that have adopted this parameter as a major outcome measure (Hinman, Bowles, Metcalf, Wrigley, & Bennell, 2012; Kim, Richards, Lidtke, & Trede, 2018). However, several studies have failed to show positive results in improving the condition with the use of this type of insole (Barrios, Crenshaw, Royer, & Davis, 2009; Bennell et al., 2011; Pham et al., 2004b), even those that use the reduction of EKAM as a way to select participants (Felson et al., 2019; Lewinson et al., 2016). Some individuals (approximately 25%) even show an increase in EKAM with the use of insoles (Butler, Marchesi, Royer, & Davis, 2007; Hinman, Bowles, & Bennell, 2009). Others don't show significant changes in clinical measures like pain and physical function (Baker et al., 2007; Bennell et al., 2011; Pham et al., 2004a). A previous meta-analysis show no significant change in pain when compared to neutral insoles (Parkes et al., 2013). The modest effect of EKAM reduction and the unsatisfactory effects of pain and physical function reduction could be due to the non-customized use of the lateral wedge insoles. Typical prescription, wide-ranging between 5-degree to 10-degree, without satisfy the correct biomechanical discrepancy between individuals (Penny, Geere, & Smith, 2013). The non-significant results may be linked with the use of the same angulation for all patients. We hypothesize that the use of a tailored lateral wedge insoles based on a reduction in EKAM promotes the results obtained.

To assess the efficacy of an adjusted degree of lateral wedge was carried out a randomised controlled trial over 12 weeks, to measure the improves on symptoms, biomechanical parameters and physical function performance tests in people with medial knee osteoarthritis.

2. Methods

2.1 Recruitment and eligibility

This study was a randomized controlled trial (ISRCTN13577116) that tested the effects of adjusted lateral wedge insoles and neutral insoles in persons with medial knee OA. Patients with symptomatic medial knee OA and varus malalignment were recruited from local hospitals and clinics between May 2018 and October 2019. The inclusion criteria were: 1) A diagnosis of medial knee OA according to the clinic and radiographic criteria established by the American College of Rheumatology (Altman et al., 1986). (Altman et al., 1986), namely: a) presence of medial knee pain; b) radiographic evidence of osteophyte in the medial joint space of the knee and; c) morning stiffness lasting more than 30 minutes and/or crepitus during motion; 2) A Kellgren & Lawrence grade of 2 or 3 and a mechanical axis angle lower than 181°, on females, or 183° on males, indicating varus alignment in the painful knee (scored by an orthopaedic doctor) on a full-length anteroposterior radiograph (Kellgren & Lawrence, 1957); 3) Age higher than 45 and lower than 80 years old; 4) A score on medial knee pain for the past week OA equal or higher than 3 using the Visual Analog Scale (VAS). The exclusion criteria were: 1) patients with symptomatic evidence of lateral compartment OA; 2) patellofemoral OA; 3) knee surgery within the past six months; 4) systemic arthritic conditions; 5) corticosteroid injection within the previous six weeks; 6) a body mass index higher than 35 (due to difficulties to accurately place body motion capture markers) and, 7) any other condition affecting lower limb function. No restrictions were applied on participants' usual medication

2.2 Procedures

Potential participants were recruited from local hospitals and clinics by study collaborators. A telephone call was made to the participants in order to explain the study purposes, potential benefits and risks and also to verify compliance with the inclusion criteria. A brief period of time was given to participants to freely

consider their participation in the study. A second telephone screening from the main researcher guaranteed the voluntary intention to participate and initiated the participation procedures. Clinical and biomechanical outcomes were measured at the laboratory for baseline assessment, (1st assessment); 15 days after baseline assessment (2nd assessment) and 12 weeks after using lateral wedge insoles (3rd assessment). During this first visit to LABIOMEP the participants read and signed the informed consent agreement, completed a brief medical health questionnaire, and became familiar with the protocol. Participants were clearly informed that different types of insoles are being tested and they will be blind to the type of insoles or their biomechanical effects. At the end of the baseline assessment, participants were allocated to the experimental or control group using block-randomization sequences in a 4:4 ratio that were generated using specific software by an independent collaborator, not directly involved in assessment of participants. In the second visit, the participants were reassessed and received a pair of adjusted lateral wedge insoles or neutral insoles to put inside their own shoe and use over 12 weeks. The insoles were costume made, with a long posterior pronating wedge and the wedge angle was adjusted after analysis of insoles biomechanical acute effects.

2.3 Outcome measures

2.3.1 Biomechanics outcomes

The primary outcome used was the first peak of EKAM measured during the stance phase of the gait cycle. A 12-camera Qualisys motion analysis system (Qualisys, Gothenburg, Sweden) operating at 200 Hz and 5 force plates (Bertec, Columbus, USA) operating at 1000 Hz were used to collect three-dimensional kinematic and kinetic data from participants walking along a 10 m walkway. The Calibrated Anatomical System Technique (CAST) (Cappozzo, Catani, Croce, & Leardini, 1995) was employed for gait analysis of body segments. Forty-two reflective markers were attached on the principal bony prominences bilaterally on the participant's lower limbs and pelvis as described in a previous study (Ferreira,

Machado, Vilaça, Leite, & Roriz, 2019). No other walking instructions were given to participants than walking at their self-selected speed to perform at least 6 valid trials for each of the experimental conditions which have been made in a randomized order. Six experimental conditions were tested: a control condition with a neutral insole (0° insole), and lateral wedge insoles with 2°, 4°, 6°, 8° and 10-degrees (**Figure 15**). Using an inverse dynamic approach in Visual 3D software (C-Motion, Rockville, USA), the first peak of EKAM, normalized to participant's body mass (Nm/kg) and averaged across the 6 trials was calculated. The lower wedge angle promoting a 5% reduction in the first peak of EKAM compared with the neutral insole was selected for each participant enrolled in the experimental group. This value was chosen by means of what is considered a conservative (Jones et al., 2013; Kim et al., 2018) since the minimal clinically important difference for EKAM is not known. A 5% decrease seems a reasonable criterion to ensure a biomechanical response.

Figure 15. An experimental insole (4-degree) used in the study

2.3.2 Clinical outcomes

The clinical outcomes measured at each visit to the laboratory were: The intensity of knee pain using the VAS; the health status using the Knee Injury and Osteoarthritis Outcome Score (KOOS); the performance in 3 tests of physical function; and information about current medication and treatments.

The VAS is a valid tool for measuring pain at one point in time (Kersten, White, & Tennant, 2014) with the extremes being “no pain at all” (0 mm) and “worst

imaginable pain” (100 mm). KOOS is a measure that was developed to assess patients with knee injuries and OA in five dimensions: pain, other symptoms, function in daily living, function in sport and recreation and knee-related quality of life (Roos, Roos, Lohmander, Ekdahl, & Beynnon, 1998). This instrument was previously translated and culturally adapt to the Portuguese population (Goncalves, Cabri, Pinheiro, & Ferreira, 2009). The tests used to assess physical function performance were the 30 second sit-to-stand test (30s-CST), the 40-m fast paced walk test (40m FPWT) and the 12-step stair-climb test (12-step SCT). These tests are the minimal core set of tests recommended by OARSI to assess physical function in people diagnosed with knee osteoarthritis (Dobson et al., 2013).

2.3.3 Assessment of adherence, discomfort and global improvement

To assesses the adherence to daily use a logbook was given to participants at baseline assessment, intended to register all days during the 12 weeks that participants have used the insoles for at least 7 hours/day. At final assessment participants were instructed to point on a scale, ranging from "no discomfort" (0 mm) to "worst possible discomfort" (100 mm), the amount of discomfort they felt by using the insoles during the 12 weeks. To assess the global perception of improvement associated to the use of insoles compared to the initial condition, participants scored on another 100 mm scale between two extremes "much worse" (0 mm) and "much better" (100 mm). The middle of the scale was considered a "roughly equal" condition.

2.4 Sample size

The sample size calculation was based on insoles acute effects from previous study (Ferreira, Machado, & Roriz, 2020). From the baseline mean of the first peak of EKAM, which was 0.482 Nm/kg with a SD of 0.182 Nm/kg, a 5% (0.024 Nm/kg) value was calculated and used to detect differences between the groups.

To detect such a difference with ANOVA repeated measures ($\alpha = 0.05$ and power of 95%) and $\eta^2 = 0.300$, the estimated sample size was 30 participants. With the assumption of a 30% loss to follow-up, it was decided to enroll 40 participants in the present study.

2.5 Statistical analysis

All data were analyzed on an intention-to-treat basis using SPSS 25.0 (IBM, Chicago, USA). Data was tested for normality suggesting use of parametric tests. A significance level of 0.05 was used for all tests. At baseline, participant characteristics that were continuous variables were compared across groups using t-test for independent variables, while categorical variables were compared across groups using a chi-square test. Differences in pain intensity, biomechanical parameters, KOOS and physical function tests over the 12-weeks period between groups were assessed using ANCOVA, adjusting for baseline values. To account for missing follow-up data (n = 7/38 participants), multiple imputation (5 imputations) was used, and a sensitivity analysis was performed by comparing ANCOVA results with and without imputation (completed cases). As results were unchanged, only data from completed cases was presented. Outcome data were compared between the insole and control group by calculating mean differences from baseline to 12 weeks' follow-up and the 95% confidence intervals (95% CI).

3. Results

3.1 Participants

From a set of 121 potential participants, 83 (68.6%) were ineligible or did not wish to participate (**Figure 16**). In total, 38 participants (20 for lateral wedge insoles group, and 18 for control insoles group) completed all initial tests and 31 (lateral wedge insoles, 80%; control insoles, 83%) completed the 12 weeks trial. Baseline descriptive characteristics of participants indicated no differences between

groups (**Table 8**) except for the number of hours of physical activity reported by participants (t = -2.910; p = 0.006).

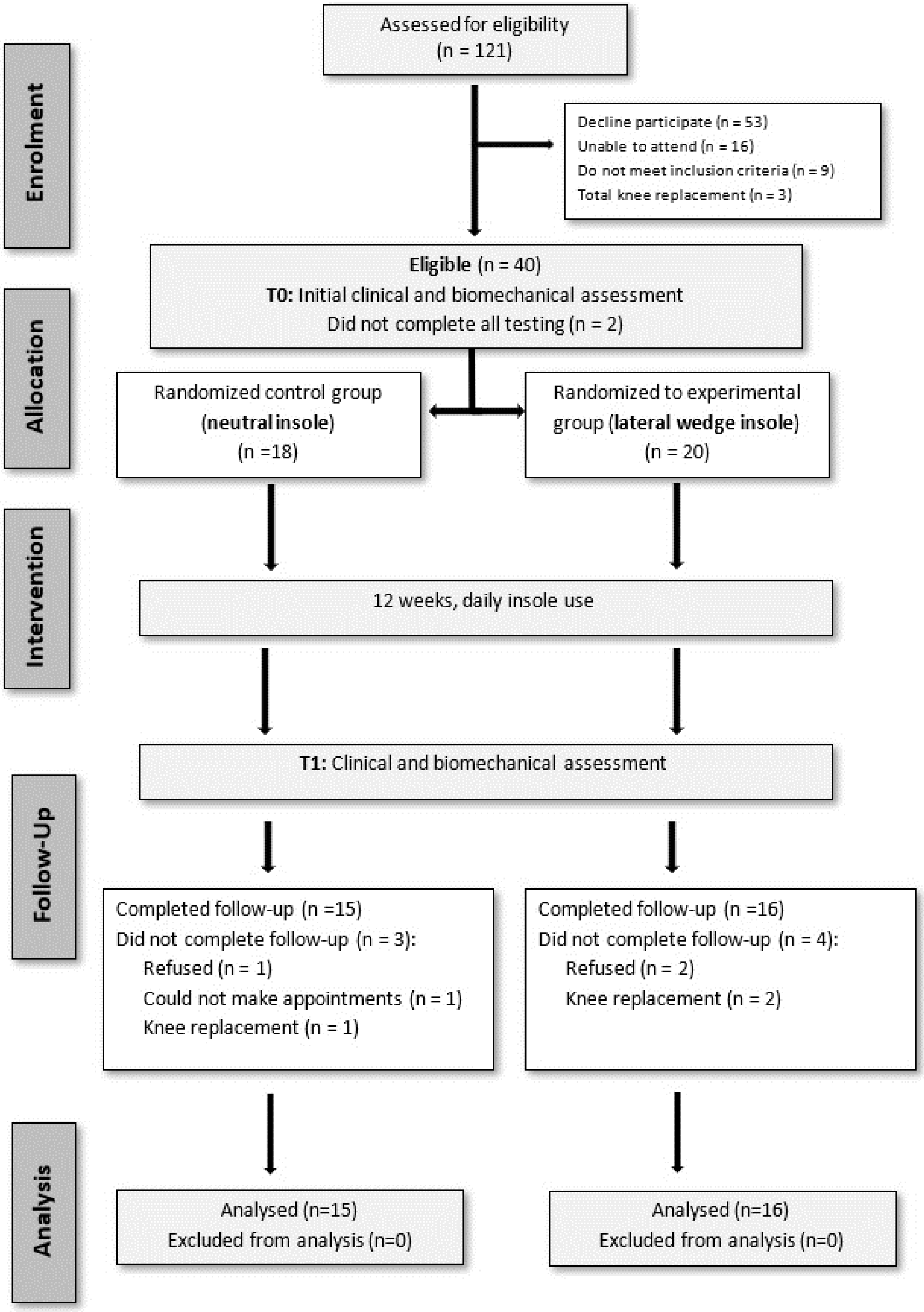


Figure 16. Flow diagram of study protocol.

Table 8. Baseline characteristics of participants, by study group. Values are numbers (SD) unless stated otherwise. P-values are shown for between group comparisons from t-test for independent variables for continuous data and chi-square tests for categorical data.

Variable	Wedge insoles (n=20)	Control insoles (n=18)	p-value
Age (years)	62.6 (8.0)	60.6 (8.9)	0.473
Female	15	8	0.054[a]
Body mass index (kg/m^2)	29.7 (5.9)	28.9 (4.2)	0.646
Hours pysical activity/week	2.0 (1.8)	0.4 (1.4)	0.006*
Radiographic disease severity			
Grade 2	9	7	
Grade 3	11	11	0,703[a]
Pain intensity			
Visual analogic scale (mm)	53.4 (23.0)	54.9 (22.9)	0.843
Biomechanical parameters			
First peak EKAM (Nm/kg)	0.496 (0.185)	0.404 (0.174)	0.126
Second peak EKAM (Nm/kg)	0.392 (0.213)	0.384 (0.170)	0.894
Knee adduction angular impulse (Nm/kg*s)	0.198 (0.101)	0.193 (0.111)	0.886
KOOS			
Pain	50.5 (16.7.3)	50.7 (12.9)	0.956
Symptom	55.3 (17.9)	64.6 (12.6)	0.077
Adl	51.0 (20.1)	60.6 (18.3)	0.134
Sport	37.5 (24.8)	35.0 (19.7)	0.735
Qol	40.8 (19.5)	39.7 (19.0)	0.870
Physical performance tests			
30-second sit-to-stand test (rep.)	12.4 (2.5)	11.4 (1.7)	0.150
40-m fast paced walk test (m/s)	1.5 (2.3)	1.4 (2.3)	0.466
12-step stair-climb test (s)	16.2 (5.2)	18.0 (7.1)	0.385

KOOS (Knee Injury and Osteoarthritis Outcome Score); rep. (repetitions); * Indicates significance; [a] Chi-square tests

3.2 Baseline measures

Looking to participants that have reduced at least 5% the EKAM in the experimental group, 13 participants (65%) achieved it with a 4-degree insole, 2 participants (10%) with a 6-degree insole and 5 participants (25%) with an 8-degree insole. When assessing baseline pain intensity (VAS), biomechanical parameters, KOOS and physical function tests no significant difference was detected (**Table 8**).

Table 9. Difference in symptomatic, biomechanical and physical function changes within and between groups from baseline to 12 weeks' follow-up. Between group mean differences were adjusted by baseline values, and so values may not equate to difference seen between the two within groups columns.

Outcome	Mean (sd) week 0		Mean (sd) week 12		Mean (sd) difference within groups (week 0 - week 12)		Between Groups Mean Difference[a] (95% CI) (week 12)
	Wedge insoles (n=20)	Control insoles (n=18)	Wedge insoles (n=16)	Control insoles (n=15)	Wedge insoles (n=16)	Control insoles (n=15)	Wedge insoles - Control insoles
Pain intensity							
Visual analogic scale	53.4 (23.0)	54.9 (22.9)	36.4 (30.7)	44.9 (22.2)	19.7 (26.1)	5.1 (20.8)	-12.5 (-29.4 to 4.4)
Biomechanical parameters							
First peak EKAM	0.496 (0.185)	0.404 (0.174)	0.479 (0.209)	0.424 (0.180)	0.019 (0.064)	0.006 (0.074)	-0.014 (-0.066 to 0.038)
Second peak EKAM	0.392 (0.213)	0.384 (0.170)	0.393 (0.224)	0.388 (0.212)	0.009 (0.096)	0.015 (0.076)	0.005 (-0.060 to 0.071)
Knee adduction angular impulse	0.198 (0.101)	0.193 (0.111)	0.175 (0.101)	0.185 (0.103)	0.024 (0.035)	0.022 (0.053)	-0.003 (-0.033 to 0.027)
KOOS							
Pain	50.5 (16.7)	50.7 (12.9)	59.1 (21.1)	49.7 (14.0)	-7.6 (14.7)	-3.1 (8.1)	4.6 (-4.4 to 13.5)
Symptom	55.3 (17.9)	64.6 (12.6)	67.2 (17.4)	60.6 (17.1)	-11.7 (12.6)	3.6 (8.9)	13.8 (5.6 to 22.0)*
Adl	51.0 (20.1)	60.6 (18.3)	56.9 (19.4)	59.1 (15.3)	-3.7 (12.8)	0.8 (13.0)	-2.4 (-11.2 to 6.3)
Sport	37.5 (24.8)	35.0 (19.7)	39.8 (23.2)	35.2 (20.7)	0.5 (21.7)	0.1 (9.0)	-1.2 (-12.6 to 10.2)
Qol	40.7 (19.5)	39.7 (19.0)	44.6 (21.1)	49.1 (20.7)	-3.9 (14.9)	-8.5 (14.9)	4.6 (-6.0 to 15.3)
Physical performance tests							
30-second sit-to-stand test	12.4 (2.5)	11.4 (1.6)	13.6 (3.1)	12.9 (2.6)	-1.1 (1.7)	-1.5 (1.5)	-0.4 (-1.7 to 0.9)
40-m fast paced walk test	1.5 (0.2)	1.5 (0.2)	1.5 (0.2)	1.5 (0.2)	0.0 (0.1)	0.0 (0.1)	-0.0 (-0.1 to 0.1)
12-step stair-climb test	16.2 (5.2)	18.0 (7.2)	13.6 (3.0)	16.3 (6.6)	1.1 (1.9)	1.1 (2.4)	-0.6 (-2.0 to 0.8)

Values reported as mean (SD). *p* value different from the 0° condition; [a] Adjusted for baseline value of variable; * Significant difference.

3.3 Follow-up outcomes

Difference in symptomatic, biomechanical and physical performance within and between groups from baseline to 12 weeks' follow-up can be found in **Table 9**. Between group mean differences were adjusted by baseline values. Change in

pain intensity, biomechanical parameters, KOOS and physical performance tests over 3-months was not significantly between the lateral wedge insole and control group, except for the subscale KOOS other symptoms.

The between group difference for the change in knee average pain measured with the VAS did not differ significantly (−12.5 mm, 95% CI, −29.4 to 4.4). Both groups showed mean reductions in pain, but these reductions were smaller than the minimal clinically important difference (MCID) (-19.9 mm) (Tubach et al., 2005). Nevertheless, the participants in the experimental group showed a reduction very close to the indicated absolute value (-19.7 mm). Change in KOOS pain over 12-weeks was not significantly different nor than the MCID between the experimental and control group when adjusted for baseline pain ($F = 1.094$; $p = 0.305$). Both groups showed mean reductions, but these reductions were again smaller than the MCID (13.4 points) (Collins, Misra, Felson, Crossley, & Roos, 2011). Change in KOOS other symptoms over 12-weeks was significantly different ($F = 11.817$; $p = 0.002$) between groups but not clinically relevant and smaller than the MCID (15.5 points) (Collins et al., 2011). Change in first peak of EKAM was not significantly different between the experimental and control group when adjusted for baseline value ($F = 0.301$; $p = 0.587$). The experimental group showed a reduction of 0.019 Nm/kg and the control group a small reduction (0.006Nm/kg) over 12 weeks (**Figure 17**).

3.4 Adherence, discomfort and global improvement to insoles

Logbook achievement rates were 70.2% for the insole group and 68.3% for the control insole group (**Table 10**). Discomfort scores were higher for those using insoles (15.3 mm in a scale 0-100 mm), than the control group (5.8 mm). On the other hand, participants in the experimental group reported a better global improvement condition than participants from the control group, which was statistically significant ($t = -2.233$; $p = 0.033$).

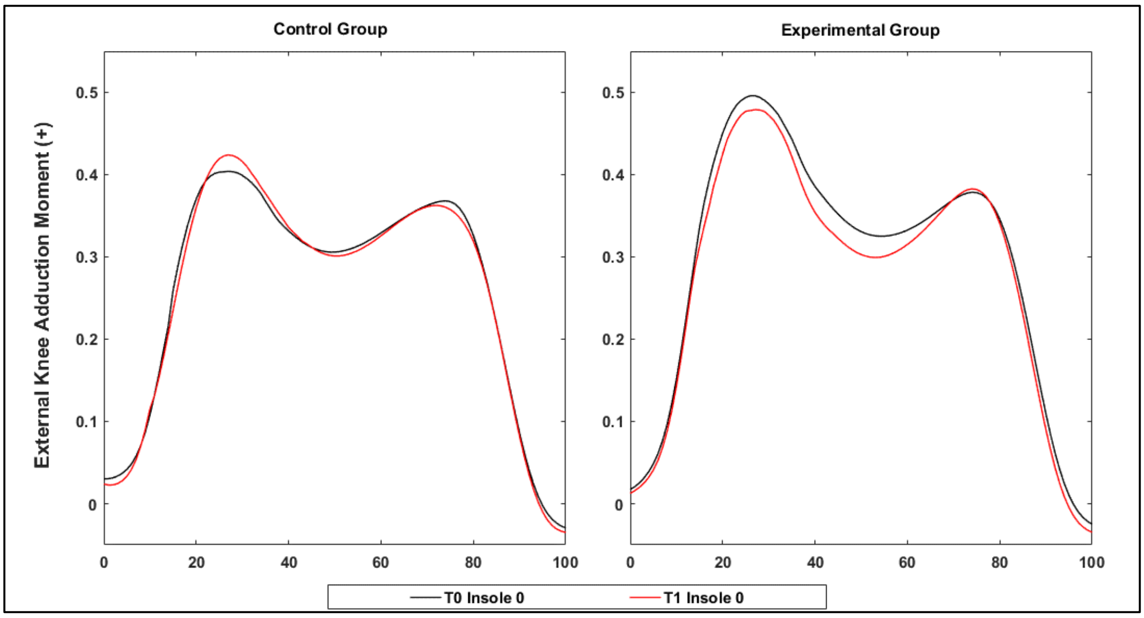


Figure 17. Differences between EKAM waveform between baseline (T0) and final (T1) assessment of control and experimental group, with 0-degree insole.

Table 10. Participant's reporting global improvement, adherence, and discomfort to insoles.

Outcome	Wedge insoles (n=16)	Control insoles (n=15)
Adherence to insoles (%)	70.2 (23.3)	68.3 (27.1)
Discomfort to insoles (mm in a scale 0-100)	15.3 (29.0)	5.8 (13.0)
Global improvement to insoles (mm in a scale 0-100)	68.3 (16.2)	56.5 (12.8)

4. Discussion

The purpose of this study was to evaluate if individualized prescription of a lateral wedge insole reduces OA symptoms and improves biomechanical parameters during 12-weeks, in individuals with medial knee osteoarthritis. The prescription was based on the biomechanical response due to slight variations on the lateral wedge angle of insoles. Our results do not support the use of tailored lateral wedge insoles since no significant differences were observed between or within the insole and control groups for pain intensity, biomechanical parameters,

KOOS and physical functions tests. Only in subscale KOOS other symptoms was observed a significant improvement of 13.8 (5.6 to 22.0, 95% CI) points in the experimental However, this value is below the MCID established (15.5 points) (Collins et al., 2011).

To the best of our knowledge, this study was the first that tried to prescribe the wedge angle of insoles based on acute biomechanical response. It was our belief that a tailored insole could be more effective improving the condition than a neutral insole. We assumed that a reduction of about 5% in first peak of EKAM could in a 12-weeks follow-up lead to positive effects reducing OA symptoms. Perhaps choosing this value as an effective biomechanical response is too ambitious. Otherwise, the evidence about the use of insoles for individuals with OA is quite controversial (Arnold, Wong, Jones, Hill, & Thewlis, 2016; Bennell et al., 2011; Chapman, Parkes, Forsythe, Felson, & Jones, 2015). A recent study (Lewinson et al., 2016) showed that even those individuals who responded to a reduction in EKAM, had no significant changes in pain reduction over 3 months. However, in that study the participants used a 6 mm lateral wedged insole, or a 6 mm medially wedged insole, based on the EKAM reduction. Though, in that study the morphology of the knees was not an inclusion criterion. The use of these insoles in individuals with a valgus morphology may be contradictory to the proposed effects. In fact, the presence of pain is more localized in the medial region of the knee in individuals with OA (Kumar, Manal, & Rudolph, 2013), and the varum alignment favours the forces exerted on the medial condyle (Sharma et al., 2001). On the other hand, an increasing degree of varus alignment is associated not only with progression of knee OA but also with development of knee OA and with greater medial joint space loss during the subsequent 18 months (Brouwer et al., 2007; Sharma et al., 2010; Sharma et al., 2001). Thus, in present study only participants with varum morphology were enrolled. However, the results on the experimental group have not been satisfactory either.

An influence of physical activity on the outcomes is possible. Cumulative load at the knee related to physical activity level was reported previously (Wallis et al., 2015). In our study it was not possible to strictly control the levels of physical

activity. Interestingly, when we compared the volume that participants reported in the baseline, we found that participants in the experimental group reported a higher number of hours of physical activity and that it was statistically significant compared to the control group. The recommended dose for patients with severe OA (grade 4 on the K/L scale) is about 70 minutes per week of moderate intensity walking (Wallis et al., 2015). In the baseline, participants in the experimental group reported about 2 hours per week. However due to the size of our sample and the lack of monitoring of physical activity levels throughout the trial it was not possible to assess to what extent differences in initial assessment could influence the results.

On the other hand, in an individual prescription study it will be important to check individual changes and whether these changes are compatible with MCID (**see supplementary table 1**). Regarding the changes in the intensity of knee pain in VAS, we found that 7 out of 16 (43.8%) participants perceived a pain reduction greater than the MCID (19.9 mm). Only 3 (20%) out of 15 participants perceived a pain reduction in control group. Concerning the changes in the intensity of KOOS pain over 12 weeks, we found that 3 out of 16 (18.6%) participants perceived a pain reduction greater than 13.4, the MCID established. Only 1 out of 15 (6.7%) participants perceived a pain reduction in control group. In individual changes of the subscale KOOS other symptoms, we found that 6 out of 16 (37.5%) participants in insoles group perceived reduction greater than the MCID (15.5 points). As the MCID for first peak EKAM is not known, it was not possible to do an individual analysis. However, considering the 5% reduction as a criterion for insole prescription, and we found that for all participants, the reduction corresponds to 0.023 Nm/kg, a value similar to the one found in the study of Kim et al. (0.02 Nm/kg) (Kim et al., 2018). In our study we found in the experimental group 8 (50%) and in the control group 5 (33.3%) participants with a reduction greater than the previous value. On the other hand, in the experimental group 3 (18.8%) participants had a first peak of EKAM worsening than 5% and 4 (26.7%) participants in the control group. Despite an account of greater discomfort with the use of the insoles, when asked about the improvement in health status compared to the beginning of the trial, more participants from the experimental

group (11 out of 16) reported they felt "with some improvements" or "much better" compared to the control group (5 out of 15).

Our findings are in agreement with other randomised controlled trials that also failed to show the efficacy of lateral wedge insoles (Baker et al., 2007; Barrios et al., 2009; Bennell et al., 2011; Lewinson et al., 2016; Pham et al., 2004b). Despite some individual improvements in the experimental group compared to the control group, present study also failed to show that an individual prescription of insole angle based in EKAM reduction, stands for a good strategy in the management of medial knee OA. Future studies should rethink EKAM reduction as a strategy for knee OA management. The study of this parameter seems to shown great variability, particularly with the use of insoles (Felson et al., 2019; Jones, Chapman, Forsythe, Parkes, & Felson, 2014; Lewinson et al., 2016). It will be important in future studies to understand this variability so that the biomechanical approach can assert itself as a valid alternative in the future.

Present study also encompasses several limitations. Firstly, it did not control physical activity levels. It is not possible to know if the participants during the trial had different levels of physical activity and if these levels have an impact on the outcomes. In the study of Bennell et al. (Bennell et al., 2011) physical activity levels were non-rated and there were no major differences between the groups. However, in our study the values at baseline were already statistically different. In future studies physical activity levels should be used in participants randomization. Secondly, the value set to define a clinically relevant reduction in first peak of EKAM needs to be found. However, the fact that a higher reduction in first peak of EKAM is required may impair participant’s adherence to daily use of the insoles. Knowing that insoles with angles greater than 8-degrees increases the discomfort and adverse effects with their use (Tipnis, Anloague, Laubach, & Barrios, 2014). Another possible limitation may be the inclusion criterion that allow participants up to 80 years old. In our study, the average age of participants was around 60 years. The inclusion of elderly participants may negatively influence the results since knee OA tissue repair capacity or mechanical correction at more advanced age will be somewhat limited (Hugle, Geurts,

Nuesch, Muller-Gerbl, & Valderrabano, 2012; Loeser, 2013). In future studies data analysis should be made by age groups. Finally, for the type of statistical analysis that needs to be performed the sample size proved to be too small. Future studies will certainly benefit from larger samples.

Conclusion

Over 12 weeks, continued use of insoles was not more effective than neutral insoles in reducing EKAM and pain intensity or improving status in KOOS and physical function. Only a significant improvement was observed in subscale KOOS other symptoms. However, the effects were small and without clinical significance. Reduction in EKAM needs to be confirmed in future studies as a primary outcome for the study of medial knee OA since it is a particularly unbalanced variable.

References

Altman, R., Asch, E., Bloch, D., Bole, G., Borenstein, D., Brandt, K., . . . et al. (1986). Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis Rheum, 29*(8), 1039-1049.

Arnold, J. B., Wong, D. X., Jones, R. K., Hill, C. L., & Thewlis, D. (2016). Lateral Wedge Insoles for Reducing Biomechanical Risk Factors for Medial Knee Osteoarthritis Progression: A Systematic Review and Meta-Analysis. *Arthritis Care Res (Hoboken), 68*(7), 936-951. doi:10.1002/acr.22797

Baker, K., Goggins, J., Xie, H., Szumowski, K., LaValley, M., Hunter, D. J., & Felson, D. T. (2007). A randomized crossover trial of a wedged insole for treatment of knee osteoarthritis. *Arthritis Rheum, 56*(4), 1198-1203. doi:10.1002/art.22516

Barrios, J. A., Crenshaw, J. R., Royer, T. D., & Davis, I. S. (2009). Walking shoes and laterally wedged orthoses in the clinical management of medial tibiofemoral osteoarthritis: a one-year prospective controlled trial. *Knee, 16*(2), 136-142. doi:10.1016/j.knee.2008.10.002

Bennell, K. L., Bowles, K. A., Payne, C., Cicuttini, F., Williamson, E., Forbes, A., . . . Hinman, R. S. (2011). Lateral wedge insoles for medial knee osteoarthritis: 12 month randomised controlled trial. *BMJ, 342*, d2912. doi:10.1136/bmj.d2912

Brouwer, G. M., van Tol, A. W., Bergink, A. P., Belo, J. N., Bernsen, R. M., Reijman, M., . . . Bierma-Zeinstra, S. M. (2007). Association between valgus and varus alignment and the development and progression of radiographic osteoarthritis of the knee. *Arthritis Rheum, 56*(4), 1204-1211. doi:10.1002/art.22515

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. *J Orthop Res, 25*(9), 1121-1127. doi:10.1002/jor.20423

Cappozzo, A., Catani, F., Croce, U. D., & Leardini, A. (1995). Position and orientation in space of bones during movement: anatomical frame definition and determination. *Clin Biomech (Bristol, Avon), 10*(4), 171-178. doi:10.1016/0268-0033(95)91394-T

Chapman, G. J., Parkes, M. J., Forsythe, L., Felson, D. T., & Jones, R. K. (2015). Ankle motion influences the external knee adduction moment and may predict who will respond to lateral wedge insoles?:

an ancillary analysis from the SILK trial. *Osteoarthritis Cartilage, 23*(8), 1316-1322. doi:10.1016/j.joca.2015.02.164
Collins, N. J., Misra, D., Felson, D. T., Crossley, K. M., & Roos, E. M. (2011). Measures of knee function: International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form, Knee Injury and Osteoarthritis Outcome Score (KOOS), Knee Injury and Osteoarthritis Outcome Score Physical Function Short Form (KOOS-PS), Knee Outcome Survey Activities of Daily Living Scale (KOS-ADL), Lysholm Knee Scoring Scale, Oxford Knee Score (OKS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Activity Rating Scale (ARS), and Tegner Activity Score (TAS). *Arthritis Care Res (Hoboken), 63 Suppl 11*(S11), S208-228. doi:10.1002/acr.20632
Dobson, F., Hinman, R. S., Roos, E. M., Abbott, J. H., Stratford, P., Davis, A. M., . . . Bennell, K. L. (2013). OARSI recommended performance-based tests to assess physical function in people diagnosed with hip or knee osteoarthritis. *Osteoarthritis Cartilage, 21*(8), 1042-1052. doi:10.1016/j.joca.2013.05.002
Felson, D. T., Parkes, M., Carter, S., Liu, A., Callaghan, M. J., Hodgson, R., . . . Jones, R. K. (2019). The Efficacy of a Lateral Wedge Insole for Painful Medial Knee Osteoarthritis After Prescreening: A Randomized Clinical Trial. *Arthritis Rheumatol, 71*(6), 908-915. doi:10.1002/art.40808
Ferreira, V., Machado, L., & Roriz, P. (2020). The effects on lower limbs kinematics of different lateral wedge insoles. *Journal of Mechanical Engineering and Biomechanics, 4*(4), 77-82. doi:10.24243/JMEB/4.4.233
Ferreira, V., Machado, L., Vilaça, A., Leite, F. X., & Roriz, P. (2019). Biomechanics performance in 30-s chair stand test in patients with medial knee osteoarthritis. *International Journal of Human Factors and Ergonomics, 6*(4), 319-330. doi:10.1504/ijhfe.2019.105359
Goncalves, R. S., Cabri, J., Pinheiro, J. P., & Ferreira, P. L. (2009). Cross-cultural adaptation and validation of the Portuguese version of the Knee injury and Osteoarthritis Outcome Score (KOOS). *Osteoarthritis Cartilage, 17*(9), 1156-1162. doi:10.1016/j.joca.2009.01.009
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 Musculoskelet Disord, 10*, 146. doi:10.1186/1471-2474-10-146
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. *Clin Biomech (Bristol, Avon), 27*(1), 27-33. doi:10.1016/j.clinbiomech.2011.07.010
Hugle, T., Geurts, J., Nuesch, C., Muller-Gerbl, M., & Valderrabano, V. (2012). Aging and osteoarthritis: an inevitable encounter? *Journal of aging research, 2012*, 950192. doi:10.1155/2012/950192
Jones, R. K., Chapman, G. J., Findlow, A. H., Forsythe, L., Parkes, M. J., Sultan, J., & Felson, D. T. (2013). A new approach to prevention of knee osteoarthritis: reducing medial load in the contralateral knee. *J Rheumatol, 40*(3), 309-315. doi:10.3899/jrheum.120589
Jones, R. K., Chapman, G. J., Forsythe, L., Parkes, M. J., & Felson, D. T. (2014). The relationship between reductions in knee loading and immediate pain response whilst wearing lateral wedged insoles in knee osteoarthritis. *J Orthop Res, 32*(9), 1147-1154. doi:10.1002/jor.22666
Kellgren, J. H., & Lawrence, J. S. (1957). Radiological assessment of osteo-arthrosis. *Ann Rheum Dis, 16*(4), 494-502.
Kersten, P., White, P. J., & Tennant, A. (2014). Is the pain visual analogue scale linear and responsive to change? An exploration using Rasch analysis. *PLoS ONE, 9*(6), e99485. doi:10.1371/journal.pone.0099485
Kim, Y., Richards, J., Lidtke, R. H., & Trede, R. (2018). Characteristics of clinical measurements between biomechanical responders and non-responders to a shoe designed for knee osteoarthritis. *Gait Posture, 59*, 23-27. doi:10.1016/j.gaitpost.2017.09.038
Kumar, D., Manal, K. T., & Rudolph, K. S. (2013). Knee joint loading during gait in healthy controls and individuals with knee osteoarthritis. *Osteoarthritis Cartilage, 21*(2), 298-305. doi:10.1016/j.joca.2012.11.008
Lawrence, R. C., Felson, D. T., Helmick, C. G., Arnold, L. M., Choi, H., Deyo, R. A., . . . National Arthritis Data, W. (2008). Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum, 58*(1), 26-35. doi:10.1002/art.23176
Lewinson, R. T., Vallerand, I. A., Collins, K. H., Wiley, J. P., Lun, V. M. Y., Patel, C., . . . Stefanyshyn, D. J. (2016). Reduced knee adduction moments for management of knee osteoarthritis:: A three month phase I/II randomized controlled trial. *Gait Posture, 50*, 60-68. doi:10.1016/j.gaitpost.2016.08.027
Loeser, R. F. (2013). Aging processes and the development of osteoarthritis. *Curr Opin Rheumatol, 25*(1), 108-113. doi:10.1097/BOR.0b013e32835a9428
London, N. J., Miller, L. E., & Block, J. E. (2011). Clinical and economic consequences of the treatment gap in knee osteoarthritis management. *Med Hypotheses, 76*(6), 887-892. doi:10.1016/j.mehy.2011.02.044

McAlindon, T. E., Bannuru, R. R., Sullivan, M. C., Arden, N. K., Berenbaum, F., Bierma-Zeinstra, S. M., . . . Underwood, M. (2014). OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis Cartilage, 22*(3), 363-388. doi:10.1016/j.joca.2014.01.003

Parkes, M. J., Maricar, N., Lunt, M., LaValley, M. P., Jones, R. K., Segal, N. A., . . . Felson, D. T. (2013). Lateral wedge insoles as a conservative treatment for pain in patients with medial knee osteoarthritis: a meta-analysis. *JAMA, 310*(7), 722-730. doi:10.1001/jama.2013.243229

Penny, P., Geere, J., & Smith, T. O. (2013). A systematic review investigating the efficacy of laterally wedged insoles for medial knee osteoarthritis. *Rheumatol Int, 33*(10), 2529-2538. doi:10.1007/s00296-013-2760-x

Pham, T., Maillefert, J. F., Hudry, C., Kieffert, P., Bourgeois, P., Lechevalier, D., & Dougados, M. (2004a). Laterally elevated wedged insoles in the treatment of medial knee osteoarthritis11This work was supported in part by the 'Programme Hospitalier de Recherche Clinique' (AOM 97 184) of the French Health Ministry. *Osteoarthritis and Cartilage, 12*(1), 46-55. doi:10.1016/j.joca.2003.08.011

Pham, T., Maillefert, J. F., Hudry, C., Kieffert, P., Bourgeois, P., Lechevalier, D., & Dougados, M. (2004b). Laterally elevated wedged insoles in the treatment of medial knee osteoarthritis: A two-year prospective randomized controlled study. *Osteoarthritis and Cartilage, 12*(1), 46-55. doi:https://doi.org/10.1016/j.joca.2003.08.011

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. *J Orthop Sports Phys Ther, 28*(2), 88-96. doi:10.2519/jospt.1998.28.2.88

Schipplein, O. D., & Andriacchi, T. P. (1991). Interaction between active and passive knee stabilizers during level walking. *J Orthop Res, 9*(1), 113-119. doi:10.1002/jor.1100090114

Sharma, L., Song, J., Dunlop, D., Felson, D., Lewis, C. E., Segal, N., . . . Nevitt, M. (2010). Varus and valgus alignment and incident and progressive knee osteoarthritis. *Ann Rheum Dis, 69*(11), 1940-1945. doi:10.1136/ard.2010.129742

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, 286*(2), 188-195. doi:10.1001/jama.286.2.188

Tipnis, R. A., Anloague, P. A., Laubach, L. L., & Barrios, J. A. (2014). The dose-response relationship between lateral foot wedging and the reduction of knee adduction moment. *Clin Biomech (Bristol, Avon), 29*(9), 984-989. doi:10.1016/j.clinbiomech.2014.08.016

Tubach, F., Ravaud, P., Baron, G., Falissard, B., Logeart, I., Bellamy, N., . . . Dougados, M. (2005). Evaluation of clinically relevant changes in patient reported outcomes in knee and hip osteoarthritis: the minimal clinically important improvement. *Ann Rheum Dis, 64*(1), 29-33. doi:10.1136/ard.2004.022905

Wallis, J. A., Webster, K. E., Levinger, P., Singh, P. J., Fong, C., & Taylor, N. F. (2015). The maximum tolerated dose of walking for people with severe osteoarthritis of the knee: a phase I trial. *Osteoarthritis Cartilage, 23*(8), 1285-1293. doi:10.1016/j.joca.2015.04.001

Chapter 4 - Discussion

4.1 General discussion

OA is a disease induced by mechanical forces for which unfortunately there is currently no cure (Felson, 2013). Therefore, nonsurgical conservative management for this disease may have a huge impact on the quality of life of those patients. The impact of osteoarthritis on disability is substantial (Vincent, Conrad, Fregly, & Vincent, 2012; Woolf & Pfleger, 2003). The risk for disability attributable to knee OA is as great as that attributable to cardiovascular disease and greater than that any other medical condition in elderly persons (Felson et al., 2000). In this population, walking, sit-to-stand or climbing stairs are naturally affected activities of daily living (ADL). In gait, these patients show slight changes in the spatiotemporal parameters (**Appendix 6**), such as decrease in velocity, stride and step length, and an increase of the stance phase and stride width, compared to a match age and no relevant multimorbidity individuals (Thaler-Kall et al., 2015). Apparently, these alterations in gait are an adaptation to changes caused by the disease in order to make walking more safer (Salzman, 2010).

Estimating the amount of change enough to produce real alterations in patients with knee OA is critical to design more effective interventions. Nevertheless, two concepts should be clarified: the minimal detectable change (MDC) and the minimal clinically important difference (MCID). The MDC can be defined as the smallest change that can be detected by the instrument beyond the standard measurement error (de Vet et al., 2006). The MCID as the smallest change in measurement that signifies an important improvement in a patient's symptom (Tubach et al., 2005). We found that the MDC for the 40-m fast paced walk test (40m FPWT) was 0.1 m/s, for the 12-step stair climb test (12-step SCT) was 1.9 s, and for the 30 second chair stand test (30s-CST) was 2.4 repetitions (**Appendix 4**). The values found are similar to a previous study (Dobson et al., 2012) and reflect that minor adjustments are relevant to detect changes in assessments. Since the disease has repercussions on the main ADL (walking, stand-to-sit and climbing stairs), a more detailed analysis on the 30s-CST (**Study III**) allowed to obtain important knowledge for understanding the biomechanical strategies used by these patients when performing the test. Despite being a short

duration test, these patients showed better outcomes in the most painful knee. On the other hand, we observed that patients with better health status show higher ability to produce power and force in the most painful knee along with other improved biomechanical outcomes. It was also possible to verify how patient's health status impacts on performance through an ADL task, as in other studies (McAlindon, Cooper, Kirwan, & Dieppe, 1992).

Present research was mainly focused on gait biomechanics changes since they seem to be associated with knee OA progression (Bennell, Bowles, Wang, et al., 2011; Hatfield, Stanish, & Hubley-Kozey, 2015). The external knee adduction moment (EKAM) has consistently emerged as a reasonable surrogate to assess dynamic load on the medial compartment of the knee (Chang et al., 2015). It has been shown to be a reliable and valid biomechanical parameter for individuals with medial knee OA (Birmingham, Hunt, Jones, Jenkyn, & Giffin, 2007). When we tried to study the reproducibility of this measurement (**Appendix 2**), we found a intraclass correlation coefficient (ICC) of 0.991, a standard error of measurement (SEM) of 0.016 Nm/kg and a MDC of 0.045 Nm/kg, within the same session. These results allowed us to ensure an excellent reproducibility in the procedures used during the data collection.

Footwear insoles/orthotics are commonly utilized as an intervention to prevent, treat or manage a variety of musculoskeletal disorders (N. Collins et al., 2009; Sahar et al., 2007; Snyder, DeAngelis, Koester, Spindler, & Dunn, 2009). Typically, the desired objective of the insole is to modify an individual’s gait pattern, particularly some kinetic variables (e.g. EKAM) that are believed to be changed. Lateral wedge insoles have been often indicated for patients with medial knee OA (McAlindon et al., 2014). As they have a higher elevation at the lateral than the medial edge, it is assumed that there is a transfer of load from the medial to the lateral knee joint during the stance phase (Mannisi, Dell'Isola, Andersen, & Woodburn, 2019). Its use is expected to promote significant biomechanical changes both immediately and in the long term. In this regard, we tried in a first approach to test slight variations in the lateral wedge insoles and see their acute effects in an individual with asymptomatic knee OA (**Appendix 1**). In this study an incremental reduction of EKAM was observed. Lateral wedge

insoles higher than 6-degree showed a significantly reduction of first peak of EKAM, second peak of EKAM and in knee adduction angular impulse (KAAI) compared with the control insole (0-degree insole). Similarly, we tried to understand if the application of lateral wedge insoles could change the alignment of the lower limbs in a static position (**Appendix 3**). In healthy individuals, we found they did not significantly change the knee, ankle or hip static alignment, which is in line with a previous study (Maly, Culham, & Costigan, 2002). This may be explained by the proposed mechanism of action for the lateral wedge insoles, which is based on the displacement of ground reaction forces (GRF) during gait (Hinman, Bowles, Metcalf, Wrigley, & Bennell, 2012). It is suggested that lateral wedges insoles may laterally shift the center of pressure (CoP) of the GRF (Kakihana, Akai, Yamasaki, Takashima, & Nakazawa, 2004). However, in our studies we have not been able to confirm that (**Study II; Study IV; Appendix 5**). A possible explanation for this disagreement may be related to different methodologies used in data analysis. On the other hand, other authors argue that the principal mechanism of action of the lateral wedge insoles is related to changes in the biomechanics of the ankle, mainly in ankle eversion (Chapman, Parkes, Forsythe, Felson, & Jones, 2015; Jones, Zhang, Laxton, Findlow, & Liu, 2013; Sawada et al., 2017). Since lateral wedge insoles are a mechanical correction under the foot, primarily increase ankle eversion and possibly deviate the GRF vector to a more medial knee position (**Study IV**). After initial contact of the foot on the ground, the CoP shifts from lateral to medial side (**FIGURE 19**), but controversially in our studies the higher angulations showed no significative differences compared with the neutral insole (**Study IV; Appendix 5**). A possible explanation may be related to use of different types of insoles. Some studies used full-length insoles (Hinman, Payne, Metcalf, Wrigley, & Bennell, 2008), half-length (Hinman, Bowles, Payne, & Bennell, 2008), without arch support (Dessery, Belzile, Turmel, & Corbeil, 2017) or with arch support (Jones, Chapman, Forsythe, Parkes, & Felson, 2014). In our study a pronating posterior long wedge was used. These slight variations of the insole shape may alter the path of the CoP, since minor modifications under the foot induce changes in the behaviour of the lower limb´s kinematics (Soares, de Castro, Mendes, & Machado, 2014).

However, in a systematic review, no significant differences were found in the main biomechanical parameters between neutral insoles and arch support insoles (Xing et al., 2017).

Although the use of lateral wedge insoles is widespread in patients with medial knee OA, several studies have shown a negligible effect on changing biomechanical parameters. A preceding meta-analysis demonstrated that lateral wedge insoles caused small reductions in the EKAM and KAAI, which could be useless in people with medial knee OA (Arnold, Wong, Jones, Hill, & Thewlis, 2016). Moreover, it is estimated that at least 20% of the individuals using lateral wedge insoles could even increase EKAM (Hinman et al., 2012; Jones et al., 2014; Lewinson et al., 2016). One reason that may contribute to these non-responders may be the patient's lack of customization of the insoles (Arnold, 2016). Numerous studies used insoles with identical angles, typically 5 or 6 degrees for all patients. Across our meta-analysis (**Study I**) we found that angulations higher than 9 degrees do not present a standardized mean difference (SMD) greater than angulations ≤ 9 degrees. In addition, it is well documented that the use of insoles with angles greater than 8 degrees cause discomfort or adverse effects, like foot pain (Tipnis, Anloague, Laubach, & Barrios, 2014; Toda, Tsukimura, & Kato, 2004). Thus, tailoring the application of insoles may allow a better biomechanical adjustment. Being the motivation of this Thesis, after a first approach in the case study (**Appendix 1**), we tried to understand if slight differences between wedges (2 degrees) induce different effects. During the course of our studies we used 6 different insoles. One with a neutral angle that served as a control (0 degrees) and 5 experimental insoles with wedges of 2, 4, 6, 8 and 10 degrees. The first approach, with healthy individuals (**Study II**), suggested that the application of the insoles on biomechanical parameters, was statistically significant only with insoles greater than 6-degrees. These insoles (> 6 degrees) when compared to the neutral insole, reduced the first peak of EKAM in 0.021Nm/kg (**Table 4**). Moreover, it was possible to see a slight reduction on first peak EKAM with each insole in an incremental direction, with the increasing angulation. In contrast, the 2-degree lateral wedge insole showed a slight increase in the first peak of EKAM. The main effect on kinematics in this study

was the increase in the ankle eversion (about 2 degrees with the 10-degree insole) at the first peak of EKAM. These results are coherent with previous studies (Chapman et al., 2015; Tipnis et al., 2014) and reinforce the assumption that this type of insoles are essentially a mechanical correction in the frontal plane (Hinman et al., 2012), promoting ankle eversion (Jones et al., 2013), and induce minor differences on the lower limb's biomechanics.

After exploring the acute effects on gait kinematics, we try to understand if the acute effects would be similar in patients with knee OA (**Study IV**). During the randomized controlled trial that was planned, we first considered the data from the baseline measurements. From the assessment of thirty-eight participants who previously had been diagnosed with symptomatic medial knee OA we found that the major changes were handled at the level of the ankle. More specifically, in the frontal plane and like in healthy individuals (**Study II**) a common increase in the angle of eversion, ankle eversion moment and ankle power absorption was observed (**Table 7**). In the eversion movement an increment of almost 2 degrees we registered, similar to the one observed in **Study II**. Also, we observed an increase of 0.040 Nm/kg in ankle eversion moment, and an increase of 0.041 W/kg in power absorption. These results were consistent to previous studies (Chapman et al., 2015; Sawada et al., 2017) and show slight changes in the foot biomechanics with the use of this type of insoles. When we look to the knee joint, fundamentally, we observe changes at the waveform of the EKAM. Surprisingly, the 2-degree insole was proved to be effective in reducing the first peak of EKAM ($p = 0.050$). The same pattern has been found in a previous study but only with healthy young participants enrolled (Tipnis et al., 2014),.

Going to the rationale of this thesis, we definitively wanted to see if an adjusted lateral wedge insole would improve the results so far disappointing, especially in the clinical outcomes. Several studies have failed to show encouraging results in improving medial knee OA with the use of lateral wedge insoles (Barrios, Crenshaw, Royer, & Davis, 2009; Bennell, Bowles, Payne, et al., 2011; Pham, Maillefert, et al., 2004b). Painful symptomatology is one of the most common symptoms in OA, and most used outcome measure for pain

intensity is visual analogue scale (VAS). However, the effects of lateral wedge insoles when compared to a neutral insole show no significant changes in pain intensity (Baker et al., 2007; Bennell, Bowles, Payne, et al., 2011; Parkes et al., 2013; Pham, Maillefert, et al., 2004a). Even those studies that use the reduction of first peak of EKAM as a way to enroll participants (Felson et al., 2019; Lewinson et al., 2016). The modest effect of EKAM reduction and the unsatisfactory effects on clinical outcomes may have been due to the lack of customization on the prescription of the insoles. For these reasons, it was hypothesized that an adequate biomechanical adjustment would lead to an improved efficiency of the lateral wedge insoles (**Study V**). In this sense, several patients were recruited from local clinics and hospitals and after baseline assessment were assigned to the experimental or control group. Afterwards, they were invited to wear the selected insoles inside their own shoes over 12 weeks. As the biomechanical intervention was well documented in previous studies, we decided to include some clinical measures recommended by international societies (Dobson et al., 2013; Pham, van der Heijde, et al., 2004). This allowed to assess the progresses on symptoms and physical function. In addition to VAS for knee pain intensity, the Knee Injury and Osteoarthritis Outcome Score (KOOS) was used. For the assessment of the performance in ADL's, the 3 physical function tests already described were used: 30s-CST, 40m FPWT and the 12-step SCT (**Study III; Appendix 4**). As in previous studies the results in our study failed to demonstrate improvements clinically significant or important with long-term use of insoles (Bennell, Bowles, Payne, et al., 2011; Felson et al., 2019; Lewinson et al., 2016). Only a significant improvement of 13.8 points (5.6 to 22.0, 95% CI) was observed in subscale KOOS other symptoms when compared to the control group. However, this value is slightly below the MCID established in a previous study (15.5 points) (N. J. Collins, Misra, Felson, Crossley, & Roos, 2011). Perhaps, by choosing a higher EKAM reduction value for selecting insoles, other results could be obtained. Nevertheless, the risk of low adherence to the use of insoles and the adverse effects could be clearly higher. To the best of our knowledge this study was the first completed in patients with OA that sought to recommend the angulation based on the biomechanical acute effects. We assume that a

reduction of about 5% in first peak of EKAM could lead to positive effects in reducing symptoms for a period of 12 weeks. Possibly choosing this value as an effective biomechanical response was too ambitious. Even when we performed a more individualized analysis, less than 50% of participants had a reduction in pain intensity higher than the MCID value. However, about 69% of participants in the experimental group reported on a global improvement scale at least "with some improvement" compared with 33% in the control group. This difference of judgment may be related to other reasons that have not been taken into account in the measures used in the study. Many patients with this condition, experience depressed mood and activity restriction with substantial impact on the Quality of Life (QoL) (Alkan, Fidan, Tosun, & Ardicoglu, 2014; Vitaloni et al., 2019). These limitations can persist even after receiving the best available treatments, like knee replacement (Noble et al., 2005). Remarkably, the problematic aspects of this condition are not fully explained by OA-related joint degeneration (Bedson & Croft, 2008). Some studies report that these patients experiences increase levels of pain as they perform activities (Harden et al., 2013). These increased levels of sensitivity to physical activity, are correlated with elevated pain catastrophizing, reduced activity tolerance, and increased disability (Sullivan et al., 2009). Interestingly, the participants in our study in the control group reporting a lower value of physical activity at baseline were the ones with the largest change in the KOOS QoL subscale (8.5 points). Along with changes reported in KOOS ADL's subscale close to the MDIC value, other clinical reasons may justify the present results.

Osteoarthritis is a challenging disease to treat because it combines mechanopathology with an inflammatory response to joint injury, both of which contribute to pain and disease progression (Felson et al., 2019). It has been unclear whether nonsurgical treatments targeting pathomechanics were likely to be major elements of the treatment regimen. Adherence to further treatments for this condition such as braces is poor (Squyer, Stamper, Hamilton, Sabin, & Leopold, 2013). This relatively inexpensive treatment compared to others has everything to be effective of the management of knee OA. However, our modest results combined to others have not yet confirmed this method of treatment as

effective. Perhaps a better association is missing between linking biomechanical findings with clinical outcomes. Maybe, the use of lateral wedge insole within non-standard footwear allows for too many degrees of freedom of the foot that mitigate the potential effect of the insole. Further refinement of the treatment with the use of specific shoes could increase the effectiveness of the device. On the other hand, using these insoles at an earlier stage of the disease and in younger individuals could improve clinical and biomechanical outcomes, in particular, because it is a relatively inexpensive treatment, simple to use and is well accepted by patients.

4.2 Limitations

The interpretation of the findings of this Thesis should be tempered considering a set of limitations.

The systematic review of the literature (**Study I**) which aggregates the data for the meta-analysis, has always some heterogeneity expressed by the methodology of the studies selected. Particularity in the selection of participants, data collection and analysis. This area of study is so sensitive to small differences that different setups in marker placement for gait analysis could affect the outputs and data comparison.

In the second study (**Study II**) the morphology of the foot was not considered. A previous study (Sawada et al., 2016) suggest that foot alignment has different effects in kinematics when wearing lateral wedge insoles because an individual with a normal foot is more likely to respond to lateral wedge insoles.

In the third study (**Study III**) the results presented are related only with individuals with knee OA. This make this study too descriptive without a comparative group. The presence of a matched group with asymptomatic pain could allow comparing the various parameters studied with these participants.

In the second and fourth study (**Study II; Study IV**) was used a rigid foot model. The use of multisegmented foot models like the Oxford model, could

provide more detailed information. However, in the study by Kim et al. (Kim, Richards, Lidtke, & Trede, 2018) a multisegmented model was used and the results are similar to others, for instance in EKAM values or percentage of non-responders.

Finally, in the randomized controlled trial (**Study V**) it was not possible to effectively control the participants' physical activity levels along the intervention period. Knowing that knee OA is a mechanically sensitive pathology, different levels of physical activity most likely influence the symptomatologic response. Another aspect to bear in mind, was that in this study the assessments were not blind to the principal investigator. This may have somehow influenced the results. Nevertheless, the assessment of gait biomechanics is by nature blind to researchers since the processing of the data is done after the fact. Also, the use of a 5% reduction in EKAM for the prescription of the insole needs further reflection. On the other hand, participants' use of their own footwear can be seen as a factor for improving external validity, but the accommodation of the insole to different types of footwear is different from participant to participant. Somehow, not controlling the use of shoes over the intervention period may have misleading the results. Another potential factor could be related to the selection of participants, either because of age or because the research took place outside hospital facilities. The age range used in this study may have been too large or otherwise the sample too small to allow more robust comparisons across variables. The evolution of the pathology is reflected in age and consequently the ability to adjustments will be limited in older ages (Hugle, Geurts, Nuesch, Muller-Gerbl, & Valderrabano, 2012; Loeser, 2013). Similarly, adherence to study out of hospital facilities may be higher in motivated participants. It will be important to understand if the results are similar in other motivation profiles. Likewise, we could also place the limitation of the intervention timeline. In our study an interval of 12 weeks was selected. However, in studies with longer follow-up the results are very similar to those of the present study (Bennell, Bowles, Payne, et al., 2011; Toda & Tsukimura, 2006; van Raaij, Reijman, Brouwer, Bierma-Zeinstra, & Verhaar, 2010).

References

Alkan, B. M., Fidan, F., Tosun, A., & Ardicoglu, O. (2014). Quality of life and self-reported disability in patients with knee osteoarthritis. *Mod Rheumatol, 24*(1), 166-171. doi:10.3109/14397595.2013.854046

Arnold, J. B. (2016). Lateral wedge insoles for people with medial knee osteoarthritis: one size fits all, some or none? *Osteoarthritis Cartilage, 24*(2), 193-195. doi:10.1016/j.joca.2015.09.016

Arnold, J. B., Wong, D. X., Jones, R. K., Hill, C. L., & Thewlis, D. (2016). Lateral Wedge Insoles for Reducing Biomechanical Risk Factors for Medial Knee Osteoarthritis Progression: A Systematic Review and Meta-Analysis. *Arthritis Care Res (Hoboken), 68*(7), 936-951. doi:10.1002/acr.22797

Baker, K., Goggins, J., Xie, H., Szumowski, K., LaValley, M., Hunter, D. J., & Felson, D. T. (2007). A randomized crossover trial of a wedged insole for treatment of knee osteoarthritis. *Arthritis Rheum, 56*(4), 1198-1203. doi:10.1002/art.22516

Barrios, J. A., Crenshaw, J. R., Royer, T. D., & Davis, I. S. (2009). Walking shoes and laterally wedged orthoses in the clinical management of medial tibiofemoral osteoarthritis: a one-year prospective controlled trial. *Knee, 16*(2), 136-142. doi:10.1016/j.knee.2008.10.002

Bedson, J., & Croft, P. R. (2008). The discordance between clinical and radiographic knee osteoarthritis: a systematic search and summary of the literature. *BMC Musculoskelet Disord, 9*(1), 116. doi:10.1186/1471-2474-9-116

Bennell, K. L., Bowles, K. A., Payne, C., Cicuttini, F., Williamson, E., Forbes, A., . . . Hinman, R. S. (2011). Lateral wedge insoles for medial knee osteoarthritis: 12 month randomised controlled trial. *BMJ, 342*, d2912. doi:10.1136/bmj.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. *Ann Rheum Dis, 70*(10), 1770-1774. doi:10.1136/ard.2010.147082

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 Rheum, 57*(6), 1012-1017. doi:10.1002/art.22899

Chang, A. H., Moisio, K. C., Chmiel, J. S., Eckstein, F., Guermazi, A., Prasad, P. V., . . . Sharma, L. (2015). External knee adduction and flexion moments during gait and medial tibiofemoral disease progression in knee osteoarthritis. *Osteoarthritis Cartilage, 23*(7), 1099-1106. doi:10.1016/j.joca.2015.02.005

Chapman, G. J., Parkes, M. J., Forsythe, L., Felson, D. T., & Jones, R. K. (2015). Ankle motion influences the external knee adduction moment and may predict who will respond to lateral wedge insoles?: an ancillary analysis from the SILK trial. *Osteoarthritis Cartilage, 23*(8), 1316-1322. doi:10.1016/j.joca.2015.02.164

Collins, N., Crossley, K., Beller, E., Darnell, R., McPoil, T., & Vicenzino, B. (2009). Foot orthoses and physiotherapy in the treatment of patellofemoral pain syndrome: randomised clinical trial. *Br J Sports Med, 43*(3), 169-171. doi:10.1136/bmj.a1735

Collins, N. J., Misra, D., Felson, D. T., Crossley, K. M., & Roos, E. M. (2011). Measures of knee function: International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form, Knee Injury and Osteoarthritis Outcome Score (KOOS), Knee Injury and Osteoarthritis Outcome Score Physical Function Short Form (KOOS-PS), Knee Outcome Survey Activities of Daily Living Scale (KOS-ADL), Lysholm Knee Scoring Scale, Oxford Knee Score (OKS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Activity Rating Scale (ARS), and Tegner Activity Score (TAS). *Arthritis Care Res (Hoboken), 63 Suppl 11*(S11), S208-228. doi:10.1002/acr.20632

de Vet, H. C., Terwee, C. B., Ostelo, R. W., Beckerman, H., Knol, D. L., & Bouter, L. M. (2006). Minimal changes in health status questionnaires: distinction between minimally detectable change and minimally important change. *Health Qual Life Outcomes, 4*, 54. doi:10.1186/1477-7525-4-54

Dessery, Y., Belzile, E., Turmel, S., & Corbeil, P. (2017). Effects of foot orthoses with medial arch support and lateral wedge on knee adduction moment in patients with medial knee osteoarthritis. *Prosthet Orthot Int, 41*(4), 356-363. doi:10.1177/0309364616661254

Dobson, F., Hinman, R. S., Hall, M., Terwee, C. B., Roos, E. M., & Bennell, K. L. (2012). Measurement properties of performance-based measures to assess physical function in hip and knee osteoarthritis: a systematic review. *Osteoarthritis Cartilage, 20*(12), 1548-1562. doi:10.1016/j.joca.2012.08.015

Dobson, F., Hinman, R. S., Roos, E. M., Abbott, J. H., Stratford, P., Davis, A. M., . . . Bennell, K. L. (2013). OARSI recommended performance-based tests to assess physical function in people diagnosed with hip or knee osteoarthritis. *Osteoarthritis Cartilage, 21*(8), 1042-1052. doi:10.1016/j.joca.2013.05.002

Felson, D. T. (2013). Osteoarthritis as a disease of mechanics. *Osteoarthritis Cartilage, 21*(1), 10-15. doi:10.1016/j.joca.2012.09.012

Felson, D. T., Lawrence, R. C., Dieppe, P. A., Hirsch, R., Helmick, C. G., Jordan, J. M., . . . Fries, J. F. (2000). Osteoarthritis: new insights. Part 1: the disease and its risk factors. *Ann Intern Med, 133*(8), 635-646. doi:10.7326/0003-4819-133-8-200010170-00016

Felson, D. T., Parkes, M., Carter, S., Liu, A., Callaghan, M. J., Hodgson, R., . . . Jones, R. K. (2019). The Efficacy of a Lateral Wedge Insole for Painful Medial Knee Osteoarthritis After Prescreening: A Randomized Clinical Trial. *Arthritis Rheumatol, 71*(6), 908-915. doi:10.1002/art.40808

Harden, R. N., Wallach, G., Gagnon, C. M., Zereshki, A., Mukai, A., Saracoglu, M., . . . Bruehl, S. (2013). The osteoarthritis knee model: psychophysical characteristics and putative outcomes. *J Pain, 14*(3), 281-289. doi:10.1016/j.jpain.2012.11.009

Hatfield, G. L., Stanish, W. D., & Hubley-Kozey, C. L. (2015). Three-dimensional biomechanical gait characteristics at baseline are associated with progression to total knee arthroplasty. *Arthritis Care Res (Hoboken), 67*(7), 1004-1014. doi:10.1002/acr.22564

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. *Clin Biomech (Bristol, Avon), 27*(1), 27-33. doi:10.1016/j.clinbiomech.2011.07.010

Hinman, R. S., Bowles, K. A., Payne, C., & Bennell, K. L. (2008). Effect of length on laterally-wedged insoles in knee osteoarthritis. *Arthritis Rheum, 59*(1), 144-147. doi:10.1002/art.23249

Hinman, R. S., Payne, C., Metcalf, B. R., Wrigley, T. V., & Bennell, K. L. (2008). Lateral wedges in knee osteoarthritis: what are their immediate clinical and biomechanical effects and can these predict a three-month clinical outcome? *Arthritis Rheum, 59*(3), 408-415. doi:10.1002/art.23326

Hugle, T., Geurts, J., Nuesch, C., Muller-Gerbl, M., & Valderrabano, V. (2012). Aging and osteoarthritis: an inevitable encounter? *Journal of aging research, 2012*, 950192. doi:10.1155/2012/950192

Jones, R. K., Chapman, G. J., Forsythe, L., Parkes, M. J., & Felson, D. T. (2014). The relationship between reductions in knee loading and immediate pain response whilst wearing lateral wedged insoles in knee osteoarthritis. *J Orthop Res, 32*(9), 1147-1154. doi:10.1002/jor.22666

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. *Hum Mov Sci, 32*(4), 596-604. doi:10.1016/j.humov.2012.12.012

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. *Am J Phys Med Rehabil, 83*(4), 273-278.

Kim, Y., Richards, J., Lidtke, R. H., & Trede, R. (2018). Characteristics of clinical measurements between biomechanical responders and non-responders to a shoe designed for knee osteoarthritis. *Gait Posture, 59*, 23-27. doi:10.1016/j.gaitpost.2017.09.038

Lewinson, R. T., Vallerand, I. A., Collins, K. H., Wiley, J. P., Lun, V. M. Y., Patel, C., . . . Stefanyshyn, D. J. (2016). Reduced knee adduction moments for management of knee osteoarthritis:: A three month phase I/II randomized controlled trial. *Gait Posture, 50*, 60-68. doi:10.1016/j.gaitpost.2016.08.027

Loeser, R. F. (2013). Aging processes and the development of osteoarthritis. *Curr Opin Rheumatol, 25*(1), 108-113. doi:10.1097/BOR.0b013e32835a9428

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. doi:https://doi.org/10.1016/S0268-0033(02)00073-6

Mannisi, M., Dell'Isola, A., Andersen, M. S., & Woodburn, J. (2019). Effect of lateral wedged insoles on the knee internal contact forces in medial knee osteoarthritis. *Gait Posture, 68*, 443-448. doi:10.1016/j.gaitpost.2018.12.030

McAlindon, T. E., Bannuru, R. R., Sullivan, M. C., Arden, N. K., Berenbaum, F., Bierma-Zeinstra, S. M., . . . Underwood, M. (2014). OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis Cartilage, 22*(3), 363-388. doi:10.1016/j.joca.2014.01.003

McAlindon, T. E., Cooper, C., Kirwan, J. R., & Dieppe, P. A. (1992). Knee pain and disability in the community. *Br J Rheumatol, 31*(3), 189-192.

Noble, P. C., Gordon, M. J., Weiss, J. M., Reddix, R. N., Conditt, M. A., & Mathis, K. B. (2005). Does total knee replacement restore normal knee function? *Clin Orthop Relat Res*(431), 157-165. doi:10.1097/01.blo.0000150130.03519.fb

Parkes, M. J., Maricar, N., Lunt, M., LaValley, M. P., Jones, R. K., Segal, N. A., . . . Felson, D. T. (2013). Lateral wedge insoles as a conservative treatment for pain in patients with medial knee osteoarthritis: a meta-analysis. *JAMA, 310*(7), 722-730. doi:10.1001/jama.2013.243229

Pham, T., Maillefert, J. F., Hudry, C., Kieffert, P., Bourgeois, P., Lechevalier, D., & Dougados, M. (2004a). Laterally elevated wedged insoles in the treatment of medial knee osteoarthritis11This work was supported in part by the 'Programme Hospitalier de Recherche Clinique' (AOM 97 184) of the French Health Ministry. *Osteoarthritis and Cartilage, 12*(1), 46-55. doi:10.1016/j.joca.2003.08.011

Pham, T., Maillefert, J. F., Hudry, C., Kieffert, P., Bourgeois, P., Lechevalier, D., & Dougados, M. (2004b). Laterally elevated wedged insoles in the treatment of medial knee osteoarthritis: A two-year prospective randomized controlled study. *Osteoarthritis and Cartilage, 12*(1), 46-55. doi:https://doi.org/10.1016/j.joca.2003.08.011

Pham, T., van der Heijde, D., Altman, R. D., Anderson, J. J., Bellamy, N., Hochberg, M., . . . Dougados, M. (2004). OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. *Osteoarthritis Cartilage, 12*(5), 389-399. doi:10.1016/j.joca.2004.02.001

Sahar, T., Cohen, M. J., Ne'eman, V., Kandel, L., Odebiyi, D. O., Lev, I., . . . Lahad, A. (2007). Insoles for prevention and treatment of back pain. *Cochrane Database Syst Rev*(4), CD005275. doi:10.1002/14651858.CD005275.pub2

Salzman, B. (2010). Gait and balance disorders in older adults. *Am Fam Physician, 82*(1), 61-68.

Sawada, T., Tanimoto, K., Tokuda, K., Iwamoto, Y., Ogata, Y., Anan, M., . . . Shinkoda, K. (2017). Rear foot kinematics when wearing lateral wedge insoles and foot alignment influence the effect of knee adduction moment for medial knee osteoarthritis. *Gait Posture, 57*, 177-181. doi:10.1016/j.gaitpost.2017.06.009

Sawada, T., Tokuda, K., Tanimoto, K., Iwamoto, Y., Ogata, Y., Anan, M., . . . Shinkoda, K. (2016). Foot alignments influence the effect of knee adduction moment with lateral wedge insoles during gait. *Gait Posture, 49*, 451-456. doi:10.1016/j.gaitpost.2016.08.011

Snyder, R. A., DeAngelis, J. P., Koester, M. C., Spindler, K. P., & Dunn, W. R. (2009). Does shoe insole modification prevent stress fractures? A systematic review. *Hss j, 5*(2), 92-98. doi:10.1007/s11420-009-9114-y

Soares, D. P., de Castro, M. P., Mendes, E., & Machado, L. (2014). Influence of wedges on lower limbs' kinematics and net joint moments during healthy elderly gait using principal component analysis. *Human Movement Science, 38*, 319-330. doi:10.1016/j.humov.2014.09.007

Squyer, E., Stamper, D. L., Hamilton, D. T., Sabin, J. A., & Leopold, S. S. (2013). Unloader knee braces for osteoarthritis: do patients actually wear them? *Clin Orthop Relat Res, 471*(6), 1982-1991. doi:10.1007/s11999-013-2814-0

Sullivan, M. J., Thibault, P., Andrikonyte, J., Butler, H., Catchlove, R., & Lariviere, C. (2009). Psychological influences on repetition-induced summation of activity-related pain in patients with chronic low back pain. *Pain, 141*(1-2), 70-78. doi:10.1016/j.pain.2008.10.017

Thaler-Kall, K., Peters, A., Thorand, B., Grill, E., Autenrieth, C. S., Horsch, A., & Meisinger, C. (2015). Description of spatio-temporal gait parameters in elderly people and their association with history of falls: results of the population-based cross-sectional KORA-Age study. *BMC Geriatr, 15*, 32. doi:10.1186/s12877-015-0032-1

Tipnis, R. A., Anloague, P. A., Laubach, L. L., & Barrios, J. A. (2014). The dose-response relationship between lateral foot wedging and the reduction of knee adduction moment. *Clin Biomech (Bristol, Avon), 29*(9), 984-989. doi:10.1016/j.clinbiomech.2014.08.016

Toda, Y., & Tsukimura, N. (2006). A 2-year follow-up of a study to compare the efficacy of lateral wedged insoles with subtalar strapping and in-shoe lateral wedged insoles in patients with varus deformity osteoarthritis of the knee. *Osteoarthritis Cartilage, 14*(3), 231-237. doi:10.1016/j.joca.2005.09.006

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. *Arch Phys Med Rehabil, 85*(4), 673-677. doi:10.1016/j.apmr.2003.06.011

Tubach, F., Ravaud, P., Baron, G., Falissard, B., Logeart, I., Bellamy, N., . . . Dougados, M. (2005). Evaluation of clinically relevant changes in patient reported outcomes in knee and hip osteoarthritis: the minimal clinically important improvement. *Ann Rheum Dis, 64*(1), 29-33. doi:10.1136/ard.2004.022905

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. *Clin Orthop Relat Res, 468*(7), 1926-1932. doi:10.1007/s11999-010-1274-z

Vincent, K. R., Conrad, B. P., Fregly, B. J., & Vincent, H. K. (2012). The pathophysiology of osteoarthritis: a mechanical perspective on the knee joint. *PM R, 4*(5 Suppl), S3-9. doi:10.1016/j.pmrj.2012.01.020

Vitaloni, M., Botto-van Bemden, A., Sciortino Contreras, R. M., Scotton, D., Bibas, M., Quintero, M., . . . Verges, J. (2019). Global management of patients with knee osteoarthritis begins with quality of life assessment: a systematic review. *BMC Musculoskelet Disord, 20*(1), 493. doi:10.1186/s12891-019-2895-3

Woolf, A. D., & Pfleger, B. (2003). Burden of major musculoskeletal conditions. *Bull World Health Organ, 81*(9), 646-656.

Xing, F., Lu, B., Kuang, M. J., Wang, Y., Zhao, Y. L., Zhao, J., . . . Ma, X. L. (2017). A systematic review and meta-analysis into the effect of lateral wedge arch support insoles for reducing knee joint load in patients with medial knee osteoarthritis. *Medicine (Baltimore), 96*(24), e7168. doi:10.1097/MD.0000000000007168

Chapter 5 – Conclusion and future work perspectives

5.1 General conclusions

Following the findings obtained in the collection of studies presented in this Thesis, it seems reasonable to highlight out the following conclusions:

I. Lateral wedge insoles have a small effect on reducing the EKAM that cross the medial knee in people with medial knee OA.
II. Angulations higher than 9-degrees do not present significative effects than angulations lower than 9-degrees in reducing the first peak of EKAM.
III. In healthy individuals, the lateral wedge insoles seem to promote a greater peak eversion on the foot, particularly at the first peak of EKAM.
IV. In individuals with knee OA, lateral wedge insoles increase ankle eversion as well which seems to be the primary mechanism of action of lateral wedge insoles.
V. Small changes under the foot can induce significant changes in the knee.
VI. The shift of CoP appears to have no influence on the mechanism responsible for reducing the first peak of EKAM.
VII. Patients with higher scores in KOOS subscales (ADL and QoL) exhibited higher capacity to produce power and force in the most painful knee for a sit-to-stand functional task.
VIII. The continuous use, during 12 weeks, of tailored wedge insoles was no more effective at improving biomechanical or clinically meaningful outcomes than neutral insoles.
IX. The reduction in the first peak of EKAM needs to be confirmed in future studies as a primary outcome as it is still a variable with little clinical significance.

5.2 Future work perspectives

Further research on medial knee OA is needed to improve biomechanical and clinical positive outcomes, particularly in the later stages of the disease. It will be important in future studies the assessment of muscle strength and motor control parameters in order to relate them with the biomechanical variables in patients with varus malalignment and knee OA and better understand the adaptive mechanisms of the pathology. To understand the complexity of knee OA and to design earlier and more appropriate treatment strategies for the disease will require continued study on the interrelationships between risk factors and appropriate models of disease progression. This analysis is particularly important in alterations in gait and in different approaches to minimize these alterations. Different types of materials or shapes of the insoles could be a way to better outcomes. Future modifications of the screening strategy or even other treatments might offer greater levels of efficacy. Because different foot morphologies can change effects to insoles, future studies that also consider foot morphology may be explore. Identification of MCID for the first peak EKAM is critical for more effective biomechanical interventions. Finally, the use of standardized footwear with the application of an adjusted insole may be a strategy to use in future studies.

Appendices

Appendix 1. The biomechanical effects of lateral wedge insoles with different heights on the knee: a preliminary study

***Vitor Ferreira* [1], *Leandro Machado* [2] *e Paulo Roriz* [3, 4]**

[1]*Health Center of Aveiro; ESSUA - School of Health, University of Aveiro, Portugal,* v.ferreira@ua.pt

[2] *FADEUP, CIFI2D, LABIOMEP, University of Porto, Portugal,* lmachado@fade.up.pt

[3] *CIDESD-ISMAI, Institute University of Maia, Portugal;* paulororiz@ismai.pt; paulororiz.labiomep@fade.up.pt

[4] *LABIOMEP, INESC-TEC, Institute for Systems and Computer Engineering, Technology and Science, Porto, Portugal*

ABSTRACT:

Knee osteoarthritis is a degenerative joint disease with no known cure that is characterized by joint pain and dysfunction. Traditional treatments have shown long-term poor effectiveness. Knee misalignment loads acting in the joint are probably the most important factors for its progression and severity. Thus, biomechanical interventions focusing on knee alignment along with reduction and redistribution of loads should contribute for a better prognosis. A typical intervention is focused on the application of lateral wedge insoles. Their use could reduce knee varus position and external knee adduction moment, leading to a better load distribution, particularly at the medial condyle. However, some individuals are non-responders, probably due to a bad choice of the wedge angle. The purpose of this study was to examine the effects of different wedge insole angles on external knee adduction moment during gait. A three-dimensional motion analysis system and force platforms were used to collect the data for seven wedge angles (0, 2, 4, 5, 6, 8 and 10 degrees). Post-processing calculation of the kinematic and kinetic data was conducted using Visual 3D software. Generally, a reduction of the external knee adduction moment is obtained with higher wedge angles. Nevertheless, the optimal angle should be obtained from individual fitting.

KEY-WORDS: Knee adduction moment; Angular impulse; Lateral wedged insole; Gait; Osteoarthritis

1 INTRODUCTION

Osteoarthritis (OA) is a major cause of chronic musculoskeletal pain and disability in the elderly population (Jordan et al., 2003). Joint loads during walking are implicated in the pathogenesis of knee OA. During walking, the forces across the knee are not transmitted equally between the medial and lateral compartments (Zhao et al., 2007). The medial compartment has a higher prevalence in subjects with tibiofemoral OA relative to the lateral compartment, especially in men (Wise et al., 2012).

The previous existence of varus malalignment of the knee (the angle formed by the hip, knee, and ankle joint centers) is described as one of the reasons for the high prevalence of OA and has been shown to increase the risk of development (Brouwer et al., 2007) and subsequent medial OA knee progression (Sharma et al., 2001). This asymmetry in the distribution of the forces over

the articular surface in the knee causes more pressure over the soft tissues and may lead to a premature degeneration (Felson, 2013).

Direct measurement of knee joint loads is not feasible because of the invasive nature of this in vivo method. However, gait analysis can calculate external joint-loading moments that are directly related to internal joint loads. The external knee adduction moment (KAM) is a method that determines load distribution across the medial and lateral tibial plateaus. The external KAM is 50% greater in OA patients (Kumar, Manal, & Rudolph, 2013), and provides a valid and reliable indication of dynamic joint load in the medial compartment during walking (Birmingham, Hunt, Jones, Jenkyn, & Giffin, 2007; Hunt & Bennell, 2011). During the stance phase, the KAM has two peaks: a 1st peak during early stance and a 2nd peak during late stance (Kutzner, Trepczynski, Heller, & Bergmann, 2013). The 1st, also the larger has a high correlation with medial tibiofemoral contact force (Kutzner et al., 2013). There is currently no cure for knee OA, nevertheless the treatment gap for the patient who is unresponsive to conservative care can be extended up to 20 years (London, Miller, & Block, 2011). The only established treatment for end-stage OA is a costly joint replacement. However, slowing of structural disease progression is essential to help reduce the personal and societal burden of knee OA. Moreover, there is great need for a cost-effective treatment option for patients with moderate to severe OA that could enjoy high patient acceptance. Recent guidelines update for the management of knee OA (McAlindon et al., 2014) recommended a combination of non-pharmacological and pharmacological methods like changes in lifestyle, exercise, pacing of activities, weight reduction and other measures to reduce the load on the damaged joint(s), such as walking aids, knee braces or insoles.

An approach that aims to reduce the external KAM is an important treatment option (K. Bennell et al., 2007; Jones, Zhang, Laxton, Findlow, & Liu, 2013). Laterally wedged insoles (LWI) have been used to treat patients with medial knee OA in the last years. This biomechanical intervention, which tries to reduce the KAM, might have the potential to decelerate the progression of OA over time. Its potential mechanism of action is to redistribute the forces across articular surface in a new fair mode. It appears that LWI result in a lateral shift of the center of pressure at the foot and this shifts the frontal plane ground reaction force vector towards the knee joint center (Hinman, Bowles, Metcalf, Wrigley, & Bennell, 2012). Recent literature shows, using gait analyses studies, that LWI reduce the KAM in individuals with OA by at least 5% (Baker et al., 2007; Hinman et al., 2012; Jones, Nester, et al., 2013). However, individuals KAM response to LWI is particularly variable. Some individuals even show an increase (worsening) in external KAM (Hinman et al., 2012). Others don’t show significant changes in clinical measures like pain and physical function (K. L. Bennell et al., 2011). One of the reasons appointed may be the widespread use of a unique lateral wedge for all individuals. The typical prescription is 5º or 6º for all individuals without requirements to correct biomechanical discrepancy between individuals.

The aim of this preliminary/case study is to understand whether and how small variations of the wedge angle change the biomechanical behaviour of the knee.

2 METHODS

2.1 SUBJECT

A sixty-nine years' old, 1.68 m of height, 79.6 kg of mass, without any neuromuscular disorders, and without history of actual ankle knee or hip pain, was volunteer. Ethical approval was gained from the University's committee and the subject provided written consent.

2.2 PROCEDURES

Seven experimental conditions were tested: a control condition (shoes with a 0º insole), and LWI with 2º, 4º, 5º, 6º, 8º and 10º degrees. The insoles were costume made with a pronating wedge posterior long (Capron Podologie; Ref.: 8004F). The insoles were worn bilaterally but only the data from the right side is presented.

2.3 DATA COLLECTION

A twelve-camera three-dimensional Qualisys Oqus (Qualisys AB, Sweden) motion analysis system sampling at 200 Hz, with four force platforms (Bertec, Columbus, USA) sampling at 1000 Hz, were used to collect the kinematic and kinetic data. Reflective markers were attached with self-adhesive tape bilaterally on the subject's lower limbs and pelvis, respectively in anterior superior iliac spine, posterior superior iliac spine, greater trochanter, medial condyles, lateral condyles, fibula head, tibial tubercle, lateral malleolus and medial malleolus. The markers at locations of calcaneus, 1st, 2nd and 5th metatarsal heads were glued on the shoes and the feet were assumed to be a rigid body. Four rigid clusters were placed bilaterally on anterior-lateral aspect of the leg and thigh. The Calibrated Anatomical System Technique (CAST) was employed to determine the movement of these segments during the walking trials (Cappozzo, Catani, Croce, & Leardini, 1995). All of the markers remained attached during the entire data collection to ensure that anatomical marker placement remained consistent to reduce marker replacement error between each condition. A static calibration of the markers was performed for each condition before any walking trials. The subject was asked to walk at their own self-selected speed and performed 6 valid trials in each of the seven conditions in a randomized order. Two minutes walking between conditions was given to allow the subject to adapt to the new insole condition.

2.4 DATA ANALYSIS

Post-processing calculation of the kinematic and kinetic time series data was conducted using Visual3D software (Version 5.02.24, C-Motion Inc., Rockville, USA). Motion and force plate data were filtered (6 Hz) using a Butterworth 4th order filter. The position and force data, alongside the inertial parameters were used to calculate the net external joint moments using three-dimensional inverse dynamics. The external KAM was expressed with respect to the tibial reference frame.

The 1st and 2nd peak (greatest magnitude) adduction moment values were identified from each of the KAM waveforms and were averaged across the 6 condition trials to obtain a single peak KAM value. External joint moment data were normalized to body mass (BM) (Nm/kg). The knee adduction angular impulse (KAAI) (Thorp et al., 2006) was also calculated by integrating the external KAM signal for the stance phase (in % BM x Time). The kinematic and kinetic data were time normalized to 100% of the stance phase.

Data was exported to SPSS 22.0 (SPSS Inc) for statistical analysis. A Mann-Whitney test was used to compare the control condition with others insoles. The differences were considered to be significant at $\alpha < 0,05$.

3 RESULTS

Figure 18 shows the average of the gait trails in different conditions compared with the control *condition.* Table 11 presents the 1st and 2nd peak external KAM and KAII. The magnitude of change and significant differences compared with the control condition are also presented.

In the control condition (insole 0º) the average of 1st peak KAM during the stance phase was 0,208 (± 0,007) Nm/kg. The average of 2nd peak KAM during the stance phase with an insole 0º was 0,237 (± 0,010) Nm/kg. The average of KAAI during the stance phase was 0,095 (± 0,004) Nm/Kg^{x}s. Generally, a reduction of the external KAM was obtained for higher wedge angles. For instance, with an insole of 5º the reduction in the 1st peak KAM was 6,7% and with an insole of 10º the reduction in the 1st peak KAM was 17,3% when compared with the control condition. These differences in external KAM and KAAI between insoles conditions were statistically significant ($p \leq 0,05$) for insoles higher than 5º in the 1st peak and insoles higher than 6º in the 2nd peak and KAAI. In this subject, for gait with an insole of 6º (**Figure 18**), the average of external KAM along the stance phase is always below the mean minus standard deviation for the control condition.

4 DISCUSSION

One of the primary reasons for investigating different wedges in insoles was the belief that different wedges can cause different reductions on external KAM. Secondly, to understand the best way to prescribe an adjusted insole to the actual knee biomechanical condition. The results suggested that higher wedge angles could produce higher reduction on the external KAM. In the analysed subject, the insole with an angle of 5° significantly reduced the 1st peak of KAM, but not the 2nd peak and the KAAI. Since these variables are the most used in studies that focus on this issue (Duivenvoorden et al., 2014; Hinman, Payne, Metcalf, Wrigley, & Bennell, 2008; Jones, Chapman, Forsythe, Parkes, & Felson, 2014; Jones, Zhang, et al., 2013; Nakajima et al., 2009), it seems pertinent to us that the prescription of an individual insole has to be adjusted in order to cause a significant reduction of these 3 variables.

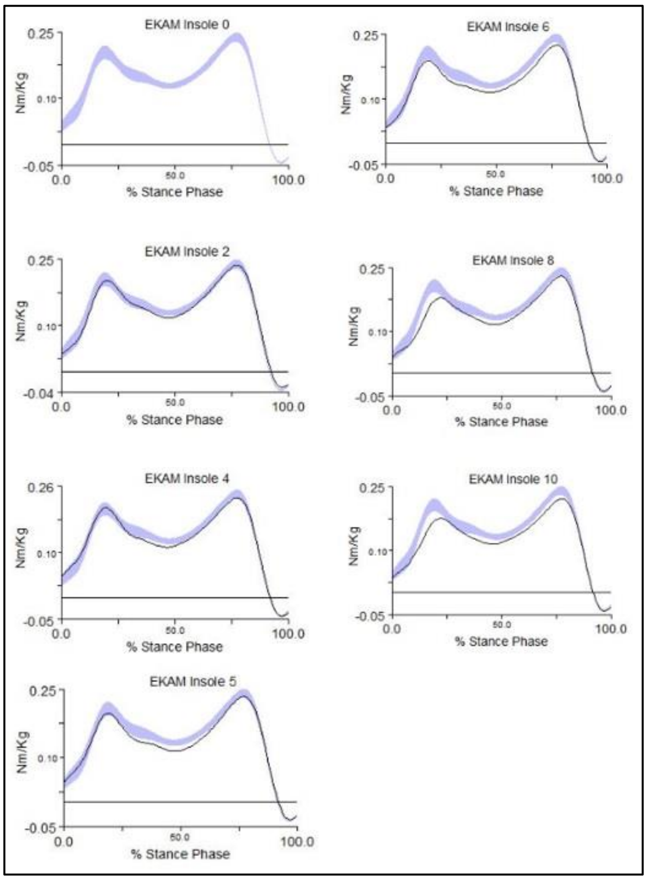


Figure 18. Comparison of various wedge insoles with the control condition. Lines represent the average of the experimental condition and shaded areas the average of the control condition ± one standard deviation.

The majority of the previous studies have been focused on a single outcome, usually the 1st peak of the external KAM (Duivenvoorden et al., 2014; Hinman et al., 2008; Jones, Chapman, et al., 2013). Increased external KAM have been linked with worsening of OA in medial compartment (Miyazaki et al., 2002) and a large number of studies adopted only the 1st peak KAM as a major outcome, where LWI reduce the 1st peak KAM in individuals with OA by at least 5%. However, a recent meta-analysis showed no significant changes in clinical outcomes, like pain or physical function (Parkes et al., 2013). One possible explanation to this fact may be that the insoles reduce the 1st peak KAM, but not the whole amount of forces to which the knee is subjected in each cycle of stance phase. Another explanation may be the prescription of equal wedge angulation for all individuals typically, 5º or 6 degrees. However, from studies that have already been carried out, some individuals did not reduce their 1st peak KAM, on the contrary it has increased with the application of the insole when compared with the control condition (Hinman et al., 2012; Hinman et al., 2008).

Table 11. 1st and 2nd peak external KAM (Nm/kg) and KAII (Nm/kg^{x}s).

Insole		Mean (SD)	Change	P value
Insole 0º (control)	Peak 1	0,208 (0,007)		
	Peak 2	0,237 (0,010)		
	KAAI	0,095 (0,004)		
Insole 2º	Peak 1	0,210 (0,011)	0,1%	0,813
	Peak 2	0,233 (0,010)	-1,7%	0,631
	KAAI	0,093 (0,004)	-2,1%	0,337
Insole 4º	Peak 1	0,206 (0,035)	-1,0%	0,423
	Peak 2	0,228 (0,010)	-3,8%	0,150
	KAAI	0,091 (0,005)	-4,2%	0,180
Insole 5º	Peak 1	0,194 (0,012)	-6,7%	0,025*
	Peak 2	0,230 (0,008)	-3,0%	0,200
	KAAI	0,089 (0,003)	-6,3%	0,055*
Insole 6º	Peak 1	0,189 (0,009)	-9,1%	0,006*
	Peak 2	0,220 (0,010)	-7,2%	0,037*
	KAAI	0,085 (0,005)	-10,5%	0,006*
Insole 8º	Peak 1	0,175 (0,011)	-15,9%	0,004*
	Peak 2	0,225 (0,004)	-5,1%	0,037*
	KAAI	0,087 (0,004)	-8,4%	0,016*
Insole 10º	Peak 1	0,172 (0,010)	-17,3%	0,004*
	Peak 2	0,217 (0,009)	-8,4%	0,010*
	KAAI	0,085 (0,002)	-10,5%	0,006*

* - Statistically significant

In the study of Hinman *et al* (Hinman et al., 2008), in forty subjects, five were non-responders to the application of insoles and even worsen their 1st peak of external KAM. Most showed a consistent reduction of the 1st peak KAM, with individual variations close to zero up to about 20%. In another study by Hinman *et al* (Hinman et al., 2012), with seventy-three participants, fifteen showed an increase of the 1st peak KAM with the application of a 5º insole as an immediate effect. So, why apply an equal insole to all individuals? In fact, assessing the response to various angulations and taking into account the discrepancy between individuals may be an effective strategy for those non-responders. In our understanding, the use of the 1st and 2nd peak KAM and impulse as the main outcomes may be the best way to achieve a real reduction in the internal forces of the knee. In the subject of our study the wedge that would better adjust to a significant reduction of the internal forces would be the 6º wedge. This angulation is consistent with other studies (Duivenvoorden et al., 2014; van Raaij, Reijman, Brouwer, Bierma-Zeinstra, & Verhaar, 2010) and this angulation is usually easy to accommodate by individuals. It is described that greater wedging is less likely to be tolerated by the wearer and is difficult to accommodate within a normal shoe (Kerrigan et al., 2002). Tailored interventions based on patient biomechanics may

improve outcomes in patients with knee OA. The search for clinical phenotypes is also an important topic in the scientific community (Iijima et al., 2015). However, the adjustment of the treatment to the individual seems ever more important due to the great diversity of characteristics that influence the outcomes. One weakness of the present study is that it is a case study. However, it allowed to demonstrate the variability of the responses to different angulations. More research is needed to address these issues and to understand the individual response to different wedges conditions.

5 CONCLUSIONS

In conclusion, compared to the control condition (insole 0º), a reduction of external KAM was obtained with higher wedge angles. In the analysed subject, a 6º insole produced a significant reduction on 1st peak, 2nd peak and KAAI. This angulation was the smallest that simultaneously reduced the three study variables in a significant way and would be the better for this individual. Because individual fitting is an important issue in clinical biomechanics, the analysis of these indicators may be a good option for an individualized adjustment for lateral wedge insoles in individuals with knee OA.

REFERENCES

Baker, K., Goggins, J., Xie, H., Szumowski, K., LaValley, M., Hunter, D. J., & Felson, D. T. (2007). A randomized crossover trial of a wedged insole for treatment of knee osteoarthritis. *Arthritis Rheum, 56*(4), 1198-1203. doi:10.1002/art.22516

Bennell, K., Bowles, K. A., Payne, C., Cicuttini, F., Osborne, R., Harris, A., & Hinman, R. (2007). Effects of laterally wedged insoles on symptoms and disease progression in medial knee osteoarthritis: a protocol for a randomised, double-blind, placebo controlled trial. *BMC Musculoskelet Disord, 8*(1), 96. doi:10.1186/1471-2474-8-96

Bennell, K. L., Bowles, K. A., Payne, C., Cicuttini, F., Williamson, E., Forbes, A., . . . Hinman, R. S. (2011). Lateral wedge insoles for medial knee osteoarthritis: 12 month randomised controlled trial. *BMJ, 342*, d2912. doi:10.1136/bmj.d2912

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 Rheum, 57*(6), 1012-1017. doi:10.1002/art.22899

Brouwer, G. M., van Tol, A. W., Bergink, A. P., Belo, J. N., Bernsen, R. M., Reijman, M., . . . Bierma-Zeinstra, S. M. (2007). Association between valgus and varus alignment and the development and progression of radiographic osteoarthritis of the knee. *Arthritis Rheum, 56*(4), 1204-1211. doi:10.1002/art.22515

Cappozzo, A., Catani, F., Croce, U. D., & Leardini, A. (1995). Position and orientation in space of bones during movement: anatomical frame definition and determination. *Clin Biomech (Bristol, Avon), 10*(4), 171-178. doi:10.1016/0268-0033(95)91394-T

Duivenvoorden, T., van Raaij, T. M., Horemans, H. L., Brouwer, R. W., Bos, P. K., Bierma-Zeinstra, S. M., . . . Reijman, M. (2014). Do Laterally Wedged Insoles or Valgus Braces Unload the Medial Compartment of the Knee in Patients With Osteoarthritis? *Clin Orthop Relat Res*, 1-10. doi:10.1007/s11999-014-3947-5

Felson, D. T. (2013). Osteoarthritis as a disease of mechanics. *Osteoarthritis Cartilage, 21*(1), 10-15. doi:10.1016/j.joca.2012.09.012

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. *Clin Biomech (Bristol, Avon), 27*(1), 27-33. doi:10.1016/j.clinbiomech.2011.07.010

Hinman, R. S., Payne, C., Metcalf, B. R., Wrigley, T. V., & Bennell, K. L. (2008). Lateral wedges in knee osteoarthritis: what are their immediate clinical and biomechanical effects and can these predict a three-month clinical outcome? *Arthritis Rheum, 59*(3), 408-415. doi:10.1002/art.23326

Hunt, M. A., & Bennell, K. L. (2011). Predicting dynamic knee joint load with clinical measures in people with medial knee osteoarthritis. *Knee, 18*(4), 231-234. doi:10.1016/j.knee.2010.05.014

Iijima, H., Fukutani, N., Aoyama, T., Fukumoto, T., Uritani, D., Kaneda, E., . . . Matsuda, S. (2015). Clinical Phenotype Classifications Based on Static Varus Alignment and Varus Thrust in Japanese Patients With Medial Knee Osteoarthritis. *Arthritis Rheumatol, 67*(9), 2354-2362. doi:10.1002/art.39224

Jones, R. K., Chapman, G. J., Findlow, A. H., Forsythe, L., Parkes, M. J., Sultan, J., & Felson, D. T. (2013). A new approach to prevention of knee osteoarthritis: reducing medial load in the contralateral knee. *J Rheumatol, 40*(3), 309-315. doi:10.3899/jrheum.120589

Jones, R. K., Chapman, G. J., Forsythe, L., Parkes, M. J., & Felson, D. T. (2014). The relationship between reductions in knee loading and immediate pain response whilst wearing lateral wedged insoles in knee osteoarthritis. *J Orthop Res, 32*(9), 1147-1154. doi:10.1002/jor.22666

Jones, R. K., Nester, C. J., Richards, J. D., Kim, W. Y., Johnson, D. S., Jari, S., . . . Tyson, S. F. (2013). A comparison of the biomechanical effects of valgus knee braces and lateral wedged insoles in patients with knee osteoarthritis. *Gait Posture, 37*(3), 368-372. doi:10.1016/j.gaitpost.2012.08.002

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. *Hum Mov Sci, 32*(4), 596-604. doi:10.1016/j.humov.2012.12.012

Jordan, K. M., Arden, N. K., Doherty, M., Bannwarth, B., Bijlsma, J. W., Dieppe, P., . . . Standing Committee for International Clinical Studies Including Therapeutic Trials, E. (2003). EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Ann Rheum Dis, 62*(12), 1145-1155. doi:10.1136/ard.2003.011742

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. *Arch Phys Med Rehabil, 83*(7), 889-893. doi:http://dx.doi.org/10.1053/apmr.2002.33225

Kumar, D., Manal, K. T., & Rudolph, K. S. (2013). Knee joint loading during gait in healthy controls and individuals with knee osteoarthritis. *Osteoarthritis Cartilage, 21*(2), 298-305. doi:10.1016/j.joca.2012.11.008

Kutzner, I., Trepczynski, A., Heller, M. O., & Bergmann, G. (2013). Knee adduction moment and medial contact force--facts about their correlation during gait. *PLoS ONE, 8*(12), e81036. doi:10.1371/journal.pone.0081036

London, N. J., Miller, L. E., & Block, J. E. (2011). Clinical and economic consequences of the treatment gap in knee osteoarthritis management. *Med Hypotheses, 76*(6), 887-892. doi:10.1016/j.mehy.2011.02.044

McAlindon, T. E., Bannuru, R. R., Sullivan, M. C., Arden, N. K., Berenbaum, F., Bierma-Zeinstra, S. M., . . . Underwood, M. (2014). OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis Cartilage, 22*(3), 363-388. doi:10.1016/j.joca.2014.01.003

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. doi:DOI 10.1136/ard.61.7.617

Nakajima, K., Kakihana, W., Nakagawa, T., Mitomi, H., Hikita, A., Suzuki, R., . . . Fukui, N. (2009). Addition of an arch support improves the biomechanical effect of a laterally wedged insole. *Gait Posture, 29*(2), 208-213. doi:10.1016/j.gaitpost.2008.08.007

Parkes, M. J., Maricar, N., Lunt, M., LaValley, M. P., Jones, R. K., Segal, N. A., . . . Felson, D. T. (2013). Lateral wedge insoles as a conservative treatment for pain in patients with medial knee osteoarthritis: a meta-analysis. *JAMA, 310*(7), 722-730. doi:10.1001/jama.2013.243229

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, 286*(2), 188-195. doi:10.1001/jama.286.2.188

Thorp, L. E., Sumner, D. R., Block, J. A., Moisio, K. C., Shott, S., & Wimmer, M. A. (2006). Knee joint loading differs in individuals with mild compared with moderate medial knee osteoarthritis. *Arthritis Rheum, 54*(12), 3842-3849. doi:10.1002/art.22247

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. *Clin Orthop Relat Res, 468*(7), 1926-1932. doi:10.1007/s11999-010-1274-z

Wise, B. L., Niu, J., Yang, M., Lane, N. E., Harvey, W., Felson, D. T., . . . Multicenter Osteoarthritis, G. (2012). Patterns of compartment involvement in tibiofemoral osteoarthritis in men and women and in whites and African Americans. *Arthritis Care Res (Hoboken), 64*(6), 847-852. doi:10.1002/acr.21606

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. *J Orthop Res, 25*(6), 789-797. doi:10.1002/jor.20379

Appendix 2. Análise da Repetibilidade do Momento Externo de Adução do Joelho Durante a Marcha

VÍTOR FERREIRA · LEANDRO MACHADO · PAULO RORIZ

Objetivo: Conhecer a repetibilidade de vários parâmetros cinemáticos e cinéticos da marcha, especialmente o momento externo de adução do joelho e os seus picos, pela utilização de um modelo biomecânico com 6 graus de liberdade.

Introdução: A repetibilidade de uma medição é a capacidade do instrumento de medição para dar, em condições de utilização definidas, respostas muito próximas quando se aplica repetidamente o mesmo processo. O seu estudo é fundamental para permitir a tomada de decisões baseadas em efeitos agudos. Os parâmetros da cinemática e da cinética da marcha são dos mais usados em estudos do movimento humano. Nos últimos anos, o momento externo de adução do joelho tem sido usado como medida indireta para avaliar as forças internas de contacto no compartimento medial do joelho.

Materiais e Métodos: Participaram no estudo doze participantes saudáveis. Foram usadas 11 câmaras tridimensionais juntamente com 4 plataformas de forças, para a recolha de dados cinéticos e cinemáticos da marcha. Os participantes foram instruídos a caminhar ao longo de um corredor à sua velocidade normal e foram recolhidos 4 ensaios válidos. Foi construído um modelo de marcha para definir os segmentos dos membros inferiores com 6 graus de liberdade. Para o processamento e tratamento dos dados foi usado o software Visual3D. O coeficiente de correlação intraclasse (ICC), o erro padrão de medida (SEM), a mínima mudança detetável (MDC) e os 95% de acordo (LoA) foram calculados para cada parâmetro.

Resultados: Foram encontrados níveis excelentes de repetibilidade para todos os parâmetros cinemáticos e cinéticos analisados, com o ICC > 0,75. Para o 1º pico do momento externo de adução do joelho foram obtidos os seguintes valores: ICC = 0,991; SEM = 0,016 Nm/kg; MDC = 0,045 Nm/kg.

Conclusão: Pelos resultados encontrados, concluímos que a utilização do modelo biomecânico construído, baseado em 6 graus de liberdade, é um modelo com excelente repetibilidade para a obtenção de medidas com valor clínico. Este modelo permite assim a tomada de decisões baseadas em efeitos agudos.

Appendix 3. Efeitos Imediatos da Aplicação de Palmilhas em Cunha Lateral na Estática do Joelho

VÍTOR FERREIRA · LEANDRO MACHADO · PAULO RORIZ

Introdução: A aplicação de palmilhas em cunha lateral é uma técnica com uma utilização crescente nos últimos anos. Tem como objetivo principal a correção de desvios dos segmentos. Têm sido usadas em utentes com osteoartrose medial do joelho e morfologia em varum. No entanto a definição da correta angulação da cunha carece ainda de evidência científica. Pela sua facilidade de utilização e baixo custo, é essencial conhecer melhor as alterações biomecânicas que a aplicação deste tipo de palmilhas pode proporcionar.

Objetivos: Estudar, em indivíduos saudáveis, os efeitos imediatos na biomecânica articular da estática do joelho, após a aplicação de palmilhas em cunha lateral com diferentes angulações: 0°; 2°; 4°; 6°; 8° e 10°.

Material e Métodos: Participaram no estudo doze indivíduos sem alterações relevantes nos joelhos. Foram colocados marcadores refletores nas principais proeminências ósseas dos membros inferiores. Os participantes foram instruídos a permanecer numa posição estática de pé, com os pés afastados numa posição confortável até a recolha de dados da cinemática estar concluída. Foram usadas 11 câmaras para a recolha de dados e análise tridimensional. As diferentes palmilhas foram aplicadas de uma forma randomizada. Foi usado um modelo biomecânico para definir os segmentos dos membros inferiores com 6 graus de liberdade. Os dados foram processados com o auxílio do software Visual 3D. Foi usada estatística não paramétrica para o cálculo da análise da variância.

Resultados: As diferenças encontradas em cada um dos ângulos articulares ao nível do joelho, tibiotársica e anca nos três planos anatómicos foram mínimas, inferiores a 4°. Foram encontradas diferenças de maior amplitude no plano horizontal nos ângulos articulares estudados. Não foram encontradas diferenças estatisticamente significativas ($p \geq 0,05$) entre as diferentes palmilhas quando comparadas com a palmilha neutra.

Conclusões: Os resultados encontrados sugerem que a aplicação de palmilhas em cunha lateral com várias angulações, não altera significativamente a estática do joelho, tibiotársica e anca nos vários planos anatómicos.

Journal Motricidade; Volume 15; nº S1; Sup. 2019 http://dx.doi.org/10.6063/motricidade.16967.

Appendix 4. Test–retest reliability of physical function tests in patients with knee osteoarthritis

Vitor Ferreira[1*], Leandro Machado[2], Adélio Vilaça[3], Francisco Xará-Leite[3], Paulo Roriz[4]

[1]Escola Superior Saúde da Universidade de Aveiro, Portugal, v.ferreira@ua.pt
[2]CIF2D, LABIOMEP, Faculdade de Desporto da Universidade do Porto, Portugal
[3]Serviço Ortopedia Hospital Santo António, Porto, Portugal
[4]CIDESD-ISMAI, INESC-TEC, LABIOMEP, Portugal

INTRODUCTION

Physical function is related to the ability to move around and perform daily activities, which is assessed using self-reported and performance-based measures (Dobson et al., 2012). The Osteoarthritis Research Society International (OARSI) recommended three minimum core set tests for outcome measures in patients with knee osteoarthritis: 30s chair stand test (CST); 40m fast-paced walk test (FWT); stair climb test (SCT) (Dobson et al., 2013). The purpose of this study was to investigate the test-retest reliability of these physical function tests in patients with knee osteoarthritis.

METHODS

The intraclass correlation coefficient (ICC) and their 95% confidence interval, the standard error of measurement (SEM), minimal detectable change (MDC) and limits of agreement were calculated for the three tests. The SEM and MDC were calculated using the following equations: $SEM = SD*\sqrt{(1-ICC)}$ and $MDC95 = 1.96*\sqrt{2}*SEM$ (de Vet, Terwee, Knol, & Bouter, 2006).

Table 12. Test–retest reliability of physical function tests.

Physical function tests	ICC	95% CI		Mean	Minimum	Maximum	Diff	SD_{diff}	SEM	MDC
30s chair stand test (s)	0.91	0.70	0.97	12.35	9.75	18.50	-0.71	1.59	0.86	2.39
40m fast-paced walk test (m/s)	0.96	0.86	0.99	1.51	1.15	1.92	0.01	0.08	0.04	0.11
Stair climb test (s)	0.98	0.93	0.99	15.60	10.33	26.03	0.51	1.35	0.68	1.89

RESULTS

This study includes 14 patients (9 females; mean age 62 ± 5.3; weight 77.6 ± 13.9 kg, and height 163 ± 8.6 cm) with diagnosed radiographic medial knee OA Kellgren/Lawrence grade 2 or 3. The results for the test-retest reliability can been seen in Table 1. The physical function tests presented an excellent reliability with the ICC > 0.90. The estimated value for SEM was 0.86 for the CST, 0.04 for FWT and 0.68 for SCT. The MDC for the CST was 2.39, for the FWT was 0.11 and for the SCT was 1.89.

CONCLUSIONS

The ICC suggests that these tests are appropriate for use in clinical practice and the values found for the SEM and MDC are useful for estimate the amount of change which is enough to produce real changes in patients with knee osteoarthritis.

REFERENCES

de Vet, H. C., Terwee, C. B., Knol, D. L., & Bouter, L. M. (2006). When to use agreement versus reliability measures. J Clin Epidemiol, 59(10), 1033-1039. doi:10.1016/j.jclinepi.2005.10.015

Dobson, F., Hinman, R. S., Hall, M., Terwee, C. B., Roos, E. M., & Bennell, K. L. (2012). Measurement properties of performance-based measures to assess physical function in hip and knee osteoarthritis: a systematic review. Osteoarthritis Cartilage, 20(12), 1548-1562. doi:10.1016/j.joca.2012.08.015

Dobson, F., Hinman, R. S., Roos, E. M., Abbott, J. H., Stratford, P., Davis, A. M., . . . Bennell, K. L. (2013). OARSI recommended performance-based tests to assess physical function in people diagnosed with hip or knee osteoarthritis. Osteoarthritis Cartilage, 21(8), 1042-1052. doi:10.1016/j.joca.2013.05.002

Appendix 5. Center of pressure alterations with the application of lateral wedge insoles

Vitor Ferreira[1*], Leandro Machado[2], Paulo Roriz[3]

[1*]Escola Superior Saúde da Universidade de Aveiro, Portugal, v.ferreira@ua.pt

[2]CIF2D, LABIOMEP, Faculdade de Desporto da Universidade do Porto, Portugal

[3]CIDESD-ISMAI, INESC-TEC, LABIOMEP, Portugal

INTRODUCTION

Laterally wedged insole (LWI) is a device inserted in the shoes with a thicker lateral border predisposing the calcaneus into a valgus position (Abdallah & Radwan, 2011). It was theorized that LWI cause a lateral shift of the center of pressure (CoP) which results in a decrease in the knee adduction moment arm reducing the external knee adduction moment (EKAM) (Hinman, Bowles, Metcalf, Wrigley, & Bennell, 2012; Yasuda & Sasaki, 1987). Understanding the changes with incremental lateral wedges in CoP is fundamental to maximize the treatment strategies of these patients.

METHODS

Twenty-three healthy volunteers (15 males, age of 21.0 ± 5.13, weight of 65.8 ± 8.7 kg, and height 170 ± 5.13 cm) were recruited. The inclusion criteria for the subjects included healthy young adults, aged 18 – 40 years, without any symptoms or neuromuscular disorders. Eleven cameras three-dimensional Qualisys Oqus motion analysis system sampling at 200 Hz, with four force platforms sampling at 1000 Hz, were used to collect the kinematic and kinetic data from participants walking along a 10-meter walkway. Reflective markers were placed on the pelvis and on both lower limbs according to the CAST protocol (Cappozzo, Catani, Croce, & Leardini, 1995). Six experimental conditions were tested: a control condition (shoes with a 0° insole), and LWI with 2°, 4°, 6°, 8° and 10 degrees. The kinematic and kinetic data were time normalized to 100% of the stance phase and all post-processing calculation was conducted using Visual3D software. The displacement of CoP was defined as distance of the CoP from the line of the foot (calcaneus to the midpoint between first and fifth metatarsals) and was calculated at the first peak, second peak and in the lower peak of the mid-stance EKAM. A negative value means that the CoP it was in the medial side and a positive value means the CoP it was in lateral side of the line of the foot (Sawada et al., 2016).

RESULTS

No differences ($p > 0.05$) were observed in the CoP at first peak, second peak and in the lower peak of the mid-stance of EKAM, with the experimental conditions compare to the control condition as can be seen in Figure 19.

CONCLUSIONS

With this design of LWI, no changes were found in the displacement of the CoP. Perhaps the displacement of CoP is not an essential condition for the reduction of the EKAM. Other factors that alter EKAM should be study.

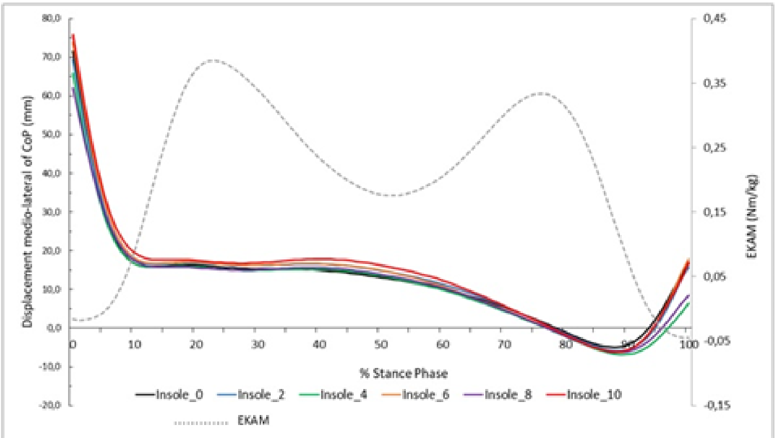


Figure 19. CoP during the stance phase by the experimental LWI conditions. Each colour line represents the mean of different LWI. Dashed lined represents the EKAM.

REFERENCES

Abdallah, A. A., & Radwan, A. Y. (2011). Biomechanical changes accompanying unilateral and bilateral use of laterally wedged insoles with medial arch supports in patients with medial knee osteoarthritis. Clin Biomech, 26(7), 783-789. doi:10.1016/j.clinbiomech.2011.03.013

Cappozzo, A., Catani, F., Croce, U. D., & Leardini, A. (1995). Position and orientation in space of bones during movement: anatomical frame definition and determination. Clin Biomech (Bristol, Avon), 10(4), 171-178. doi:10.1016/0268-0033(95)91394-T

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. Clin Biomech (Bristol, Avon), 27(1), 27-33. doi:10.1016/j.clinbiomech.2011.07.010

Sawada, T., Tokuda, K., Tanimoto, K., Iwamoto, Y., Ogata, Y., Anan, M., . . . Shinkoda, K. (2016). Foot alignments influence the effect of knee adduction moment with lateral wedge insoles during gait. Gait Posture, 49, 451-456. doi:10.1016/j.gaitpost.2016.08.011

Yasuda, K., & Sasaki, T. (1987). The mechanics of treatment of the osteoarthritic knee with a wedged insole. Clin Orthop Relat Res(215), 162-172.

Appendix 6. Spatiotemporal parameters of gait in patients with knee osteoarthritis

Vitor Ferreira[1], Leandro Machado[2], Adélio Vilaça[3], Francisco Xará-Leite[4], Paulo Roriz[5]

[1]School of Health Sciences, University of Aveiro (ESSUA), Portugal, v.ferreira@ua.pt

[2]CIF2D, LABIOMEP, Faculdade de Desporto da Universidade do Porto, Portugal, lmachado@fade.up.p

[3]Serviço Ortopedia Hospital Santo António, Porto, Portugal, adeliovilaca@gmail.com

[4]Serviço Ortopedia Hospital Santo António, Porto, Portugal, franciscoxdl@gmail.com

[4]CIDESD-ISMAI, INESC-TEC, LABIOMEP, Portugal, paulororiz@ismai.pt

ABSTRACT

Introduction: Gait is used to quantify physical function, quality of life and health status since is the most frequently performed physical activities in daily life (Afiah, Nakashima, Loh, & Muraki, 2016). Knee osteoarthritis (OA) is a complex disease influenced by many factors, including the loading environment. Analyzing biomechanics during walking is therefore particularly relevant (Favre & Jolles, 2016) and the study of spatiotemporal parameters in various pathologies a relevant topic of attention (Herssens et al., 2018). Objectives: This study aimed to study spatiotemporal parameters of gait the in patients with knee OA. Methods: A laboratory, analytic and cross-sectional study was design. A 3D motion analysis system, consisting of 11 infrared cameras (Qualisys, Gothenburg, Sweden), was used to collect kinematic data at 200 Hz. Forty-two trajectory passive markers were attached to the lower body segments of each participant. Participants were asked to walk with own shoes on a flat surface for 10 m at a self-selected speed. Three trials of each participant were recorded to eliminate variation in walking speed and to enhance the reliability and accuracy of the average. Post-processing calculation of all gait parameters were studied using Visual3D software (Version 6.00.12, C-Motion, Rockville, USA). Several gait parameters were measured in this study: walking speed, stride and step length, cadence, duration of 1 gait cycle double limb support, duration and percentages of swing and stance phase. Results: This study includes 15 patients (10 females; mean age 62 ± 7,1; weight 77,2 ± 12,9 kg, and height 162 ± 8,1 cm) with diagnosed radiographic medial knee OA Kellgren/Lawrence (K/L) grade 2 or 3, recruited in hospitals. The mean walking speed was 1.16 m/s (± 0.15), the cycle time was 1.08 s (± 0.16) and other gait parameters are similar to a population of the same age. No significant differences were found between right and left side. Conclusions: This study shows that the analysis of spatiotemporal parameters of gait can serve as a basis for understanding of possible changes in gait in patients with osteoarthritis of the knee. The gait analysis provides critical information needed to understand the knee OA development and to design therapeutic interventions.

Keywords: *Biomechanics, gait, osteoarthritis, knee*

References:

Afiah, I. N., Nakashima, H., Loh, P. Y., & Muraki, S. (2016). An exploratory investigation of changes in gait parameters with age in elderly Japanese women. *SpringerPlus, 5*(1), 1069. doi:10.1186/s40064-016-2739-7

Favre, J., & Jolles, B. M. (2016). Gait analysis of patients with knee osteoarthritis highlights a pathological mechanical pathway and provides a basis for therapeutic interventions. *EFORT Open Rev, 1*(10), 368-374. doi:10.1302/2058-5241.1.000051

Herssens, N., Verbecque, E., Hallemans, A., Vereeck, L., Van Rompaey, V., & Saeys, W. (2018). Do spatiotemporal parameters and gait variability differ across the lifespan of healthy adults? A systematic review. *Gait Posture, 64*, 181-190. doi:10.1016/j.gaitpost.2018.06.012

Annex's

Annex 1. Ethics opinion of the Ethics Committee of the FADEUP

U.PORTO
FACULDADE DE DESPORTO
UNIVERSIDADE DO PORTO

Ethics Committee

ETHICS OPINION

Process **CEFADE 10.2016**

The Ethics Committee of the Faculty of Sport from the University of Porto analyzed the project entitled "The effects of application of lateral wedge insole on medial osteoarthritis of the knee", presented by MSc. Vitor Ferreira. Considering the project's characteristics, as well as the competence of the research team, the Ethics Committee addresses a positive opinion, because the ethical principles that govern this type of scientific work are respected.

Porto and Faculty of Sport, 24th March, 2017

The chairman of the Ethics Committee,

José Alberto Ramos Duarte

Annex 2. Ethics opinion of the Ethics Committee of the CHP

DEFI
DEPARTAMENTO DE ENSINO, FORMAÇÃO E INVESTIGAÇÃO

centro hospitalar do Porto

OS EFEITOS DA APLICAÇÃO DE UMA PALMILHA EM CUNHA LATERAL NA OSTEOARTROSE MEDIAL DO JOELHO

097-17 (088-DEFI/086-CES) Trabalho académico de investigação realizado no âmbito do programa de Doutoramento em Fisioterapia ministrado pela Faculdade de Desporto da Universidade do Porto (FADEUP)

Data de Receção no Gabinete Coordenador da Investigação (GCI): 25/05/2017

Aluna e Investigadora Principal:
Vitor Manuel Fontes Ferreira – Aluno do 3º ano de doutoramento da FADEUP

Investigador Responsável no Centro Hospitalar do Porto (CHP):
Adélio Vilaça – Médico, Serviço de Ortopedia do CHP

Orientador da tese de doutoramento:
Paulo Roriz – Professor Auxiliar; Instituto Universitário da Maia; LABIOMEP e INESC-TEC´

Co-Orientador da tese de doutoramento:
Leandro José Rodrigues Machado – Professor Auxiliar; FADEUP

Resumo do Estudo:

- **Local:** Serviço de Ortopedia do CHP.
- **Desenho do estudo:** Nacional, multicêntrico, experimental e prospetivo.
- **Classificação do estudo segundo a lei da investigação clínica** (Dec. Lei n.º 21/2014): Estudo clínico com intervenção de dispositivo médico (classe I)
- **Objetivo geral do estudo:** estudar os efeitos da aplicação de uma palmilha com cunha lateral ajustada à biomecânica dos indivíduos com osteoartrose medial do joelho na dor e na função física.
- **Participantes no estudo:** Indivíduos com dor medial e critérios radiológicos de osteoartrose no joelho.
  Critérios de inclusão: 1) *Score* 2 ou 3 na classificação de Kellgren & Lawrence; 2) Idade entre os 40 e os 80 anos; 3) rigidez matinal e/ou crepitação durante movimentos; 4) Joelhos com configuração normal ou em varo (avaliação radiológica).
  Critérios de exclusão: 1) Dor no joelho de predomínio lateral; 2) osteoartrose na patelofemural; 3) história de cirurgia ao joelho nos últimos 6 meses; 4) presença de condição sistémica; 5) infiltração com corticosteroide nas últimas 6 semanas; 6) Índice de massa corporal superior a 35; 7) outra condição que afete a marcha.
- **Tamanho da amostra:** Não estimado.
- **Duração do estudo:** Início: setembro/2017 Conclusão: julho 2018 (período de recrutamento
- **Metodologia:**
  - A seleção dos pacientes a incluir no CHP será realizada pelo Investigador Responsável no CHP (Dr. Adélio Vilaça) com base nos utentes seguidos na consulta externa de Ortopedia.
  - Do processo clínico serão colhidos dados como o contacto e identificação, bem como, elementos que confirmem que o paciente cumpre os critérios de seleção estabelecidos.
  - Os potenciais participantes serão depois contactados telefonicamente pelo investigador para agendar uma avaliação inicial.
  - Os participantes serão distribuídos em dois grupos através de um processo de aleatorização da amostra. O grupo 1 será o grupo de intervenção no qual será fornecido aos participantes um par

de palmilhas com cunha lateral e biomecanicamente ajustado ao seu joelho que utilizarão durante 12 semanas. O grupo 2 será o grupo controlo e aos participantes será fornecido um par de palmilhas com angulação neutra, que utilizarão durante 12 semanas.

- Os procedimentos no âmbito do estudo serão realizados no Laboratório de Biomecânica da FADEUP, onde os participantes terão de se deslocar para avaliação, por três vezes no decorrer do estudo.
- Na primeira visita será obtido o consentimento informado dos participantes. Todos eles serão avaliados com palmilhas com angulação em cunha de 0º, 2º, 4º, 6º, 8º e 10º. Nesta fase, não será dado conhecimento aos participantes dos resultados preliminares obtidos.
- Após a primeira avaliação, o participante é distribuído de forma aleatória por um dos grupos.
- A segunda visita será realizada após uma semana, onde serão distribuídas as palmilhas correspondentes ao grupo em que o participante foi alocado. Será realizada em avaliação biomecânica e clínica com e sem palmilha, devidamente descrita na proposta de investigação submetida.
- A terceira visita ocorrerá 12 semanas após o início da intervenção e constituirá uma avaliação similar à da segunda visita.
- Não está prevista qualquer compensação aos participantes no estudo, pelas deslocações que terão de efetuar
- Será pedido consentimento informado aos participantes.

ASPETOS FINANCEIROS:

Não foram referidos aspetos financeiros a considerar.

Requisitos Preenchidos:

- ☑ Pedidos de autorização dirigidos ao Conselho de Administração, DEFI e Comissão de Ética
- ☑ Termo de Responsabilidade e *Curriculum Vitae* do Investigador Principal (Dr. Vitor Ferrera)
- ☑ Termo de Responsabilidade do Investigador Responsável no CHP (Dr. Adélio Vilaça)
- ☑ Termo de Responsabilidade do Orientador da tese de doutoramento (Prof. Doutor Paulo Roriz)
- ☑ Autorização do Diretor do Departamento de Ortofisiatria (Prof. Doutor António Oliveira)
- ☑ Autorização do Diretor do Serviço de Ortopedia (Prof. Doutor António Oliveira)
- ☑ Comprovativo de frequência no curso de doutoramento
- ☑ Formulário de recolha de dados
- ☑ Questionário KOOS sobre o joelho

QUESTÕES A CLARIFICAR PELOS INVESTIGADORES:

A proposta de investigação "*Os efeitos da aplicação de uma palmilha em cunha lateral na osteoartrose medial do joelho*" foi avaliada pelo Gabinete Coordenador de Investigação, que coloca as seguintes questões:

a) **Instituições participantes**: Para além do CHP serão recrutados participantes em outras instituições? Quais?

b) **Tamanho da amostra**: Qual a dimensão prevista da amostra? Quantos participantes serão incluídos em cada grupo? Que metodologia será utilizada na aleatorização dos participantes?

c) **Recrutamento dos participantes**: Como será realizado o recrutamento dos participantes no CHP? O investigador responsável no CHP (Dr. Adélio Vilaça) apresentará primeiro o estudo aos

participantes e pedirá a sua permissão para fornecer o contacto telefónico ao investigador e avisará que serão contactados pela equipa de investigação? Ou apenas fornecerá ao investigador uma lista com os potenciais participantes e os seus contactos, sem aviso prévio dos utentes?

d) **Custos:** Quem suportará os custos das palmilhas? Os doentes? Os investigadores?

e) **Disponibilização das palmilhas**: Como serão disponibilizadas as palmilhas aos participantes? Pelos investigadores? Ou haverá algum tipo de prescrição?

f) **Dispositivos médicos:** Tendo em conta que as palmilhas são considerados dispositivos médicos de classe I, solicita-se o envio da declaração CE de conformidade (de acordo com os procedimentos a efetuar pelo fabricante referidos decreto-lei nº 145/2009 de 17 de junho).

O Gabinete Coordenador da Investigação aguarda que sejam enviados os esclarecimentos e documentos solicitados no sentido de dar seguimento ao processo

Centro Hospitalar do Porto, 31 de maio de 2017

José Manuel Pereira, Gabinete Coordenador da Investigação

Isabel Fonseca, Responsável pela área da análise científica dos estudos de investigação
DEFI/ Gabinete Coordenador da Investigação