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Gait modifications for medial knee osteoarthritis

Ulrich Baptiste

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Faculté de biologie
et de médecine

Département de l'Appareil Locomoteur
Swiss BioMotion Lab

Gait Modifications for Medial Knee Osteoarthritis

Thèse de doctorat ès sciences de la vie (PhD)

présentée à la

Faculté de biologie et de médecine
de l'Université de Lausanne

par

Baptiste ULRICH

Master of Science MSc in Mechanical Engineering
École Polytechnique Fédérale de Lausanne

Jury

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Lausanne
(2021)

UNIL | Université de Lausanne
Faculté de biologie
et de médecine

Ecole Doctorale
Doctorat ès sciences de la vie

Imprimatur

Vu le rapport présenté par le jury d'examen, composé de

Président·e	Monsieur	Prof.	Olivier	**Borens**
Directeur·trice de thèse	Madame	Prof.	Brigitte	**Jolles-Haeberli**
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le Conseil de Faculté autorise l'impression de la thèse de

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intitulée

Gait modifications for medial knee osteoarthritis

Date de l'examen : 12 juillet 2021

Date d'émission de l'imprimatur : Lausanne, le 29 juillet 2021

pour le Doyen
de la Faculté de biologie et de médecine

Prof. Niko GELDNER
Directeur de l'Ecole Doctorale

Remerciements

En premier lieu, mes remerciements vont au **Dr Julien Favre** pour sa confiance et son accompagnement durant cette thèse et au sein du Swiss BioMotion Lab (SBML). Sa grande expertise et son obsession des détails ont été extrêmement formatrices. Merci également à ma directrice de thèse, **Prof. Brigitte Jolles-Haeberli** pour sa supervision et pour son travail qui permet au SBML d'exister.

Deuxièmement, je tiens à remercier mes expert·e·s de thèse, **Prof. Katherine Boyer** et **Dr François Luthi**, ainsi que le président **Prof. Olivier Borrens**, pour avoir accepté d'évaluer mon travail. Mes remerciements vont également au **Fonds National Suisse de la Recherche Scientifique,** à la **Fondation Profectus**, et à la **Lausanne Orthopedic Research Foundation** pour leur soutien financier durant cette thèse, ainsi qu'à toutes et tous les **co-auteur·e·s** des études présentées dans ce mémoire et avec qui j'ai eu le plaisir de collaborer.

En troisième lieu, mes remerciements vont à mes collègues et ancien·ne·s collègues au SBML : **Margaux Baron**, **Dr Shannon Edd**, **Johann Heches**, **Guillaume Christe**, **Luìs Pereira**, et plus particulièrement à **Killian Cosendey** pour sa relecture et pour m'avoir supporté comme voisin de bureau toutes ces années, et au **Dr Hugo Babel** qui a ouvert la voie en devenant le premier doctorant diplômé du SBML.

Je tiens également à remercier mes athlètes au sein du Stade Lausanne Athlétisme qui, au travers de leur implication et de leur persévérance tant à l'entrainement qu'en compétition, me motivent au quotidien.

Ensuite, j'aimerais particulièrement remercier ma famille, notamment mes frères et ma sœur, **Camille**, **Guillaume** et **Vincent**, qui m'ont permis d'aiguiser mon sens critique au fil des années, ainsi qu'à **Maé** qui m'a relu, soutenu et supporté durant la fin de ma thèse. Finalement, je souhaite dédier cette thèse à mes parents, **Catherine** et **Didier**, qui m'ont donné accès à l'éducation et m'ont offert tout l'encadrement nécessaire pour mon développement intellectuel et personnel. Sans eux, je n'aurais jamais été en mesure de faire ce doctorat.

Veuillez excuser mes fautes de frappe, elles sont surement
la faute de Sirius, Arwen ou Lupin…

Abstract

Knee osteoarthritis is a prevalent disease worldwide, inducing pain and limiting daily function. No cure exists for knee osteoarthritis and there is a necessity for therapeutic solutions to slow down disease progression, notably through non-surgical interventions. While knee osteoarthritis is a disease of the entire joint, the medial compartment is often more severely affected.

Modifying patients' gait, through lateral wedge insoles or by retraining, is a promising option for the management of knee osteoarthritis, as it could change the mechanics at the knee, an important factor in disease development. Specifically, there is an interest in reducing the peak of the knee adduction moment because this parameter has been associated with disease progression, severity and symptoms. Secondary knee moment parameters have also been partially associated with the disease. However, they were only marginally targeted in the context of gait modification for medial knee osteoarthritis.

This PhD thesis aimed at (1) improving our understanding of the effects of lateral wedge insoles and gait retraining on knee moments, (2) proposing and assessing options to modify gait individually, and (3) providing a global assessment of knee moments relative to disease severity.

Throughout its four studies, this thesis has shown in particular that lateral wedge effect differs with respect to the natural foot progression angle, and that modifying stride length is a pertinent option to change knee moments. Moreover, by demonstrating associations between secondary knee moment parameters (others than the peak of the knee adduction moment) and disease severity, the thesis highlighted the necessity for a more global consideration of knee moments when changing the gait of medial knee osteoarthritis patients. Finally, this thesis showed the possibility of combining knee moment parameters into a severity index.

To conclude, the results of this thesis highlighted the relevance and possibility to personalize gait modifications for patients with medial knee osteoarthritis. This doctoral research also provided insight on how such modifications could be induced.

Résumé

La gonarthrose est une maladie très répandue dans le monde, qui induit douleur et limitations fonctionnelles. Aucun remède n’existe pour la gonarthrose et il est nécessaire de trouver des solutions pour ralentir sa progression, notamment au travers d’interventions non-chirurgicales. Alors que la gonarthrose est une maladie qui touche l’entier de l’articulation, la forme fémoro-tibiale interne est la plus répandue.

Modifier la marche des patients, à l’aide de cales latérales ou par réentrainement, est une option prometteuse pour le traitement de la gonarthrose, car cela peut induire des changements dans la mécanique du genou, un facteur important dans le développement de la maladie. Particulièrement, il y a un intérêt à réduire le pic du moment d’adduction du genou, car ce paramètre a été associé avec la progression, la sévérité et les symptômes de la gonarthrose. Des paramètres secondaires décrivant les moments du genou ont aussi été partiellement associés à la maladie. Cependant, ils n’ont été que marginalement ciblés dans le contexte de modification de la marche en cas de gonarthrose fémoro-tibiale interne.

Cette thèse avait pour but de (1) améliorer nos connaissances sur les effets des cales latérales et du réentrainement à la marche sur les moments du genou, (2) proposer et évaluer des options pour modifier la marche individuellement, et (3) fournir une évaluation globale des moments du genou par rapport à la sévérité de la maladie.

Au travers de ses quatre études, cette thèse a notamment montré que l’effet des cales latérales différait en fonction de l’angle naturel d’ouverture du pied, et que modifier la longueur de pas est une option pertinente pour changer les moments du genou. De plus, en démontrant des associations entre divers paramètres décrivant les moments du genou (autres que le pic du moment d’adduction) et la sévérité de la maladie, cette thèse a mis en évidence la nécessité de considérer les moments du genou de façon plus globale lors de la modification de la marche chez des patients avec gonarthrose. Finalement, cette thèse a montré la possibilité de combiner divers paramètres des moments du genou en un indice de sévérité.

En conclusion, les résultats de cette thèse ont mis en évidence la pertinence et la possibilité de personnaliser les modifications de la marche pour les patients avec gonarthrose fémoro-tibiale interne. Cette recherche doctorale a également fourni des pistes sur la manière dont de telles modifications pourraient être induites.

Contents

List of Tables

List of Figures

Abbreviations

BW	Bodyweight
COP	Center of pressure
FPA	Foot progression angle
GRF	Ground reaction force
Ht	Height
KAM	Knee adduction moment
KERM	Knee external rotation moment
KFM	Knee flexion moment
LWI	Lateral wedge insole
MCF	Medial compartment force
OA	Osteoarthritis
SL	Stride length
SW	Step width
TJM	Total joint moment

I Introduction

I.1 Knee osteoarthritis

Knee osteoarthritis (OA) is one of the most common musculoskeletal diseases worldwide (March et al., 2014) affecting tens of millions of people in Europe only (Safiri et al., 2020). This disease is among the leading causes of disability and induces pain, stiffness and loss of function at the joint (Cross et al., 2014). Moreover, it also represents a real economic burden for society with annual costs estimated in Europe at over one hundred billion euros (Safiri et al., 2020; Salmon et al., 2016). With the aging of the population and the increase of obesity prevalence, knee OA prevalence increased significantly during the last decades and is expected to continue increasing in the future (Safiri et al., 2020). The knee joint is affected non uniformly in knee OA, with the medial compartment of the knee being more often affected, partially because it undergoes more mechanical load (Ahlbäck, 1968). In consequence, medial knee OA is the most common form of the disease.

No cure exists for medial knee OA and the disease end-stage often leads to major surgery with total knee arthroplasty (Rönn et al., 2011). Therefore, there is a need for better management of the disease to avoid reaching end-stage, or at least to slow down its progression and reduce associated symptoms.

I.2 Pathomechanics of knee osteoarthritis

Knee OA is a complex disease with biological, mechanical and structural factors acting together (Andriacchi et al., 2015). While the mechanism leading to disease initiation is not fully understood, the load applied on the cartilage during walking have been shown to play an important role in disease progression (Figure 1) (Andriacchi and Mündermann 2006; Felson 2013). After disease initiation, non-adapted repetitive mechanical stress during walking have been associated with faster disease progression.

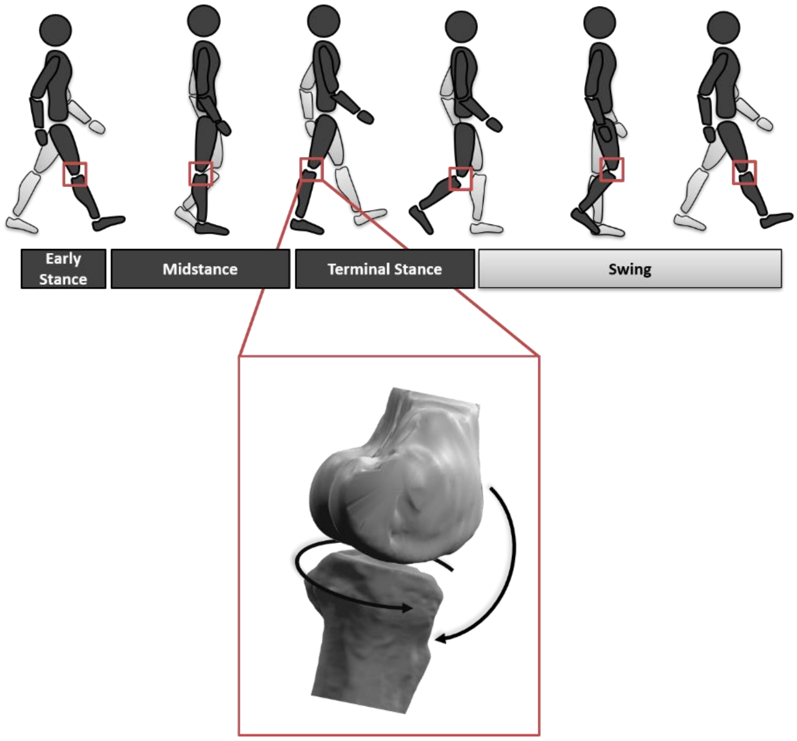


Figure 1: *Gait mechanics play an important role in medial knee osteoarthritis progression.*

Internal knee load during gait being difficult to measure, the knee adduction moment (KAM) has been proposed as a surrogate measure. It corresponds to the medial-lateral distribution of loading at the knee (Schipplein and Andriacchi, 1991). The KAM presents a typical m-shape, and is commonly described by its peak during the first half of stance phase (KAM_{first}) and by the area under its curve ($KAM_{impulse}$) (Figure 2). Larger KAM values indicate that a larger proportion of the total load is transmitted through the medial compartment, meaning that larger mechanical constrains are exerted on this compartment, which in turn contributes to the degradation of medial tissues in medial knee OA patients. This mechanism is supported by literature, which consistently reported that larger KAM_{first} and $KAM_{impulse}$ values were associated with faster progression in patients suffering from medial knee OA. Indeed, cartilage thickness loss was associated with higher baseline KAM_{first} and $KAM_{impulse}$ (Chang et al., 2015; Chehab et al., 2014). Additionally, KAM values were also associated with medial knee OA severity and symptoms (Amin et al., 2004; Astephen et al., 2008; Astephen Wilson et al., 2017; Mills et al., 2013). This motivated the design of interventions aiming at decreasing KAM_{first} and $KAM_{impulse}$ to slow down disease progression and reduce pain and symptoms (Reeves and Bowling, 2011; Waller et al., 2011).

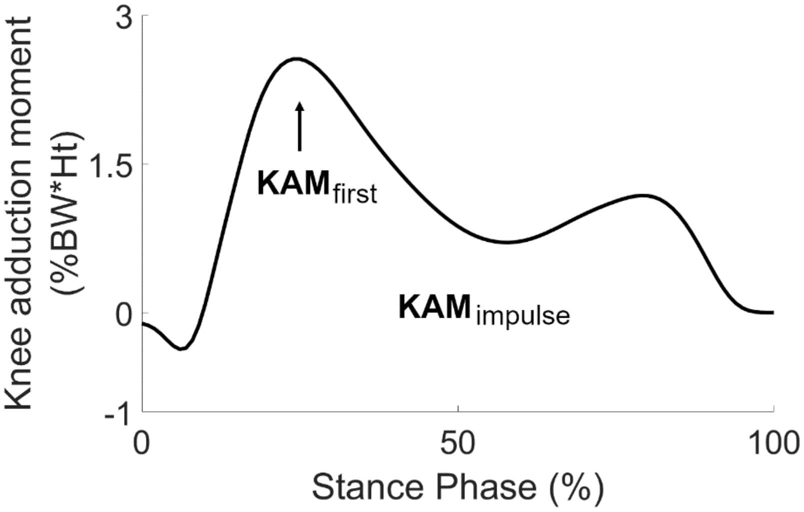


Figure 2: *Knee adduction moment (KAM) over stance phase.*

More recently, the knee flexion moment (KFM), and especially the peak value during the first half of stance (KFM_{first}) (Figure 3), gained in interest, and association between KFM_{first} and disease progression were also reported in literature. Higher baseline KFM_{first} was associated with greater cartilage thickness loss in a five-year longitudinal study (Chehab et al., 2014). Moreover, studies showed that a combination of KFM_{first} and KAM_{first} better estimates the contact forces acting on the medial compartment than KAM_{first} does alone (Walter et al., 2010). Finally, KFM_{first} was also associated with disease severity and pain (Astephen et al., 2008; Boyer et al., 2011; Henriksen et al., 2010; Huang et al., 2008). This suggests that KFM_{first} should also be considered when designing interventions aiming at decreasing the KAM.

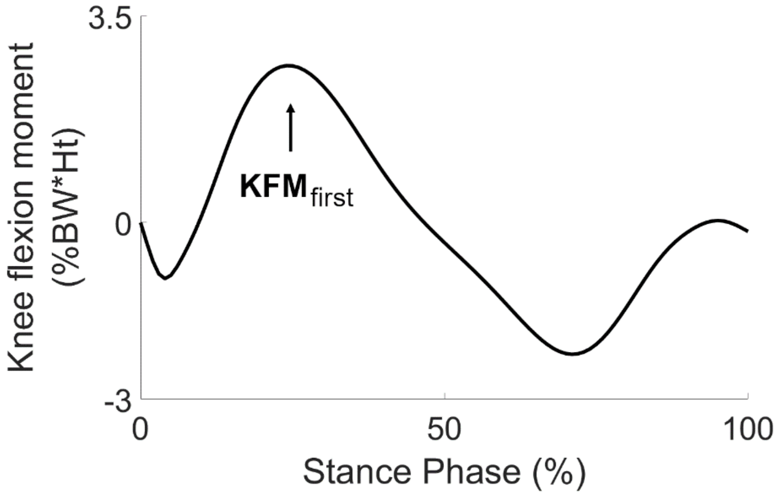


Figure 3: *Knee flexion moment (KFM) over stance phase.*

I.3 Gait interventions

The association between the KAM, particularly the KAM_{first}, and disease progression, severity and symptoms motivated the design of a range of interventions to decrease this kinetic measure during walking, including footwear modification and gait retraining (Reeves and Bowling, 2011; Waller et al., 2011).

I.3.1 Lateral wedge insoles

Footwear modification through the addition of a lateral wedge insole (LWI) in the shoe is among the most attractive interventions to reduce the KAM, because it is non-invasive and does not require the patients to do anything special, which is critical for compliance and long-term success (Figure 4). Furthermore, LWI could be highly cost-effective (Segal, 2012). LWI studies systematically reported overall KAM_{first} and $KAM_{impulse}$ decreases in healthy individuals and in medial knee OA patients (Arnold et al., 2016; Radzimski & Mündermann, 2012; Shaw et al., 2018). Concerning the KFM_{first}, literature did not report any overall effect in group statistics (Fischer et al., 2018).

While LWI is very interesting in terms of compliance and overall KAM reduction, important variations exist among individuals, ranging from patients drastically reducing their KAM to patients increasing their KAM

(Kakihana et al., 2007). Moreover, clinical trials conducted on LWI seem to agree on the absence of overall symptoms improvement (Parkes et al., 2013; Zhan et al., 2018). However, these results are contrasted with more recent work that showed significant pain reduction with the wear of LWI in patients who were pre-screened as KAM responders, i.e., with at least a certain amount of KAM_{first} decrease when wearing LWI (Felson et al., 2019). Therefore, there is a need to better understand who would be more likely to decrease their KAM_{first} with the wear of LWI to benefit from it, and to investigate if an individual characteristic that would help to find responding individuals exists.

Figure 4: *Lateral wedge insoles.*

I.3.2 Gait retraining

Another therapeutic intervention proposed for the management of medial knee OA is gait retraining, consists in teaching patients new ways of walking (Figure 5). This intervention is also particularly interesting, as it does not require long-term device usage. Moreover, the modification of several gait parameters has been shown to efficiently decrease the KAM for the overall population (Favre et al., 2016; Simic et al., 2011). Indeed, KAM_{first} can be decreased by toeing-in, walking with wider steps, or using other strategies such as medial knee thrust or increasing trunk sway (Favre et al., 2016; Simic et al., 2011). Additionally, the $KAM_{impulse}$ and KFM_{first} are also altered by such gait modifications (Favre et al., 2016; Simic et al., 2011). However, as with LWI, the KAM changes induced by the gait modifications vary among individuals (Uhlrich et al., 2018).

One main advantage of gait retraining is that several gait modification strategies exist and are adjustable to the patients to give more opportunities to reach a specific KAM decrease. More recently patient-specific gait modification approaches were suggested and showed better results than when the same modification was suggested to all patients. These studies consistently reducing the KAM_{first} reported symptom improvements in OA patients with patient-specific approaches (Cheung et al., 2018; Richards et al., 2018a; Shull et al., 2013a).

Indeed, KAM_{first} values and clinical outcomes (WOMAC scores) were significantly improved with 6-week retraining programs using personalized strategies including foot progression angle (FPA) and step width (SW) modifications, and these improvements appear to last with reduction still seen after 1-month (Shull et al., 2013a) and 6-month follow-ups (Cheung et al., 2018; Richards et al., 2018a). These studies were based on biofeedback systems to modify only one or two parameters, mainly the FPA and the SW.

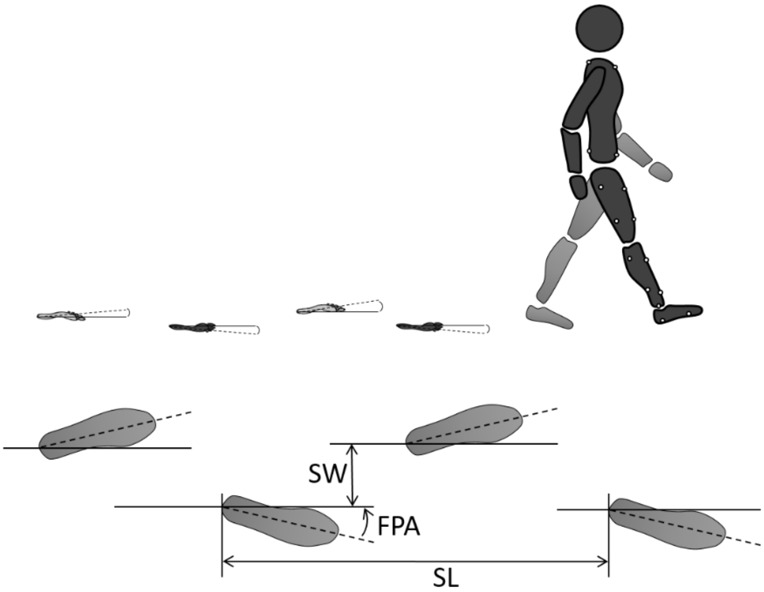


Figure 5: *Representation of footprint parameters: foot progression angle (FPA), step width (SW) and stride length (SL).*

A gait retraining system using augmented reality to modify footprint parameters was developed in our laboratory (Bennour et al., 2018). This system displays target footprints on the floor therefore allowing simultaneous modification of the three main footprint parameters: the FPA, the SW, and the stride length (SL). While the effect of modifying the two first footprint parameters on knee moments has been previously described (Favre et al., 2016), kinetic changes due to modification of the SL remain unknown and need to be characterized in medial knee OA patients. Moreover, a system with footprint instructions displayed directly on the floor was never tested for gait retraining in OA patients.

I.4 A more global evaluation of knee moments

The KAM_{first} has been the main target of gait interventions for medial knee OA. Recent gait modifications studies also considered the KFM_{first}, but mostly to verify that there was no negative effect. Unfortunately, on a group level, some KAM_{first} decreasing gait modifications induces a KFM_{first} increase (Favre et al., 2016; Jenkyn et al., 2008). Additionally, even if the KFM_{first} is not significantly changed at a group level, it can be at an individual level with some patients experiencing KFM_{first} increase (Kakihana et al., 2007). Based on these observations, interventions aiming at decreasing the KAM_{first} should not increase the KFM_{first} at both group level and individual level. Achieving such KAM_{first} and KFM_{first} dual kinetic change is not straightforward and necessitates more personalized interventions or better selection of responding patients.

While the KAM_{first}, and the KFM_{first} to a lesser degree, were widely studied in literature, the knee moments are not limited to these parameters. Indeed, additionally to the KAM_{first}, the KAM curve presents other peaks: a peak of abduction during early stance (KAM_{onset}), a peak of adduction during late stance (KAM_{second}) and a minimum of adduction between KAM_{first} and KAM_{second} ($KAM_{central}$) (Figure 6B). Some of these frontal-plane knee moment parameters have been associated with the disease. Indeed, differences between some of these knee moment parameters were reported among groups of patients with different severities of medial knee OA (Astephen et al., 2008; Thorp et al., 2006), and associations with disease symptoms were also reported (Astephen Wilson et al., 2016). Moreover, $KAM_{central}$ was associated with disease progression (Costello et al., 2020).

Concerning the KFM curve, it also presents other parameters than KFM_{first}: a peak of extension during early stance (KFM_{onset}) and a peak of extension during late stance (KFM_{second}) (Figure 6A). Scattered studies also reported associations between these peaks of extension and disease severity (Astephen et al., 2008; Baert et al., 2013).

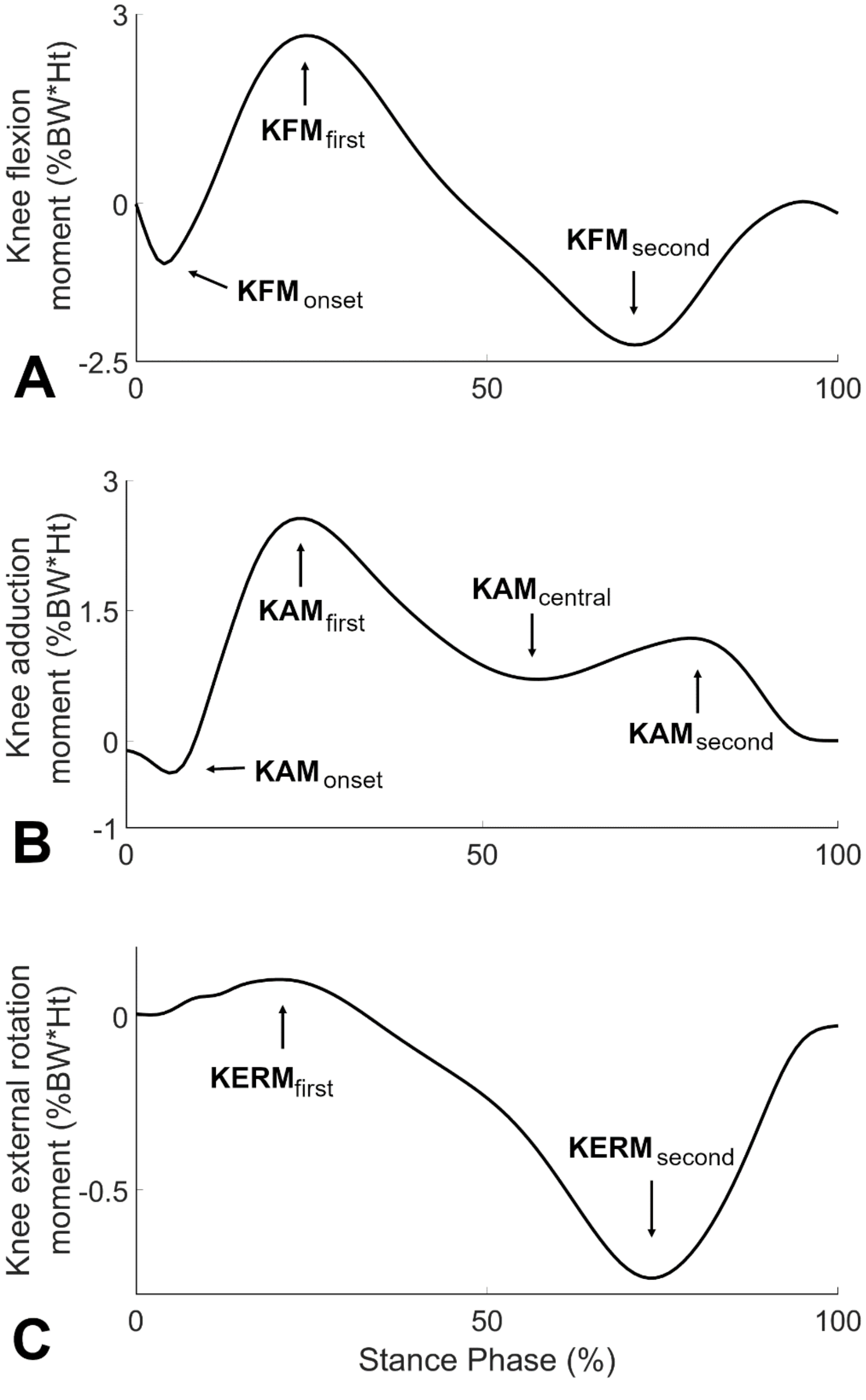


Figure 6: *Knee flexion (KFM) (top, A), adduction (KAM) (middle, B) and external rotation (KERM) (bottom, C) knee moments representation and corresponding knee moment parameters.*

Finally, while literature mainly focused on frontal-plane and sagittal-plane knee moments, transverse-plane knee moment has been neglected in medial knee OA literature. The knee external rotation moment (KERM) curve presents two peaks: a peak of external rotation during midstance ($KERM_{first}$) and a peak of internal rotation during late stance ($KERM_{second}$) (Figure 6C). Once again, little is known in the association between these knee moment parameters and medial knee OA (Astephen et al., 2008).

These secondary knee moment parameters also seem to be related to the disease, notably with its severity. However, related studies being scattered in literature and with non-uniform designs, there is a need for a more complete analysis on all nine usual knee moment parameters (Figure 6) to get a more global picture of the relationship between the disease severity and the knee moment parameters.

Additionally, as with the KFM_{first}, the secondary knee moment parameters could be negatively impacted by interventions designed to decrease KAM_{first}. For example, toe-in gait seems to induce KAM_{first} reductions associated with KAM_{second} increases (Bowd et al., 2019; Simic et al., 2011), which might decrease the impact of such a gait modification. It would then be very interesting to be able to control all knee moment parameters to ensure interventions do not induce counterproductive changes. However, controlling all knee moment parameters while decreasing KAM_{first} could become almost impossible. Therefore, it would be interesting to combine all nine knee moment parameters to get an index that would provide knowledge on the global impact of the intervention on knee moments.

I.5 Thesis overall aims

The above literature review highlighted the potential of gait modification to decrease knee loadings and improve clinical outcomes for medial knee OA patients. However, variations among patients remain and almost only the KAM_{first} was targeted by such gait modifications. It follows the need for a better understanding of gait modifications, including LWI and gait retraining, and stresses out the importance to get more personalized solutions that would lead to more consistent knee loading reductions among patients, in terms of KAM_{first} reduction, but also of reductions of other knee moment parameters. Finally, it revealed the lack of global and uniform knowledge on the relationship between medial knee OA and all nine usual knee moment parameters, and the necessity to group these parameters into a severity index.

This PhD thesis aimed at (1) improving our understanding of the effects of lateral wedge insoles and gait retraining on knee moments, (2) proposing and assessing options to modify gait individually, and (3) providing a global assessment of knee moments relative to disease severity.

The following thesis is composed of four studies, each one corresponding to a chapter, with the following specific aims:

- **Lateral wedge insole and foot progression angle (Chapter II):**

  This study aimed at determining if the KAM changes induced by LWI differed with respect to the natural FPA. A second objective was to compare KAM-related gait parameters between individuals walking with smaller and larger natural FPA to improve our understanding of the mechanism leading to KAM reductions.

- **Dual kinetic change (Chapter III):**

  This study aimed at characterizing the feasibility of decreasing the KAM_{first} by 10% or more without increasing the KFM_{first} through modifications in footprint parameters. A second aim was to evaluate the added value of modifying SL while maintaining normal walking speed.

- **Stride length modifications (Chapter IV):**

  This study aimed at providing first insights into the effects of SL reductions, at constant walking speed, on the KAM_{first}, $KAM_{impulse}$ and KFM_{first} in patients with medial knee OA. The effects were characterized both for a group of patients and at an individual level.

- **Severity index (Chapter V):**

  This study aimed at characterizing the nine usual parameters of knee moments during walking with respect to medial knee OA severity, through comparison and correlation analyses. A second objective was to assess the possibility of developing a severity index combining all nine parameters.

This thesis was written personally by Baptiste Ulrich, except for the studies in Chapters II to V, which were co-authored with peers.

II Lateral wedge insoles and foot progression angle

The following chapter is an adaptation of the study *"Changes in ambulatory knee adduction moment with lateral wedge insoles differ with respect to the natural foot progression angle"* published in Journal of Biomechanics (Ulrich et al., 2020a).

II.1 Introduction

LWI have been proposed to decrease the KAM. At first, this approach seemed promising, with multiple studies reporting KAM_{first} and $KAM_{impulse}$ reductions in groups of individuals with or without knee OA (Arnold et al., 2016; Shaw et al., 2018). However, literature failed to demonstrate clear improvements in disease outcomes (Penny et al., 2013; Zhang et al., 2018). The uncertainty of clinical benefits with LWI could find its origin in the fact that the KAM changes with LWI are inconsistent among individuals and that prior studies did not pay enough attention to inter-individual variations. Indeed, while a majority of individuals decreases both OA-related KAM parameters with LWI, in some individuals, LWI increase these parameters (Hinman et al., 2012; Jones et al., 2014; Kakihana et al., 2007). Additionally, the magnitude of the KAM changes strongly varies among persons (Hinman et al., 2012; Jones et al., 2014). The need to better understand these inter-individual variations is further supported by the fact that heterogeneous changes were consistently reported, independently of the LWI design and study population (Arnold et al., 2016; Hinman et al., 2008).

Interestingly, a recent study defined patients as responder if they decreased their KAM_{first} with the use of LWI, and showed significant pain reductions with LWI in these patients (Felson et al., 2019). Therefore, whereas earlier research showed that LWI are not a universal solution (Arnold et al., 2016; Kakihana et al., 2007), this recent work indicates that LWI could be clinically beneficial for the patients who actually decrease the KAM with this intervention. This observation of clinical improvements in case of KAM reductions is well supported by gait retraining studies where improvements in pain and function were also reported in patients who decreased the OA-related KAM parameters (Cheung et al., 2018; Richards et al., 2018a; Shull et al., 2013a).

Consequently, in view of the significant impact that LWI could make in the management of medial knee OA if recommended to the right (responder) patients, there are definite interests to develop screening procedures to differentiate between individuals who reduce sufficiently their KAM_{first} and $KAM_{impulse}$ with LWI and those who do not, without having to perform full instrumented gait analysis. To do so, a necessary first step is to better understand the underlying mechanism of LWI and identify easy-to-measure predictive parameters.

Only a few studies so far investigated individual factors that could influence the KAM changes with LWI (Chapman et al., 2015; Sawada et al., 2016), and to the authors knowledge no study analyzed the effect the natural foot progression angle (FPA) could have on the KAM changes. The FPA is a classical spatio-temporal gait parameters quantifying the amplitude of foot opening (toeing-in or toeing-out) during the stance phase of walking (Murray et al., 1964; Saggini et al., 1998; Scherer et al., 2006; Woolley, 2001). It significantly gained in interest during the last decades with advance in knee OA research. In fact, it is among the gait parameters the most frequently associated to the KAM, with numerous studies reporting KAM changes with modifications of the FPA (Favre et al., 2016; Simic et al., 2013). Moreover, the reductions in KAM_{first} and $KAM_{impulse}$ with LWI were recently shown to be larger when the participants toed-in compared to when they walked with their natural FPA (Khan et al., 2018). Therefore, there is a possibility that the natural FPA influences the changes in KAM with LWI.

This study aimed at determining if the KAM changes induced by LWI differed with respect to the natural FPA. Specifically, it tested the hypothesis that individuals walking with smaller FPA have greater KAM_{first} and $KAM_{impulse}$ reductions than individuals walking with larger

FPA. A second objective was to compare KAM-related gait parameters between individuals walking with smaller and larger natural FPA to improve our understanding of the mechanism leading to KAM reductions.

II.2 Methods

II.2.1 Participants

Twenty-two healthy subjects (8 women) without history of serious lower extremity injury or gait impairments took part in this IRB-approved study after providing informed consent. Their mean (± standard deviation) age, height and weight were of 24 ± 3 years old, 1.76 ± 0.10 m and 70.8 ± 11.6 kg, respectively. A sample size calculation for the t-test used for the primary hypothesis indicated a minimum of 11 participants per group, considering an effect size (Cohen's d) greater than 1.2 (Felson et al., 2019; Radzimski et al., 2012), a power of 80% and an alpha level of 5% (G*Power, DE).

II.2.2 Experimental Protocol

Participants performed a series of gait trials at normal self-selected speed with neutral frontal plane stability shoes (gel-beyond, Asics, JP), and with the same shoes in which custom full-length LWI (Fischer et al., 2018) were inserted bilaterally under the comfort insoles. Footwear order was random. LWI were made of high-density ethylene vinyl acetate (EVA) with a durometer of 60 (Shore C) and wedged at 5° following literature recommendations (Tipnis et al., 2014). Only the biomechanics of the right leg was recorded and analyzed in this study.

Gait trials consisted of straight-line walking across a 10m-long gait lab instrumented with a motion capture system (Vicon, UK) and ground-embedded force plates (Kistler AG, CH) recording synchronously at 120Hz and 1200Hz, respectively. For both footwear conditions, three successful trials were recorded. A trial was considered successful when the right foot of the participant fully stepped on one force plate with no other step occurring on that force plate. The biomechanics of the participant was analyzed during these particular stance phases with the right foot on a force plate.

Prior to the gait trials, clusters of reflective markers were fixed on the participants following a common protocol (Chehab et al., 2017). The clusters were used to embed a technical frame in each lower-limb segment (Andriacchi et al., 1998). Anatomical landmarks, identified by palpation during a standing reference pose, were used to define the anatomical frame of the thigh, shank and foot segments (Favre et al., 2016), as well as the technical-to-anatomical transformations (Favre et al., 2009). During the gait trials, the position and orientation of the anatomical frames were calculated using the marker cluster trajectories and the technical-to-anatomical transformations (Andriacchi et al., 1998).

The KAM was calculated following a standard inverse dynamics approach based on the anatomical frame dynamics, force plate data and inertia properties of the segments (Zabala et al., 2013). The KAM was expressed as an external moment and normalized to percent bodyweight and height (%BW*Ht). Three parameters were used to describe the KAM during the stance phase of interest of each trial: the maximum values during the first (KAM_{first}) and second (KAM_{second}) halves of stance phase, as well as the impulse ($KAM_{impulse}$) over the entire stance phase (Chehab et al., 2014). The foot progression angle parameter (FPA) was calculated as the average horizontal-plane angle between the posterior–anterior axis of the foot anatomical frame and the forward axis of the walkway during the middle 50% of each stance phase of interest (Favre et al., 2016).

Four additional biomechanical metrics related to the KAM were computed to better understand the LWI mechanism. They included the magnitude of the ground reaction force (GRF), the lever arm, the angle between the GRF and the longitudinal shank axis, and the position of the center of pressure (COP), all measured in the frontal-plane of the shank anatomical frame (Table 1). Three parameters, coinciding with the KAM parameters, were used to analyze each of these additional metrics. They corresponded to the values of the metrics at the time of KAM_{first} and KAM_{second} and to the average value of the metrics during stance phase.

Table 1: *Definition of the additional biomechanical metrics related to the knee adduction moment (KAM).*

Metric	**Unit**	**Description**
Frontal-plane GRF magnitude	%BW	Magnitude of the GRF in the frontal plane of the shank anatomical frame
Frontal-plane lever arm	mm	Perpendicular distance between the GRF and the knee joint center in the frontal-plane of the shank anatomical frame
Frontal-plane GRF-shank angle	degree	Angle between the GRF and the distal-proximal axis of the shank in the frontal plane of the shank anatomical frame (positive values indicate that the GRF is medial to the shank)
Medio-lateral COP position	mm	Medio-lateral position of the COP in the shank anatomical frame (positive values indicate that the COP is lateral to the knee joint center)

Three parameters, corresponding to the values of the metrics at the time of the KAM_{first} *and* KAM_{second} *and to the average value of the metrics during stance, were used for statistical analysis.*

GRF = Ground reaction force

COP = Center of pressure

Finally, the data were averaged over the three trials recorded with each footwear condition to have only one data point per participant, footwear condition and parameters of interest. Computations were done using the software BioMove (Standford, CA, US) and custom scripts in Matlab (Mathworks, Natick, MA, USA).

II.2.3 Statistical analysis

Participants were divided into two groups of same size according to their FPA when walking without LWI. The split was done using the median FPA of the 22 subjects, yielding a group with the 11 “smaller natural FPA” participants and a group with the 11 “larger natural FPA” participants. For each group, two-sided paired t-tests were performed to compare the parameters of interest between the two footwear conditions (with and without LWI). Unpaired two-sided t-tests were also done to compare the parameters of interests and their changes with LWI between the two groups. To allow a thorough interpretation of these comparisons between conditions and groups, the unstandardized and standardized effect sizes were calculated. Cohen’s d was used to report the standardized effect sizes (Cohen, 2013; Cooper et al., 2019). All data were previously tested for normality using Kolmogorov-Smirnov tests. Statistical significance level was set a-priori at 5%.

II.3 Results

When walking without LWI, the FPA was, on average, 9.6° larger in the larger natural FPA group (mean ± standard deviation: 20.0 ± 3.0°) than in the smaller natural FPA group (10.4 ± 3.1°). With this footwear condition, neither the speed nor the KAM parameters differed statistically significantly between the two groups ($p \geq 0.47$) (Table 2).

Walking with LWI significantly decreased the KAM_{first} in the smaller natural FPA group ($p < 0.01$; Cohen's d = -0.30), whereas no significant changes in the KAM_{first} were observed in the larger natural FPA group ($p = 0.14$) (Figure 7, Table 2). Furthermore, the changes in the KAM_{first} were significantly different between both groups ($p = 0.04$; Cohen's d = -0.93). The LWI induced significant decreases in the KAM_{second} and $KAM_{impulse}$ in both the smaller ($p = 0.01$; Cohen's d = -0.46 and $p < 0.01$; Cohen's d = -0.47, respectively) and larger ($p < 0.01$; Cohen's d = -0.56 and $p < 0.01$; Cohen's d = -0.32, respectively) natural FPA groups, without significant differences in the changes between the groups ($p \geq 0.59$).

Table 2: *Foot progression angle (FPA), walking speed, and knee adduction moment (KAM) parameters for the smaller and larger natural FPA groups with both footwear conditions.*

	Smaller natural FPA group			Larger natural FPA group						
	Value without LWI	Changes with LWI		Value without LWI	Changes with LWI		Inter-group differences in gait without LWI		Inter-group differences in changes with LWI	
		Unstandardized (U) and standardized (S) changes	p-value		Unstandardized (U) and standardized (S) changes	p-value	Unstandardized (U) and standardized (S) differences	p-value	Unstandardized (U) and standardized (S) differences	p-value
FPA (°)	10.4 ± 3.1	U: 0.9 (0.3, 1.4) S: 0.27 (-0.57, 1.11)	**0.014**	20.0 ± 3.0	U: 1.5 (0.5, 2.5) S: 0.49 (-0.36, 1.34)	**0.015**	U: 9.6 (7.0, 12.1) S: 3.11 (1.87, 4.35)	**< 0.001**	U: 0.6 (-0.5, 1.8) S: 0.45 (-0.40, 1.30)	0.30
Speed (m/s)	1.47 ± 0.17	U: 0.01 (-0.04, 0.05) S: 0.04 (-0.80, 0.87)	0.81	1.48 ± 0.21	U: 0.00 (-0.04, 0.04) S: 0.01 (-0.82, 0.85)	0.90	U: 0.01 (-0.15, 0.17) S: 0.06 (-0.78, 0.90)	0.89	U: -0.00 (-0.07, 0.06) S: 0.05 (-0.79, 0.89)	0.91
$\text{KAM}_{\text{first}}$ (%BW*Ht)	2.73 ± 1.09	U: -0.32 (-0.50, -0.15) S: -0.30 (-1.14, 0.54)	**0.005**	2.96 ± 0.65	U: -0.09 (-0.02, 0.20) S: -0.14 (-0.98, 0.70)	0.14	U: 0.23 (-0.53, 0.98) S: 0.25 (-0.59, 1.09)	0.56	U: 0.23 (0.02, 0.44) S: 0.93 (0.05, 1.81)	**0.042**
$\text{KAM}_{\text{second}}$ (%BW*Ht)	1.86 ± 0.62	U: -0.29 (-0.47, -0.10) S: -0.46 (-1.31, 0.38)	**0.012**	1.85 ± 0.60	U: -0.33 (-0.43, -0.24) S: -0.56 (-1.41, 0.29)	**< 0.001**	U: -0.02 (-0.52, 0.49) S: -0.03 (-0.87, 0.81)	0.95	U: -0.05 (-0.26, 0.16) S: -0.19 (-1.03, 0.65)	0.67
$\text{KAM}_{\text{impulse}}$ (%BW*Ht*s)	0.79 ± 0.28	U: -0.13 (-0.21, -0.06) S: -0.47 (-1.32, 0.37)	**0.006**	0.89 ± 0.34	U: -0.11 (-0.15, -0.07) S: -0.32 (-1.34, 0.36)	**< 0.001**	U: 0.10 (-0.16, 0.36) S: 0.32 (-0.52, 1.16)	0.47	U: 0.02 (-0.06, 0.11) S: 0.23 (-0.61, 1.07)	0.59

Measures are reported as 'mean ± one standard deviation'.

Changes and differences are reported as 'effect size (95% confidence interval)'. Standardized effect sizes are Cohen's d.

Bolded numbers indicate significant p-values (p<0.05).

LWI = Lateral wedge insoles.

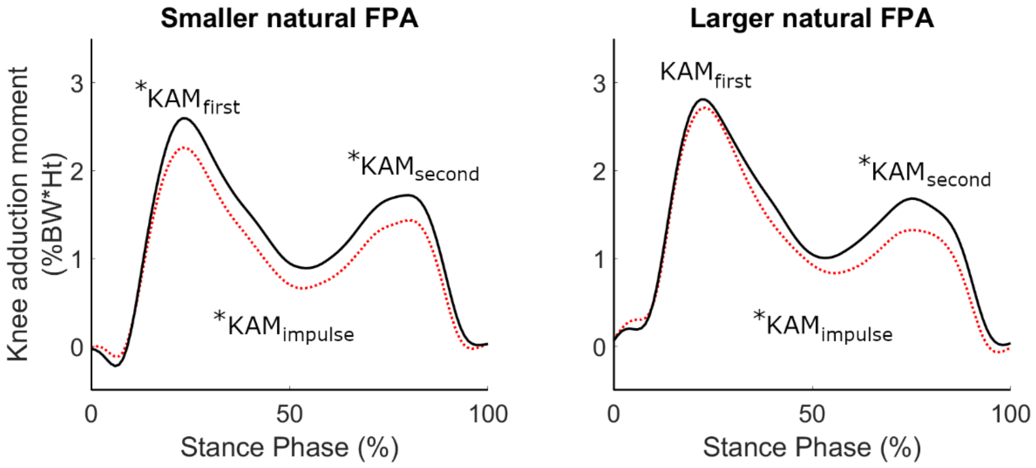


Figure 7: *Mean knee adduction moment (KAM) over stance phase for the smaller (left) and larger (right) natural foot progression angle (FPA) groups. In both plots, the continuous black and the dotted red lines correspond to the walking conditions without lateral wedge insole (LWI) and with LWI, respectively. Stars (*) indicate significant difference between LWI conditions ($p \leq 0.02$; Table 2).*

Walking with LWI also changed the FPA, with significant increases in both the smaller ($p = 0.014$; Cohen's d = -0.27) and the larger ($p = 0.015$; Cohen's d = -0.49) natural FPA groups. The FPA increases induced by the LWI did not significantly differ between the groups ($p = 0.30$). Finally, speed was not significantly different when walking with or without LWI for neither group ($p \geq 0.81$).

Analyzing the additional KAM-related metrics at the time of the KAM_{first} allowed better understanding the differences between the two groups in the KAM_{first} changes with LWI (Figure 8, Table 3). First, when comparing the two main components of the KAM, this analysis indicated statistically significant differences in the lever arm changes between groups ($p = 0.04$; Cohen's d = 0.93), but no group differences in the GRF magnitude changes ($p = 0.63$). Indeed, while the lever arms were reduced with the LWI in both groups, the reductions were larger in the smaller ($p < 0.01$; Cohen's d = -0.31) than in the larger ($p = 0.04$; Cohen's d = -0.19) natural FPA group.

Second, when comparing the main components of the lever arm, statistically significant group differences were observed in the GRF-shank angle changes ($p = 0.04$; Cohen's d = 0.97), whereas the changes in the COP position were not significantly different between groups ($p = 0.75$). The differences in the GRF-shank angle changes are explained by significant increases in the GRF-shank angle with LWI in the larger natural FPA group ($p = 0.01$; Cohen's d = 0.29), with non-significant changes in the smaller natural FPA group ($p = 0.31$).

Table 3: *Additional biomechanical metrics at the time of first peak of knee adduction moment (*KAM_{first}*) for the smaller and larger natural foot progression angle (FPA) groups with both footwear conditions.*

	Smaller natural FPA group			Larger natural FPA group						
	Value without LWI	Changes with LWI		Value without LWI	Changes with LWI		Inter-group differences in gait without LWI		Inter-group differences in changes with LWI	
		Unstandardized (U) and standardized (S) changes	p-value		Unstandardized (U) and standardized (S) changes	p-value	Unstandardized (U) and standardized (S) differences	p-value	Unstandardized (U) and standardized (S) differences	p-value
Frontal-plane GRF magnitude (%BW)	112.78 ± 11.96	U: 0.04 (-3.03, 3.12) S: 0.00 (-0.83, 0.84)	0.98	111.83 ± 7.00	U: 1.09 (-1.78, 3.97) S: 0.16 (-0.68, 0.99)	0.47	U: -0.95 (-9.14, 7.23) S: -0.10 (-0.93, 0.74)	0.82	U: 1.05 (-3.16, 5.26) S: 0.21 (-0.63, 1.05)	0.63
Frontal-plane lever arm (mm)	42.62 ± 15.90	U: -4.87 (-6.63, -3.11) S: -0.31 (-1.15, 0.53)	< **0.001**	49.00 ± 11.14	U: -2.10 (-3.86, -0.33) S: -0.19 (-1.03, 0.65)	**0.042**	U: 6.38 (-5.10, 17.85) S: 0.46 (-0.38, 1.31)	0.29	U: 2.77 (0.28, 5.27) S: 0.93 (0.05, 1.81)	**0.041**
Frontal-plane GRF-shank angle (°)	7.09 ± 2.16	U: 0.07 (-0.06, 0.21) S: 0.03 (-0.80, 0.87)	0.31	7.74 ± 1.47	U: 0.42 (0.15, 0.69) S: 0.29 (-0.55, 1.13)	**0.012**	U: 0.65 (-0.90, 2.20) S: 0.35 (-0.49, 1.19)	0.42	U: 0.35 (0.05, 0.65) S: 0.97 (0.08, 1.85)	**0.035**
Medio-lateral COP position (mm)	15.85 ± 3.33	U: 6.15 (4.06, 8.24) S: 1.84 (0.85, 2.84)	< **0.001**	18.82 ± 7.23	U: 6.62 (4.68, 8.56) S: 0.92 (0.04, 1.79)	**< 0.001**	U: 2.96 (-1.74, 7.67) S: 0.53 (-0.32, 1.38)	0.23	U: 0.48 (-2.37, 3.33) S: 0.14 (-0.70, 0.98)	0.75

Measures are reported as 'mean ± one standard deviation'.

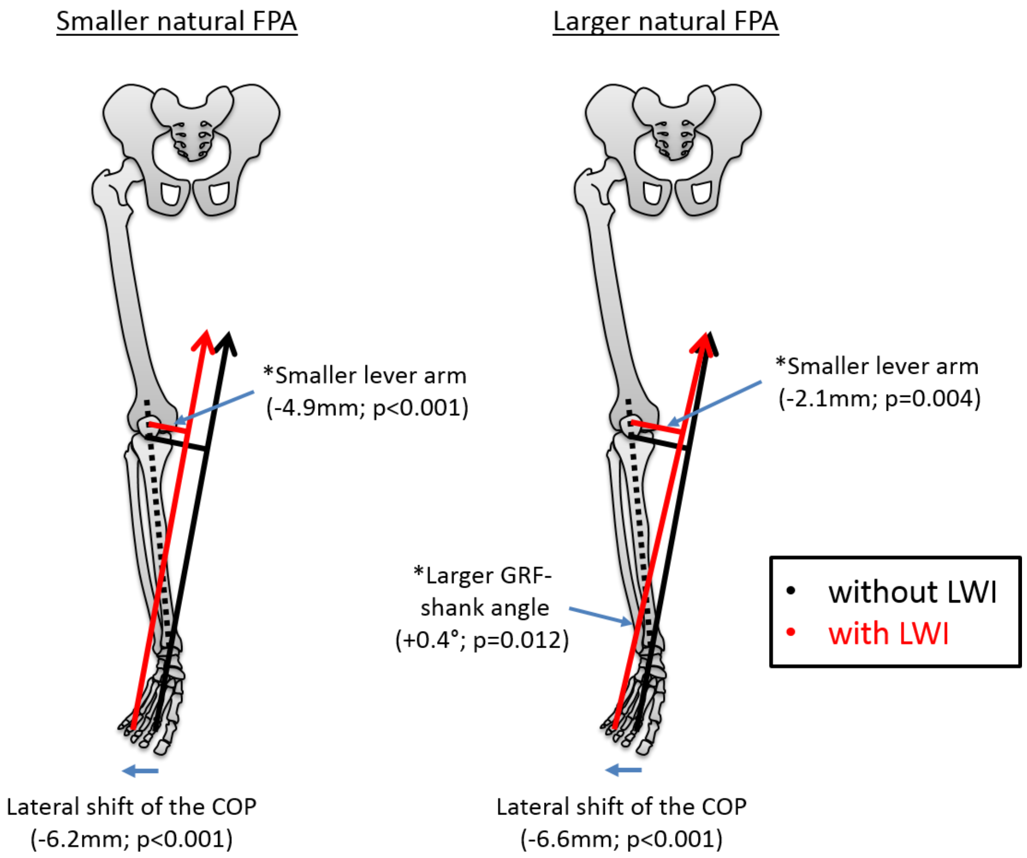
Changes and differences are reported as 'effect size (95% confidence interval)'. Standardized effect sizes are Cohen's d.

Bolded numbers indicate significant p-values (p<0.05).

LWI = Lateral wedge insoles

GRF = Ground reaction force

COP = Center of pressure



Smaller natural FPA

Larger natural FPA

*Smaller lever arm
(-4.9mm; p<0.001)

*Smaller lever arm
(-2.1mm; p=0.004)

*Larger GRF-shank angle
(+0.4°; p=0.012)

Lateral shift of the COP
(-6.2mm; p<0.001)

Lateral shift of the COP
(-6.6mm; p<0.001)

Figure 8: *Illustration of the significant changes in KAM-related biomechanical metrics at the time of the KAM$_{first}$ with lateral wedge insoles (LWI) in the smaller (left) and larger (right) natural foot progression angle (FPA) groups. Numbers reported into brackets correspond to the mean changes with LWI (Table 3). Stars (*) indicate changes that are statistically significantly different from the changes occurring in the other group (p≤0.04).*

GRF = Ground reaction force

COP = Center of pressure

II.4 Discussion

This study showed that the changes in KAM_{first} with LWI are related to the natural FPA. Specifically, a statistically significant decrease in this peak was only observed in the group of participants walking with smaller natural FPA, and the standardized effect size of the changes with LWI was twice as large in the smaller natural FPA group than in the other group (Cohen’s d of -0.30 vs. -0.14). While no effect size recommendation exists regarding KAM_{first} decreases in the case of medial knee OA, mainly because there have been too few longitudinal studies on gait intervention with KAM measurement, the difference in effect size with respect to the FPA is certainly clinically relevant. In fact, the effect sizes in prior studies that reported clinical improvements with LWI were comprised between -0.25 and -0.20 (Hinman et al., 2008; Felson et al., 2019), and gait retraining studies aimed for reductions equivalent to effect sizes between -0.45 and -0.30 (Richards et al., 2018a; Shull et al, 2013a). Comparing the present results with the literature thus suggests an adequate effect size in the smaller natural FPA group and an insufficient effect size in the other group.

Consequently, the FPA could help to screen patients who should be more likely to decrease their KAM_{first} with LWI and therefore for who LWI could improve clinical outcomes. In this regard, it should be noted that the FPA could be measured using much simpler instrumentation than in the present study, therefore making its use in routine practice totally possible. For example, the FPA can be measured using pressure mats (Menz et al., 2004) or inertial sensors (Huang et al., 2016).

The relationship between the natural FPA and the $\text{KAM}_{\text{first}}$ changes with LWI highlighted in the present study could also shed light on the inter-individual variability in the KAM changes with LWI reported in literature (Arnold et al., 2016; Kakihana et al., 2007). In fact, to the authors' knowledge, none of the prior studies on LWI accounted for participants variations in natural FPA. While this is unfortunate, it might also be very encouraging for the treatment of medial knee OA. Indeed, this supports a shift toward personalized management where the differences among patients are acknowledged and each patient is proposed the best biomechanical intervention for him/herself. With this approach, as shown in this work, the effect size of existing interventions could be significantly improved. Additional research will nonetheless be required to establish which intervention suits which patient profiles best.

Analyzing the underlying mechanism of the changes in $\text{KAM}_{\text{first}}$ with LWI showed that the decreases in the smaller natural FPA group were related to decreased lever arms and not to decreased GRF magnitudes. The analysis further indicated that the lever arms were decreased by lateral shifts of the COP (Figure 8 left).

In the larger natural FPA group, the lever arms were also decreased with the wear of LWI, but the decreases were smaller than in the other group. The smaller decreases in lever arm were explained by increases in the frontal-plane GRF-shank angles with LWI in the larger natural FPA group (Figure 8 right).

Consequently, the difference of changes in KAM_{first} with LWI between groups was related to less decreased lever arms induced by increased frontal-plane GRF-shank angles in the larger natural FPA group. Further research will be necessary to determine if other interventions could be combined with LWI to avoid the increase of the frontal-plane GRF-shank angle. For example, in the future, we could imagine that LWI will not simply be given to the patients, but that a clinician will help the patients improve their gait patterns when walking with LWI. Interestingly, a recent study showed that the effect of LWI can be improved if walking instructions are given to the patients (Khan et al., 2018).

Medial knee OA literature suggests reducing the $KAM_{impulse}$, in addition to the KAM_{first} (Chehab et al., 2014; Mündermann et al., 2004; Thorp et al., 2007). However, when discussing the effect of the FPA, the $KAM_{impulse}$ appears of lesser importance since this parameter statistically significantly decreased in both groups, without difference between groups. Consequently, there is no counterargument between the two KAM parameters, and screening for smaller FPA could help identify patients more likely to improve their ambulatory loading with LWI and thus to benefit from this intervention.

This study has a few limitations that should be discussed. First, while testing healthy, young, normal weight subjects was justified by the aim to understand the biomechanics of LWI, the finding that FPA could be used to determine which individuals are more likely to have KAM reductions with LWI should be confirmed with medial knee OA patients. Second, this study separated participants in two groups of same size according to their natural FPA, which led to a separation value of about 15° of natural FPA. Further works are needed to determine if a strict threshold is the most effective method to differentiate individuals. Third, additional studies are also necessary to determine whether the response to LWI is equivalent between an individual naturally walking with a small FPA and someone with a larger natural FPA but toeing-in to actually walk with the same smaller FPA.

Finally, while the number of subjects was sufficient for the primary objectives and provided valuable insights on LWI mechanism, further studies on larger populations will be necessary for more precise estimation of the effect sizes as well as to analyze multiple factors simultaneously and establish a responder profile. Indeed, while this study focused on FPA, other factors have been suggested to influence the KAM changes induced by LWI, including foot posture, ankle kinematics and OA severity (Chapman et al., 2015; Sawada et al., 2016; Shimada et al., 2006), and it is likely that other factors, for example describing demographics, alignment and/or walking mechanics, will be associated to the KAM changes in the future. Nevertheless, later, when the questions of comparing factors and building a responder profile will come, it will be important to take into account the possibility to estimate the natural FPA in routine practice (Huang et al., 2016; Menz et al., 2004).

II.5 Conclusion

This study showed a relationship between the natural FPA and the changes in KAM_{first} occurring with LWI. Specifically, statistically significant decreases, of adequate effect size, in KAM_{first} were only observed in the group walking with smaller natural FPA. The different response in the larger natural FPA group was related to an increased frontal-plane GRF-shank angle. Consequently, this study suggested that screening based on the natural FPA could become a simple procedure to identify medial knee OA patients more likely to benefit from LWI. More generally, this study highlighted the needs to better understand the factors influencing the response to LWI and determine if the biomechanical and clinical outcomes could be enhanced by combining LWI with walking rehabilitation.

III Dual kinetic change

The following chapter is an adaptation of the study *"Decreasing the ambulatory knee adduction moment without increasing the knee flexion moment individually through modifications in footprint parameters: a feasibility study for a dual kinetic change in healthy subjects"* published in Journal of Biomechanics (Ulrich et al., 2020b).

III.1 Introduction

The previous chapter (Chapter 2) showed that LWI have the potential to decrease the KAM, and that screening based on the FPA could help to select patients more likely to clinically benefit from this intervention. However, as with braces or tibial osteotomies, the degrees of freedom with this intervention are limited and it focused on reducing only the KAM_{first} (Hussain et al., 2016; Reeves and Bowling, 2011). Among the other approaches to reduce the KAM_{first}, diverse gait retraining systems using biofeedback have been proposed to help individuals modify their walking patterns and the results are encouraging both biomechanically (as summarized in Table 4) and clinically (Cheung et al., 2018; Richards et al., 2018a; Shull et al., 2013a). Gait retraining is different from insoles, braces, or tibial osteotomies, as it has the potential to induce more complex changes than simply $\mathrm{KAM}_{\mathrm{first}}$ reductions. This is noteworthy since disease progression has also been associated with the $\mathrm{KFM}_{\mathrm{first}}$ (Chehab et al., 2014). Additionally, since medial-compartment loading has been related to both the $\mathrm{KAM}_{\mathrm{first}}$ and the $\mathrm{KFM}_{\mathrm{first}}$ (Manal et al., 2015; Walter et al., 2010), reducing the $\mathrm{KAM}_{\mathrm{first}}$ without considering the $\mathrm{KFM}_{\mathrm{first}}$ does not guaranty a decrease in medial-compartment loading, as looked for in the treatment of medial knee OA (Reeves and Bowling, 2011). Indeed, if an intervention increases the $\mathrm{KFM}_{\mathrm{first}}$ while it reduces the $\mathrm{KAM}_{\mathrm{first}}$, it could result in an increase in medial-compartment loading (Walter et al., 2010).

Today, the exact relationship between changes in $\mathrm{KAM}_{\mathrm{first}}$, $\mathrm{KFM}_{\mathrm{first}}$ and medial-compartment loading is unknown. Therefore, a conservative reading of the literature suggests that gait interventions for medial knee OA should reduce the $\mathrm{KAM}_{\mathrm{first}}$ by 10% or more without increasing the $\mathrm{KFM}_{\mathrm{first}}$. Yet, it is unknown if this more specific change, referred here as dual kinetic change, is feasible through gait retraining because prior studies focused on $\mathrm{KAM}_{\mathrm{first}}$ reductions. In fact, as shown in Table 4, previous studies that analyzed the $\mathrm{KFM}_{\mathrm{first}}$ either reported no statistically significant changes or reported $\mathrm{KFM}_{\mathrm{first}}$ increases. Since these studies analyzed the change at the group level, the absence of significant change indicates that the changes differed among participants, with a portion of them increasing the $\mathrm{KFM}_{\mathrm{first}}$. Consequently, it is clear that gait modifications used to reduce the $\mathrm{KAM}_{\mathrm{first}}$ could increase the $\mathrm{KFM}_{\mathrm{first}}$, and there is a need to determine the feasibility of achieving the dual kinetic change to help the design of future gait retraining protocols.

Modifications in foot progression angle (FPA) and step width (SW) have been shown to change the KAM_{first} (Favre et al., 2016) and have been frequently used in gait retraining for medial knee OA (Table 4). Surprisingly, modifying stride length (SL) received much less attention, although this could change knee kinetics (Russell et al., 2010) and is regularly used in other applications, such as prevention of running injury (Schubert et al., 2014). Since prior medial knee OA gait retraining studies have shown that the responses to gait modifications are subject-specific (Favre et al., 2016, Uhlrich et al., 2018), it could be extremely valuable to have the possibility to modify a third parameter (SL) in addition to FPA and SW, especially when targeting more specific change, like the dual kinetic change. Furthermore, a gait retraining system using augmented reality was recently introduced to facilitate simultaneous modifications in FPA, SW and SL (Bennour et al., 2018), meaning that it could be possible to optimize knee OA rehabilitation by combining these modifications (Favre et al., 2016; Shull et al., 2011). It is important that gait retraining maintains normal walking speed for everyday quality of life and long-term general health. Therefore, it is understood that SL modifications go along with inverse modifications in cadence (Grieve and Gear, 1966).

Table 4: *Overview of prior biofeedback gait retraining studies for knee osteoarthritis (OA).*

Study	**Overall retraining objectives**	**Strategy**	**Feedback**	**Experiment**		**Results**	
				Population	**Observation period**	**Change in KAM$_{first}$***	**Change in KFM$_{first}$ ***
Barrios et al., 2010	KAM decrease	Indirect - decrease FPKA	FPKA displayed on a screen	8 AP	Immediate	**-20% (p=0.027)**	N/R
					1 month follow-up	**-20% (p=0.019)**	N/R
Dowling et al., 2010	KAM decrease	Indirect - medial weight transfer at the foot	Vibration at the shoe based on plantar pressure	9 AP	Immediate	**-14% (p<0.01)**	N/R
Hunt et al., 2011	KAM decrease	Indirect - TL of 4°	TL displayed on a screen	9 AP	Immediate	-7% (p-value not reported)	N/R
		Indirect - TL of 8°				**-21% (p<0.05)**	N/R
		Indirect - TL of 12°				**-25% (p<0.05)**	N/R
Shull et al., 2011	>30% KAM decrease	Indirect - modify FPA, TS and TA	Vibration at the back, knee and foot based on TS, TA and FPA	9 AP	Immediate	**-1.5 %BW*Ht (p<0.001)**	N/R
Wheeler et al., 2011	KAM decrease	Direct - decrease KAM	KAM displayed on a screen	16 AP	Immediate	**-20% (p<0.001)**	N/R
			Vibration at the arm based on KAM			**-21% (p<0.001)**	N/R
Shull et al., 2013a	10% KAM decrease	Indirect - decrease FPA and/or increase TS	Vibration at the arm and back based on TA and TS	10 KOAP	Post-training (6 weeks)	**-0.5 %BW*Ht (p<0.01)**	-0.28 %BW*Ht (p=0.35)
					1 month follow-up	**-0.44 %BW*Ht (p<0.05)**	-0.52 %BW*Ht (p=0.08)
Shull et al., 2013b	KAM decrease, without KFM increase	Indirect - decrease FPA	Vibration at the arm based on TA	12 KOAP	Immediate	**-13% (p<0.01)**	-0.03 %BW*Ht (p=0.85)
Hunt and Takacs, 2014	KAM decrease	Indirect - increase FPA	FPA displayed on a screen	15 KOAP	Post-training (10 weeks)	-0.26 %BW*Ht (p=0.12)	+0.13 %BW*Ht (p=0.67)
Ferrigno et al., 2015	KAM decrease, without KFM increase	Indirect - medial weight transfer at the foot	Sound based on plantar pressure	22 AP	Immediate	**-15% (p<0.001)**	-0.20 %BW*Ht (p=0.34)
Van den Noort et al., 2015	KAM decrease	Direct - decrease KAM	KAM displayed on a screen (diverse visual feedbacks)	12 AP	Immediate	**Between -56% and -45% (all p≤0.01)**	N/R
		Indirect - increase HIR	HIR displayed on a screen (diverse visual feedbacks)			Between -5% and -19% (all p≥0.19)	N/R
Erhart-Hledik et al., 2017	KAM decrease	Indirect - medial weight transfer at the foot	Vibration at the shoe based on plantar pressure	10 KOAP	Immediate	**-6% (p=0.04)**	+0.03%BW*Ht (p=0.90)

(continued on next page)

Charlton et al., 2019	KAM change	Indirect - FPA of -10°	FPA displayed on a screen	15 KOAP	Immediate	-0.08 Nm/kg (no statistics for comparison with natural walking)	N/R
		Indirect - FPA of 0°				-0.04 Nm/kg (no statistics for comparison with natural walking)	N/R
		Indirect - FPA of 10°				+0.00 Nm/kg (no statistics for comparison with natural walking)	N/R
		Indirect - FPA of 20°				+0.03 Nm/kg (no statistics for comparison with natural walking)	N/R
Cheung et al., 2018	>20% KAM decrease	Direct - decrease KAM	KAM displayed on a screen	10 KOAP	Post-training (6 weeks)	**-22% (p<0.001)**	N/S (p-value not reported)
					6 months follow-up	**-25% (p=0.01)**	N/S (p-value not reported)
Jackson et al., 2018a	>20% KAM decrease	Direct - decrease KAM	KAM displayed on a screen	11 AP	Immediate with feedback	**-23% (p=0.007)**	+33% (p-value not reported)
					Immediate without feedback	**-21% (p=0.009)**	+25% (p-value not reported)
					5 minutes after immediate	**-24% (p=0.008)**	**+35% (p=0.04)**
Richards et al, 2018a	10% KAM decrease, with limited KFM increase	Direct - decrease KAM	KAM displayed on a screen	16 KOAP	Post-training (6 weeks)	**-0.22 %BW*Ht (p=0.05)**	+0.11 %BW*Ht (p=0.53)
					3 months follow-up	-0.31 %BW*Ht (p=0.18)	+0.02 %BW*Ht (p=1.00)
					6 months follow-up	-0.21 %BW*Ht (p=0.26)	+0.20 %BW*Ht (p=0.24)
Richards et al., 2018b	10% KAM decrease	Direct - decrease KAM	KAM displayed on a screen (version 1)	40 KOAP	Immediate	-0.10 %BW*Ht (p=0.15)	-0.02 %BW*Ht (p=1.00)
			KAM displayed on a screen (version 2)			**-14% (p<0.001)**	**+22% (p=0.005)**
			Sound based on KAM			-0.11 %BW*Ht (p=0.06)	+0.01 %BW*Ht (p=1.00)
Uhlrich et al., 2018	KAM decrease	Indirect - modify FPA	Vibration at the tibia based on FPA	20 AP	Immediate	**-19% (p-value not reported)**	**+12% (p=0.023)**

The studies summarized in this table were selected based on the inclusion/exclusion criterion of two recent systematic literature reviews on knee OA gait retraining (Bowd et al., 2019; Richards et al., 2017).

Abbreviations: KAM = knee adduction moment; KFM = knee flexion moment; HIR = hip internal rotation; FPKA = frontal plane knee angle; FPA = foot progression angle; TS = trunk sway; TL = trunk lean; TA = tibia angle; AP = asymptomatic participant; KOAP = knee osteoarthritic patient; N/R = not reported; N/S = average change not reported, but change indicated as statistically non-significant.

*Average change of the study population (group level).

Bold: change statistically significant.

The primary objective of this study was to characterize the feasibility of achieving the dual kinetic change individually through modifications in footprint parameters. This study also aimed at evaluating the added value of modifying SL while maintaining normal walking speed. Healthy participants were tested in this preliminary work involving the recording of many gait trials, to avoid pain or fatigue. It was hypothesized that participants could achieve the dual kinetic change of a KAM_{first} reduction of 10% or more without KFM_{first} increase and that, for some participants, the dual kinetic change would be achievable with SL modifications. No hypothesis was formulated regarding the directionality of FPA, SW and SL modifications necessary to reach the dual kinetic change because prior literature showed the modifications to be participant-specific (Favre et al., 2016; Jackson et al., 2018; Uhlrich et al., 2018).

III.2 Method

III.2.1 Participants

Eleven healthy subjects (7 males), without history of lower-limbs surgery, knee pain or locomotion difficulty, participated in this IRB-approved study after providing informed consent. Participants were of mean (± standard deviation) age, height and weight of 24.9 ± 2.5 years old, 1.82 ± 0.08 m and 68.7 ± 9.3 kg, respectively. Since the study objectives were of descriptive nature, the sample size was defined based on prior gait modification studies with comparable objectives (Cheung et al., 2018; Favre et al., 2016; Jackson et al., 2018; Shull et al., 2013a).

III.2.2 Experimental procedure

The participants were equipped with reflective markers and performed multiple gait trials with their own casual shoes on a 10 m long instrumented walkway (Bennour et al., 2018). A motion capture system (Vicon, Oxford, UK) and floor-embedded forceplates (Kistler, Winterthur, CH) were used to measure the kinetics of the right knee (KAM_{first} and KFM_{first}) and the spatio-temporal parameters (FPA, SW, SL and walking speed) during one cycle in the middle of the trials following common methods (Bennour et al., 2018; Favre et al., 2009; Zabala et al., 2013). In addition, two projectors were used to display instruction footprints on the floor that could be modified in terms of FPA, SW and SL (Figure 9) (Bennour et al., 2018).

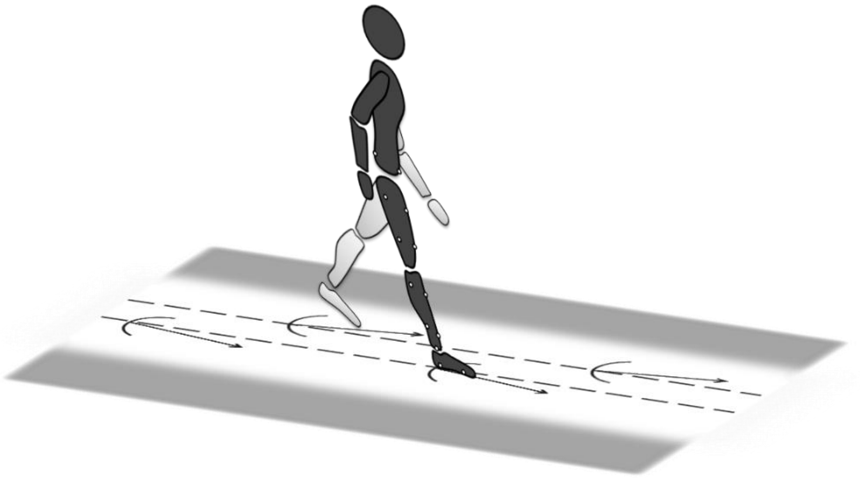


Figure 9: *Illustration of the experimental setup with a participant walking on ground-projected instruction footprints.*

Gait was recorded in two phases. During the first phase, five trials at self-selected normal walking speed were collected. No footprint instructions were provided to the participants at this point. The five trials were then analyzed to determine the normal FPA, SW, SL and walking speed of the participants. Next, instruction footprints corresponding to the normal FPA, SW and SL of the participants were displayed on the floor and time was given to the participants to practice walking on the projected footprints (Edd et al., 2020a). To help the participants stepping following the instruction footprints, each time a trial was completed during the practice period, the foot placements of the participants were displayed on top of the instruction footprints (Bennour et al., 2018). The participants needed about 5 minutes and 10 trials to get used to walking on the projected footprints. The second phase of gait recording started after the participants felt confident walking on footprint instructions. During this phase, the participants were asked to walk on modified footprint instructions. Twelve modifications with respect to normal gait were recorded in the following order for all the participants: -20, -13, -6 and +10° in FPA; +0.20, +0.13, +0.06 and -0.10 m in SW; and -0.20, -0.13, -0.06 and +0.10 m in SL. These modifications were defined based on pilot data and prior publications to span the modifications susceptible to trigger KAM_{first} reductions of 10% or more without causing discomfort (Bennour et al., 2018; Cheung et al., 2018; Favre et al., 2016; Richards et al., 2018a). The modifications were applied to both, left and right, footprints. The participants could practice each modification as many times as they wanted, before the recording of three trials. When the participants were unsatisfied with a trial, it was recorded again. The participants were asked to maintain their normal walking speed during the trials with modifications, and trials with speed differing from the normal speed by more than 10% were repeated. After each modification, a single-answer multiple choice question was asked to the participants to classify the modification as either “I could walk like this in everyday living” or “I am not willing nor able to walk like this in everyday living”.

III.2.3 Statistical analysis

For each participant, the $\mathrm{KAM}_{\mathrm{first}}$ and $\mathrm{KFM}_{\mathrm{first}}$ measures were averaged per walking condition (normal and 12 modifications) and these average values were used to calculate the relative changes induced by the modifications with respect to the normal condition. Then, for each participant and each modification, it was determined if the dual kinetic change of $\mathrm{KAM}_{\mathrm{first}}$ reduction by 10% or more without $\mathrm{KFM}_{\mathrm{first}}$ increase was achieved and descriptive statistics was used to report these results. Additionally, bilateral Wilcoxon signed rank tests were performed to determine if the overall change in $\mathrm{KAM}_{\mathrm{first}}$ for the group of participants was different from a decrease of 10%. Similar tests were done to determine if the changes in $\mathrm{KFM}_{\mathrm{first}}$ differed from zero. Significance level was set a priori at 5% for these tests. Data processing and statistical analyses were done with MATLAB version R2018b (MathWorks, Natick, MA).

III.3 Results

When walking normally (without instructions), the participants walked at a median {interquartile range; IQR} speed of 1.55 {0.20} m/s, with FPA of 4.7 {5.3}°, SW of 0.10 {0.02} m and SL of 1.62 {0.14} m. The average ± standard deviation differences between instructions and actual footprints during the 396 trials recorded with modifications were -0.3 ± 3.2° for FPA, 0.001 ± 0.023 m for SW, and 0.007 ± 0.019 m for SL.

Individual analyses showed that the 11 participants could reduce their KAM_{first} by 10% or more without increasing their KFM_{first} with the modifications tested in this study (Table 5). For nine of them, this dual kinetic change could be achieved with modifications classified as possible in everyday living. Modifications leading to the dual kinetic change varied among participants. In fact, with the modifications participants could adopt in everyday living, the dual kinetic change could be achieved for seven participants by modifying FPA (#2, #3, #5, #6, #7, #9 and #11) or SL (#1, #2, #6, #7, #9, #10 and #11) and for three participants by modifying SW (#1, #2 and #10). The averaged KAM and KFM curves of the participants achieving the dual kinetic change are presented separately for each modification in Figure 10.

Table 5: *Feasibility of reducing the first peak knee adduction moment (KAM_{first}) by 10% or more, without increasing the first peak knee flexion moment (KFM_{first}).*

Participant	**Foot progression angle modification, °**				**Step width modification, m**				**Stride length modification, m**			
	-20	**-13**	**-6**	**+10**	**-0.10**	**+0.06**	**+0.13**	**+0.20**	**-0.20**	**-0.13**	**-0.06**	**+0.10**
1					**x**				x	**x**		
2	(x)	x	**x**		**x**				x	**x**		
3		**x**										
4	(x)											
5			**x**	x								
6	(x)	**x**							**x**			
7	x	x	**x**						x	x	**x**	
8	(x)	(x)										
9		**x**							x	**x**		
10					(x)	**x**			x	**x**		
11	(x)	**x**									**x**	x
Number of participants achieving the dual change	1 (5)	6 (1)	3	1	2 (1)	1	0	0	6	5	2	1

Modifications achieving the dual kinetic change are marked by an "x". For sake of clarity, modifications not achieving the dual kinetic change are let blank. Marks into brackets, "(x)", indicate modifications that the participants classified as "not be willing or able to adopt in everyday living". For each modification parameter, the smallest absolute amplitude of modification achieving the dual kinetic change and classified as possible in everyday living is marked in bold, "**x**". The actual KAM_{first} and KFM_{first} changes for the gait modifications in bold are reported in Table 6.

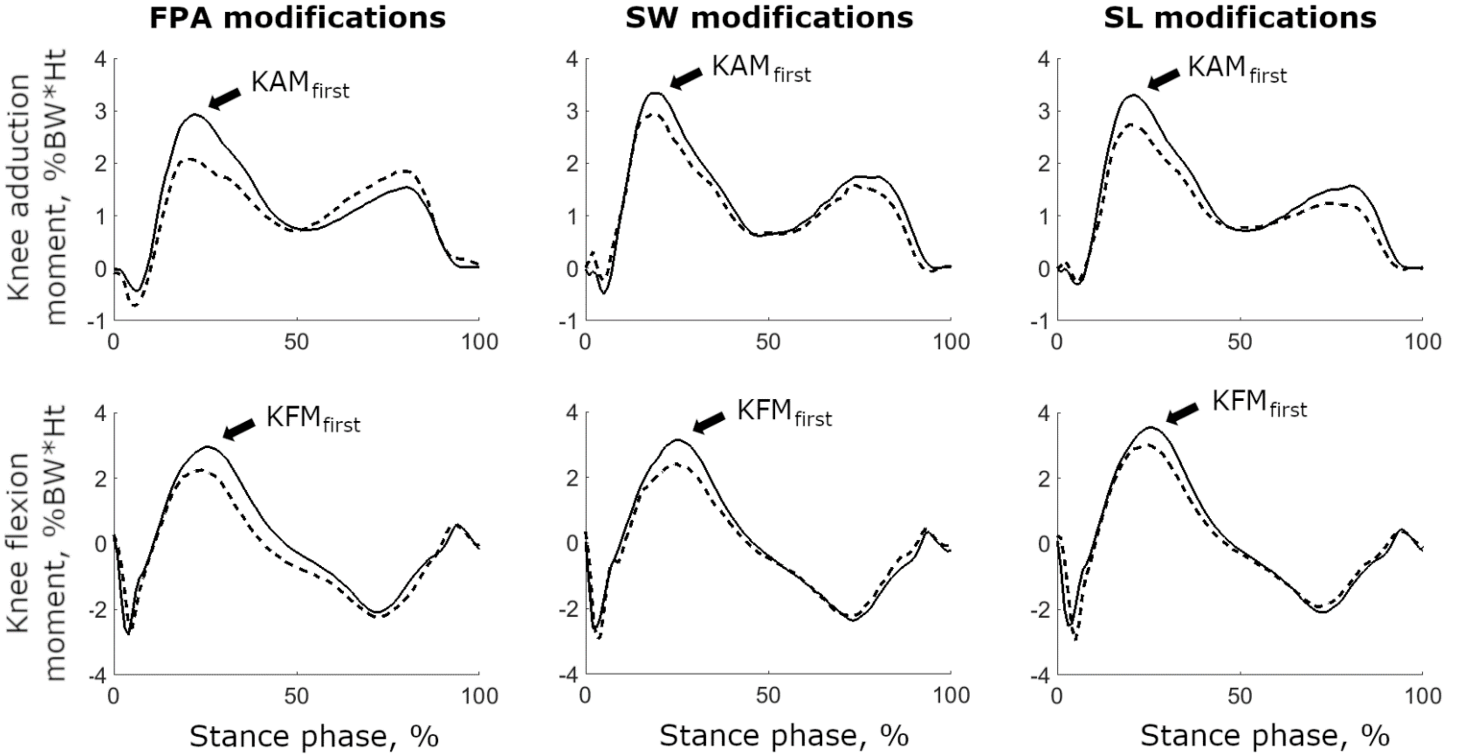


Figure 10: *Average knee adduction moment (KAM, top) and knee flexion moment (KFM, bottom) for the participants achieving the dual kinetic change with modifications in foot progression angle (FPA, left), step width (SW, middle), and stride length (SL, right). Continuous lines correspond to the normal walking trials (without modification), and dash lines to the walking trials with the modifications of interest. The arrows indicates the peaks of interest (KAM$_{first}$ and KFM$_{first}$).*

When looking at the results from the participant stand points, one participant (#2) could achieve the dual kinetic change by modifications in any of the three footprint parameters, six participants (#1, #6,#3, #9, #10 and #11) could achieve it by modifications in one or two footprint parameters, and two participants (#3 and #6) could achieve it only with FPA modifications (Figure 11).

Among the seven participants who achieved the dual kinetic change with FPA modifications classified as possible in everyday living, the smallest absolute amplitudes of modification were toeing-in by 6° for three participants and toeing-in by 12° for the remaining four participants (Table 5). These modifications resulted in a median {IQR} KAM_{first} reduction of 19.4 {10.1}% and a median KFM_{first} reduction of 16.1 {7.4}% (Table 6).

Regarding the three participants achieving the dual kinetic change with modifications in SW classified as possible in everyday living, the smallest absolute amplitudes of modification were SW narrowing by 0.1 m for two participants and SW widening by 0.06 m for the remaining participant (Table 5). These modifications induced in median KAM_{first} and KFM_{first} reductions of 12.0 {1.4}% and 23.5 {17.2}% (Table 6).

For the seven participants who achieved the dual kinetic change with SL modifications classified as possible in everyday living, the smallest absolutes amplitudes of modification were SL shortening by 0.06 m for two participants, SL shortening by 0.13 m for four participants, and SL shortening by 0.2 m for the remaining participant (Table 5). These modifications resulted in median KAM_{first} and KFM_{first} reductions of 16.3 {4.2}% and 9.3 {21.7}% (Table 6).

Table 6: *Changes in first peak of knee adduction moment (KAM_{first}) and first peak of knee flexion moment (KFM_{first}) for the smallest absolute amplitude of modification achieving the dual kinetic change and classified as possible in everyday living (modifications in bold in Table 5).*

Participant	**Foot progression angle modification**		**Step width modification**		**Stride length modification**	
	KAM_{first}	**KFM_{first}**	**KAM_{first}**	**KFM_{first}**	**KAM_{first}**	**KFM_{first}**
1			-12.0	-1.0	-15.2	-16.9
2	-15.7	-29.2	-10.5	-35.4	-17.8	-32.7
3	-17.8	-12.4				
4						
5	-19.4	-12.9				
6	-42.7	-15.2			-23.6	-2.1
7	-13.9	-24.2			-17.9	-0.4
8						
9	-25.2	-18.5			-12.1	-33.3
10			-13.4	-23.5	-11.2	-4.1
11	-28.4	-16.1			-16.3	-9.3
Median { IQR} changes	-19.4 {10.1}	-16.1 {7.4}	-12.0 {1.4}	-23.5 {17.2}	-16.3 {4.2}	-9.3 {21.7}

Changes are reported in percent of the values measured during the normal walking condition. The median and interquartile range {IQR} changes of the participants achieving the dual change are reported at the bottom of the table. Blank cells indicate modifications that did not achieve the dual kinetic change in a manner classified as possible in everyday living, whatever their amplitudes, for the given participant.

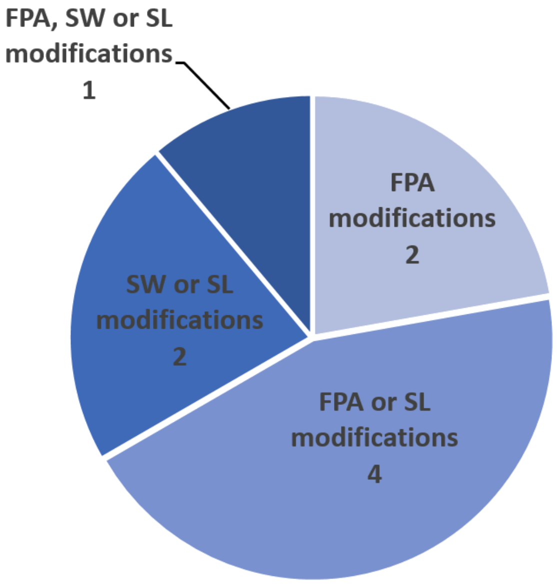


Figure 11: *Distribution, among participants, of the footprint modifications that allowed achieving the dual kinetic change while being classified as possible in everyday living. The number in each slice corresponds to the number of participants who achieved the dual kinetic change with modifications in foot progression angle (FPA), step width (SW) and/or stride length (SL).*

Analyzing the kinetic changes of the group of participants indicated that seven of the 12 modifications (FPA-6, SW-0.1, SW+0.06, SW+0.13, SL-0.2, SL-0.13 and SL-0.06) induced changes in KAM_{first} not statistically significantly different from a reduction of 10% and two modifications (FPA-20 and FPA-13) reduced the KAM_{first} by more than 10% (Figure 12, upper graph). None of these nine modifications induced a significant group increase in KFM_{first}, with two of them (FPA-13 and SW-0.1) even reducing the KFM_{first} (Figure 12, lower graph).

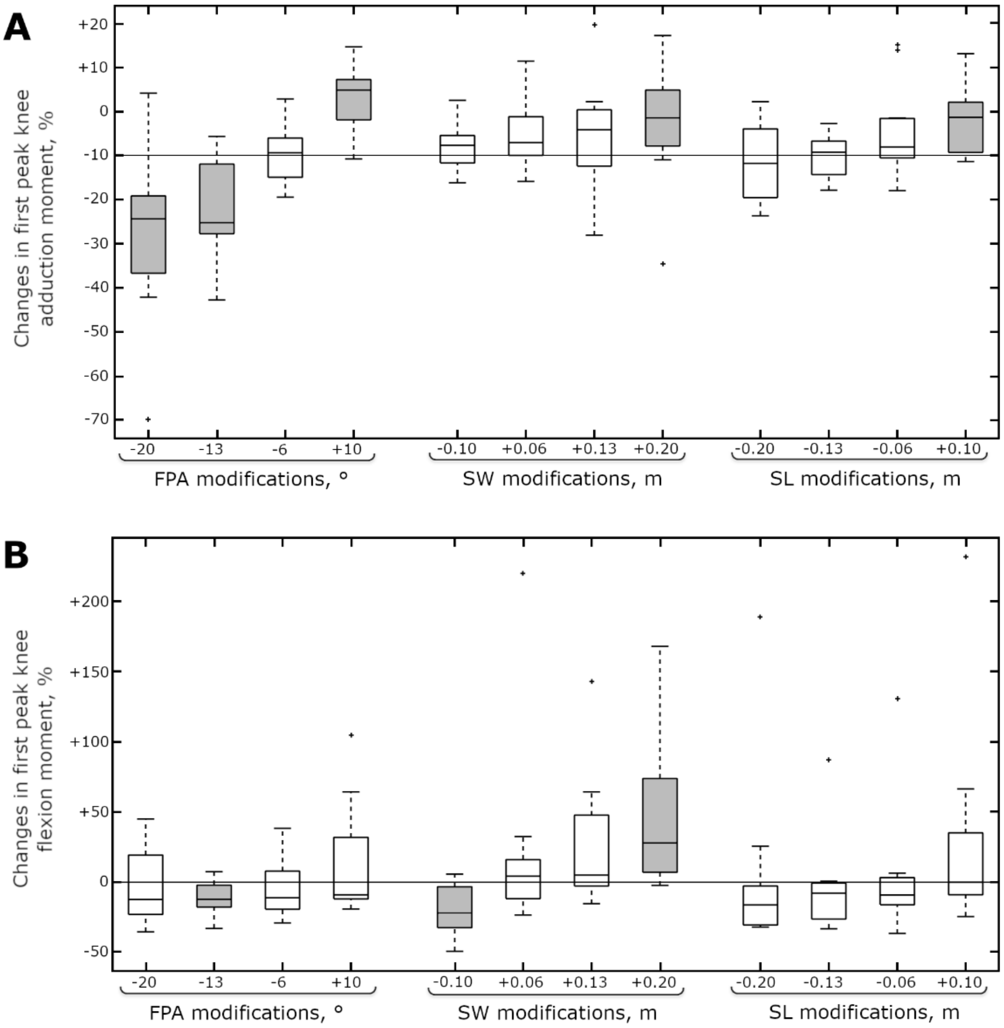


Figure 12: *Boxplots of the changes in (A, upper) first peak of knee adduction moment (KAM_{first}) and (B, lower) first peak of knee flexion moment (KFM_{first}) induced by foot progression angle (FPA), step width (SW) or stride length (SL) modifications. Changes are expressed in percent of the values measured during the normal walking condition. Shaded boxplots represent modifications inducing changes significantly different (smaller or larger) from -10% in KAM_{first} or from 0% in KFM_{first} ($p<0.05$).*

III.4 Discussion

This study showed that the dual kinetic change, consisting in reducing the KAM_{first} by 10% or more without increasing the KFM_{first}, is individually feasible through modifications in footprint parameters. This result is important because it suggests that gait retraining for medial knee OA could aim for more specific kinetic changes than simply KAM_{first} reduction, as it has been the case so far. This result reveals even more important when we consider that medial knee OA literature recommends no KFM_{first} increase (Manal et al., 2015: Walter et al., 2010) and that prior gait retraining studies clearly indicate that the KFM_{first} can increase if no enough attention is paid to it (Table 4). Consequently, since the dual kinetic change is feasible, future gait retraining intervention for medial knee OA should probably target a reduction in KAM_{first} without increase in KFM_{first} for each participant.

The second hypothesis was also supported, with seven out of the 11 participants being able to achieve the dual kinetic change through SL modifications. This result is also substantial, as SL modifications were as effective as FPA modifications and twice as effective as SW modifications, when considering the modifications classified as suitable for everyday living. Although comparing modification parameters is tricky because testing modifications of other amplitudes could have changed the results, the value of considering SL modifications in medial knee OA gait retraining appears undeniable both for their capacity to change knee kinetics and their acceptability potential. The dual kinetic change was always achieved by shortening SL. Since walking speed was maintained during the experiment, these SL modifications could also be seen as cadence increases (Grieve and Gear, 1966). This relationship could reveal very useful in the future, particularly for routine rehabilitation, as cadence modifications could be easy to initiate (Nijs et al., 2020) and wearable devices already exist to measure walking speed and cadence (Fasel et al., 2017). Moreover, it is worth mentioning that, while modifying SL is novel in knee OA gait retraining, SL modifications have already been considered for other applications, such as running injuries (Schubert et al., 2014).

The footprint modifications to achieve the dual kinetic change differed among participants. This observation well agrees with prior research that already reported participant-specific changes in knee kinetics in response to footprint modifications (Favre et al., 2016; Uhlrich et al., 2018). Therefore, widening the range of modifications that could be used for medial knee OA by acting on SL, in addition to FPA and SW, could be valuable. In the present study, FPA, SW and SL were modified in isolation. However, in the future, combining them could improve the retraining procedure. For example, instead of modifying one or another parameter by a large amplitude, it could be interesting to modify two or three parameters by smaller amplitudes (Shull et al., 2011). In addition to personalizing the intervention, further research will also be necessary to improve our understanding of the variability among individuals, as did the previous chapter on LWI that reported an association between the natural FPA and the KAM changes in response to the intervention.

Another originality of this study is the use of augmented reality to help the participants modifying their footprint parameters in the framework of knee OA gait retraining. Previously, gait retraining systems for knee OA based on footprint modifications have all been designed using biofeedback, either visual, haptic or auditory (Table 4). With the biofeedback approach, the modifications are not demonstrated to the participants; participants have to modify their walking patterns based on signals dissociated from their physical meaning. While biofeedback could be beneficial during the learning process taking place once the modifications for a given individual have been identified (Richards et al., 2018c), this approach could complicate the identification of the individual modifications necessary to induce the biomechanical changes because concurrent modifications in FPA, SW and SL could be tedious to achieve with biofeedback (Chen et al., 2017). The augmented-reality approach used in the present study is therefore promising for knee OA gait retraining because FPA, SW and SL modifications can be demonstrated and easily achieved by the participants. Gait retraining for knee OA is still at an early stage and further works will be necessary to improve the systems and protocols, as well as determining which strategies are best for which patients.

The present data also highlight the ambiguity that group statistics can generate when reporting biomechanical changes after gait retraining. For example, as a group of participants, the modification consisting in decreasing the FPA by 13° statistically significantly reduced the KAM_{first} by more than 10% and statistically significantly reduced the KFM_{first}. This modification therefore appears as plainly achieving the dual kinetic change. However, only seven participants (64% of the study population) actually achieved the dual kinetic change with this modification. The other participants either did not achieve 10% KAM_{first} decrease (one participant) or had KFM_{first} increases (three participants). This ambiguity between the changes as a group and as individuals could be prejudicial when interpreting the clinical improvements after a gait retraining program because, as with the present example, reporting that the targeted biomechanical changes was achieved for the group does not mean that every participant individually achieved the target. In consequence, future gait retraining studies are encouraged to report the percentage of participants reaching the target and, when appropriate, to analyze separately the subgroup of participants that achieved the target and the subgroup that did not.

This study has some limitations that should be discussed. First, while it is extremely encouraging that the 11 participants could achieve the dual kinetic change with at least one of the modifications, this result should not be over interpreted as: "every individual can achieve the dual kinetic change". The present study aimed to test a limited number of individuals with a limited number of predefined modifications to characterize the feasibility of the dual kinetic change. Now, that the feasibility has been demonstrated, further studies with larger sample size and personalized footprint modifications will be necessary to define the percentage, and maybe the profile, of the individuals capable of achieving and maintaining the dual kinetic change. For example, it is interesting to note that, while all the participants achieved the dual kinetic change, about a fifth said that they would not be willing nor able to walk with the modification(s) inducing this change in everyday living. Again, although instructive, this percentage should be interpreted with caution as testing other modifications or other individuals could have led to a different percentage.

Although the dual kinetic change was selected conservatively based on prior literature (Butler et al., 2007; Manal et al., 2015; Richards et al., 2018a; Shull et al., 2013a; Walter et al., 2010), it constitutes a second limitation, as no clear target for KAM_{first} and KFM_{first} changes has yet been defined for medial knee OA. Nevertheless, adjusting the KAM_{first} and KFM_{first} targets would not modify the main findings of this study.

Asymptomatic participants were tested to facilitate the recording of numerous trials without pain or fatigue. This constitutes another limitation, and future studies are therefore necessary to confirm the results in patients with medial knee OA. Finally, longitudinal studies will also be needed to evaluate the effects learning and long-term practice of the footprint modifications could have on knee kinetics.

III.5 Conclusion

In conclusion, this study demonstrated the feasibility of reducing the KAM_{first} by 10% or more without increasing the KFM_{first} individually through modifications in footprint parameters. This suggests that more specific changes than simply KAM_{first} reductions can be targeted in footprint-based gait retraining. The results also confirmed the need for subject-specific retraining approaches, where the footprint parameter modifications are defined individually for each patient. Additionally, the study showed that the dual kinetic change could be achieved with SL modifications, therefore widening the range of modifications that could be used for gait retraining of medial knee OA. Finally, this work introduced a new, augmented-reality, approach to help the modification of footprint parameters in the framework of knee OA rehabilitation.

IV Stride length modification

The following chapter presents the study "*Effects of stride length reductions on ambulatory knee kinetics in patients with medial knee osteoarthritis*" which in preparation for publication in a brief report format. This study was done in collaboration with Stanford University.

IV.1 Introduction

The previous chapter (Chapter III) showed that SL reduction can help a portion of healthy individuals to achieve the dual change. Moreover, another recent study showed that walking with SL shorter by 0.14 m while maintaining the same walking speed (a modification equivalent to a cadence increase) induces KAM_{first} group decrease in healthy subjects (Edd et al., 2020b). Gait retraining is known to be highly patient-specific, therefore increasing the number of parameters that could be modified could reveal very useful to find enhanced walking patterns for a larger proportion of patients (Favre et al., 2016; Uhlrich et al., 2018). Therefore, there is an interest to characterize the effect of SL reductions on the KAM_{first} of medial knee OA patients.

Although gait retraining for medial knee OA started with the sole objective of decreasing the KAM_{first}, more recently, attention has been payed to KFM_{first} (Edd et al., 2020b; Ulrich et al., 2020b). In fact, the KFM_{first} was related to disease progression (Chehab et al., 2014) and increase in KFM_{first} was suggested to counteract the benefits of reducing the KAM_{first} (Manal et al., 2015; Ulrich et al., 2020b; Walter et al., 2010). The $KAM_{impulse}$ is also particularly relevant for the present study, since it has been associated with disease progression as well (Chang et al., 2015). Consequently, for a better understanding of SL reductions in patients with medial knee OA, there is an additional need to assess the effects on the KFM_{first} and $KAM_{impulse}$.

This study aimed at providing first insights into the effects of SL reductions, at constant walking speed, on the KAM_{first}, $KAM_{impulse}$ and KFM_{first} in patients with medial knee OA. Following Edd and colleagues (Edd et al., 2020b), reductions of 0.10 and 0.15 m were tested. Furthermore, in accordance with prior observations that gait modifications could induce patient-specific changes, the effects were characterized both for a group of patients and at the individual level (Uhlrich et al., 2018, Ulrich et al., 2020b).

IV.2 Methods

IV.2.1 Participants

Fifteen patients (5 women) with medial knee OA were enrolled in this IRB-approved study after providing written informed consent. Inclusion criteria were unilateral or bilateral medial knee OA of Kellgren-Lawrence grades I to III (Kellgren and Lawrence 1957) and age between 20 and 70 years old. Individuals with a BMI over 30 kg/m^2, a history of lower limbs surgery, neurological disorders or using walking aids were excluded. Participants were of mean (± SD) age, height, and weight of 55.5 ± 8.7 years old, 1.74 ± 0.12 m, and 74.5 ± 15.3 kg, respectively. A previous study in healthy individuals reported KAM$_{\text{first}}$ changes of large effect size (Cohen’s d of 0.85) with 0.14 m SL reductions (Edd et al., 2020b). A sample size calculation based on this prior observation indicated a minimum of 14 participants to detect changes between the normal and the two shorter SL walking conditions, with a power of 80% and an alpha level of 5% (G*Power, DE).

IV.2.2 Experimental procedure

Patients performed 10m-long walking trials in a laboratory equipped with a motion capture system (Vicon, UK) and floor-embedded force plates (Kistler, CH) recording synchronously at 120 and 1200 Hz, respectively (Bennour et al., 2018). Two projectors were used to display target footprints on the ground (Bennour et al., 2018). As explained below, this served to induce SL modifications. Following a standard protocol (Chehab et al., 2017), reflective markers were fixed on the patients and a standing reference pose was captured before the gait trials. The $\mathrm{KAM}_{\mathrm{first}}$, $\mathrm{KAM}_{\mathrm{impulse}}$ and $\mathrm{KFM}_{\mathrm{first}}$ were calculated following a common inverse dynamics procedure (Zabala et al., 2013) and expressed as external moments normalized to percent bodyweight and height (%BW×Ht). Footprint parameters, including SL, SW and FPA, as well as walking speed were also computed according to previously described methods (Bennour et al., 2018). All biomechanical calculations were done using the software application BioMove (Stanford, US).

The gait protocol first included the capture of five trials at self-selected normal walking speed without footprint displayed on the floor. The average footprint parameters and speed of these five trials defined the normal footprint parameters and speed for the rest of the experiment. Then, target footprints were displayed on the ground and patients were given time to get used walking on it (Bennour et al., 2018). Once patients felt confident walking according to the target footprints, footprints corresponding to their normal footprint parameters were displayed on the ground and three trials were recorded. Next, the target footprints were modified to induce SL reductions of 0.10 and 0.15

m bilaterally and three trials were recorded for each condition. Target footprints remained at the patients' normal SW and FPA. Patients were free to practice each footprint configuration as many times as they wanted and trials they felt have been improperly executed were recorded again. Patients were asked to maintain their normal walking speed during the trials with footprint displayed on the floor, and trials with speed differing by more than 10% from the normal speed were repeated.

IV.2.3 Statistics

The KAM_{first}, $KAM_{impulse}$ and KFM_{first} were averaged over the three trials recorded for each SL condition in order to have one value per kinetic measure, SL condition and patient. For each kinetic measure, paired t-tests were performed to compare the SL reductions to the normal condition. Paired t-test were also performed, secondarily, to compare both SL reductions. Descriptive statistics were used to report the effects of SL reductions at the patient level. Data were tested for normality using Kolmogorov-Smirnov tests before using parametric statistics. Significance level was set a-priori at $p < 0.05$, with a Bonferroni correction for the testing of two SL modifications.

IV.3 Results

The average (± SD) walking speed and SL in the normal walking condition were 1.42 ± 0.21 m/s and 1.48 ± 0.17 m, respectively. When patients were asked to reduce their SL by 0.10 and 0.15 m, they performed the gait modifications with an accuracy of 0.004 m and a precision of 0.022 m. Walking with reduced SL induced statistically significant $KAM_{impulse}$ decreases of 6.7 ± 13.0 % ($p = 0.017$) for 0.10 m reduction and of 8.2 ± 14.6 % ($p = 0.005$) for 0.15 m reduction (Table 7). No significant change was observed in the KAM_{first} and KFM_{first} with either SL reductions ($p \geq 0.075$). Additionally, no significant change was found between the two reduced SL conditions, neither in the KAM_{first} ($p = 0.43$), $KAM_{impulse}$ ($p = 0.22$) nor KFM_{first} ($p = 0.62$).

Individual analysis of the responses indicated that 67% (10 out of 15) and 73% (11 out of 15) of the patients decreased their KAM_{first} with SL reductions of 0.10 and 0.15 m, respectively (Figure 13). Similarly, 0.10 and 0.15 m reductions in SL resulted in a $KAM_{impulse}$ decrease in 67 % (10 out of 15) and 80 % (12 out of 15) of the patients, respectively. A simultaneous decrease in the KAM_{first} and the $KAM_{impulse}$ was observed in 33% (5 out of 15) of the patients with SL reduction of 0.10 m and in 60% (9 out of 15) of the patients with 0.15 m reduction. Among the patients decreasing simultaneously the KAM_{first} and the $KAM_{impulse}$, 40 %

(2 out of 5) and 56% (5 out of 9) also decreased the KFM_{first} with 0.10 and 0.15 m SL reductions, respectively.

Table 7: *Kinetic measures of the 15 patients*

		Absolute values of the kinetic measures	Relative changes with respect to the normal SL condition	
		Mean ± SD	**Mean ± SD**	**P-value**
Normal SL	KAM_{first}	3.21 ± 0.80 %BW*Ht	n/a	
	$KAM_{impulse}$	0.99 ± 0.34 %BW*Ht*s	n/a	
	KFM_{first}	2.85 ± 1.78 %BW*Ht	n/a	
SL reduced by 0.10 m	KAM_{first}	3.06 ± 0.86 %BW*Ht	-5.12 ± 9.53 %	p = 0.095
	$KAM_{impulse}$	0.92 ± 0.34 %BW*Ht*s	**-6.67 ± 12.96 %**	**p = 0.017**
	KFM_{first}	2.71 ± 1.92 %BW*Ht	-5.42 ± 26.08 %	p = 0.41
SL reduced by 0.15 m	KAM_{first}	3.02 ± 0.79 %BW*Ht	-5.37 ± 11.15 %	p = 0.075
	$KAM_{impulse}$	0.90 ± 0.33 %BW*Ht*s	**-8.17 ± 14.59** %	**p = 0.005**
	KFM_{first}	2.63 ± 1.74 %BW*Ht	-9.62 ± 27.71 %	p = 0.24

Bold values indicate statistically significant changes compared to the normal stride length (SL) walking condition ($p<0.025$). KAM: knee adduction moment; KFM: knee flexion moment.

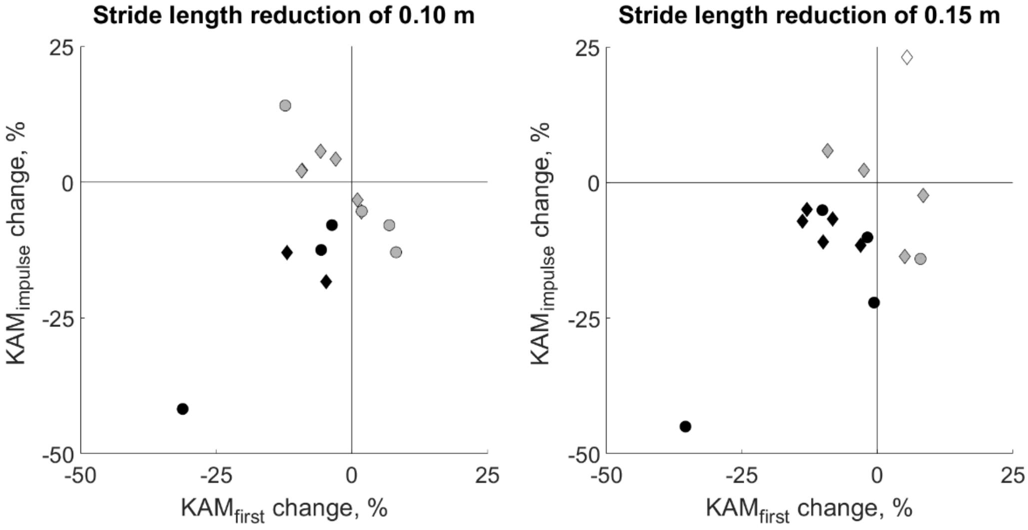


Figure 13: *Graphical representation of the individual kinetic changes with stride length reductions of 0.10 (left) and 0.15 (right) m. Each mark corresponds to one patient. Changes in the first peak and the impulse of the knee adduction moment (KAM$_{first}$ and KAM$_{impulse}$) are reported along the horizontal and vertical axes, respectively, while changes in the first peak of the knee flexion moment (KFM$_{first}$) are indicated by symbols (diamonds: KFM$_{first}$ decreases, circles: KFM$_{first}$ increases). Black marks indicate patients with a decrease in both KAM$_{first}$ and KAM$_{impulse}$, grey marks patients with a decrease in KAM$_{first}$ or KAM$_{impulse}$, and white marks patients with an increase in both KAM$_{first}$ and KAM$_{impulse}$.*

IV.4 Discussion

This first study to assess SL modifications in patients with medial knee OA confirmed the potential of such modifications to enhance mechanical loading at the knee in this patient population. Reducing SL induced statistically significant decreases in the $KAM_{impulse}$ at the group level, and all patients decreased at least one KAM measure when walking with shorter SL. Moreover, for more than half of the participants, one or both SL reductions decreased both the KAM_{first} and the $KAM_{impulse}$. Forty percent of the patients even reduced the KAM_{first} and the $KAM_{impulse}$ without increasing the KFM_{first}, with at least one of the SL reductions. Now that this study showed the potential of SL modifications in the rehabilitation of medial knee OA, further research will be required to characterize the dose-response relationships. In this regard, it is worth mentioning that while improvement in clinical outcomes have been reported following gait interventions primarily aiming at reducing the KAM_{first} (Cheung et al., 2018; Felson et al., 2019; Richards et al., 2018a; Shull et al., 2013a), there is no guideline regarding the kinetic changes that should be sought. For instance, regarding the KAM_{first}, prior works aimed for decreases of any magnitudes to decreases of at least 10% (Ulrich et al., 2020b).

The possibility of enhancing knee kinetics through SL modifications is especially appealing because SL modifications, or equivalently cadence modifications, could be easily taught to the patients. For example, a simple smartphone app measuring walking speed with the built-in GPS and producing sounds or vibrations at the desired cadence could be a simple option to help patients learn and maintain new SL (cadence).

Patients with medial knee OA followed the footprint instructions on the floor with comparable accuracy and precision than previously reported for healthy individuals (Edd et al., 2020a). This finding is also very encouraging as it supports the use of augmented reality for gait retraining of patients with knee OA.

The results of this study also highlighted the necessity of analyzing individual responses, as group statistics alone could be misleading in applications with large inter-patient variability, like in medial knee OA gait retraining. For example, the absence of statistically significant decrease in the KAM_{first} for the group of patients could mask the potential of SL reductions, which is far to be negligible with KAM_{first} decreases in two third of the patients.

This study has a few limitations. First, since it aimed at providing insights into the effects of SL reductions in medial knee OA, it tested a limited number of SL modifications on a relatively small population. Additional studies with larger sample sizes and ranges of modifications will be necessary. Second, longitudinal works will also be required to determine the long-term effects of SL reductions on ambulatory mechanics as well as on clinical outcomes. Finally, the possibility to combine SL modifications with modifications in other parameters, such as foot progression angle or step width, will need to be investigated in the future.

IV.5 Conclusion

This study confirmed the potential of SL reductions to enhance the mechanical loading at the knee in patients with medial OA. While further research will be necessary notably to determine the dose-response relationships and the long-term effects, this finding is particularly encouraging because simple solutions could be developed to help patients walk with modified SL.

V Knee moments and severity index

The following chapter presents the study "*Comprehensive evaluation of ambulatory knee moment in medial knee osteoarthritis*" which in preparation for publication. This study is a collaboration with Stanford University.

V.1 Introduction

The maximum values (peaks) of the knee adduction (KAM_{first}) and flexion (KFM_{first}) moments during the first half of stance have been the main focused of the literature as these knee moment parameters have been related to disease severity and progression (Chehab et al., 2014; Kean et al., 2012; Erhart-Hledik et al., 2015). Gait modifications based on these parameters showed improvement in clinical outcomes (Cheung et al., 2018; Richards et al., 2018a). These encouraging results motivate further efforts notably toward a more comprehensive characterization of ambulatory knee moments with medial knee OA. Indeed, the large majority of previous studies focused on the KAM_{first} and KFM_{first}, and little is known about the seven other parameters usually used for a full description of knee moments during walking, as illustrated in (Figure 14)

(Benedetti et al., 1998; Chehab et al., 2017). While analyzing the KAM_{first} and KFM_{first} was well motivated in prior works, the disregard of the other parameters was rarely justified. This is even more intriguing as there is evidence scattered in literature, from studies with heterogeneous designs, that the other parameters vary with medial knee OA (Astephen et al., 2008; Baert et al., 2013; Huang et al., 2008; Mills et al., 2013; Thorp et al., 2006). Consequently, there is a need for additional studies analyzing all nine usual parameters over the full range of disease severity to establish a global picture of ambulatory knee moments with respect to medial knee OA severity. Such complete studies would also provide a basis to consolidate prior observations dispersed in literature.

While considering more parameters will enhance the description of knee moments, having a larger number of parameters to deal with could render the analysis and use of knee kinetics more complex. For example, assessing the effect of a treatment could become difficult when the results diverge among parameters. The situation could be even more arduous with personalized interventions, such as insoles or gait retraining (Reeves and Bowling 2011), where it could be impossible to find solutions fulfilling modifications on several parameters (Edd et al., 2020b; Ulrich et al., 2020b). In fact, the increase in complexity when describing knee moments with a higher number of parameters could well be the main reason why most of prior works focused on the KAM_{first} and

KFM_{first}. Therefore, to benefit from a more complete characterization of knee moment without increasing the complexity-of-use, there is a need to combine the parameters into indices associated with specific features of the disease, such as severity. Prior works have already shown the relevance of combining knee moment parameters. For instance, the total joint moment (TJM) combination was introduced to assess the moments at particular time points without consideration for the anatomical planes (Zabala et al., 2013) and the medial contact force (MCF_{first}) parameter to estimate the peak force applied on the medial tibial plateau during the first half of stance (Manal et al., 2015; Walter et al., 2010).

This study first aimed at characterizing the nine usual parameters of knee moments during walking with respect to medial knee OA severity, through comparison and correlation analyses. A second objective was to assess the possibility of developing a severity index combining all nine parameters.

V.2 Methods

V.2.1 Study population

For this study, the database of the Stanford BioMotion lab was screened for individuals aged 40 years old or older, with a body mass index (BMI) lower than 35 kg/m^2, and who got their gait analyzed following a standard procedure (see below) at the same time they were evaluated for symptoms and imaging signs of knee OA. From those, non-OA individuals, defined as individuals without self-reported pain or significant injury in the lower limb or lower back and without evidence of cartilage loss, osteophytes, subchondral bone marrow lesions, bone attrition, or meniscal pathology (subluxation, maceration, degeneration) in any knees, were selected for the present study (Hunter et al., 2011). Structural alterations of the knees were determined based on magnetic resonance imaging exams, including a three-dimensional fat-suppressed spoiled-gradient recalled echo sequence (3D SPGR; plane= sagittal, TR = 50 ms, TE = 7 ms, flip angle = 30°, field of view = 140 × 140 mm2, slice thickness = 1.5 mm, number of slices = 60, acquisition matrix = 256 × 256) and a fat-suppressed proton density fast spin echo sequence (PDFSE; plane = sagittal, TR = 4000 ms, TE = 13 ms, flip angle = 90°, field of view = 140 × 140 mm2, slice thickness = 2.5 mm, number of slices = 33, acquisition matrix = 256 × 256), using a 1.5T machine (GE Medical Systems, Milwaukee, WI).

Individuals with medial compartment knee OA were also selected for the present study. These persons were characterized by persistent self-reported pain and radiographic confirmation of the presence of primarily medial compartment OA in at least one knee, no primarily lateral or trochlea OA or arthroplasty in any knees, Kellgren and Lawrence (K/L) grading of both knees (Kellgren and Lawrence 1957), no diagnosis or symptoms of OA in other lower extremity joints, no serious ankle, hip or back injury or surgery, no gout or recurrent pseudogout, and no use of ambulatory aids. All individuals selected for the present study got their data recorded in the framework of researches approved by the internal review board of Stanford University and gave their consent for further analysis of their data. Data from the most recent testing were used for individuals with multiple records in the database.

In total, 98 individuals (43 males) were available for this study. They were of mean (± standard deviation) age, height and weight of 58.7 ± 9.2 years old, 1.69 ± 0.09 m, and 76.9 ± 14.5 kg, respectively. One knee per individual was analyzed. For non-OA individuals, the study knee was randomly chosen, while the knee with the highest K/L grade was analyzed for OA individuals. In case of equal K/L grade for both knees, the study knee was randomly chosen. For comparison analyses, knees with K/L grade of I or II were considered mild OA and knees with K/L grade of III or IV severe OA, resulting in three severity groups of 22 to 38 knees each (Table 8). There was no statistically significant demographic difference among the severity groups, except for age, with younger individuals in the non-OA group compared to the two other groups ($p < 0.001$). A sample size calculation based on the large to stronger effect sizes reported in prior studies comparing ambulatory knee moments with respect to OA severity (Cohen's d between 0.8 and 1.2) (Astephen et al., 2008; Mills et al., 2013) suggested groups of 15 to 30 knees for the present study, considering a power of 80% and a Bonferroni-corrected alpha level of 5% (G*Power, DE).

Table 8: *Characteristics of the three severity groups.*

	Non-OA n = 22	**Mild OA** n = 38	**Severe OA** n = 38
Gender (number)	W: 13, M: 9	W: 20, M: 18	W: 22, M: 16
KL grade (number)		I: 26, II: 12	III: 19, IV: 19
Age (years)*	50.5 ± 5.5	59.3 ± 8.6	62.8 ± 8.6
Height (m)	1.70 ± 0.09	1.70 ± 0.10	1.70 ± 0.09
Weight (kg)	74.3 ± 14.7	74.5 ± 14.4	81.0 ± 13.8

Data are presented as mean ± SD or as numbers.

* Non-OA individuals were statistically significantly younger than mild and severe OA individuals ($p < 0.001$)

V.2.2 Gait analysis

All knees in this study were tested following the same standardized procedure including the recording of three 10m-long straight-line trials at self-selected normal gait speed with personal walking shoes across a walkway instrumented with an optoelectronic motion capture system (Qualisys Medical, Gothenburg, SE) and a force plate (Bertec, Columbus, OH) operating synchronously at 120 Hz. Only trials with a clear step of the foot below the knee of interest on the force plate were recorded. Before recording the gait trials, clusters of reflective markers were fixed on the individuals and a calibration based on anatomical landmarks was performed, following a common protocol (Chehab et al., 2017). During the gait trials, the position and orientation of the lower-limb segments were calculated using the cluster marker trajectories and the calibration information (Andriacchi et al., 1998; Favre et al., 2009). The moments in the knee during the stance phases with the foot of interest on the force plate were calculated following a standard inverse dynamics approach (Zabala et al., 2013). They were time-normalized to 0-100% during stance and expressed as external moments in percentage of bodyweight and height (%BW×Ht). Nine usual parameters were used to describe the moments during each stance phase (Table 9, Figure 14). Finally, the parameters were averaged over the three trials to have one value per parameter and knee. All biomechanical processing was done using the software application BioMove (Stanford, CA).

V.2.3 Severity index

The severity index was computed by multinomial logistic regression with the severity groups as nominal response and the nine knee moment parameters as predictors (McCullagh and Nelder, 2019). The parameters were standardized using a z-score transformation before performing the regression and a sigmoid transformation was applied to the regressed data to have indices ranging between 0 and 100. The regression was calculated by bootstrapping which allowed determining confidence intervals for the regression coefficients and assessing the reliability of the index (Efron and Tibshirani, 1994). Reliability was characterized using the intraclass correlation coefficient (ICC) and the standard error of measurement (SEM) (Weir, 2005).

For completeness with literature, two previously proposed combinations of knee moment parameters, the total knee joint moment and the medial contact force, were also computed. For the total knee joint moment, the square root of the sum of the squared knee flexion, adduction and external rotation moments was calculated for each time point of each stance (Zabala et al., 2013). Then, the maximal values during the first and second halves of each stance were extracted (TJM_{first} and TJM_{second}, respectively). Regarding the medial contact force, the maximum value during the first half of each stance (MCF_{first}) was estimated based on the KAM_{first} and KFM_{first} using a formula determined with instrumented knee prostheses (Manal et al., 2015; Uhlrich et al., 2018; Walter et al., 2010). Similar to the other moment parameters, TJM_{first}, TJM_{second} and MCF_{first} were averaged over the three trials recoded for each knee.

V.2.4 Statistical analysis

Since the data were not normally distributed (Kolmogorov-Smirnov tests), they were analyzed using non-parametric statistics. Specifically, comparisons of the nine knee moment parameters, the severity index and the three prior combination parameters among the severity groups were performed using Kruskal-Wallis tests with post-hoc ranksum tests. Associations with disease severity, for the knee moment parameters, the severity index and the prior combination parameters, were assessed using Spearman correlations across severity groups. Significance level was set a-priori at $p<0.05$, with Bonferroni corrections for multiple comparisons during post-hoc analyses (effective $p<0.017$).

V.3 Results

Kruskal-Wallis tests showed statistically significant effect of disease severity on six of the nine knee moment parameters (KFM_{first}, $p = 0.034$; $KERM_{second}$, $p = 0.039$; KFM_{second}, KAM_{onset}, $KAM_{central}$ and KAM_{second}, all $p < 0.001$). Post-hoc ranksum tests showed significant incremental differences in the $KAM_{central}$ and KAM_{second} from non-OA to mild OA, to severe OA, with larger values in more severely affected knees. The KAM_{onset} was significantly larger in the severe OA group compared to both the non-OA and the mild OA groups. The KFM_{second} was significantly larger in severe OA knees compared to both the non-OA and the mild OA knees, while the KFM_{first} was significantly smaller in mild OA than in non-OA knees. Finally, the $KERM_{second}$ was significantly smaller in the severe OA than in the non-OA group (Table 9, Figure 14).

Statistically significant correlations with disease severity were found for five of the nine moment parameters: $KAM_{central}$ ($rs = 0.59$, $p < 0.001$), KAM_{second} ($rs = 0.49$, $p < 0.001$), KAM_{onset} ($rs = 0.48$, $p<0.001$), KFM_{second} ($rs = 0.35$, $p < 0.001$), $KERM_{second}$ ($rs = -0.24$, $p = 0.016$) and $KERM_{first}$ ($rs = -0.23$, $p = 0.021$) (Table 9).

Table 9: Values of the knee moment parameters for the three severity groups, as well as Spearman correlation between the parameters and disease severity.

Parameter	Definition	Values per severity group: median (1st quartile; 3rd quartile)			Correlation with disease severity, n = 98	
		Non-OA, n = 22	Mild OA, n = 38	Severe OA, n = 38	Correlation coefficient (95% CI)	p-value
KAM$_{\text{central}}$	Minimum adduction moment between KAM$_{\text{first}}$ and KAM$_{\text{second}}$	0.61 (0.30; 0.86)$^{\#\S}$	0.98 (0.77; 1.56)*§	1.69 (1.17; 2.55)$^{*\#}$	0.59 (0.43; 0.71)	<0.001
KAM$_{\text{second}}$	Maximum adduction moment during second half of stance	1.32 (0.91; 1.69)$^{\#\S}$	1.62 (1.40; 2.05)*§	2.40 (1.64; 2.89)$^{*\#}$	0.49 (0.31; 0.63)	<0.001
KAM$_{\text{onset}}$	Minimum adduction moment before KAM$_{\text{first}}$	-0.87 (-0.55; -1.19)§	-0.83 (-0.40; -0.94)§	-0.37 (-0.13; -0.54)$^{*\#}$	0.48 (0.30; 0.63)	<0.001
KFM$_{\text{second}}$	Minimum flexion moment during second half of stance	-2.34 (-2.92; -1.87)§	-2.58 (-3.15; -1.87)§	-1.56 (-2.38; -0.79)$^{*\#}$	0.35 (0.16; 0.52)	<0.001
KERM$_{\text{second}}$	Minimum external rotation moment during second half of stance	-0.79 (-1.00; -0.70)§	-0.94 (-1.07; -0.74)	-0.96 (-1.19; -0.76)*	-0.24 (-0.42; -0.04)	0.016
KERM$_{\text{first}}$	Maximum external rotation moment during first half of stance	0.19 (0.11; 0.26)	0.16 (0.11; 0.22)	0.12 (0.07; 0.19)	-0.23 (-0.42; -0.03)	0.021
KFM$_{\text{onset}}$	Minimum flexion moment before KFM$_{\text{first}}$	-2.42 (-2.93; -1.68)	-2.08 (-2.49; -1.60)	-1.88 (-2.33; -1.64)	0.18 (-0.02; 0.37)	0.077
KFM$_{\text{first}}$	Maximum flexion moment during first half of stance	3.00 (2.21; 3.61)$^{\#}$	2.06 (1.47; 2.52)*	2.05 (0.85; 3.43)	-0.17 (-0.36; 0.03)	0.095
KAM$_{\text{first}}$	Maximum adduction moment during first half of stance	3.01 (2.34; 3.24)	2.49 (2.16; 3.22)	3.16 (2.50; 3.82)	0.13 (-0.07; 0.32)	0.189

Parameters are ordered according to the magnitude of the correlation coefficients. All parameters are reported in %BW*Ht. See Figure 14 for an illustration of the parameters and their differences with disease severity.

* = significantly different compared to the non-OA group ($p < 0.017$)

$^{\#}$ = significantly different compared to the mild OA group ($p < 0.017$)

§ = significantly different compared to the severe OA group ($p < 0.017$)

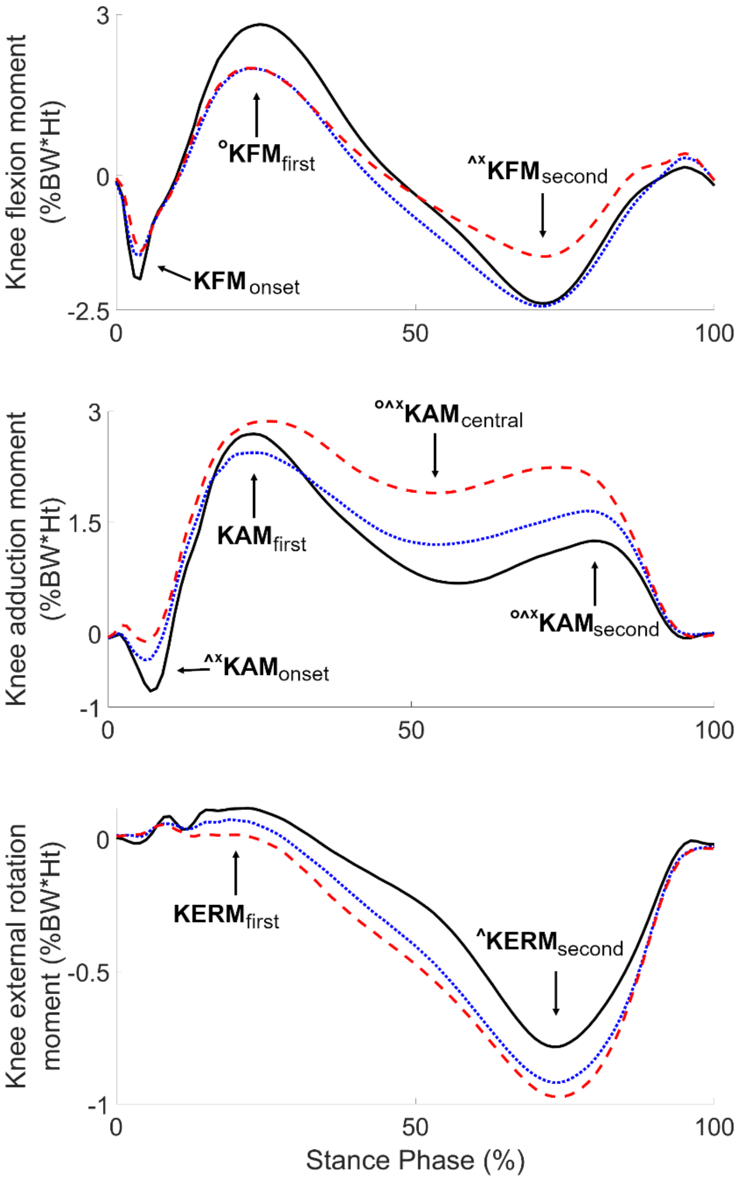


Figure 14: *Average knee moments of the three severity groups (black solid lines: non-OA, blue dotted lines: mild OA, red dashed lines: severe OA), with indication of the nine usual parameters. Symbols indicate significant differences between groups (°: non-OA different from mild OA, ^: non-OA different from severe OA, ^{x}: mild OA different from severe OA) ($p<0.017$).*

The proposed regression method allowed compiling a severity index showing an excellent reliability, with ICC of 0.96 and SEM of 6.78 units (Koo and Li, 2016). Moreover, Kruskal-Wallis test showed statistically significant differences among severity groups ($p < 0.001$), with post-hoc analyses indicating significant difference between the three groups. Indeed, the non-OA group had significantly lower severity indices than the mild OA and severe OA groups, and the mild OA group had significantly lower severity indices than the severe OA groups (Table 10). Additionally, a significant correlation was found between the severity index and disease severity (rs = 0.70, $p < 0.001$).

Since the moment parameters were standardized before calculating the severity index, the coefficients of the regression leading to the severity index can be analyzed to compare the contribution of the nine moment parameters to the severity index. Doing so, indicated that the $KAM_{central}$ had the biggest effect on the index with a coefficient of -1.52, contributing 27.0% to the severity index, followed by the KFM_{second} and the KAM_{first} with coefficients of -1.00 and 0.98 and contributing for 17.7% and 17.4% of the severity index, respectively (Table 11, Figure 15). On the opposite, the KFM_{onset}, $KERM_{first}$ and KAM_{second} had the least impact on the index, with coefficients of 0.095, -0.178, and -0.304 and contributions of 1.7%, 3.2% and 5.4% to the severity index, respectively.

Table 10: *Values of the severity index and of three prior moment combination parameters for the three severity groups, as well as Spearman correlation between these measures and disease severity.*

Combination parameter	**Definition; unit**	**Values per severity group: median (1st quartile; 3rd quartile)**			**Correlation with disease severity, n = 98**	
		Non-OA, n = 22	**Mild OA, n = 38**	**Severe OA, n = 38**	**Correlation coefficient (95% CI)**	**p-value**
Severity index	Severity index; -	10.0 (3.7; 21.0)$^{\#§}$	42.9 (25.3; 58.2)*§	84.2 (62.5; 94.4)$^{*\#}$	0.70 (0.57; 0.80)	<0.001
TJM$_{second}$	Maximum total knee joint moment during second half of stance; %BW*Ht	2.72 (2.27; 3.01)	3.27 (2.42; 3.82)	3.06 (2.72; 3.46)	0.11 (-0.09; 0.30)	0.277
MCF$_{first}$	Maximum medial contact force during first half of stance; BW	2.07 (1.90; 2.27)	1.87 (1.72; 2.08)§	2.12 (1.79; 2.25)$^{\#}$	0.03 (-0.16; 0.23)	0.734
TJM$_{first}$	Maximum total knee joint moment during first half of stance; %BW*Ht	4.11 (3.53; 4.75)	3.29 (2.90; 4.25)	3.95 (3.20; 4.95)	0.01 (-0.19; 0.21)	0.893

Combination parameters are ordered according to the magnitude of the correlation coefficients.

* = significantly different compared to the non-OA group ($p < 0.017$)

$^{\#}$ = significantly different compared to the mild OA group ($p < 0.017$)

§ = significantly different compared to the severe OA group ($p < 0.017$)

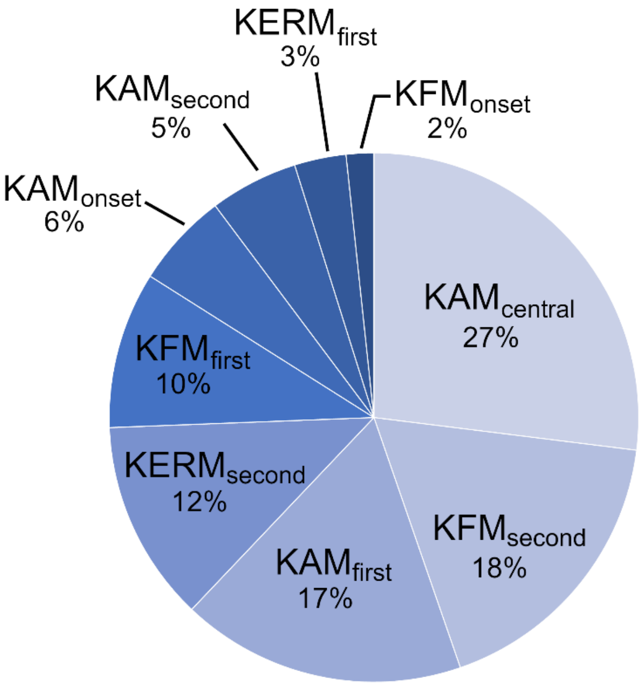


Figure 15: *Contribution of the nine moment parameters to the severity index.*

Additionally, Kruskal-Wallis tests showed no statistically significant difference among severity groups for any of the three prior combinations parameters (TJM_{first}, p = 0.079; TJM_{second}, p = 0.168; MCF_{first}, p = 0.061). Finally, no statistically significant correlation was found with disease severity for MCF_{first} (rs = 0.04, p = 0.73), TJM_{first} (rs = 0.01, p = 0.89) or TJM_{second} (rs = 0.11, p = 0.28) (Table 10).

Table 11: *Coefficient of the nine moment parameters in the severity index regression.*

Parameter	Regression coefficient (95% CI)
$KAM_{central}$	-1.52 (-1.58; -1.47)
KFM_{second}	-1.00 (-1.03; -0.97)
KAM_{first}	0.98 (0.94; 1.02)
$KERM_{second}$	0.69 (0.65; 0.74)
KFM_{first}	0.54 (0.51;0.57)
KAM_{onset}	-0.33 (-0.37; -0.28)
KAM_{second}	-0.30 (-0.37; -0.24)
$KERM_{first}$	-0.18 (-0.21; -0.15)
KFM_{onset}	0.09 (0.07; 0.12)

Parameters are ordered according to the magnitude of the regression coefficients. Please refer to Table 9 and Figure 14 for a definition and an illustration of the parameters, respectively.

V.4 Discussion

This study confirmed that multiple knee moment parameters differ with respect to the severity of medial knee OA. Compared to prior works, the present study, testing all usual parameters over the entire spectrum of disease severity, provided a basis to assemble the pieces disseminated in literature. Various factors, including participants' characteristics or analysis protocols, could influence knee moments and lead to diverging results among studies (Chehab et al, 2017; Messier et al., 2005; Schrijvers et al., 2021). Nevertheless, even with such possible methodological variations among studies, strong consensuses could be identified for four parameters. These included smaller KFM_{first} in mild OA compared to non-OA (asymptomatic) knees and in severe OA compared to mild OA knees, although the severe-mild difference was not observed in the present study (Astephen et al., 2008; Huang et al., 2008; Weidow et al., 2006). Consistent observations also existed for larger KFM_{second} in severe OA than in non-OA (asymptomatic) and mild OA knees (Astephen et al., 2008; Baert et al., 2013), as well as larger $KAM_{central}$ and KAM_{second} in mild OA than in non-OA (asymptomatic) and in severe OA than in mild OA (Astephen et al., 2008; Huang et al., 2008; Thorp et al., 2006). No consensus existed for the KAM_{first}, which was already shown to have highly inconsistent results among studies (Mills et al., 2013), and no consolidation could be attempted for the other parameters due to lacking data in literature. Altogether, the present study shed light on three parameters, the $KAM_{central}$, KAM_{second} and KFM_{second}, which were frequently disregarded in prior works. This suggests that future research should not limit the analysis to the KAM_{first} and the KFM_{first}. This suggestion is particularly well supported by two recent studies relating the $KAM_{central}$ with disease progression and symptoms (Astephen Wilson et al., 2017; Costello et al., 2020).

With the consideration of more than two parameters appearing wise for the characterization of the knee moments, the possibility to combine the parameters into an index reflecting disease severity constitutes another important finding of the present study. Indeed, while considering a larger number of parameters will contribute to better descriptions, having a larger number of independent parameters to manage could increase study design complexity and make gait interventions more complex (Edd et al., 2020b). Therefore, the possibility of combining the parameters, as demonstrated in this study, is interesting practically. However, beyond practical considerations, indices could be especially relevant for the global assessments of the knee moments they allow. For example, in personalized interventions, such as gait retraining (Cheung et al., 2018; Richards et al., 2018a; Ulrich et al., 2020b), it could become possible to aim for a global change, instead of aiming for changes in one or two moment parameters, without consideration for the others.

The second objective of assessing the possibility of developing a severity index was fully achieved, with the design of an index reliable, significantly different among the three severity groups and showing a large correlation with disease severity. Further research will now be necessary to assess the validity of the proposed index. The techniques to record and calculate knee moments differ among institutions (Benedetti et al., 2013; Schrijvers et al., 2021). Therefore, the sensitivity of the severity index to variations in gait analysis protocols will need to be determined. It is well possible that the index will be little sensitive to such methodological differences, as it is an aggregate of standardized parameters. It will also be necessary evaluating the index longitudinally and characterizing its relationships with key features of knee OA, such as pain or disease progression (Felson, 2009).

It is interesting to note that the KAM_{first} accounted for 17% of the severity index (third most important contributor to the index), although it was not significantly different among severity groups nor correlated with disease severity. While such an important role in the severity index could appear peculiar in view of its relationship with disease severity, this role well agrees with medial knee OA literature, where the KAM_{first} is a prevalent parameter and the primary focus of gait interventions (Favre and Jolles, 2016; Mills et al., 2013; Reeves and Bowling, 2011). Thus, it is possible that the severity index actually captured the global essence of disease severity. Three combination parameters were already proposed in literature, the TJM_{first}, TJM_{second} and MCF_{first} (Manal et al., 2015; Walter et al., 2010; Zabala et al., 2013), but the severity index in this study is the first to have been designed to reflect disease severity.

This study has some limitations, including the use of a single cross-sectional dataset, as discussed above. Another point worth mentioning is the multinomial logistic regression used to determine the severity index. While this is a common method, which successfully combined the moment parameters, one cannot exclude that there could be other ways to combine the parameters. Depending on the results of the validity studies to follow, in the future, it might be necessary to compare different combination methods. Finally, since the severity groups differed in age, it is possible that a fraction of the severity index reflects the variations in moment parameters with respect to age.

V.5 Conclusion

This study confirmed that multiple knee moment parameters differ with disease severity. In particular, differences among severity groups were found to be consistent across studies for four parameters, including three that were frequently disregarded in prior works ($KAM_{central}$, KAM_{second}, KFM_{second}). Future studies are therefore recommended to not limit the analysis to the KAM_{first} and the KFM_{first}. Another important finding of this study was the possibility to combine the parameters into a severity index, which opens promising perspectives based on a single figure assessing the knee moments in their entirety. While the proposed index was shown to be reliable and correlated with disease severity, further research will be necessary to assess its validity.

VI Conclusions and perspectives

VI.1 Achieved results

Through its four studies (Chapters II to V), the present thesis achieved several results. First, it brought additional knowledge on LWI, notably on the effect of baseline FPA on induced knee kinetic changes (Chapter II). It also brought new knowledge on gait retraining based on footprint parameters, notably by showing the relevance of SL modifications and the possibility to aim for global kinetic changes (Chapters III and IV). Additionally, it highlighted the importance of inducing more specific kinetic changes than KAM_{first} decrease only, as other knee moment parameters were also associated with the disease (Chapter V). It was also shown that such more specific changes could be achieved, notably with footprint parameter modifications (Chapters III & IV). Finally, a way to group all knee moment parameters to allow a global assessment of knee kinetics was proposed (Chapter V).

Several key topics were addressed through these results. Gait modifications were studied with LWI and gait retraining. Secondary knee moments were also associated with medial knee OA and led to a global assessment of knee moments. Finally, all the studies in this thesis stressed the need and the potential of combining and personalizing the interventions. The contributions of each of the four studies to these key topics are summarized in Table 12 and discussed below.

Table 12: *General topics addressed by this thesis.*

	LWI	Gait retraining	Secondary knee moment parameters	Global assessment of knee moments	Personalized gait modifications	Combination of gait modifications
II LWI and FPA	X				X	X
III Dual kinetic change		X		X	X	X
IV SL modification		X		X	X	X
V Severity index			X	X	X	X

LWI = Lateral wedge insoles; SL = Stride length

VI.2 Lateral wedge insoles

The study in Chapter II (Ulrich et al., 2020a) showed that LWI had a better effect on knee loadings in individuals walking with a smaller natural FPA, than the ones naturally walking with a larger FPA. This observation could help to identify the patients more likely to reduce knee loading and thus to benefit from LWI. This observation also provided an explanation for the large variations reported in prior studies.

Moreover, a finer analysis of the underlying mechanism brought a better comprehension of why some patients are more likely to benefit from the insole. It is due to an increase in the frontal-plane GRF-shank angle. This result could lead to the finding of ways to get better LWI effects, such as pairing the wear of LWI with walking instructions or coupling it with other gait modifications to enhance its effects.

VI.3 Gait retraining based on footprint parameters

Footprint parameters are easily changeable and teachable to the patients. Among them, SL was left aside by literature. At the author’s knowledge, the work of Chapter IV is the first study investigating the effect of SL modification in medial knee OA population. Together with the study in Chapter III (Ulrich et al., 2020b), it highlighted the interests for SL reduction, as it decreased several KAM parameters in healthy individuals and in medial knee OA patients.

These results provide a new and additional intervention to induce kinetic changes for the purpose of personalized treatment of medial knee OA. SL modifications is all the more interesting, as a reduced SL with constant speed corresponds to a frequency increase, which is quite easy to measure and therefore to change, notably with accelerometers that are included in almost every smartphone nowadays.

VI.4 Secondary knee moment parameters

Most of gait modifications for medial knee OA focused on reducing the KAM_{first}, often with a secondary objective of not increasing the KFM_{first}. Unfortunately, benefits in terms of clinical outcomes were not always present, especially in the case of LWI (Penny et al., 2013; Zhang et al., 2018). A part of the explanation for these mitigated clinical results may come from negative repercussions of KAM_{first} changes on kinetic parameters in other planes (Jackson et al., 2018; Richards et al., 2018b) or at other time points of the gait cycle (Favre et al., 2016; Jenkyn et al., 2008; Simic et al., 2011). The results of the study in Chapter V consolidate the scattered results present in literature, with other knee moment parameters also being associated with medial knee OA. Indeed, several knee moment parameters have been associated with the disease severity (Chapter V; Astephen et al., 2008; Baert et al., 2013; Thorp et al., 2006) or with symptoms (Astephen Wilson et al., 2016) and the KFM_{first} and $KAM_{central}$ were also associated with disease progression (Costello et al., 2020). Therefore, this highlighted the interest in also considering other knee moment parameters in gait modification for medial knee OA.

VI.5 Global assessment of knee moments

Targeting a finer kinetic change than just KAM_{first} decrease, notably decreasing the KAM_{first} by a specific amount or combining KAM_{first} reduction with KFM_{first} reduction and $KAM_{impulse}$ reduction, increases the complexity of interventions. Studies of Chapters III and IV (Ulrich et al., 2020b) showed that this was possible, notably through gait retraining. With the degrees of freedom offered by footprint parameter modifications, this thesis showed that it was totally possible to aim for simultaneous changes in the KAM_{first}, $KAM_{impulse}$ and KFM_{first}, or to change the KAM_{first} by at least a certain amount without KFM_{first} increase. Although the long-term effects on clinical outcomes need to be estimated, more complex kinetic changes than just KAM_{first} decrease should be considered in future gait modification studies.

Inducing a multiparametric kinetic change through modifying two, or even three knee moment parameters is more challenging than reducing the KAM_{first} alone (Edd et al., 2020b; Ulrich et al., 2020b). While it is very relevant to modify the KAM_{first}, the KFM_{first}, or even the $KAM_{impulse}$ according to specific literature, the study of Chapter V showed that other knee moment parameters are also associated with the disease. Therefore, it would become very complicated or almost impossible to consider every parameter individually.

The severity index proposed in Chapter V presents a new way to group all usual knee moment parameters and therefore to consider knee moments in a global way. Indeed, this index was associated with medial knee OA severity. The association with disease progression or symptoms still needs to be investigated. However this index could allow a simplification in the search for solutions to the multiparametric moment change problem, because instead of changing each knee moment parameter individually, it would induce a beneficial global moment change at the knee.

VI.6 Personalized gait modifications

Benefits in terms of clinical outcomes are not always present in gait modification studies. A part of the explanation was discussed above with possible negative repercussions of KAM_{first} changes on other knee moment parameters. Another possible explanation comes from KAM_{first} change inconsistencies in gait modification studies. It is especially the case in LWI, where the KAM_{first} reductions are particularly inconsistent among participants, ranging from large decreases to increases (Hinman et al., 2012; Jones et al., 2014; Kakihana et al., 2007), but also in gait retraining studies (Ulrich et al., 2020b).

A trend towards more personalized gait modifications is more and more present in literature and gave particularly interesting results in terms of clinical improvements in gait retraining studies (Cheung et al., 2018; Richards et al., 2018a; Shull et al., 2013a), but also insights with LWI (Felson et al., 2019). This personalized approach, where the differences among individuals are recognized and acknowledged, consists in finding a personalized gait modification inducing the wanted kinetic change for each patient individually, or equivalently to find the right individuals more likely to benefit from a specific intervention. This approach is especially interesting when targeting a multiparametric moment change. Indeed, while several solutions for most individuals exist to decrease one knee moment parameters, the possibilities decrease when targeting more complex moment changes (Edd et al., 2020b; Ulrich et al., 2020b). Therefore, personalizing the gait modification offers the possibility to find a solution for more individuals (Edd et al., 2020b).

Gait retraining based on footprint parameter modifications is particularly suitable for personalized interventions with the high number of degrees of freedom offered by such intervention. Indeed, the possibility to change different parameters helps to find modifications more likely to benefit to each patient. The interest of SL modification to change knee moment parameters highlighted in this thesis (Ulrich et al., 2020b; Chapter IV) even gives more opportunities to find personalized gait retraining solutions.

In the case of LWI, the personalized approach is more complicated as there are less degrees of freedom to induce individual specific changes. However, it is possible to find the right individuals for the modifications, which was recently shown to lead to clinical outcomes improvements (Felson et al., 2019), and the study in Chapter II (Ulrich et al., 2020a) gave inputs to find responder individuals. However, it could become even more complicated to find the responders if a multiparametric moment change was targeted. To help personalize footwear modifications, it could be interesting to develop an adjustable insole that could be individually adjusted to each patient (Elbaz et al., 2010; Fisher et al., 2007), or to combine the LWI with instructions or with other gait modification.

VI.7 Combination of gait modifications

With the increased complexity induced by the necessity to consider more knee moment parameters than the KAM_{first} only (Ulrich et al., 2020b; Chapters IV & V), finding a personalized intervention fulfilling specific multiparametric moment change for each patient will become difficult. This increase in complexity motivates the combination of several gait modifications to help find personalized interventions. Indeed, a recent study showed that combining footprint parameter modifications allowed to get multiparametric moment changes for more individuals than if the gait modifications were used separately (Edd et al., 2020b). Moreover, combining gait modifications could also lead to smaller amplitudes of gait modifications, which could therefore be more likely to be accepted by the patients (Ulrich et al., 2018). It could also be possible to couple the footprint parameter modifications with LWI or braces for example. Indeed, the study in Chapter II showed that there was an interaction between LWI effect and baseline FPA (Ulrich et al., 2020a).

VI.8 Perspectives

This thesis allowed a better understanding of gait modifications for medial knee OA. This consolidates the trend towards more personalized gait modifications. It also showed a great interest in having a more global vision of gait modifications, as combined effects of modifications exist and as the interventions should probably aim for more complex changes than simply KAM_{first} reductions. Other knee moment parameters were also associated with the disease and this thesis showed that it was possible to change them in a more global way. This leads to a more global approach of medial knee OA management with the need to find the right modification for each patient, through the multitudes of possible combinations. Results on healthy participants still need to be confirmed on medial knee OA patients, and longitudinal studies are necessary to investigate mid-term and long-term effects on knee moments and on clinical outcomes. However, the results of this thesis motivate the design of new customizable interventions targeting multiparametric knee moment changes, such as footwear intervention that could be adjusted to each patient in order to optimize their knee moment changes. It also motivates to study the combined effects of gait modifications, or the combined effects of a gait modification with specific instructions on how to walk with it, in order to improve the effects of such interventions.

An augmented-reality system was shown capable of helping the participants modify their footprint parameters in the framework of knee OA gait retraining. This system is not based on a feedback, but on one unique target regrouping several footprint parameter modifications together. This kind of system may be useful for other gait modifications or for coupling footprint parameter changes with other gait modifications, such as LWI. Therefore, the results of this thesis also motivate the design and development of less complicated systems to retrain more patients in simpler labs, or even to find portable solution for everyday training at home.

VI.9 Final conclusion

This thesis showed that there is a great interest in finding personalized gait modifications as intervention for the management of medial knee OA. Indeed, considering individual modifications leads to consistent knee moment changes in a larger portion of persons. Moreover, this thesis highlighted the importance of other knee moment parameters also associated with the disease, and showed that it was possible to target more specific changes than only KAM_{first} decreases, notably through gait retraining. Certainly, this increases the complexity to find suitable interventions, however this thesis proposed solutions to reduce this complexity, notably with SL modifications, a novel gait modification for medial knee OA patients, or with the severity index, a way to group all knee moment parameters in one figure associated with the disease severity.

Publications pertaining to the PhD thesis

Peer-reviewed journal articles

Ulrich B., Hoffmann, L., Jolles, B. M., Favre, J., 2020a. Changes in ambulatory knee adduction moment with lateral wedge insoles differ with respect to the natural foot progression angle. *Journal of Biomechanics*, 103, 109655.

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Award

Movement Analysis (BTS) Award, International Society of Physical and Rehabilitation Medicine World Congress, Paris, France. Study: Ranges of modifications in step width and foot progression angle for everyday walking.

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