Aalborg Universitet

Investigation of bracing to unload muscle and knee contact forces for knee oteoarthritis patients

Modelling, workflow, prototype design and evaluation

Stoltze, Jonas Stensgaard

DOI (link to publication from Publisher):
10.54337/aau470864014

Publication date:
2022

Document Version
Publisher's PDF, also known as Version of record

Link to publication from Aalborg University

Citation for published version (APA):
Stoltze, J. S. (2022). *Investigation of bracing to unload muscle and knee contact forces for knee oteoarthritis patients: Modelling, workflow, prototype design and evaluation*. Aalborg Universitetsforlag.

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal -

Take down policy
If you believe that this document breaches copyright please contact us at vbn@aub.aau.dk providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from vbn.aau.dk on: December 05, 2025

INVESTIGATION OF BRACING TO UNLOAD MUSCLE AND KNEE CONTACT FORCES FOR KNEE OTEOARTHRITIS PATIENTS

MODELLING, WORKFLOW, PROTOTYPE DESIGN AND EVALUATION

BY
JONAS STENSGAARD STOLTZE

DISSERTATION SUBMITTED 2022

AALBORG UNIVERSITY
DENMARK

Investigation of bracing to unload muscle and knee contact forces for knee oteoarthritis patients

Modelling, workflow, prototype design and evaluation

PhD dissertation by

Jonas Stensgaard Stoltze

AALBORG UNIVERSITY
DENMARK

Dissertation submitted February 24, 2022

Dissertation submitted: February 2022

PhD supervisor: Assoc. Prof. Michael Skipper Andersen
Aalborg University

Assistant PhD supervisor: Prof. John Rasmussen
Aalborg University

PhD committee: Professor Erik Lund (chair)
Aalborg University, Denmark

Associate Professor Tine Alkjaer
University of Copenhagen, Denmark

Associate Professor Luc Labey Mechanical
KU Leuven, Belgium

PhD Series: Faculty of Engineering and Science, Aalborg University
Department: Department of Materials and Production

ISSN (online): 2446-1636
ISBN (online): 978-87-7573-939-4

Published by:
Aalborg University Press
Kroghstræde 3
DK – 9220 Aalborg Ø
Phone: +45 99407140
aauf@forlag.aau.dk
forlag.aau.dk

© Copyright: Jonas Stensgaard Stoltze

Printed in Denmark by Rosendahls, 2022

Individualized Osteoarthritis Interventions

Innovation Fund Denmark

The work presented in this PhD dissertation was carried out at Aalborg University in the Biomechanics Group at the Department of Materials and Production. The work was part of the Individualized Osteoarthritis Interventions project and has received funding from the Innovation Fund Denmark.

Publications in peer-reviewed scientific journals

1. Stoltze J.S., Rasmussen J., Andersen M.S., 2018. On the biomechanical relationship between applied hip, knee and ankle joint moments and the internal knee compressive forces, *International Biomechanics*, https://doi.org/10.1080/23335432.2018.1499442

2. Stoltze J.S., Palari J., Eskandari B., Oliveira A.S.C., Pirscoveanu C.I., Rasmussen J., Andersen M.S., 2021. Development and Functional Testing of An Unloading Concept for Knee Osteoarthritis Patients: A Pilot Study, *Journal of Biomechanical Engineering*, https://doi.org/10.1115/1.4051847

3. Stoltze J.S., Oliveira A.S.C., Rasmussen J., Andersen M.S., 2022. Evaluation of an Unloading Concept for Knee Osteoarthritis: A Pilot Study in a Small Patient Group, *Osteoarthritis and Cartilage*, under review

Publications in proceedings and monographs

1. Stoltze J.S., Rasmussen J., Andersen M.S., 2017. How internal knee compressive forces are most effectively reduced by applied hip, knee and ankle joint moments. Presented at XXVI Congress of the International Society of Biomechanics, Brisbane, Australia

2. Stoltze J.S., Rasmussen J., Andersen M.S., 2017. Correlation between internal knee joint loads and vibroarthrography for detecting knee-joint disorders A pilot study. Presented at XVI International Symposium on Computer Simulation in Biomechanics, Gold Coast, Australia

3. Stoltze J.S., Rasmussen J., Andersen M.S., 2017. On the biomechanical relationship between applied hip, knee and ankle joint moments and the internal knee compressive forces. Presented at XVI International Society of Prothetics and Orthoses (ISPO) World Congress, Cape Town, South Africa

English Summary

This PhD study was part of a collaboration project named Individualized Osteoarthritis Intervention (IOI), which was funded by the innovation fund Denmark. The main goal with the IOI project was to conduct research within treatment of knee osteoarthritis (KOA) and develop a workflow for optimal individualised non-surgical intervention by using advanced computational and measuring technologies. This workflow is expected to improve the management of KOA and postpone the need for surgery.

This dissertation focusses on knee brace intervention and the design and development of a patient-specific prototype with the aim of reducing joint loads and thereby relieve joint pain in KOA patients during gait. The main aims with the PhD study was 1) to analyse various approaches for efficiently unloading the knee joint and 2) to develop and experimentally test a subject-specific knee brace prototype using a concept based on the findings from the first step. It is believed that the findings in this thesis have the potential to advance the state-of-the-art within knee braces, which will improve the quality-of-life for the patients.

The first three chapters cover the opening of the dissertation, with the first chapter as an introduction, which outlines the background and motivation for the project. This describes the epidemiology of KOA including currently known risk factors for disease development and common treatment methods for early and late stage KOA. Next, the latest research within knee bracing is presented, where the state-of-the-art knee brace methods are discussed, pointing out the limitations of the currently available options on the market. Finally, the overall aims with the project, and how these are achieved, are presented with three scientific studies. Additionally, the methods for evaluating the effects of a developed knee brace prototype are described including pain score, electromyography (EMG) and musculoskeletal (MS) modeling.

In Chapter 4, the first paper is presented, which investigated how applied moments in the lower extremity affect the knee compressive forces (KCF). This was based on recorded gait data of ten healthy subjects and MS models, which were used to apply moments *in silico* around all three joint axes for the hip, knee and ankle joints. The moments were applied whenever needed with a magnitude defined as a percentage of the net moment around the respective axis during normal gait without any intervention. Combinations of applied moments and a percentage value were examined and for each combination, the total, medial and lateral KCF were computed and compared with a baseline case with no external moments applied. All results presented here are

for combinations of 40% net moment. Generally, the moments acting in the sagittal plane, hip flexion-extension (HFM), knee flexion-extension (KFM) and ankle plantarflexion-dorsiflexion (APM), provided the largest reduction of the total KCF during the stance phase. HFM and KFM mainly affected the first peak of the total KCF, revealing reductions of 8.8% and 13.5%, respectively, by compensating for rectus femoris and quadriceps muscle activation, respectively. APM solely reduced the second peak with 11.4% through a reduced gastrocnemius muscle activation during the late stance. Although, the results from the first paper did not reveal a clear suggestion of the best suited brace intervention, which will most likely vary between patients, the KFM was chosen as the basis for the developed prototype in the next papers.

Chapter 5 presents the second paper, which is considered as a proof-of-concept case study describing the design and experimental testing of the prototype brace. The brace applies a knee extension moment from stored potential energy in springs and the stiffness of these can be chosen individually. A built-in switch mechanism ensures that the brace moment is only applied in the early stance phase to target the first peak KCF and to avoid interference during swing phase. A workflow to adjust the brace and choose the correct spring stiffness was established and the prototype was tested on a single healthy subject to investigate the effect on muscle activity and internal KCF during normal gait. Before the experimental tests, the brace concept was tested *in silico* using MS models revealing a 35.9% reduction of the first peak total KCF and a 38.2% reduction of the impulse illustrating the potential of the unloading concept. The experimental tests were conducted with the use of EMG measurements and motion capture recordings to support the simulated results, and the main target muscles were vastus medialis (VM), vastus lateralis (VL) and rectus femoris (RF). The peak activation of VM was reduced with up to 37% whereas VL and RF peak activation increased with up to 43.8% and 7.7% respectively. According to the MS models, the prototype brace reduced the first peak KCF and the impulse with up to 24% and 9.1% respectively. This paper concluded that the concept of applying a knee extension moment has the potential to effectively reduce the total KCF by compensating muscle activation.

The last paper is presented in Chapter 6 and this paper examined a small group of KOA patients. The brace concept was tested *in silico* on all the patients with the same approach as in the second paper. The reduction of the first peak total KCF varied from 3.5% to 33.8% and the medial and lateral first peak KCF reduction ranged from 0.1% to 24.4% and 18.4% to 56%, respectively. These results illustrated the importance of including biomechanical analyses to determine whether a patient is suited for a specific intervention. Additionally, experimental tests were conducted on one of the patients with the same prototype brace as in the second paper. A VAS pain score was evaluated after each test condition, but no effect was observed for this measure. However, the EMG measurements revealed a VM muscle activity reduction of up to 28.7% whereas the VL and RF peak muscle activation increased with up to 2% and 18.3%, respectively. The MS models estimated the first peak total KCF to be reduced with up to 26.3%, although the impulse increased with up to 13.7%. The findings of this paper concluded that not all KOA patients are suited for this unloading concept so initial gait analyses are needed before prescribing this intervention type. The experimental results illustrated the potential of reducing KCF, and although no immediate pain relief was detected in this thesis, long-term studies may observe a pain reduction.

The final chapter includes a summary of key results from the publications within this dissertation and a discussion regarding the methods and outcomes of the studies. Additionally, limitations of these studies are addressed and recommendations for future research are outlined. The research conducted during this PhD is only the initial step for implementing an unloading knee brace concept, which aims to decrease KCF through muscle compensation. The results seem promising but more patient tests are required to draw any conclusions. The prototype brace need to be redesigned to obtain a lighter and more slim product in order to conduct long-term studies. Additionally, the gait data of the KOA patients from the third paper highlight the importance of including biomechanical analyses in the prescription of unloading interventions, since the source to internal joint loads is highly individual. If the clinicians have the tools to detect these individual factors, and the brace can be adjusted to each patient like the prototype in this PhD study, the developed intervention concept is expected to have a positive effect and will improve the quality-of-life for the majority of patients.

Dansk Resumé

Dette ph.d.-studium var del af et samarbejdsprojekt ved navn Individualized Osteoarthritis Intervention (IOI), som var finansieret af Innovationsfonden. Det overordnede mål med IOI projektet var forskning indenfor behandling af knæartrose og udvikling af et workflow til optimal individuel ikke-kirurgisk intervention ved brug af avancerede computer- og måleteknologier. Dette workflow forventes at forbedre behandlingen af knæartrose og udsætte behovet for operation.

Denne afhandling fokuserer på intervention med knæortose samt design og udvikling af en patientspecifik prototype med det formål at reducere ledkræfter og dermed lindre ledsmerte for knæartrosepatienter under gang. Hovedformålet med ph.d.-studiet var 1) at analysere forskellige fremgangsmåder til effektivt at aflaste knæleddet og 2) at udvikle og eksperimentielt teste en personspecifik knæortose prototype ved at bruge et koncept baseret på resultaterne fra den første del. Det vurderes, at resultaterne i denne afhandling har potentiale til at avancere state-of-the-art indenfor knæortoser, hvilket vil forbedre livskvaliteten for patienterne.

De første tre kapitler dækker over indledningen af afhandlingen, hvor første kapitel er en introduktion, som fremhæver baggrunden og motivationen for projektet. Dette beskriver knæartroseepidemiologien og inkluderer nuværende risikofaktorer for udvikling af sygdommen samt typiske behandlingsmetoder til tidlig stadie og senstadie knæartrose. Dernæst præsenteres den seneste forskning indenfor ortosebehandling, hvor state-of-the-art knæortosemetoder bliver diskuteret, hvor begrænsningerne af de nuværende tilgængelige muligheder på markedet udpeges. Til sidst præsenteres de overordnede mål med projektet og hvordan disse opnås med tre videnskabelige studier. Derudover er metoderne til at evaluere effekten af en udviklet ortoseprototype beskrevet, hvilket inkluderer smertemål, elektromyografi (EMG) og muskelskeletal (MS) modelering.

I kapitel 4 er den første artikel præsenteret, som undersøger, hvordan pålagte momenter i underekstremiteten påvirker kompressionskræfterne inde i knæet. Dette var baseret på optaget gang data af ti raske personer og MS modeller, som blev brugt til at pålægge momenter *in silico* rundt om alle tre ledakser i hofte-, knæ- og ankelleddet. Momenterne blev pålagt, når det var krævet med en størrelse defineret som en procentdel af netmomentet omkring den respektive akse, som var krævet under normal gang uden intervention. Forskellige procentværdier og kombinationer af momenter blev undersøgt, og for hver belastningseksempel blev den totale, mediale og laterale knækraft beregnet og sammenlignet med en udgangsværdi uden eksternt pålagte momenter. Alle

resultater, som præsenteres her, er for 40% pålagt moment. Generelt viste momenterne i det sagittale plan, hofte fleksion-ekstension (HFM), knæ fleksion-ekstension (KFM) og ankel plantarfleksion-dorsifleksion (APM), den største reduktion af den totale knækraft i løbet af standfasen. HFM og KFM påvirkede hovedsageligt den første maksimalværdi af den totale knækraft, hvilket resulterede reduktioner på henholdsvis 8.8% og 13.5% ved at kompensere for henholdsvis rectus femoris og quadriceps muskelaktivering. APM reducerede udelukkende den anden maksimalværdi med 11.4% ved at reducere gastrocnemius muskelaktivering i løbet af den sidste del af standfasen. Selvom resultaterne fra den første artikel ikke gav et klart billede af den bedst egnede ortoseintervention, hvilket højest sandsynligt vil variere mellem patienterne, så blev KFM valgt som basis til den udviklede prototype i de næste artikler.

Kapitel 5 præsenterer den anden artikel, der kan betraktes som et proof-of-concept case studie, der beskriver designet og eksperimentelt test af prototypeortosen. Ortosen pålægger et knæekstensionsmoment fra lagret potentiel energi i fjedre og stivheden af disse kan vælges individuelt. En indbygget koblingsmekanisme sikrer at ortosemomentet kun pålægges i den tidlige standfase for at påvirke den første maksimalværdi af knækompressionskraften og for at undgå indblanding under svingfasen. Et workflow til at justere ortosen og vælge den rette fjederstivhed blev etableret, og prototypen blev testet på en enkelt rask forsøgsperson for at undersøge effekten på muskelaktivitet og interne knæledskræfter under normal gang. Før de eksperimentielle tests blev ortosekonceptet testet *in silico* vha. MS modeller, og disse afslørede en 35.9% reduktion af den første maksimalværdi af den totale knækompressionskraft og en 38.2% reduktion af impulsen, hvilket illustrerer potentialet af aflastningskonceptet. De eksperimentielle tests blev udført med brug af EMG målinger og bevægelsesoptagelser til at underbygge de simulerede resultater, og hovedfokus var på vastus medialis (VM), vastus lateralis (VL) and rectus femoris (RF). Den maksimale aktivering for VM blev reduceret med op til 37%, hvorimod maksimalværdierne for VL og RF steg med op til henholdsvis 43.8% og 7.7%. Ifølge MS modellerne reducerede prototypeortosen den første maksimalværdi af knækompressionskraften og impulsen med op til henholdsvis 24% og 9.1%. Den anden artikel konkluderede, at konceptet med at pålægge et knæekstensionsmoment har potentialet til effektivt at reducere den totale knækompressionskraft ved at kompensere for muskelaktivering.

Den sidste artikel præsenteres i kapitel 6 og undersøger en lille gruppe af knæartrosepatienter. Ortosekonceptet blev testet *in silico* på alle patienterne med den samme fremgangsmåde som i den anden artikel. Reduktionen af den første maksimalværdi af den totale knækompressionskraft varierede fra 3.5% til 33.8% og reduktionen af den tilsvarende værdi for medial og lateral kompressionskraft varierede fra henholdsvis 0.1% til 24.4% og 18.4% til 56%. Disse resultater illustrerer vigtigheden i at inkludere biomekaniske analyser til at bestemme om en patient er egnet til en specifik intervention. Derudover blev der udført eksperimentielle tests på én af patienterne med den samme ortoseprototype som i den anden artikel. En VAS smertevurdering blev noteret efter hver forsøgsbetingelse, men der blev ikke observeret nogen effekt for dette mål. EMG målingerne derimod viste en reduktion af VM muskelaktivitet på op til 28.7% hvorimod maksimal muskelaktivitet for VL og RF steg med op til henholdsvis 2% og 18.3%. MS modellerne estimerede en reduktion af den første maksimalværdi af den totale knækompressionskraft på op til 26.3%, dog steg impulsen med op til 13.7%. Resultaterne fra denne artikel konkluderede, at ikke alle knæartrosepatienter egner sig til dette aflastningskoncept, så indledende ganganalyser er nødvendige for at kunne ordinere denne interventionstype. De eksperimentielle resultater illustrerede potentialet til at reducere knækompressionskræfter, og selvom ingen øjblikkelig smertelindring blev raporteret i denne afhandling, så vil langtidssigtede studier muligvis detektere en smertereduktion.

Det sidste kapitel inkluderer et resume af hovedresultaterne fra publikationerne i denne afhandling og en diskussion omhandlende metoderne og udbyttet af studierne. Derudover bliver begrænsninger i disse studier diskuteret og anbefalinger til fremtidig forskning bliver fremlagt. Forskningen i denne afhandling er kun det indledende skridt til implementering af en aflastningskonncept, som forsøger at reducere knækompressionskræfter vha. kompensering af muskler. Resultaterne er lovende men endelige konklusioner kræver flere patienttests. Ortoseprototypen er nødt til at blive redesignet til et lettere og mindre klodset produkt for at kunne udføre langtidssigtede studier. Ydermere understreger gangdata fra knæartrosepatienterne i den tredje artikel vigtigheden af at inkludere biomekaniske analyser i ordineringen af aflastningsinterventioner, eftersom at kilden til de interne knælaster er meget individuel. Hvis sundhedspersonalet har værktøjerne til at detektere disse individuelle faktorer, og ortosen kan justeres til hver enkel patient ligesom prototypen i denne ph.d. afhandling, så forventes det, at det udviklede interventionskoncept har en positiv effekt og vil forbedre livskvaliteten for størstedelen af patienterne.

Preface

This PhD thesis has been submitted to the Faculty of Engineering and Science at Aalborg University, Denmark, in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Mechanical Engineering. The work has been accomplished at the Department of Materials and Production from December 2015 until February 2022 under the supervision of Associate Professor Michael Skipper Andersen and Professor John Rasmussen. The research was carried out as part of the Individual Osteoarthritis Intervention (IOI) project funded by Innovation Fund Denmark. I would like to acknowledge everyone in the IOI consortium for the collaboration and knowledge share at symposiums, which encouraged me to the pursuit of my PhD.

First of all, a big thank you to my two supervisors for all the guidance and assistance, which always motivated me to work hard to achieve the best results. It has been a great pleasure to work under your supervision and I have learned a lot during the past six years. I am very grateful that you, Michael, insisted to meet for playing music together, which resulted in a university band with an annual gig at the department's Christmas Party. Also, thanks to you, John, for encouraging me to start up playing tennis again and providing enjoyable training sessions. I am very grateful that both of you gave me the opportunity to receive a PhD degree and I hope that our paths will meet again in the future for further collaborations.

A huge thank to Associate Professor Anderson Oliveira and research assistant Cristina Ioana who have provided invaluable help and support to conduct experiments in the gait laboratory for collecting data used in papers II and III. Without their assistance this dissertation would not have been possible. Additionally, a thank to Sebastian Laigaard Skals for sharing gait data and models used for paper I.

Furthermore, I would like to thank my colleagues at Aalborg University for all the collaborations and cosy hours with cake and coffee. A great thank to my fellow colleagues, both former and current, in the Biomechanics Research Group who have made the office a very pleasant place to work for the past four years.

Furthermore, I would like to extend my gratitude to Jari Pallari and Behrokh Eskandari for supervision during my external visit at Peacocks Medical Group in Newcastle Upon Tyne, UK. Their expertise within design of medical equipment was essential for the development of the knee brace prototype for papers II and III.

Finally, a huge thanks to my girlfriend Eva for the support and love through this journey. You were always willing to help with rehearsing presentations and provided encouragement in the late hours of experimental testing. Thank you so much for your support and patience.

Jonas Stensgaard Stoltze
Aalborg University, February 24, 2022

Contents

Part I

Introduction

1. Knee Osteoarthritis

1.1 Background and Motivation

Osteoarthritis (OA) is a chronic long-term synovial joint disease causing inflammation of the synovial membrane, which produces inflammatory mediators that contribute to cartilage degradation and affect joint homoeostasis (Maniar et al. [2018], Chen and Tuan [2008]). Homoeostasis is the balance between the repair and destruction of joint tissues driven primarily by mechanical factors (Moelgaard [2015]) for which reason these factors influence the initiation, progression, and treatment of OA (Wilson et al. [2009]). The balance between tissue repair and deterioration is shown in Figure 1.1 by means of a stable and unstable state.

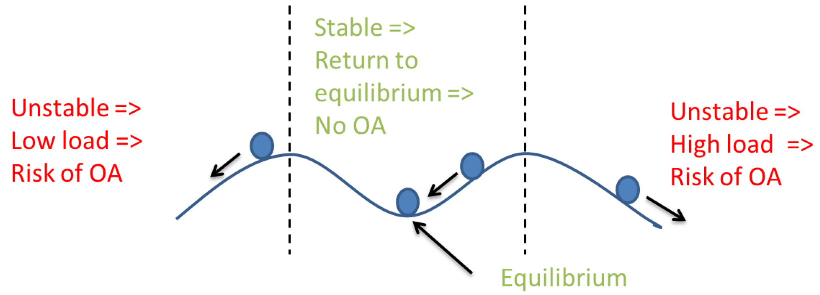


Fig. 1.1: Illustration of joint homoeostasis, where abnormal mechanical loading can cause the soft tissue deterioration to exceed the repair process (unstable state) (Moelgaard [2015]).

Once an imbalance in the homeostasis between the repair and destruction of joint tissues occurs, the risk for OA development increases and the chance for reversing the cartilage deterioration is minimal (Moelgaard [2015]).

The number of OA patients is currently growing and this is expected to continue in the following years (Kiadaliri et al. [2018], Wallace et al. [2017]). Since no cure currently exists (Fransen et al. [2015]), the need for managing the symptoms increases. In UK, OA ranks as the fourth most demanding disease regarding general practice time within the health care system but still, most General Practitioners (GPs) wish for more time with the patients to provide sufficient treatment (Kingsbury and Conaghan [2012]). Despite most GPs use the NICE recommendations (Conaghan et al. [2008]), providing guidance in patient management, educational material with common guidelines is still in demand (Kingsbury and Conaghan [2012]). Due to this, OA treatment is often based on experiences and intuition with varying results (Bhatia et al. [2013], Brooks [2014], Jamtvedt et al. [2008]), for which reason several consultations between the patient and the healthcare system are required to achieve a satisfactory result (Kingsbury and Conaghan [2012], Paskins et al. [2014]).

The main risk factor for a joint to lose homeostasis and initiate OA is believed to be ageing since the chondrocytes (cells in the articular cartilage) loses the function of maintaining the articular cartilage (Buckwalter et al. [2004]). The effect of age can be seen in Figure 1.2 showing the prevalence of knee OA (KOA) for different age groups.

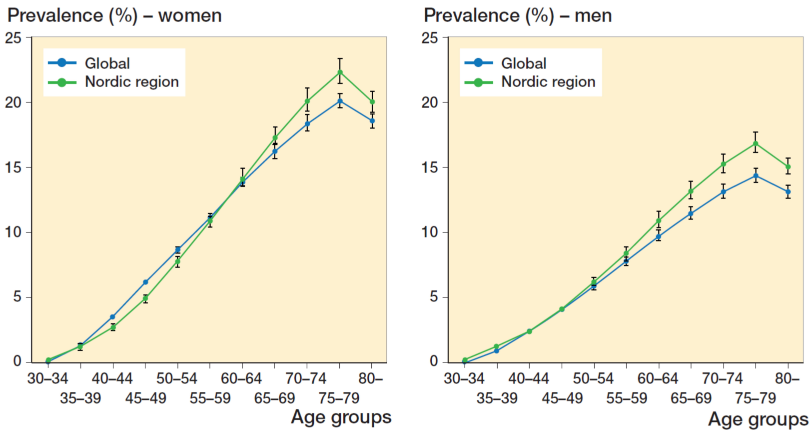


Fig. 1.2: Prevalence of KOA patients as percentage of age groups for men and women, both globally and locally in the Nordic region (Kiadaliri et al. [2018]).

Additional biomechanical factors also contribute to the risk of developing KOA. Studies have identified multiple phenotypes, depending on the joint, representing different mechanisms of the disease (Dell'Isola et al. [2016], Bierma-Zeinstra and Van Middelkoop [2017], Deveza et al. [2017]). These includes pain sensitization, radiographic severity, body mass index, muscle strength and inflammation among others, for which reason the underlying cause can vary and therefore also the necessary treatment, depending on the patient.

Once OA initiates, it is difficult to return to a stable state in the affected joint, and the disease will cause pain and stiffness due to synovial inflammation and cartilage degeneration (Richard Steadman et al. [2016]). The disease progresses gradually over time from mild to more severe cartilage degeneration, which can lead to bone-on-bone contact causing even more pain and stiffness to the joint (Buckwalter et al. [2004],Peters et al. [2005]). These symptoms limit the joint range-of-motion and thereby joint mobility. In most cases, the quality-of-life is affected negatively due to a slowly decreased activity level (Heidari et al. [2016]), which has a psychological effect (Dell'Isola et al. [2016]).

The most widely affected joint regarding OA is the knee (Arthritis Research

UK [2013], Martel-Pelletier et al. [2016]), which is considered as a biomechanically and anatomically complex joint (Turner and Craig [1980]). It consists of the tibiofemoral joint between femur (thigh) and tibia (shank) and the patellofemoral joint between patella (knee cap) and femur (Turner and Craig [1980]). The former is responsible for allowing bending (flexion-extension) of the leg and the patellofemoral joint allows patella to slide in a groove on the distal end of the femur during flexion and extension. This allows the quadriceps muscles to transfer the contraction force from thigh to tibia without spanning the knee and getting damaged by sharp bony edges.

This thesis mainly focuses on the tibiofemoral joint, which is shown below in Figure 1.3 for a healthy knee (A) and a knee affected by OA (B).

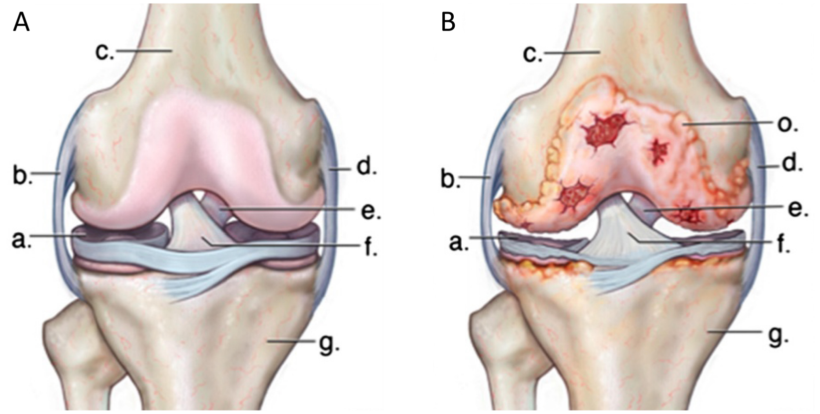


Fig. 1.3: A healthy knee joint (A) and a knee with cartilage deterioration caused by OA (B). The figure includes meniscus (a), lateral collateral ligament (b), femur bone (c), medial collateral ligament (d), posterior cruciate ligament (e), anterior cruciate ligament (f) and tibia bone (g). Modified figure from (Boyan et al. [2013]).

The joint connects the two longest bones of the human skeleton, and for this reason the flexor-extensor muscles around the knee often have to balance a large external moment in the sagittal plane created by gravity and inertia loads. These muscles also assist the ligaments in preventing undesirable displacement of tibia relative to femur, which can lead to loading of poorly suited structures damaging the surrounding cartilage and meniscus (Richard Steadman et al. [2016]). Even though the pathophysiology of the joint degeneration leading to clinical OA symptoms is still poorly understood (Buckwalter et al. [2004]), abnormal joint kinematics is considered as one of the most common reasons for knee OA (KOA) initiation (Andriacchi and Mündermann [2006a], Richard Steadman et al. [2016]). These kinematic changes are often caused by knee joint injuries, such as cruciate ligament rupture (Van Der Esch et al. [2005], Barenius et al. [2014]), which increases the laxity (joint looseness) of the knee, causing joint instability. In this case, physical training of the surrounding muscles becomes crucial to maintain stability and avoid KOA initiation, since knee instability changes the original load-bearing contact location to a new region, which may not be suited for these loads (Andriacchi and Mündermann [2006a]).

It has been shown that knee joint contact forces are not increased for early KOA patients (Meireles et al. [2016], Baert et al. [2013], Duffell et al. [2014]), which supports abnormal load pattern as a cause of KOA initiation and not the changes in joint load magnitude. However, once KOA initiates, the knee structures are particularly vulnerable to stress and wear, and since meniscus and cartilage deterioration rate depend on internal joint loads and stress distribution (Radin et al. [1991], Bennell et al. [2011]), mechanical overloading is considered as a cause for disease progression (Miyazaki et al. [2002], Andriacchi and Mündermann [2006b], Meireles et al. [2016]). This can lead to loss of meniscal tissue, which can permanently affect the knee homoeostasis to become unstable and accelerating OA progression (Vannini et al. [2016]).

Generally, the knee is one of the main weight-bearing joints in the human body (Segal [2012]) and plays a central role during most activities of daily living due to the frequently large external knee moment (Gross and Hillstrom [2008]). The flexor-extensor muscles must provide substantial muscle contraction forces to balance the large external moments around the knee joint, and this contributes to the internal joint compressive forces. According to *in vivo* studies, the knee is exposed to loads of approximately 2-3 times body weight (BW) in the tibiofemoral joint during gait (Fregly et al. [2012]). Higher knee compressive forces have been observed in females than male subjects (Ro et al. [2017]), which may be the cause of KOA being 2-3 times more prevalent in female patients (McKean et al. [2007]). Furthermore, women have smaller cartilage volume (Cicuttini et al. [1999]) and a smaller contact area in the knee to distribute the stresses (Lonner et al. [2008]). This is shown in Figure 1.4 with the ratio between femur medial-lateral and anterior-posterior dimensions for males and females. Despite the relatively low R^2 values, the trend indicates a generally smaller knee contact area for women, inducing higher stresses in the joint tissue, which is especially critical for woman above 50 years (Nicolella et al. [2012]).

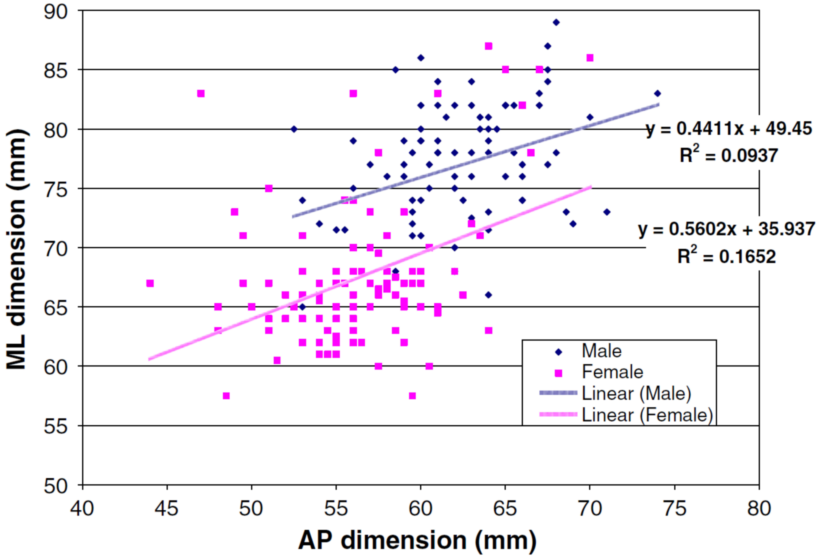


Fig. 1.4: The ratio between medial-lateral (ML) and anterior-posterior (AP) dimensions has been shown to be larger for males than females (Lonner et al. [2008]).

Due to the critical impact of mechanical overloading after KOA initiation in both males and females, biomechanical factors governing the loading and the load distribution of the tibiofemoral joint, such as obesity (Neogi [2013], Gabay et al. [2008]), joint malalignment (Mündermann et al. [2005], Isola et al. [2017]) and muscle activation (Fantini Pagani et al. [2013]), are considered risk factors for disease progression. Therefore, a common treatment of KOA is to unload the joint to stop the progression and to avoid the need for surgery, which is usually only considered when the disease is at a critical stage and no other options are available. To define the stage of OA, the progression severity can be evaluated by e.g. the Kellgren-Lawrence (KL) scale (Kellgren and Lawrence [1957]) using five OA grades from none (0) to severe (4). The grade level is based on the visual amount of degenerated tissue evaluated from an X-ray image like the ones below.

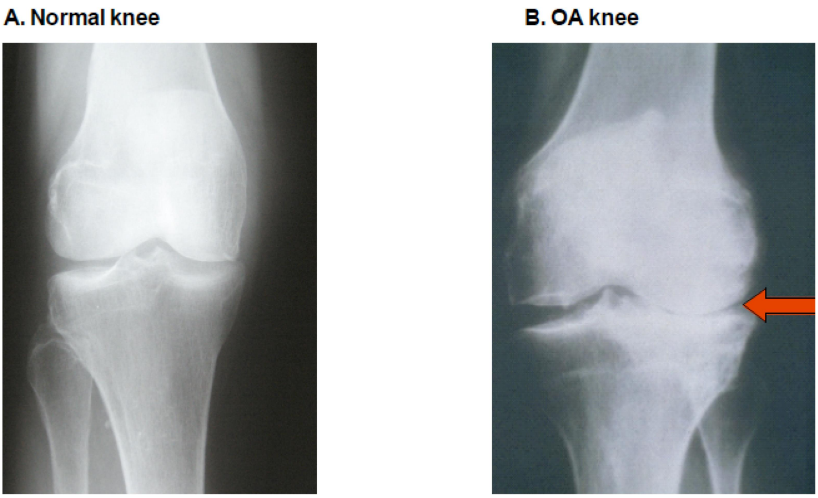


Fig. 1.5: X-ray images of A) a healthy knee and B) a knee joint affected by OA on the lateral compartment (red arrow) (Sofat et al. [2011]).

Figure 1.5 shows an example of X-ray images of a healthy knee joint (A) and a knee affected by OA (B) in the tibiofemoral joint. The dark space between the bones in Figure 1.5A indicates a healthy layer of soft tissue and meniscus for shock absorption, which is not visible in X-ray images. In Figure 1.5B, the space between femur and tibia's articular surfaces on the lateral side is reduced due to the loss of cartilage, and this joint space narrowing is used to evaluate a KL score. The lack of this stabilising tissue at the articular surfaces leads to instability and malalignment of the bones at the affected joint (Van Der Esch et al. [2005]) influencing the internal load distribution in the tibiofemoral joint. This can lead to abnormal load patterns for which reason knee malalignment is considered a risk factor for disease progression (Tanamas et al. [2009]). This is supported by Isola et al. [2017] who showed that varus alignment in medial knee OA patients alone is not responsible for increased medial contact force unless medial compartment degeneration is already present. This implies that knee malalignment is not responsible for KOA initiation but only disease progression, i.e. a consequence of KOA.

Often a poor correlation between x-ray findings and symptoms is observed (Bosomworth [2009],Bedson and Croft [2008]) regardless of the OA severity, meaning that some patients experience extensive pain despite of a low KL-score and vice versa. Especially pain affects the mobility during activities-of-daily-living and reduces quality-of-life (Bosomworth [2009], Segal et al. [2009]) for which reason it is the major complaint from KOA patients (Dessery et al. [2014]). Therefore, a scale to evaluate subjective pain is a common tool to investigate the effect of an intervention compared to baseline in research studies (Fransen et al. [2015]). Two frequently used pain evaluation schemes are "visual analogue scale" (VAS) (McCormack et al. [1988]) and "Western Ontario and McMaster Universities Osteoarthritis Index" (WOMAC) (Bellamy et al. [1988], McConnell et al. [2001]). These are further elaborated upon in Section 2.2.1.

As mentioned previously, most patients experience multiple consultations with the health care system before reaching a satisfactory result, which might be due to the many risk factors for developing KOA and causing disease progression. Therefore, a concept of phenotyping has been developed (Dell'Isola et al. [2016]), which makes it possible to divide KOA patients into subgroups based on individual risk factors. This helps doctors to classify the patients and choose the right treatment with the best possible outcome.

1.2 Common Treatments of KOA

Regardless of the cause for developing KOA, the main purpose of the available interventions is to reduce pain, since this is the symptom with the largest effect on activities-of-daily-living (Segal et al. [2009]). A reduced pain will increase mobility and the possibility to remain as active as their ability and condition allows to maintain a healthy lifestyle (Bennell et al. [2014]). Physical exercise keeps the joint tissue occasionally loaded, which can prevent the knee joint from unstable homoeostasis, since underloading is a critical factor regarding KOA progression (Moelgaard [2015]) (see Figure 1.1 on page 3). This has also been demonstrated by Wellsandt et al. [2016] who found a correlation between reduced knee joint loads during gait and development of KOA in a group with anterior cruciate ligament injury. This highlights the complexity of the disease and how the patient always must evaluate the pain symptoms against the physical ability.

Early intervention of KOA is one of the key factors to reduce disease progression and maintain quality-of-life (Duffell et al. [2014]), and if the soft tissue damages are still at an early stage, the disease is reversible, particularly in younger people (Ding et al. [2010]). This means that an intervention can change the joint from an unstable state to stable homoeostasis (see Figure 1.1 on page 3). Thus, identifying patients with early KOA is crucial to maintain the possibility for reversing disease progression or at least manage the symptoms through early intervention. According to recent findings, the early detection of KOA, or risk factors for developing KOA, should be done with magnetic resonance imaging (MRI) since the early knee structural changes, such as cartilage defects, meniscal tears, subchondral bone expansion and bone marrow lesions, are best assessed with MRI scans (Ding et al. [2010],Lowitz et al. [2013]). These early structural changes ultimately lead to more severe cartilage loss over time, causing irreversible radiographic osteoarthritis at a later stage as illustrated in Figure 1.5.

Variants of treatment are available to manage the symptoms for KOA patients, depending on the stage of the disease. These treatments include physical activity (Fitzgerald et al. [2016]), pharmaceuticals such as non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen (paracetamol) (McAlindon et al. [2014]), shoe insoles (Skou et al. [2013]), knee braces (Brooks [2014]) and surgery (Gardiner et al. [2016]). However, as mentioned previously, the main cause of disease, and therefore also the right treatment, can be difficult to determine (Dell'Isola et al. [2016]).

1.2.1 Physical Training

One of the core treatments to manage KOA and most often the first approach is physical training, either on land or in water, to obtain weight loss, muscle strengthening and joint flexibility (Kingsbury and Conaghan [2012], McAlindon et al. [2014]). The treatment is recommended for all OA patients regardless of disease severity, age, pain and functional status (Bennell et al. [2014]), and it usually consists of lower extremity muscular strength training, joint mobility, and aerobic exercises Fitzgerald et al. [2016].

Since most KOA patients are obese, weight loss through physical training is crucial for these patients to reduce the load burden and pain in the knee joints (Messier et al. [2005], Richette et al. [2011]). This intervention has also shown to improve pain and physical function (Richette et al. [2011], Fransen et al. [2015], Skou and Roos [2017]), and Hanna et al. [2007] showed a positive effect on knee cartilage in healthy women aged 40 to 67 years using solely physical training. However, most studies claim that this treatment only provides small to moderate effect for KOA patients regarding physical function and pain is even less affected (Bosomworth [2009], Fransen et al. [2015], Yusuf [2016]). Some patients do not experience any improvements at all to physical training (Yusuf [2016], Bennell et al. [2014]), and those who respond well to the treatment often only experience a short-term effect in the duration of the intervention due to lack of adherence to the exercise therapy (Bosomworth [2009], Bennell et al. [2014]).

The findings above suggest a more structured and personalised training program is needed taking individual needs and preferences into account to maintain participation from the patients. This has been achieved with a Danish supervised neuromuscular exercise program by certified physiotherapists under the name "Good Life with osteoArthritis in Denmark" (GLA:D^{TM}) (Skou and Roos [2017]). Such a program provides a relatively cost-effective approach to exercise prescription and maximises the adherence to the exercises (Bennell et al. [2014]). Furthermore, the continuous monitoring by physiotherapists maintains the quality of the performance and enhances positive exercise beliefs and self-efficacy in people with KOA (Skou and Roos [2017]).

1.2.2 Pharmaceutical Treatment

The missing compliance with physical training may be due to the option of pharmaceutical treatment, which is often as effective and therefore makes it tempting for the patient to take the easy way (Bennell et al. [2014], Fransen et al. [2015], Yusuf [2016]). This type of pain medicine is often used as the mainstay for managing KOA symptoms starting with mild paracetamol and moving on to stronger NSAIDs (Sofat et al. [2011]), and 56% of the included KOA patients in the Danish GLA:D^{TM} project used pain medicine within three month before the study (Skou and Roos [2017]). Oral NSAIDs are among the most common pharmaceutical approaches for KOA treatment (Carlson et al. [2018]), and in 2012, this type of drugs was prescribed to 65% of all American KOA patients (Gore et al. [2012]).

As opposed to the physical treatment, pharmaceuticals mainly reduce pain, whereas the functional effects varies in the literature (Miller et al. [2020]). Despite OA is an inflammatory disease and NSAIDs have anti-inflammatory functionality acting as a disease-modifying agent at higher doses (Haroon et al. [2012]), currently no scientific evidence exists suggesting drugs to effectively alter or prevent the progression of osteoarthritis (Croff [2013]).

Despite limiting side effects using small doses, a long-term use of NSAIDs can accumulate the amount of toxicity and increases the risk of gastrointestinal complications (Miller et al. [2020]). For this reason, oral NSAIDs are generally recommended for intermittent or cyclic use and the OARSI guidelines strongly advise against oral NSAIDs for patients with high comorbidity risk (McAlindon et al. [2014]). This recommended limited use results in a reduced therapeutic effectiveness of a pharmaceutical treatment since KOA patients most often experience continuous pain (Gallelli et al. [2013]).

1.2.3 Orthoses

Since the physical and pharmaceutical treatments often only provide small to moderate effects, orthoses can be used as additional low-cost intervention to manage KOA. These mainly include knee braces and laterally wedged insoles with the aim to mechanically unload the critical loaded joint structures, which is expected to improve function and relieve knee pain (Brooks [2014], Brand et al. [2017]). Since the centre-of-mass of the body is located medially with respect to the knee joints, a knee varus moment, known as the knee adduction moment (KAM), is generated during most activities of daily living. This moment contributes to an uneven load distribution in the knee causing the medial compartment to carry up to 2.2 times more load than the lateral compartment during midstance of gait in normally aligned knees (Gohal et al. [2018]).

Due to this influence on the internal load distribution, KAM is often used as a surrogate for the internal medial-lateral load distribution in the knee joint

(Gohal et al. [2018]) and therefore a target measurement for orthotic interventions. Furthermore, both peak and mean KAM during normal gait is larger in medial KOA patients than in healthy subjects (Baghaei Roodsari et al. [2017]), for which reason both knee braces and insoles most often aim to reduce KAM. This is believed to shift the compartment loads more laterally from infected areas to healthy structures. However, this intervention type is still debated in the literature with inconclusive results, both regarding shoe insoles (Parkes et al. [2013], Xing et al. [2017], Shaw et al. [2018], Felson et al. [2019]) and knee braces (Richard Steadman et al. [2016], Moyer et al. [2017], Gohal et al. [2018], Moyer et al. [2015b]). Researchers are still in contradiction whether insoles or knee braces are the most efficient treatment for KOA patients (Baghaei Roodsari et al. [2017]), but studies indicate that the two intervention types combined have a greater effect on KAM than if used individually (Moyer et al. [2013], Moyer et al. [2017]). Insoles have been reported to be more comfortable and less bulky than knee braces (Baghaei Roodsari et al. [2017]), which may be the main reasons for a higher compliance in insole groups compared to brace groups (Duivenvoorden et al. [2015b]).

1.2.4 Surgery

If a patient experiences severe KOA accompanied with poor quality-of-life and all of the above non-invasive pharmacological therapies are no longer effective, a total knee replacement, also known as a total knee arthroplasty (TKA), can be used as a last resort (Bourne et al. [2010], Bruyère et al. [2014]). The treatment is cost-effective (Dakin et al. [2012]) and a very common procedure, which is expected to increase in rate (Ravi et al. [2012], Chawla et al. [2017]). However, TKA is an invasive procedure that puts patients at risk for complications such as infection and venous thromboembolism (Healy et al. [2013]). Furthermore, some patients experience postoperative pain (wen Li et al. [2019]), infection (Le et al. [2014]) and aseptic loosening of the implants (Zimmerman et al. [2016]) after surgery, leading to mechanical instability and the need for revision surgery (Pedersen et al. [2012], Le et al. [2014]). Revision rates after 10 years have been estimated to 12% (Labek et al. [2011]), and a study by Bourne et al. [2010] reported dissatisfaction in 19% of the patients receiving a TKA, especially the patients below 70 years of age. This may be due to a significantly higher risk of revision for this patient group (Bayliss et al. [2017]), since younger and more active patients increase wear of the implants (Fernandez-Fernandez and Rodriguez-Merchan [2015]). Thus, TKA is reserved for the older patients with severe OA, which proves the importance of non-invasive treatment to slow down disease progression delaying the onset of late-stage KOA and thereby postpone the need for surgery.

1.3 Knee Braces

This PhD thesis deals with knee braces as a treatment for managing KOA symptoms, and this section presents the concepts currently available on the market and latest research within clinical tests. Additionally, the missing elements in the current state-of-the-art braces are presented to identify how the work and results of this thesis can contribute to the research area.

As written in Section 1.2.3 on page 11, the main goal with a knee brace is to unload the internal knee structures of the KOA patient. This can be done in several ways and, according to the American Academy of Orthopaedic Surgeons, knee braces can be fitted into four categories covering different target groups and needs (France and Paulos [1994]):

1. **Prophylactic** - prevent or reduce the severity of knee injuries in contact sports, most often through protection against lateral impact causing damage to the medial collateral ligaments (MCL)

2. **Rehabilitative** - stabilization of injured knees during rehabilitation by limiting and controlling the joint motion, mainly extension angle after a cruciate ligament injury to avoid hyper-extension

3. **Functional** - has the same stabilization properties as category 2 and additionally applies a load

4. **Patellofemoral** - designed to protect patella from abnormal motion, mainly medial/lateral, and relieve anterior knee pain

Since this thesis deals with KOA patients, the most interesting brace group is category 3, functional braces, however most knee braces relate to multiple groups. Knee braces can be divided into soft and hard types of which the former typically refers to an elastic neoprene sleeve, which compresses around the knee joint. Hard knee braces has a more advanced design and provides stability, movement limitation, or passively applies an external load to reduce internal joint loads and ensure joint alignment. These additional functionalities provide protection against injuries, instability during activities and prevention of a previous or current disease from developing (Beaudreuil et al. [2009]). Thus, hard brace types have more potential to affect the related symptoms in KOA patients and a study from Kirkley et al. [1999] evaluated hard knee braces to be more efficient regarding pain relief than neoprene sleeves.

The main focus in this thesis is on hard braces since this is the type that will be developed in the project, but soft braces are explained shortly in the following section.

Soft Knee Braces

These elastic protection sleeves are simple braces with minor mechanical actions including compression from its elastic synthetic fiber material such as neoprene or elastic cotton (Segal [2012]), which passively applies a very small extension moment during knee flexion. It is designed to stretch in certain directions to provide joint stability and is therefore often recommended when returning from a ligament injury.

Studies on OA patients wearing sleeves have demonstrated pain relief (Kirkley et al. [1999], Mazzuca et al. [2004]), but the stiffness and mechanical action of these have been reported to be very low and basically negligible compared to hard brace types (Pierrat et al. [2014b], Pierrat et al. [2014a], Birmingham et al. [2008]). Pain reduction may be caused by an increase in blood flow due to the tight material and retaining of body heat in the joint. However, Mazzuca et al. [2004] compared a normal sleeve with one specially fabricated for retaining body heat but found no significant difference in pain relief between the two groups. Therefore, the cause for pain reduction is unclear but placebo effect may have an influence. Another explanation can be homeostasis (Gardiner et al. [2016]), which is explained in Section 1.1 on page 3.

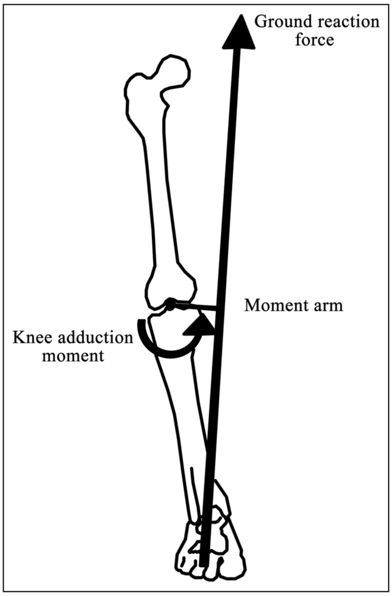
Research indicates that knee sleeves are efficient for treating patellofemoral OA due to realignment of the patella, which increases the contact area with the femur, leading to reduced stresses in this joint (Hunter et al. [2011], Callaghan et al. [2015]). Nevertheless, a knee sleeve is a low cost solution and due to its simple design, it fits more easily and is less bulky than a hard knee brace, which may be the main reasons for the slightly higher compliance for soft knee braces among OA patients (Birmingham et al. [2008]).

Hard Knee Braces

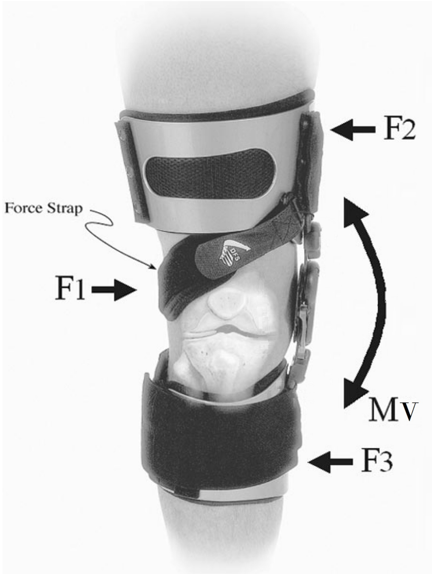
This type of brace (referred to as brace in the rest of the thesis) can have a sleeve base made of elastic fabric such as neoprene with a solid surrounding frame of aluminium, polymer or carbon composite (Brooks [2014]). Stiff protection sidebars are attached on either both sides (bilateral or dual upright brace) or only one side (unilateral or single upright brace) of each brace cuff. These sidebars are connected with a dual/biaxial hinge to connect the thigh and shank cuffs (Brooks [2014]), and adjustable Velcro straps are used to tighten and ensure best possible fit.

Two sidebars and a hinge joint combined is called an upright, and if the main purpose of a brace is to avoid abnormal knee kinematics between femur and tibia (category 1), it is usually a dual upright brace to increase the stiffness and stability. If the brace is solely for stabilising (category 2), blocks in the hinge joints are used to limit the extension angle to avoid hyper-extension of the knee. This kind of brace is often needed for patients with prior ligament injuries leading to increased laxity of the joint, for which reason the brace should prevent abnormal joint loadings. This is, as mentioned in Section 1.1 on page 3, a risk factor for developing KOA. These two brace categories apply no mechanical actions and are referred to as simple hinge braces. Although, the ability to improve confidence and function in KOA patients during gait has been demonstrated with a simple hinge brace, unloading braces (category 3) have shown higher benefits regarding pain relief and knee joint load reduction during walking (Richards et al. [2005], Gohal et al. [2018]). Thus, it seems like an additional unloading function is necessary when dealing with KOA patients.

As mentioned in Section 1.2.3 on page 11, the medial knee compartment carries twice the load compared to the lateral, partly due to the external KAM. This varus moment is generated from the ground reaction forces (GRF) between the foot and the ground during stance phase (Kaufman et al. [2001]), which is illustrated in Figure 1.6a. The size of the GRF depends on body mass and the dynamical impact between foot and ground, whereas the lever arm to the knee centre is controlled through the mechanical alignment of the thigh and shank bones. Additionally, cartilage deterioration rate depends highly on joint loads (Radin et al. [1991]) for which reason the risk of having medial KOA is much higher than lateral KOA (Segal [2012]). Therefore, most of the unloader knee braces on the market are designed to unload the medial compartment (Duivenvoorden et al. [2015a]). Furthermore, due to the aforementioned focus on KAM, the most common brace type is a valgus brace, which applies an external valgus moment to counteract KAM (Brooks [2014], Moyer et al. [2015a]). This moment is believed to redistribute the internal joint loads to less affected structures and thereby slow down the disease progression and increase the mobility of the joint. The counteracting brace moment can be applied in different ways, but the most common is the so-called three-point leverage system (Ebert et al. [2014]), which is shown in Figure 1.6b. This approach uses an adjustable force strap to produce a medially directed force (F1) on the lateral side and two laterally directed forces (F2 and F3) at the side bar ends on the medial side, transferring a valgus moment through the joint (Pollo et al. [2002]).



(a)



(b)

Fig. 1.6: A right leg illustrating a) KAM, which depends on the ground reaction force and the moment arm (picture from Khalaj et al. [2014]), and b) the three-point leverage system for applying a counteracting valgus moment (Mv) by means of the three forces F1, F2 and F3 (modified picture from Pollo et al. [2002]).

Although the majority of KOA patients suffer from medial OA, obviously the unloading principle in Figure 1.6b is also applicable for lateral KOA patients by using the same principle to apply a varus moment to unload the lateral compartment.

1.3.1 Latest Research

Knee brace treatment is cost-effective with the potential to postpone the need for surgery (Lee et al. [2017]), and especially valgus knee braces have shown positive results regarding pain relief, knee compressive force reduction and functionality during gait in medial KOA patients (Brandon et al. [2019], Brand et al. [2017], Ostrander et al. [2016]). However, although the positive outcome supports brace use, there is currently no biomechanical evidence suggesting that the reduction of knee compartment loads significantly slows down disease progression (Richard Steadman et al. [2016]). Furthermore, some studies found none or only small effect from the use of knee bracing (Ebert et al. [2014], Duivenvoorden et al. [2015b], Moyer et al. [2015c]), which highlights the inconclusive evidence of bracing treatment.

Knee Adduction Moment

The varying effect from knee braces may be due to the predominant focus on the external KAM when evaluating the effect (Richard Steadman et al. [2016], Petersen et al. [2016], Brand et al. [2017]), which is based on the intuitive link between KAM and the compressive forces in the medial compartment. However, these two biomechanical factors may not be directly related since a reduced KAM does not guarantee a reduction of medial knee contact forces (Walter et al. [2010]). The correlation between KAM and cartilage damage has been investigated by Brisson et al. [2016] who only observed a correlation for obese subjects with a Body Mass Index (BMI) above 30. However, obese patients can be challenging to treat with knee braces due to the thickness of soft tissues.

When combining findings from Fantini Pagani et al. [2010b] with *in vivo* measurements, the reduction of the external KAM is 2-3 times higher than the observed reduction in medial KCF (Kutzner et al. [2011]). This correlates well with (Baghaei Roodsari et al. [2017]) who estimated a 3% reduction in KAM would cause a reduction in medial KCF of 1%, which may be the reason for the varying effect from valgus braces. Fantini Pagani et al. [2010a] tested a neutral brace and a 4 degrees valgus brace and, despite a lower KAM for the valgus brace, the same effect was observed regarding pain and functionality. *In vivo* knee load data from Walter et al. [2010] revealed the best correlation between the two variables at late stance (second peak), whereas Kutzner et al. [2013] found the strongest correlation during early stance (first peak), also using *in vivo* data.

Another approach for assessing brace effect *in vivo* is using fluoroscopy to evaluate bone separation. Nadaud et al. [2005] reported medial condyle separation in most subjects with a valgus brace at heel strike, midstance and toe-off. However, at these stages the knee experiences the lowest compressive loads during the gait cycle (Kutzner et al. [2011]), and therefore the separation significantly decreased when taken an average over the whole stance phase. A study by Haladik et al. [2014] did not report any condyle separation during valgus bracing, which underlines the need for including additional biomechanical factors other than KAM.

Knee Flexion-Extension Moment

The findings above illustrate the inconclusive relationship between KAM and medial KCF and *in vivo* studies suggest that additional biomehanical factors influence the joint loads and thereby affect brace effectiveness (Walter et al. [2010], Kutzner et al. [2011], Meyer et al. [2013]). An alternative predictor of peak medial compartment force was proposed to be the knee flexion-extension moment (KFM), which has also been suggested based on *in silico* studies (Kumar et al. [2013], Manal et al. [2015a], Meireles et al. [2016], Stoltze et al.

[2018], Richards et al. [2018]). The KFM has been proposed to be an indicator of the net muscular contraction across the knee joint (Meyer et al. [2013]), and each muscle contraction contributes to the internal joint loads (Herzog et al. [2003], Walter et al. [2010], Meyer et al. [2013]). Thus, both the KAM and KFM need to be considered to evaluate the effect from an orthosis, which may explain the varying response from KOA patients wearing valgus braces.

An increased concern regarding the role of KFM on KCF has been observed in the literature when dealing with valgus braces (Creaby [2015]), since the influence of the muscle contractions makes it hard to know if the medial compartment is unloaded by the applied valgus moment (Moyer et al. [2017]). As mentioned, *in vivo* knee load data suggests, that a reduction of medial compartment load requires 2-3 times higher reduction of KAM for which reason it may require an uncomfortably large applied valgus moment to obtain a satisfied load reduction. Simulations by Miller et al. [2015] show that the joint contact force is reduced almost twice as much from gait modifications minimising both KAM and knee flexor muscle activity compared to only minimising KAM. This indicates that both KAM and KFM play a role in the joint loads but despite of these findings, knee braces are often evaluated on the ability to decrease KAM. Several studies claim to unload the medial compartment with a valgus brace during walking based on a reduction of KAM, both in OA patients (Baghaei Roodsari et al. [2017], Maleki et al. [2016], Jones et al. [2013], Dessery et al. [2014]) and healthy subjects (Hall et al. [2019], Orishimo et al. [2013]). Furthermore, a review by Petersen et al. [2016] has KAM outcome as an inclusion criterion, which limits the brace evaluation significantly since other biomechanical factors, which potentially could lead to a larger load reduction, are not considered.

Both peak KAM and peak KFM has been demonstrated as significant predictors of the medial KCF (Manal et al. [2015b]), but a combination of the two improves the prediction significantly (Walter et al. [2010], Manal et al. [2015b]). This correlates well with *in silico* results in a study by Stoltze et al. [2018] showing how a reduction in KAM and KFM affects the KCF, both individually and combined. The study demonstrated the potential for unloading the first peak total KCF through KFM reduction in early-stance whereas a reduced KAM only shifts the load from one compartment to the other.

According to (Manal et al. [2015b]), the Grand Challenge 2012 *in vivo* data set revealed an increase of peak medial contact force from 1.80 BWs during normal gait to 2.57 BWs during medial thrust gait despite a reduction in peak KAM. This is expected to be due to an increased knee flexion angle at the first peak, which is common when performing this type of gait modification (Walter et al. [2010], Fregly et al. [2007]). A larger flexion angle requires a larger knee extension moment when approaching mid-stance leading to higher KCF. Thus, if a valgus brace causes a patient to walk with medial thrust due to the applied moment, it may not have the intended effect. An increase of KFM has been observed during normal gait when wearing a valgus brace (Moyer et al. [2017], Jafarnezhadgero et al. [2018]), which may increase joint loads despite a reduced KAM. This is consistent with a study by Walter et al. [2010] who also observed reduced first peak KAM but not a reduced medial compartment load, whereas the second peak medial compartment load was reduced despite no change in second peak KAM. Similarly, an increase in KAM has been observed in gait strategies which reduce KFM (Jenkyn et al. [2008], Favre et al. [2016]), concluding that a reduction of one may cause the other to increase and the KCF could be unchanged or increased.

Unloading Concepts

An alternative to the traditional three-point leverage system for applying a valgus moment was presented by Hangalur et al. [2018], who developed an upright, which was used to apply an adjustable moment. The moment was solely applied from potential energy stored in the pre-tensioned uprights eliminating the need for the force strap in Figure 1.6 on page 16. The new design was reported to be more comfortable than a conventional valgus brace and thus could be used for longer periods of time.

Another way of reducing the medial compartment load is simply by distraction of tibia and femur as attempted with the Odra brace (Orthoconcept Inc., Laval, QC, Canada). This has a rack and pinion gear inducing translational motion when the knee is extended and no effect when the knee is fully flexed (Dessery et al. [2014], Laroche et al. [2014]). However, it seems unlikely that an applied distraction force to femur and tibia would efficiently unload the knee due to soft tissue and possible migration of the brace up or down the leg. Additionally, the Odra brace has external rotation of tibia during knee extension which may be inspired from studies showing that altering the foot progression angle laterally, known as toe out, decreases the KAM during walking and stair climbing (Guo et al. [2007], Jenkyn et al. [2008]). Both Dessery et al. [2014] and Laroche et al. [2014] indicate a decreased KAM with the Odra brace but as previously mentioned, this does not provide sufficient information about the joint loads.

Recent studies have investigated two different knee braces providing knee extension assistance to reduce the KFM; the OA Rehabilitator™ brace (Guardian Brace, Pinellas Park, Florida) (Cherian et al. [2015]) and the Levitation® Tri-Compartment Unloader (Spring Loaded Technology Inc., Halifax, Nova Scotia, Canada) (McGibbon et al. [2021]). Both braces store potential energy during knee flexion and assist knee extension. The Rehabilitator brace was compared to standard of care treatments in a prospective, randomized trial study including patients with Kellgren-Lawrence grades 3 to 4 (Cherian et al. [2015]). The braced patients demonstrated significant improvements in muscle strength, several functional tests, and patient-reported outcomes when compared to the matched cohort. It seems contradictory to obtain increased muscle strength when using an intervention with the aim of assisting muscle activation, but maybe the ability to be more active provides the additional muscle activation compared to the control group. The levitation brace has been tested *in silico* based on deep knee bend motion data providing a reduction in total KCF of up to 27% body weight (McGibbon et al. [2021]). Budarick et al. [2020] compared the applied moment for angles 0-90 degrees revealing that the Levitation brace provides the largest assistive moment indicating this brace to be the most efficient in reducing muscle loads among those currently on the market.

1.3.2 Limitation of Current Knee Braces

Despite the extensive research and development work of knee braces, some limitations are still present. Both regarding the scientific studies and the function of the common braces on the market, which are presented in the following sections.

Subject-specific Data

As previously explained, the scientific evidence for bracing is missing and the mechanical effects and the biomechanical understanding remains unclear (Duivenvoorden et al. [2015a], Gohal et al. [2018]). Furthermore, the pain reduction and biomechanical behaviour vary with both the intervention device and the patient (Pierrat et al. [2014b], Segal [2012], Duivenvoorden et al. [2015b]). Since all humans are unique, individual assessment and intervention for musculoskeletal dysfunctions are typically required, which is also the case for KOA (Zhang et al. [2010]). As mentioned in Section 1.3.1, the intervention depends on the cause of KOA, since only certain phenotype groups respond positively to specific treatments (Dell'Isola et al. [2016], Deveza et al. [2017]). Thus, identifying the different phenotypes can optimise the treatment, so a pre-screening of the patients would provide valuable clinical information to include the correct subjects for the investigated treatment in clinical studies. If e.g. mechanical overloading is responsible for the disease progression, the patient most likely responds well to knee bracing whereas patients with chronic pain due to central sensitisation or high levels of inflammatory biomarkers may obtain a more efficient effect from NSAIDs. A pre-screening session, analysing activities-of-daily-living with motion capture and MS modeling, could be a way to identify the patient group who experiences mechanical overload of the knee joint. These biomechanical analyses provide information on the individual patient's anatomy, gait pattern and joint properties, which can be used to assess the most suitable type of orthosis to match the specific patient. However, very few studies consider the cause of KOA when including patients, indicating the lack of evidence may be a consequence of missing in-depth understand of what factors have initiated the condition, and how this influences the individual biomechanical behavior in the affected joint.

The expression "custom brace" is often seen in the literature (Petersen et al. [2016]) demonstrating the effort to match a brace to the individual patient. Although studies rarely specify what has been customised or fitted to the included subjects (Ramsey et al. [2007], Moyer et al. [2013], Dessery et al. [2014], Jafarnezhadgero et al. [2018]), it is assumed to be based on limb size and morphology (Moyer et al. [2015a]). Arazpour et al. [2014] custom-moulded knee braces from a cast of each subjects lower extremity, whereas Draganich [2006] made custom braces based on anthropometric measurements. The custom-made braces are believed to improve the fitting and comfort compared to off-the-shelf braces and thus enhance compliance. However, fitting a brace according to the outer leg contour only takes the leg surface and knee alignment into account. The brace is not fitted to the size of the applied loads and external moments, which would be possible to take into account by using MS models. Roberts et al. [2017] identified three KOA subgroups based on gait characteristics; biphasics, flexors and counter-rotators. The biphasic group exhibited a larger knee extension moment in the early stance phase and a significantly larger KAM than the other two groups, indicating that this group is best suited for conservative treatments designed to apply an external moment. MS models can be used to identify which group a patient falls under and determine which treatment is most appropriate.

According to Brooks [2014], 42 OA-specific knee braces existed on the market in January 2013, including both custom and off-the-shelf braces, which has increased since then. The large amount of different braces makes it difficult to select the correct type and design for the specific patient. Physiotherapists and GPs highly rely on patient feedback, which mostly depends on the comfort of wearing the brace. However, a study from Pierrat et al. [2014b] indicated that the most comfortable brace is not necessarily the best choice regarding stability and function. This emphasizes the need for subject-specific biomechanical analyses to determine the best-suited orthosis, which has the potential to reduce consultant time with the health care system.

Compliance

Most studies are limited to examining immediate brace effect without including long-term effects and compliance, which highly affect the treatment (Gohal et al. [2018] ,Parween et al. [2019]). Large variability in compliance has been observed, ranging from one to 27 hours a week (Hart et al. [2016]) and below two to more than eight hours a day (YU et al. [2015]). Despite pain relief, brace compliance for KOA patients has been reported to decrease already beyond one-month period (Moyer et al. [2015a], Squyer et al. [2013]) and the chance for continued use of brace beyond the first year has been estimated to be approximately 25% (Squyer et al. [2013]). However, according to Lee et al. [2017] it requires at least two years of bracing to avoid surgery.

Another challenge in long-term studies is the high dropout rate. A study by Brouwer et al. [2006] experienced discontinued bracing from more than 30% of the participants within the 12 months completion period, and similarly less than 60% of the total amount of participants completed week 52 in a study by (YU et al. [2015]).

Multiple reasons for lack of compliance have been reported such as discomfort (Brandon et al. [2019], Jones et al. [2013]), bad fit (Van Raaij et al. [2010]), skin irritation (Van Raaij et al. [2010]) and aesthetic aspects (Squyer et al. [2013]). Discomfort may arise from the applied valgus moment acting in an "unatural" direction of the knee motion. Most medial KOA patients have a varus-aligned knee (Brouwer et al. [2006]), and thus it would seem obvious to apply a valgus moment to realign the knee joint. However, Van Raaij et al. [2010] failed to reduce varus malalignment using a valgus brace, which may require a large valgus moment to achieve. A valgus adjustment of up to 10 degrees is possible with e.g. the Donjoy Defiance OA brace (DJO Global, Guildford, UK). However, wearing a brace with eight degrees for a longer durations of time have shown discomfort in patients (Kutzner et al. [2011]), which most likely causes lower compliance. Thus, some patients with large malalignment might be more suited for an alternative bracing approach, which MS models would be able to detect. Furthermore, reduced flexion angle wearing a valgus brace during gait has been reported by Dessery et al. [2014], which could be due to unwanted limitation or discomfort from the brace.

Placebo

The effect size of placebo in KOA treatment has been estimated to 0.52 (Zhang et al. [2008]), which mostly affects the subjective measurements. This makes it difficult to determine whether outcome measures are changing due to the function of a knee brace, or because the subject expects the device to improve functionality. The latter was investigated by Balsamo et al. [2018] who tested two identical braces on healthy subjects who were told one brace could dynamically adapt to the specific gait. The study did not observe any differences in gait kinematics between the two braces, but most participants preferred the altered stiffness brace, both before and after testing. This is called "placebo analgesia" and highlights the importance of including a placebo group when subjective measurements, such as pain, are used to evaluate orthotic devices. However, out of 198 included studies in a meta-analysis by Zhang et al. [2008], only three studies included a placebo group in addition to untreated control groups and those three studies confirmed the effect of placebo based on improvement from baseline.

Placebo effect from braces can be evaluated by comparing measurements with a passive/neutral brace without any function. A study from Moyer et al. [2015b] observed a significant reduction in pain and functional improvement between a valgus brace group and a non-brace control group. However, the standardized mean difference for pain dropped 60% and the functional effect was omitted when comparing the brace group with knee braces in neutral position. Furthermore, Fantini Pagani et al. [2013] investigated muscle activity in KOA patients while comparing a neutrally aligned brace with a 4 degrees valgus brace and trials without brace. The neutrally aligned brace increased stability and functionality from reduced co-contractions, which may be due to psychological reasons of enhanced confidence when wearing a device. Similarly, in a previous study by Fantini Pagani et al. [2010a], the same neutral brace had the same effect as a 4 degrees valgus brace regarding pain relief and improvement in function. The same effect was observed by Ramsey et al. [2007] who found no difference between a neutrally aligned knee brace and a valgus brace. Similarly, Haladik et al. [2014] found bracing to be effective in improving pain and function through WOMAC scores but no change was observed in medial nor lateral compartment joint space based on *in vivo* fluoroscopy measurements. A placebo condition would have demonstrated whether the improved outcome was caused by the applied valgus moment.

KOA patients often show increased level of muscle co-contractions compared to healthy subjects (Trepczynski et al. [2018]), for which reason patients are sensitive to reduced activation of antagonist muscle groups leading to lower KCF. It is well known that muscle co-contractions are reduced in the lower extremity muscles for patients wearing an unloader brace (Ramsey et al. [2007], Fantini Pagani et al. [2013], Brandon et al. [2019]), for which reason the effect from conventional valgus braces may partly be caused by decreased muscle contractions rather than the applied valgus moment. This may be the reason why valgus bracing on healthy adults does not lead to reduced KCF (Hall et al. [2019]), indicating a potential placebo effect is partly responsible for positive patient feedback from bracing. This may be caused by reduced muscle co-contractions through psychological effects, which could be investigated by including a placebo condition. Generally, the inclusion of blinded placebo investigation will enhance the level of evidence in clinical studies using subjective measurements for evaluation.

Total Load Reduction

The main purpose of valgus braces is to shift the load from one compartment to the other without any reduction of the total KCF. Thus, long-term use of a valgus brace for medial KOA patients may have a negative effect on the lateral compartment and vice versa due to the redistributed load from the applied valgus moment (Brandon et al. [2019], Felson et al. [2019]).

As mentioned previously, the Levitation brace from Spring Loaded Technology applies a passive knee extension moment, using liquid compression springs to reduce muscle loads with the purpose of reducing the total KCF (Budarick et al. [2020]). However, the applied moment is limited when used for gait due to a large flexion angle in the swing phase, which has been reported to be approximately 60 degrees for KOA patients (Richards et al. [2005]). At this angle the Levitation brace applies approximately 11 Nm (Budarick et al. [2020]), which most likely affects the lower limbs negatively during swing phase regarding toe clearance. This forces the tibialis anterior muscle to apply ankle dorsi-flexion and increased activation of the knee flexor muscles. Since the KCF are usually relatively small during swing phase (Kutzner et al. [2011]), increased muscle loads in this phase will increase the loads and stresses in articular surfaces, which are not suited for high loads. Thus, it would be preferable to limit the applied extension moment to the stance phase only, although this would make the brace design more complicated.

The Levitation brace has only been tested *in silico* assuming rigid connection between brace and leg, and only for healthy subjects performing large knee flexion angles during deep knee bends (Budarick et al. [2020], McGibbon et al. [2021]). Soft tissue movements will influence the load transfer from the brace to the leg and reduce the effect from the applied moment, which would be much smaller during gait compared to a deep knee bend. The peak knee flexion angle during stance phase of gait has been reported to be 19 degrees in early stance for KOA patients (Heiden et al. [2009], Richards et al. [2005]) and at this angle, the Levitation brace would apply an extension moment of approximately 5 Nm (Budarick et al. [2020]). The required extension moment in early stance is highly individual, so 5 Nm may be sufficient to significantly reduce the KCF in some patients, but clinical tests of this type of knee brace are needed to validate the approach in KOA patients.

2. Aim of Study

Due to the lack of evidence for knee bracing, the overall aim with this thesis is to provide a better understanding of the biomechanical factors for optimising a subject-specific intervention and thereby improve the treatment through bracing. The main aims with the work of this project are to 1) analyse various approaches for efficiently unloading the knee joint and 2) develop and experimentally test a subject-specific prototype knee brace using a concept based on the findings in step 1) and investigate the effect on pain during gait. The prototype brace should have an adjustable design, which can be fitted individually and thereby improve the brace treatment of KOA compared to existing braces on the market. Most of these conventional braces aim to shift the load from one compartment to the other, whereas the prototype should be able to reduce the total knee compressive forces (KCF). The individual adjustment of the prototype is based on measured parameters, which are collected in a workflow using advanced biomechanical analyses to minimise the loads in the affected joint. Thus, the outcome from this project is expected to have the potential to advance the state-of-the-art by ensuring the intervention to effectively minimise the joint loads for every patient. This provides the patients a greater chance for initially choosing the correct intervention, improving quality-of-life without multiple consultations with the healthcare system.

The aim above will be achieved with three studies of which the first has analysed how applied moments around the hip, knee and ankle joints affect the knee compressive forces. The second study explains the development and testing of a prototype knee brace on a healthy subject, using a novel unloading approach and, in the third study, the same prototype is tested on a KOA patient. The introduced unloading concept is not limited to a single compartment, like a conventional valgus brace, but reduces the KCF of the entire knee joint. Furthermore, the prototype is adjustable to obtain individual treatment, which is tested to validate the potential of the unloading concept.

2.1 Concept of New Device

The concept of the prototype knee brace is similar to the aforementioned Levitation brace, which applies a passive knee extension moment from stored potential energy. The amount stored increases with flexion angle and is released during knee extension compensating for the extensor muscles.

Based on the current research, presented in Section 1.3.1 on page 16, a reduced muscle activation is expected to decrease the internal KCF relieving pain in KOA patients. However, as described in Section 1.3.2 on page 20, the Levitation brace is limited in function due to large knee flexion angles in the swing phase during gait, which restricts the constantly applied extension moment. Therefore, the developed prototype has an activation switch allowing the applied extension moment to operate only through stance phase and being disabled during swing phase. This gives the opportunity to apply a much larger extension moment achieving a greater effect than possible with current braces. A similar brace activation was presented by Reinsdorf et al. [2019], who added the activation switch to a valgus brace and only applied an abduction moment during stance phase to avoid discomfort. The brace concept developed for this project is illustrated in Figure 2.1.

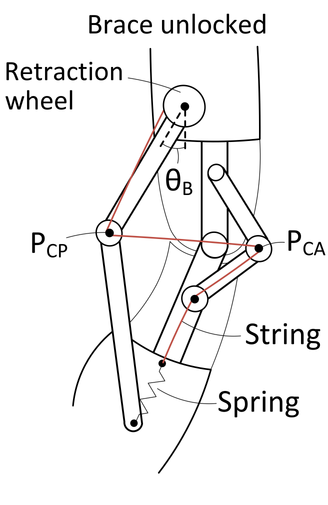


Fig. 2.1: Illustration of the brace concept which uses stored spring force during flexion to apply a knee extension moment. This compensates for muscle forces causing a reduction of the internal knee compressive forces.

Individual 3D CAD models of the brace cuffs are constructed based on a surface scan of the leg to obtain the best possible fit and comfort, which is expected to improve compliance. These cuffs have been manufactured with 3D printing, which is a common manufacturing technique within custom foot orthoses, ankle-foot orthoses and prosthetics (Chen et al. [2016]). Despite the advantages of additive manufacturing compared to traditional casting (Chen et al. [2016]) and accurate scanning tools are available for 3D surface scans (Dessery and Pallari [2018]), the manufacturing approach is rarely seen for knee braces (Dessery and Pallari [2018]). The use of cuffs based on 3D leg surface scans is to ensure a proper brace fitting and comfort when wearing the brace. The two cuffs are connected on each side with commercial OAK hinges (Fillauer LLC, Chattanooga, USA).

Furthermore, the intervention is adjusted individually based on patient-specific gait analyses, which is expected to improve the brace intervention for knee OA patients. As shown in Figure 2.1, the applied moment is generated from stored energy in springs and the spring stiffness is chosen according to the individual KFM estimated with musculoskeletal (MS) models of the initial biomechanical gait analyses. The models predict the KCF *in silico* by including biomechanical properties, ground reaction forces (GRF) and motion data, and the estimated joint loads are used to define the optimal set of brace parameters for the specific patient. Additionally, the timing of the activation switch is based on the available gait data to ensure the moment is applied correctly. The amount of individual data, used to fine-tune the intervention, will provide greater knowledge about the biomechanical interaction between the brace and the subject. Thus, a more valid choice of parameters can be made to reduce muscle activation and minimise KCF for each patient.

An illustration of the workflow for brace adjustment and testing is shown in Figure 2.2.

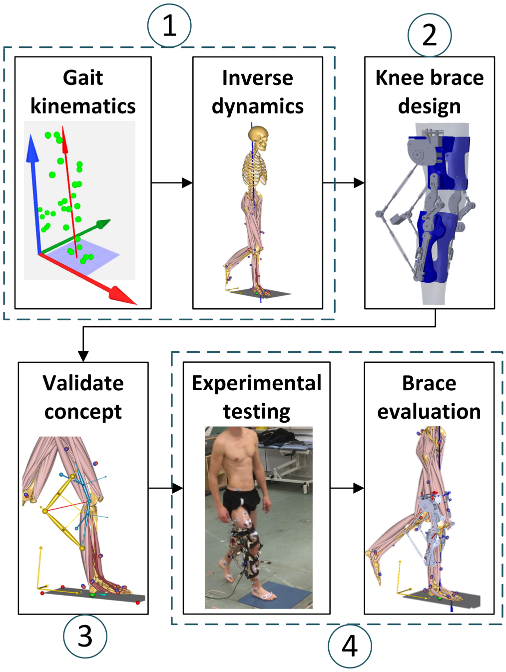


Fig. 2.2: The workflow for obtaining individual data to adjust and test the brace prototype. Step 1) includes gait data recording and musculoskeletal modeling to identify the necessary brace moment and other brace settings. In Step 2), the prototype brace is designed based on leg surface scans, and the chosen settings are evaluated with *in silico* analyses in Step 3). Finally, the prototype brace is experimentally tested in Step 4).

2.2 Evaluation Methods

The knee joint complexity entails great challenges when designing a new intervention for which reason the biomechanical effects of the prototype have been analysed and validated with experimental tests. This section presents the tools for obtaining the data to evaluate the brace concept developed in this PhD project.

2.2.1 Pain score

Despite the high influence of joint load on KOA, many studies focus on pain as a frame-of-reference when validating knee braces (Baghaei Roodsari et al. [2017]) since this is the leading cause of chronic disability and reduced quality-of-life (Heidari [2011]). Furthermore, self-reported physical functioning is mainly governed by pain in KOA patients (Nur et al. [2018]) since this is the most important outcomes to improve, according to the patients (Gohal et al. [2018]).

Pain is a very challenging subjective sensation, which easily can be obscured by placebo effects (Doherty and Dieppe [2009]). Different pain measurement scales have been proposed (Bellamy et al. [1999]). The standardized Western Ontario and McMaster Osteoarthritis Scale (WOMAC) is widely used within OA research (McConnell et al. [2001], Bellamy [2005]) evaluating three subscales; pain, stiffness and physical function based on health status questionnaires, which are answered with a score (McConnell et al. [2001]). The score interval can vary depending on the used version, but generally the outcome measure of the WOMAC questionnaire gives a good indication of whether an intervention has had an effect or not (Duivenvoorden et al. [2015a]). The included submeasures are convenient for long-term interventions to evaluate the overall effect over time. Alternatively, if solely pain is validated during a temporal intervention, the visual analogue scale (VAS) is a common tool (McCormack et al. [1988], Bellamy et al. [1999]). This is a visual continuous 100 mm long pain score ranging from 0 to 10, but is often scaled to 0-100 (Downie et al. [1978]). 0 is no pain at all and 10 (or 100) is the most unbearable pain ever experienced, which works well to investigate an instant change in pain between baseline and an intervention. Since the prototype brace is planned to be tested as a short temporal intervention to investigate the influence on muscle activation, the VAS score is used to evaluate the brace effect on pain. This pain score is a simple subjective measure and has been widely used in the literature to evaluate knee valgus braces (Fan et al. [2020]).

2.2.2 Electromyography

The concept of applying a knee extension moment is similar to the function of knee exoskeletons, which assist the motion of the lower limbs for various activities and reduces muscle activity (Park et al. [2014], Karavas et al. [2015], Shepherd and Rouse [2017]). Therefore, studies on exoskeletons usually measure electromyography (EMG) activities to validate the effect (Yan et al. [2015]) and the same method will be used to validate the effect from the prototype brace.

Since KOA patients exhibit altered muscle activation characteristics compared to asymptomatic controls (Heiden et al. [2009]), an EMG protocol is required taking into account patient anthropometrics, pain, ability to repeat trials and difficulties in producing maximal effort activations during some activities (Hubley-Kozey et al. [2013]). If these factors are considered when designing the study, EMG measurements on KOA patients have shown to be reliable outcomes for test-retest studies (Hubley-Kozey et al. [2013]). Therefore, the prototype brace has been designed for easy modification to test different settings and to reduce study duration.

2.2.3 Musculoskeletal modeling

Although muscle contractions contribute to the internal KCF, a poor relation has been shown between EMG signals and internal knee joint loads during gait (Meyer et al. [2013]). Therefore, MS models will be used to estimate how the prototype brace affects the KCF, since this is expected to affect pain and disease progression. The accuracy of MS models depends on several parameters to estimate realistic muscle and joint loads (Lund et al. [2015], Marra et al. [2015]) and the more subject-specific parameters included in the models, the more accurate results will be obtained. However, the main purpose of the included studies is to investigate a load reduction compared to baseline and not necessarily predict very precise joint loads, so the amount of subject-specific data will be limited in this work. Additionally, different validation techniques have been proposed to ensure the validity of the models (Lund et al. [2012], Hicks et al. [2015]) and if these are considered, MS models are capable of evaluating the joint kinetics accurately during gait (Marra et al. [2015]).

3. Thesis Outline

This chapter presents the main outlines for the remaining chapters of the thesis.

Chapter 4 analyses *in silico* how applied moments around the lower extremity joints affect the knee compressive forces (KCF). The study presents both the joint loads when applying individual moments and when combined moments are applied simultaneously and the results demonstrate how muscle contractions affect internal KCF.

Chapter 5 describes a developed prototype knee brace with a concept based on the study presented in Chapter 4 and explains the workflow to obtain an individual adjusted brace to efficiently reduce KCF and pain. The study includes experimental tests of the prototype on a single healthy subject for a proof-of-concept and the results seem promising for the chosen unloading concept.

In **Chapter 6**, six KOA patients are analysed during gait to investigate the muscle activation and gait characteristics for this patient group. Additionally, the prototype brace from Chapter 5 is tested on one of the patients by applying the workflow presented in Chapter 5. The aim of this study was firstly to apply the new concept on a patient and secondly to examine the brace effect on pain.

The final **Chapter 7** presents the key findings of the thesis and how this thesis contributes to the research within the area. Additionally, the limitations and future work are discussed, and concluding remarks wrap up the thesis outcome.

4. Paper I

On the biomechanical relationship between applied hip, knee and ankle joint moments and the internal knee compressive forces

Stoltze, J. S., Rasmussen, J., Andersen, M. S.

The paper has been published in
International Biomechanics Vol. 5(1), pp. 63–74, 2018

https://doi.org/10.1080/23335432.2018.1499442

© 2018 Taylor & Francis

INTERNATIONAL BIOMECHANICS
https://doi.org/10.1080/23335432.2018.1499442

Taylor & Francis
Taylor & Francis Group

OPEN ACCESS

Check for updates

On the biomechanical relationship between applied hip, knee and ankle joint moments and the internal knee compressive forces

Jonas Stensgaard Stoltze, John Rasmussen and Michael Skipper Andersen

Material and Production, Aalborg University, Aalborg, Denmark

ABSTRACT
Mechanical devices are common treating methods for knee osteoarthritis. It has the purpose of reducing the internal joint forces and unloading the damaged structure. The reduction is often achieved by alterations in the frontal plan, shifting the contact force from one compartment to the other, leaving the total compressive force unchanged. The aim of this study was to investigate how internal knee joint forces depend on applied external moments during gait. Musculoskeletal models of the gait of 10 healthy subjects were developed in the AnyBody Modelling System and used to simulate applied joint moments about different axes (load cases), each with the magnitude to compensate the net moment about the respective axis by a specified percentage. For each load case, the total, medial and lateral knee compressive force were computed and compared with a baseline case with no external moments applied. Among the investigated moments, hip flexion-extension, knee flexion-extension and ankle plantarflexion-dorsiflexion moment compensations have the most positive impact on the total knee joint compressive force, and combining the 3, each with a 40% compensation of the muscle moments, reduced the first peak by 23.6%, the second by 30.6% and the impulse by 28.6% with respect to no applied moments.

ARTICLE HISTORY
Received 6 December 2017
Accepted 4 April 2018

KEYWORDS
Knee joint forces; internal vs. external moment; inverse dynamics; in-silico; lower extremity; musculoskeletal modelling

Introduction

Osteoarthritis (OA) is a chronic, progressive, long-term and multifactorial joint disease with obesity, joint malalignment and joint laxity as some of the risk factors. The illness causes pain, stiffness and joint malalignment due to soft tissue deterioration in the affected joint (Amin et al. 2005), which limits mobility during activities of daily living and reduces quality-of-life (Silverwood et al. 2015). The number of OA patients has been growing and is expected to continue growing (Neogi 2015). In the absence of a cure (Hinman et al. 2012), there is a high demand for symptom management.

Several intervention methods have been developed with the aim of reducing pain, increasing mobility and slowing down the progression of OA. These include physical therapy (Fitzgerald et al. 2016), shoe insoles (Skou et al. 2013), knee braces (Brooks 2014), ankle-foot orthoses (AFO) (Fantini Pagani et al. 2013) and surgery (Gardiner et al. 2016). This study deals with non-surgical treatment and focuses on the mechanical devices available for the lower extremity to reduce internal knee joint forces, since the knee is the most widely affected joint (Felson and Zhang 1998).

Internal joint forces are rarely measurable but crucial for treating OA since meniscus and cartilage deterioration rates depend on these contact forces and stress distribution among others (Johnson et al. 1980). Therefore, since OA often initiates in the medial compartment of the knee, the functionality of the main part of mechanical devices on the market is to shift the condyle force laterally to unaffected structures, often by reducing the external knee adduction moment (KAM), which can be achieved with both knee braces (Fantini Pagani et al. 2010) and AFOs (Fantini Pagani et al. 2013). However, the correlation between KAM and medial contact force has been debated in the literature. According to Walter et al. (2010), a reduced KAM does not guarantee a reduced internal medial compartment force during gait, since the joint compression forces from muscle contraction are not taken into account. Still, they found a good correlation for the second peak during stance phase whereas Kutzner et al. (2013) found the strongest correlation during early stance, which illustrates a non-conclusive relationship between the two variables. Furthermore, a correlation between KAM and cartilage damage was observed in a study by Brisson et al. (2016) but only for obese subjects with a body mass index over 30.

CONTACT Jonas Stensgaard Stoltze jss@m-tech.aau.dk

© 2018 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group.
This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

In general, interventions using mechanical devices have shown varying results, and scientific evidence of their biomechanical effect is still missing (Penny et al. 2013; Brooks 2014). One of the reasons might be that most devices, designed to relieve the contact forces in the knee joint, mainly focus on unloading one compartment and therefore applies moment in the frontal plane. However, this does not compensate for the contributions to the joint reaction forces caused by muscle contraction necessary to balance the joint moment in other planes. For both the knee (Jun et al. 2015) and the ankle (Collins et al. 2015), some devices have been designed to compensate moments in the sagittal plane, but it is not clear what externally applied moment reduces the internal knee joint load most efficiently. We present an investigation of the relationship between internal joint forces – both medial, lateral and total compressive forces – and external joint moments in both frontal and sagittal planes and taking into account active muscle forces. The purpose is to gain knowledge on how to reduce knee joint forces most efficiently, and since several of the muscles spanning the knee joint are bi-articular, interventions on the hip and ankle joints are assumed to affect the knee joint compressive forces as well. Therefore, we included interventions on the hip, knee and ankle by applying moments in-silico during gait while taking muscle contraction into account. To this end, we used musculoskeletal (MS) models developed in the AnyBody Modelling System (AMS) 6.0 (AnyBody Technology A/S, Aalborg, Denmark).

Methods

Computational methods

MS models developed in AMS from a previous study by Skals et al. (2017) of 10 healthy subjects (8 males and 2 females, age: 25.7 ± 1.5 years, height: 180.8 ± 7.4 cm, weight: 76.9 ± 10.4 kg), who performed, among others, 3 gait trials each, were applied with minor adjustments as will be explained later. The models were driven by full-body 3-D kinematics based on trajectories from 35 surface-mounted reflective markers (29 placed on the skin and 3 on each shoe) recorded with 8 infrared cameras (Oqus 300 series, Qualisys AB, Gothenburg, Sweden), sampled at 250 Hz. The ground reaction force (GRF) was sampled at 2000 Hz using two force plates (Advanced Mechanical Technology, Inc., Watertown, MA, USA). The study was performed in accordance with the regulations of the regional ethics committee.

The MS models were based on the GaitFullBody template from the AnyBody Managed Model Repository v. 1.6.3 and a detailed description of these can be found in the supplementary material.

Initially, AMS was used to perform inverse dynamic analysis of each gait trial for three different load cases in the sagittal plane: hip flexion/extension moment (M_{HFE}), knee flexion/extension moment (M_{KFE}) and ankle plantarflexion/dorsiflexion moment (M_{APD}). For each load case, a parameter study was conducted in order to investigate how the reduction of internal knee joint force depends on the amount of the externally applied moment. This applied moment was specified to be between 0% and 100% of the moment generated by the muscles spanning the respective joint and incremented in steps of 20%. For example, when applying M_{KFE}, this applied moment is equal to the specified percentage of the moment generated by the muscles responsible for creating the flexion/extension rotation about the knee joint, and thereby unloads the affected muscles in this particular direction throughout the entire gait cycle. These results were used to select the magnitude of the externally applied moment for the rest of the study, where the same type of inverse dynamics analysis was performed with the chosen compensation on four additionally load cases: Normal gait with no applied moments (Normal), applied hip abduction/adduction moment (M_{HAA}), knee abduction/adduction moment (M_{KAA}) and subtalar inversion/eversion moment (M_{SIE}). The reason for only using one compensation percentage is based on the assumption of a close-to-linear trend between the amount of compensation and the amount of joint load reduction, and the amount was chosen as 40%, which is arbitrarily chosen since it depends on the application. All moments were applied in such a way that they either compensated for the muscles normally responsible for creating the movements (when applying M_{HAA}, M_{HFE}, M_{KFE}, M_{APD} and M_{SIE}) or counteracted the knee abduction/adduction (when applying M_{KAA}) generated by the GRF, muscle contraction, inertia, gyroscopic and gravitational forces. After evaluating these seven load cases (Normal, M_{HAA}, M_{HFE}, M_{KFE}, M_{KAA}, M_{APD}, M_{SIE}), combinations of the three with the largest reduction in the impulse during gait, based on MS analyses, were evaluated.

For each load case, the total compressive knee joint force, F_{TC} and M_{KAA} were computed in AMS from which the medial and lateral compressive forces on the condyles, F_{MC} and F_{LC}, respectively, were found in the tibial coordinate system by means of static equilibrium equations (1) in the frontal plane based on the free body diagram in Figure 1.

$$F_{MC} = -\frac{F_{TC}L_L + M_{KAA}}{L_L + L_M} \quad F_{LC} = -\frac{F_{TC}L_M - M_{KAA}}{L_L + L_M} \tag{1}$$

The medial and lateral moment arms, L_M and L_L, respectively, were estimated from the relationships between internal knee geometry and the maximum width of the femoral condyles from medial to lateral sides as reported in Seedhom (1972).

Data analysis

Each subject was represented by a mean contact force curve of the three gait trials normalized to bodyweight for each of the three contact force types (F_{TC}, F_{MC} and F_{LC}). These were used for further analysis to find the mean and the first and second peak values in the range of 10–20% gait cycle and 40–60% gait cycle, respectively, and also the impulse of each contact force type was found with numerical integration of the force curve by means of the trapezoidal method with unit spacing.

Results

Graphs on how the total compressive force, F_{TC}, depends on the compensation percentage through the gait cycle are shown in Figure 2, and how the two peaks and impulse of the total compressive force is affected by compensation is illustrated in Figure 3. These two plots illustrate an almost linear relation between joint compression force and external moment compensation in the sagittal plane if the compensated muscles are activated during the investigated parameter. For example, when applying M_{HFE} or M_{KFE}, the first peak decreases linearly with compensation percentage whereas M_{APD} does not influence the first peak. The same linear trend is present for the impulse where M_{KFE} has the biggest influence.

The chosen compensation of 40% was applied for further analysis to compare the effect across the different load cases for each compression force: Total (F_{TC}), medial (F_{MC}) and lateral (F_{LC}). Graphs on how these contact forces were affected through the gait cycle for each load case when applying single moment compensation of 40% are depicted in Figure 4 and illustrated with boxplots in Figures 5 and 6.

In general, the applied moments in the sagittal plane showed the largest effects. Both M_{HFE} and M_{KFE} significantly reduced the first peak mean of

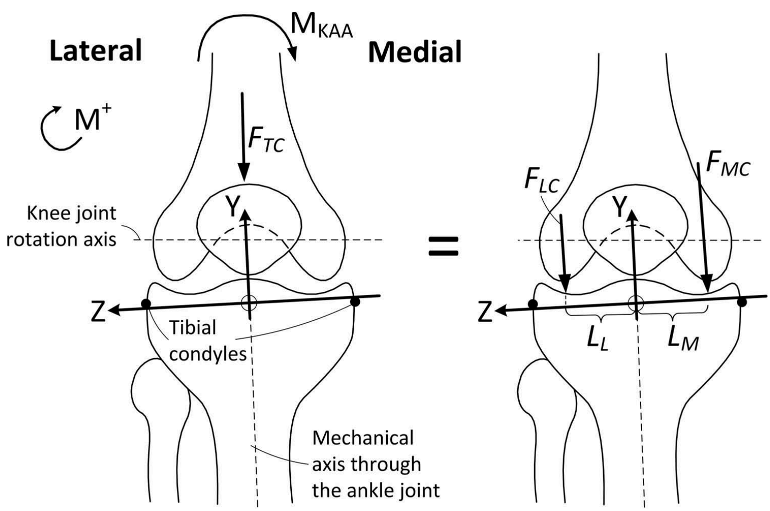


Figure 1. The tibial coordinate system in which all presented loads are defined. It is based on Grood and Suntay (1983) and a more detailed description can be found in the supplementary material. F_{TC} = total compressive force, F_{MC} = medial compressive force, F_{LC} = lateral compressive force, L_M = moment arm for the medial contact force, L_L = moment arm for the lateral contact force and M_{KAA} = the abduction/adduction moment about the *X*-axis, including contributions from external ground reaction loads, muscle forces, inertia forces, gyroscopic forces and gravity. M_{KAA} and F_{TC}, given as $F_{TC} = F_{MC} + F_{LC}$, are computed in AMS. M^+ indicates the positive moment direction when formulating Equation (1).

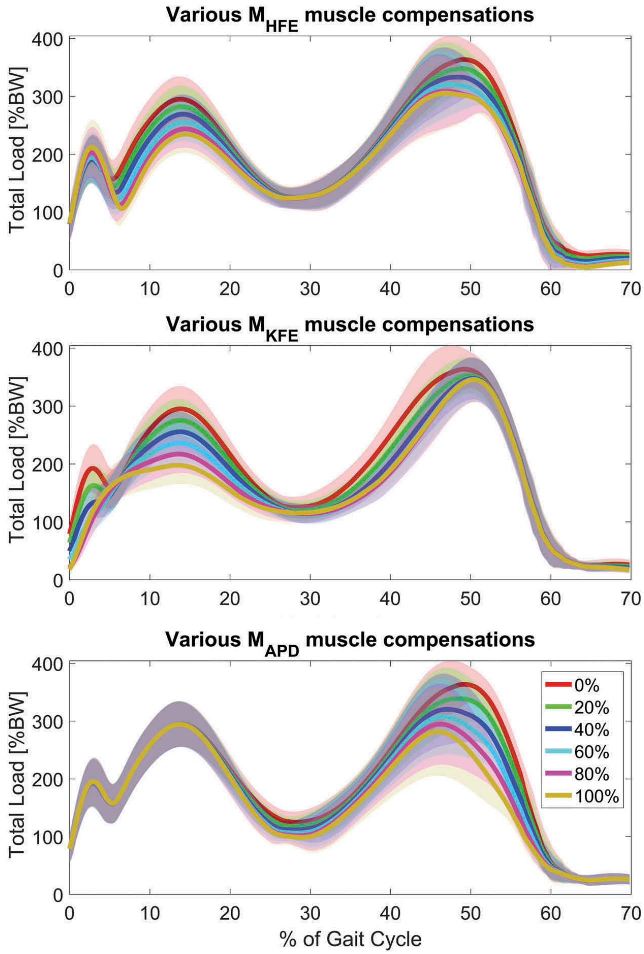


Figure 2. The total knee compressive joint load for muscle compensations of 0%, 20%, 40%, 60%, 80% and 100% of the three moments in the sagittal plane. The shaded area indicates ±1 standard deviation. According to the graphs, the potential for reducing internal joint loads, for applied moments in the sagittal plane, depends on the muscle activity.

total compressive force relative to Normal by 8.8% and 13.5%, respectively (see Figures 4 and 5 top), whereas M_{APD} mainly affected the second peak by a reduction of 11.4%, which M_{HFE} reduced by 7.7% (see Figures 4 and 6 top).

Regarding condyle forces, M_{KAA} decreased the mean of first and second peak of medial force with 13.5% and 11.5%, respectively (see Figure 4–6 middle), but likewise increased the lateral force by 30.1% and 23.8% for the first and second peaks respectively (see Figures 4–6 bottom).

Plots of combined load cases are shown in Figures 7-9 which showed, that a combination of only M_{HFE} and M_{KFE} reduced the first peak mean of total compressive force with 23%, which is more or less the same as when including M_{APD}. The second peak depends more on the number of combined moments. M_{HFE} + M_{KFE} and M_{HFE} + M_{APD} reduce the second peak by 15.5% and 16.7%, respectively, which is about half of the reduction when combining all three moments. However, M_{KFE} + M_{APD} increases the reduction to 21.7%. A major reduction was seen for medial, lateral and total compressive force when combining M_{HFE}, M_{KFE} and M_{APD} which decreased the mean (over the trials) of the first peak (~13% gait

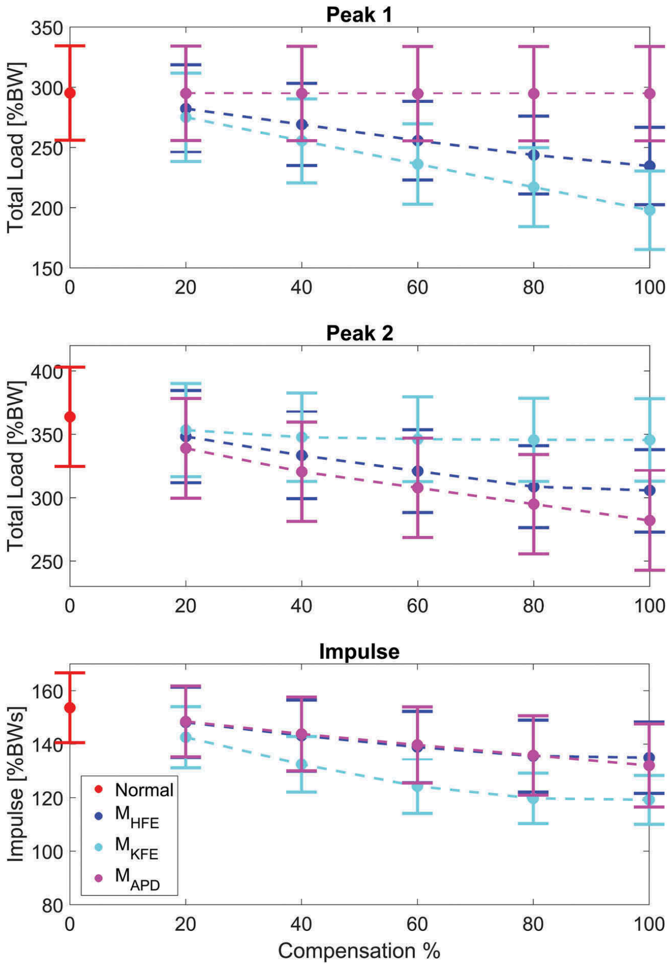


Figure 3. The mean peak values and impulse of the total load for the three moments in the sagittal plane as function of the amount of compensation. The whiskers indicates ±1 standard deviation and the dashed lines are visualising the trend between each simulated muscle compensation percentage. If any effect is present for the moment compensation, the relation is, according to the graphs, close to linear.

cycle) and second peak (~50% gait cycle) for total compressive force by 23.6% and 30.6%, respectively, and the impulse was reduced by 28.6%.

Again, the M_{HFE} + M_{KFE} combination performed as well as M_{HFE} + M_{KFE} + M_{APD} on the first peak for both condyle forces: 15.4% and 39% mean reduction for medial and lateral condyle force, respectively. The second peak of the medial condyle force was reduced by 13.6% and 15.2% for M_{HFE} + M_{APD} and M_{KFE} + M_{APD}, respectively, which a combination of all three moments increased to 21.7%. This combination reduced the second peak of the lateral condyle force by 47.9%, and reduced the impulse by 30.6%, 21.7% and 47.9% for total, medial and lateral force, respectively. However,

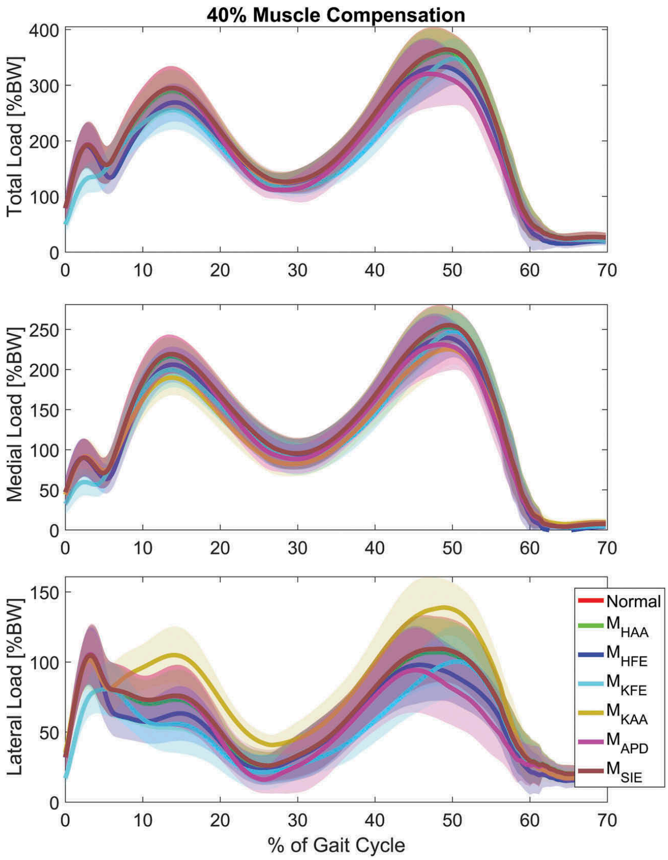


Figure 4. The mean internal knee joint load curves for normal gait when no external loads are applied (Normal) and single load cases applying 40% moment compensations for top: the total compressive force, middle: the medial condyle compressive force and bottom: the lateral condyle compressive force. The shaded area indicates ±1 standard deviation. The full gait cycle is from heel strike to heel strike but the swing phase has been omitted since the internal loads in this part are approaching zero for all load cases. As expected, the M_{SIE} and M_{HAA} have a very small influence in all three compressive force types for which reason they coincide with the red Normal line. Similarly, M_{KAA} also coincides with this line in the top figure since this applied moment only shifts the internal loads laterally leaving the total compressive load unaffected.

the second best intervention regarding impulse was either M_{HFE} + M_{KFE} or M_{KFE} + M_{APD}, which caused very similar reductions in all three investigated joint forces.

Discussion

The purpose of this study was to investigate the relationship between externally applied joint moments and the internal joint forces at the knee, which provides information for the design of mechanical devices for unloading the knee joint in Knee OA (KOA) patients. When dealing with KOA, the medial contact force is mostly in focus since this is where the disease typically initiates; applying an external abduction moment seems like an obvious solution to shift the force laterally. Since this force

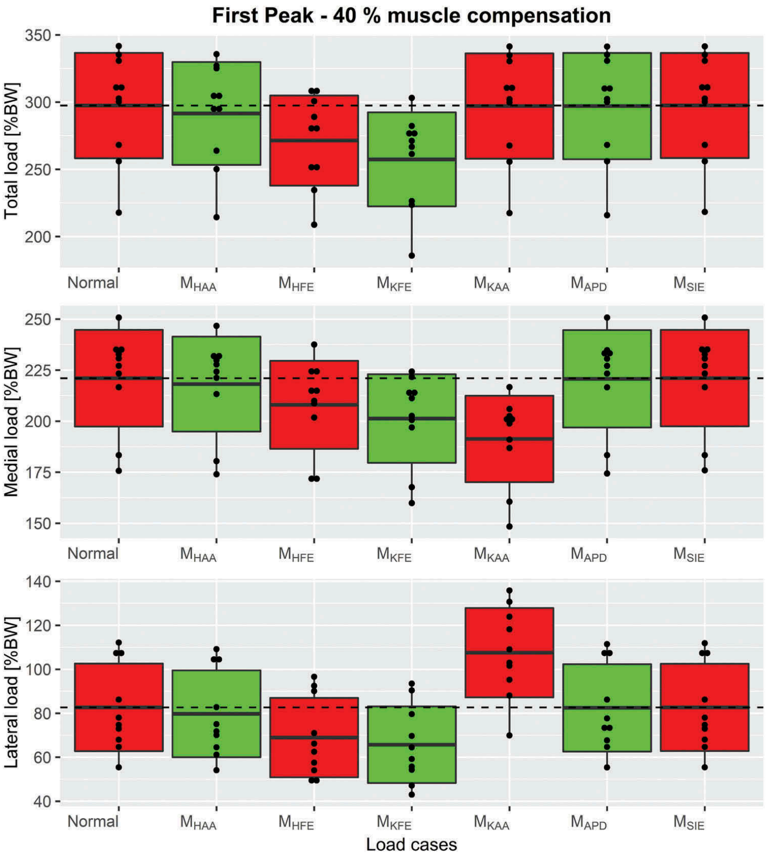


Figure 5. Boxplots, indicating the mean ± 1 standard deviation, of the first peak including Normal and the single load cases for each of the 3 compressive force types, top: the total compressive force, middle: medial force and bottom: lateral force. The dashed line represents the mean of Normal for visual comparison.

distribution is not directly measurable, it is most often evaluated based on the external KAM, which, as reported by Walter et al. (2010), can be reduced without reducing the medial contact force. This can also be interpreted from Figure 4, which shows the second peak of the medial force to be the highest, mainly due to gastrocnemius muscle contraction (Schmitz et al. 2009), whereas the first KAM peak commonly is the highest during the weight acceptance phase.

Figures 2 and 3 show that for the three moments in the sagittal plane, the total knee compressive force reduction depends on the muscle activation; the more activation the larger force reduction is seen. For example, the APD load case only affects the second peak due to high gastrocnemius muscle activation, whereas this muscle has low activation during first peak (Schmitz et al. 2009) and hence no force reduction is observed at this state of the cycle for APD.

Our results indicate that an efficient approach regarding an overall reduction of medial, lateral and total compressive forces and impulse during gait, is applying a combination of hip and knee flexion/extension moment, knee flexion/extension and ankle plantar-flexion/dorsiflexion moment, or a combination of all three. However, the practical application of combined hip flexion/extension, knee flexion/extension and/or ankle plantar-/dorsiflexion moments can be challenging

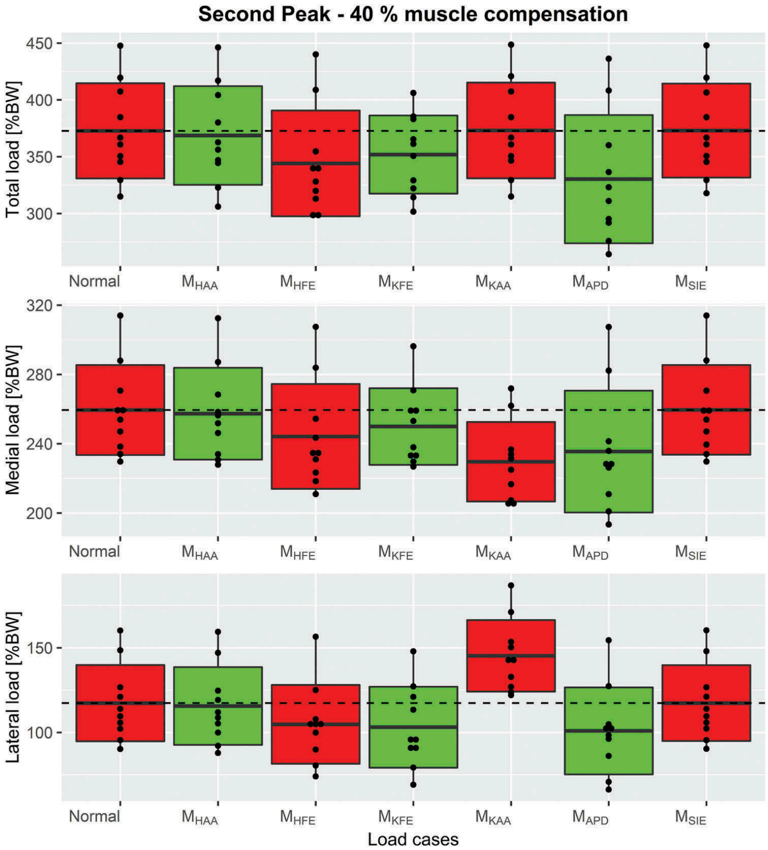


Figure 6. Boxplots, indicating the mean ± 1 standard deviation, of the second peak including Normal and the single load cases for each of the 3 compressive force types, top: the total compressive force, middle: medial force and bottom: lateral force. The dashed line represents the mean of Normal for visual comparison.

since they each need to be active at different times during the gait cycle. As mentioned previously, the first load peak is purely affected by M_{HFE} and M_{KFE} since the hip and thigh muscles are mainly active here, but when approaching toe off and second load peak, the gastrocnemius muscle is activated more, for which reason the applied M_{APD} moment decreases the second peak more than M_{KFE} and M_{HFE}. Based on this information, an orthosis can be developed which targets first peak by either compensating knee or hip flexion/extension moment and second peak by compensating either hip, knee or ankle joint moments in the sagittal plane of which the ankle, according to Figure 3, leads to the largest reduction. However, Wellsandt et al. (2016) concluded that decreased knee joint loading is associated with KOA for people who has suffered from anterior cruciate ligament injury, and reduced muscle strength is also considered as a risk factor for developing KOA (Thorstensson et al. 2004), which indicates that unloading of the knee joint should be done with care.

There are some limitations and uncertainties related to MS models and several parameters influences the joint loads (Moissenet et al. 2017). As shown in this study, the joint loads are highly affected by the surrounding muscles so the chosen muscle parameters have a big impact on the load reduction. Also, the muscle recruitment in AMS is based on an optimisation

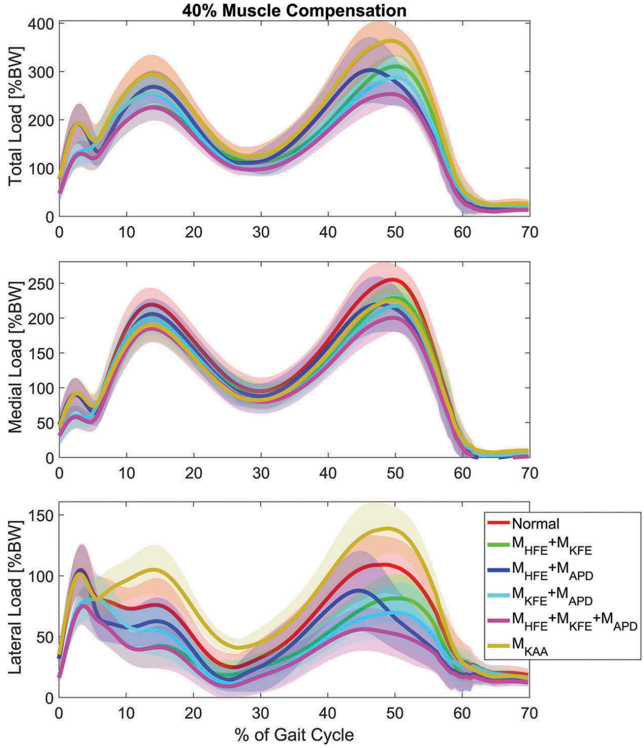


Figure 7. The mean internal knee joint load curves for normal gait when no external loads are applied (Normal) and combinations of applied 40% moment compensations for top: the total compressive force, middle: the medial condyle compressive force and bottom: the lateral condyle compressive force. The shaded area indicates ± 1 standard deviation. Similar to Figure 2, the swing phase has been omitted and the Normal load case is represented with the red lines for comparison.

criterion (Damsgaard et al. 2006), which is an estimation of the real muscle configuration. When wearing a mechanical device applying external forces and/or moments to the lower extremity, the kinematics are most likely affected compared to an unbraced condition but since the moments in this study are applied in-silico, gait alteration is not taken into account. These changes most likely affect the joint forces since the contact with the ground, and thereby the muscle recruitment, changes. Lastly, the kinematics of the knee joint are highly complex during walking (Marra et al. 2015), which are not taken into account since the knee was modelled as an ideal hinge joint, in our simulations. However, despite these uncertainties the results clearly demonstrate, presuming ideal external moment application, a potential for substantial reduction in the internal knee joint forces while performing the same movement. Since the study only includes healthy subjects, it is uncertain if similar results are seen for KOA patients, which can be tested with similar analyses.

Since the knee internal–external (IE) muscle moment is relatively small compared to the other two knee moments, external IE moment was assumed to have only a minor effect on the compressive forces, and was therefore omitted. IE motion is often considered through foot progression angle since this changes the external KAM (Guo et al. 2007) by modifying the contact point between foot and the ground. IE motion in bracing has been introduced with the Odra brace (Orthoconcept Inc., Laval, QC, Canada), which additionally applies a distraction force to the knee during knee extension. To investigate the effect of IE motion, the knee joint in the MS model must be less constrained by the idealized joints and rather stabilized by the

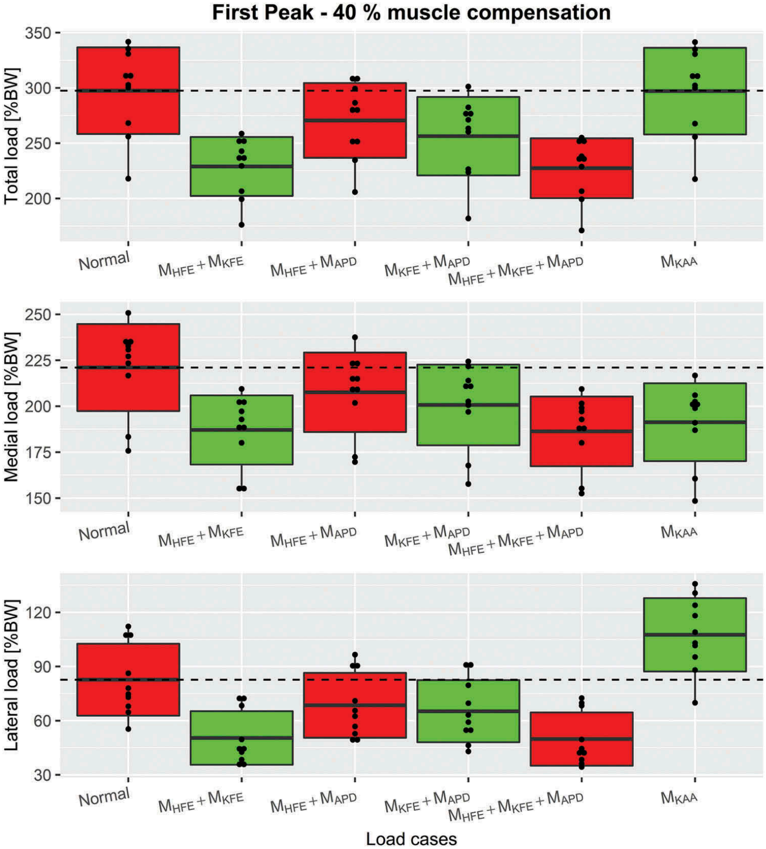


Figure 8. Boxplots, indicating the mean ± 1 standard deviation, of the first peak including Normal, M_{KAA} and combined load cases for each of the three compressive force types, top: the total compressive force, middle: medial force and bottom: lateral force. The dashed line represents the mean of Normal for visual comparison.

surrounding ligaments in the moveable directions. This is technically possible but will require a more advanced and computationally demanding model.

The results from this study indicate the contributions and ideal timing of external moments for reduction of internal knee compressive forces. Even though the highest reduction is seen for M_{HFE} + M_{KFE} + M_{APD} and combinations of two moments, these approaches seem technically challenging to realize with bracing. Thus, it might be necessary to limit the device to single moment compensation or two moments active separately, for example, M_{HFE} or M_{KFE} compensation for reducing first peak and M_{APD} for reducing second peak.

Acknowledgements

We thank Sebastian Laigaard Skals for sharing the models.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work received funding from the Innovation Fund Denmark under the Individualized Osteoarthritis Intervention project [Project title: Advanced biomechanical tools for

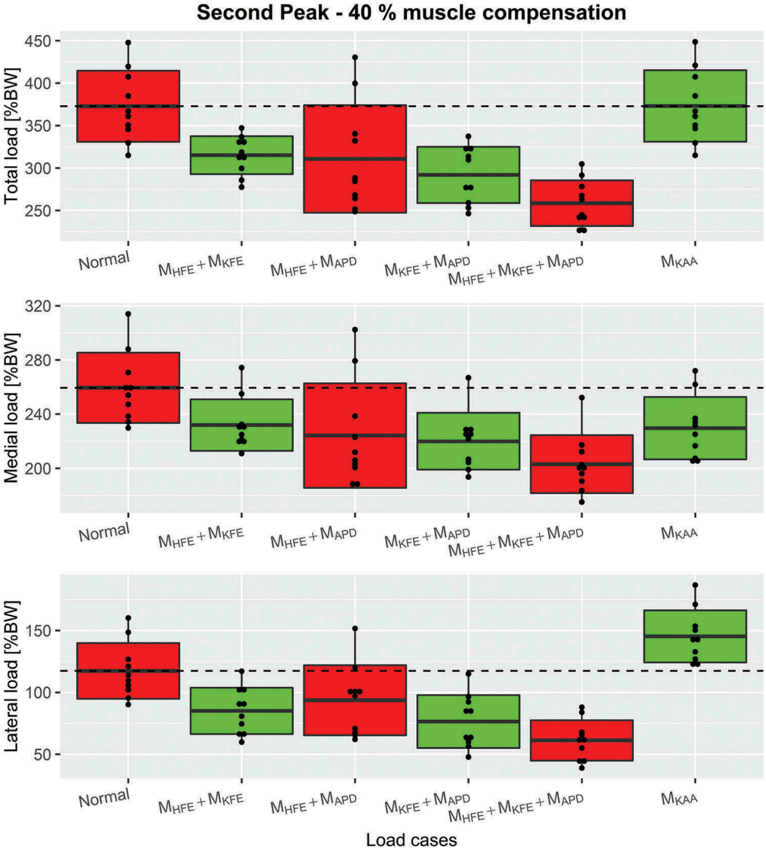


Figure 9. Boxplots, indicating the mean ± 1 standard deviation, of the second peak including Normal, M_{KAA} and combined load cases for each of the 3 compressive force types, top: the total compressive force, middle: medial force and bottom: lateral force. The dashed line represents the mean of Normal for visual comparison.

optimal individualised, nonsurgical management of knee osteoarthritis].

ORCID

Jonas Stensgaard Stoltze http://orcid.org/0000-0002-1525-2484
John Rasmussen http://orcid.org/0000-0003-3257-5653
Michael Skipper Andersen http://orcid.org/0000-0001-8275-9472

References

Amin S, LaValley MP, Guermazi A, Grigoryan M, Hunter DJ, Clancy M, Niu J, Gale DR, Felson DT. 2005. The relationship between cartilage loss on magnetic resonance imaging and radiographic progression in men and women with knee osteoarthritis. Arthritis Rheum. 52(10):3152–3159.

Brisson NM, Wiebenga EG, Stratford PW, Beattie KA, Totterman S, Tamez-Peña JG, Callaghan JP, Adachi JD, Maly MR. 2016. Knee mechanics interact with body mass index to predict cartilage loss over 2.5 years in people with clinical knee osteoarthritis. Osteoarthr Cartil. 24:S47.

Brooks KS. 2014. Osteoarthritic knee braces on the market: a literature review. J Prosthetics Orthot. 26(1):2–30.

Collins SH, Wiggin MB, Sawicki GS. 2015. Reducing the energy cost of human walking using an unpowered exoskeleton. Nature. 522(7555):212–215.

Damsgaard M, Rasmussen J, Christensen ST, Surma E, de Zee M. 2006. Analysis of musculoskeletal systems in the anybody

modeling system. Simul Model Pract Theory. 14(8):1100–1111.
Fantini Pagani CH, Potthast W, Brüggemann G. 2010. The effect of valgus bracing on the knee adduction moment during gait and running in male subjects with varus alignment. Clin Biomech. 25(1):70–76.
Fantini Pagani CH, Willwacher S, Benker R, Brüggemann G. 2013. Effect of an ankle–foot orthosis on knee joint mechanics: a novel conservative treatment for knee osteoarthritis. Prosthet Orthot Int. 38(6):481–491.
Felson DT, Zhang Y. 1998. An update on the epidemiology of knee and hip osteoarthritis with a view to prevention. Arthritis Rheum. 41(8):1343–1355.
Fitzgerald GK, Fritz JM, Childs JD, Brennan GP, Talisa V, Gil AB, Neilson BD, Abbott JH. 2016. Exercise, manual therapy, and use of booster sessions in physical therapy for knee osteoarthritis: a multi-center, factorial randomized clinical trial. Osteoarthr Cartil. 24(8):1340–1349.
Gardiner BS, Woodhouse FG, Besier TF, Grodzinsky AJ, Lloyd DG, Zhang L, Smith DW. 2016. Predicting knee osteoarthritis. Ann Biomed Eng. 44(1):222–233.
Grood ES, Suntay WJ. 1983. A joint coordinate system for the clinical description of three-dimensional motions application to the knee. J Biomech Eng. 105(2):136–144.
Guo M, Axe MJ, Manal K. 2007. The influence of foot progression angle on the knee adduction moment during walking and stair climbing in pain free individuals with knee osteoarthritis. Gait Posture. 26(3):436–441.
Hinman RS, Bowles KA, Metcalf BB, Wrigley TV, Bennell KL. 2012. Lateral wedge insoles for medial knee osteoarthritis: effects on lower limb frontal plane biomechanics. Clin Biomech. 27(1):27–33.
Johnson F, Leitl S, Waugh W. 1980. The distribution of load across the knee. A comparison of static and dynamic measurements. J Bone Jt Surg. 62(3):346–349.
Jun S, Zhou X, Ramsey DK, Krovi VN. 2015. Smart knee brace design with parallel coupled compliant plate mechanism and pennate elastic band spring. J Mech Robot. 7(4):041024-1-041024-12.
Kutzner I, Trepczynski A, Heller MO, Bergmann G. 2013. Knee adduction moment and medial contact force – facts about their correlation during gait. PLoS ONE. 8(12):1–8.
Marra MA, Vanheule V, Fluit R, Koopman BH, Rasmussen J, Verdonschot N, Andersen MS. 2015. A subject-specific musculoskeletal modeling framework to predict in vivo mechanics of total knee arthroplasty. J Biomech Eng. 137(2):020904-1-020904-12.
Moissenet F, Modenese L, Dumas R. 2017. Alterations of musculoskeletal models for a more accurate estimation of lower limb joint contact forces during normal gait: a systematic review. J Biomech. 63:8–20.
Neogi T. 2013. The epidemiology and impact of pain in osteoarthritis. Osteoarthr Cartil. 21(9):1145–1153.
Penny P, Geere J, Smith T. 2013. A systematic review investigating the efficacy of laterally wedged insoles for medial knee osteoarthritis. Rheumatol Int. 33(10):2529–2538.
Schmitz A, Silder A, Heiderscheit B, Mahoney J, Thelen DG. 2009. Differences in lower-extremity muscular activation during walking between healthy older and young adults. J. Electromyogr Kinesiol. 19(6):1085–1091.
Seedhom B. 1972. Dimensions of the knee. Radiographic and autopsy study of sizes required by a knee prosthesis. Ann Rheum Dis. 31(1):54–58.
Silverwood V, Blagojevic-Bucknall M, Jinks C, Jordan JL, Protheroe J, Jordan KP. 2015. Current evidence on risk factors for knee osteoarthritis in older adults: a systematic review and meta-analysis. Osteoarthr Cartil. 23(4):507–515.
Skals S, Jung M, Damsgaard M, Andersen MS. 2017. Prediction of ground reaction forces and moments during sports-related movements. Multibody Syst Dyn. 39(3):175–195.
Skou ST, Hojgaard L, Simonsen OH. 2013. Customized foot insoles have a positive effect on pain, function, and quality of life in patients with medial knee osteoarthritis. J Am Podiatr Med Assoc. 103(1):50–55.
Thorstensson CA, Petersson F, Jacobsson LTH, Boegård TL, Roos EM. 2004. Reduced functional performance in the lower extremity predicted radiographic knee osteoarthritis five years later. Ann Rheum Dis. 63(4):402–407.
Walter JP, D'Lima DD, Colwell CW, Fregly BJ. 2010. Decreased knee adduction moment does not guarantee decreased medial contact force during gait. J Orthop Res. 28(10):1348–1354.
Wellsandt E, Gardinier ES, Manal K, Axe MJ, Buchanan TS, Snyder-Mackler L. 2016. Decreased knee joint loading associated with early knee osteoarthritis after anterior cruciate ligament injury. Am J Sports Med. 44(1):143–151.

Supplementary for the paper "On the biomechanical relationship between applied hip, knee and ankle joint moments and the internal knee compressive forces"

Methods

Experimental Procedure

The experimental study was conducted by Skals et al. (2017) at the Department of Health Science and Technology, Aalborg University, Denmark, where ten healthy subjects (8 males and 2 females, age: 25.70 ± 1.49 years, height: 180.80 ± 7.39 cm, weight: 76.88 ± 10.37 kg) volunteered to participate. During measurements, subjects wore tight fitting shorts, sports-brassiere for females and Brooks Ravenna 2 running shoes (Brooks Sports Inc., Seattle, WA, US) in preferred size.

Initially, a 5 min warm-up at 160 W was completed on a cycle ergometer before the gait cycle starting position was found through trial-and-error approach until the subjects were able to consistently impact the two force plates. Following, 29 markers were taped to their skin and three on each shoe; two representing the position of the first and fifth metatarsal and one maker at the top of the calcaneus bone. The reason for the excessive amount of markers is that the purpose of the experiment was to predict ground reaction forces and moments (GRF&Ms) for different activities, which requires full body kinematics. The marker locations are listed in Table 1 and illustrated in Figure 1, which indicates that no markers were placed on the head. Each subject completed five gait trials.

Table 1: The marker label, position and whether the marker positions were fixed (Fix.) or optimized (Opt.) in the anterior-posterior (A-P), medial-lateral (M-L) and proximal-distal (P-D) directions.

Label	Position	A-P	M-L	P-D
RTHI	Right thigh	Opt.	Opt.	Opt.
LTHI	Left thigh	Opt.	Opt.	Opt.
RKNE	Right lateral epicondyle	Fix.	Fix.	Fix.
LKNE	Left lateral epicondyle	Fix.	Fix.	Fix.
RPSI	Right posterior superior iliac spine	Fix.	Fix.	Fix.
LPSI	Left posterior superior iliac spine	Fix.	Fix.	Fix.
RASI	Right anterior superior iliac spine	Fix.	Fix.	Fix.
LASI	Left anterior superior iliac spine	Fix.	Fix.	Fix.
RANK	Right lateral malleolus	Fix.	Fix.	Fix.
LANK	Left lateral malleolus	Fix.	Fix.	Fix.
RHEE	Right calcaneus	Fix.	Fix.	Fix.
LHEE	Left calcaneus	Fix.	Fix.	Fix.
RTIB	Right tibia	Opt.	Opt.	Opt.
LTIB	Left tibia	Opt.	Opt.	Opt.
RTOE	Right metatarsus	Fix.	Fix.	Fix.
LTOE	Left metatarsus	Fix.	Fix.	Fix.
RMT5	Right fifth metatarsal	Fix.	Fix.	Fix.
LMT5	Left fifth metatarsal	Fix.	Fix.	Fix.
RELB	Right lateral epicondyle	Fix.	Fix.	Fix.
LELB	Left lateral epicondyle	Fix.	Fix.	Fix.
RWRA	Right wrist bar thumb side	Fix.	Fix.	Fix.
LWRA	Left wrist bar thumb side	Fix.	Fix.	Fix.
RFINL	Right first metacarpal	Fix.	Fix.	Fix.
LFINL	Left first metacarpal	Fix.	Fix.	Fix.
RFINM	Right fifth metacarpal	Fix.	Fix.	Fix.
LFINM	Left fifth metacarpal	Fix.	Fix.	Fix.
RUPA	Right triceps brachii	Opt.	Opt.	Opt.
LUPA	Left triceps brachii	Opt.	Opt.	Opt.
RSHO	Right Acromio-clavicular joint	Fix.	Fix.	Fix.
LSHO	Left Acromio-clavicular joint	Fix.	Fix.	Fix.
STRN	Xiphoid process of the sternum	Opt.	Opt.	Opt.
CLAV	Jugular Notch	Opt.	Opt.	Opt.
C7	7th Cervical Vertebrae	Fix.	Fix.	Fix.
RILC*	Right iliac crest	-	-	-
LILC*	Left iliac crest	-	-	-

*Excluded

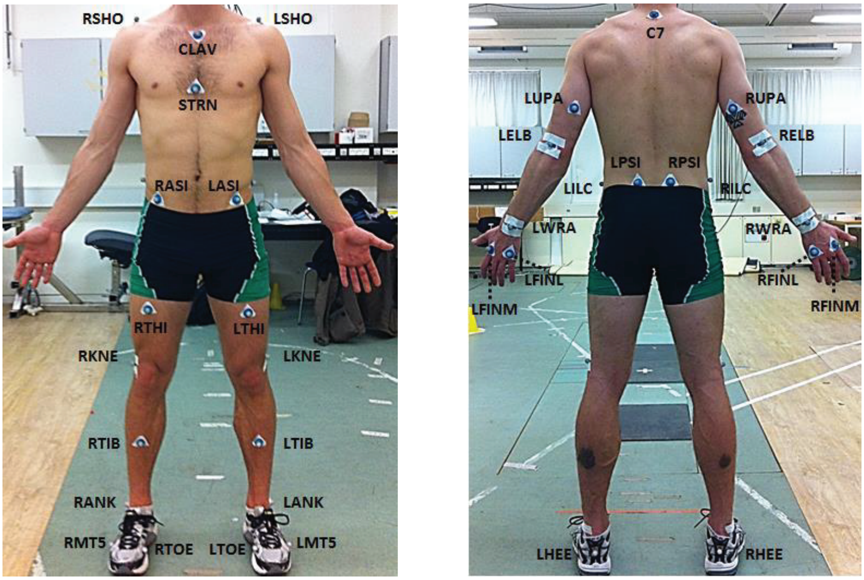


Figure 1: The marker placements used in Skals et al. (2017).

Data Collection

The marker trajectories were recorded for the study in Skals et al. (2017) with eight infrared cameras (Oqus 300 series, Qualisys AB, Gothenburg, Sweden) sampling at 250 Hz and analyzed in Qualisys Track Manager v. 2.9. The laboratory had two force plates (width/length = 464/508 mm) (Advanced Mechanical Technology, Inc., Watertown, MA, US) embedded in the floor measuring the ground reaction force at 2000 Hz.

Experimental Data Processing

A low-pass filter with second order, zero-phase Butterworth filters was used for the force plate and marker data using a cut-off frequency of 15 and 10 Hz respectively. The three of the five successful gait trials were included for further analysis, yielding a total of 30 trials used to investigate the effects of applied moments on internal joint loads. Trials were excluded due to occasional marker occlusion or inadequate impact of the force plates, i.e., the whole foot was not in complete contact or the impact occurred too close to the edges of the force plate surface.

Musculoskeletal Model

The musculoskeletal (MS) models, used in this study, were developed by Skals et al. 2017 in the AnyBody Modeling System v. 6.0.4 (AMS) (AnyBody Technology A/S, Aalborg, Denmark) based on the GaitFullBody template from the AnyBody Managed Model Repository v. 1.6.3. The lower extremity model is based on the cadaver dataset of Klein Horsman et al. (2007), the lumbar spine model is based on the work of de Zee et al. (2007), and the shoulder and arm models are based on the work of the Delft Shoulder Group (Van der Helm et al. 1992, Veeger et al. 1991 and Veeger et al. 1997). The full MS model had a total of 29 degrees-of-freedom (DOFs); 2x1 DOFs for the ankle revolute joints, 2x1 DOFs for the subtalar revolute joints, 2x1 DOFs for the knee revolute joints, 2x3 DOFs for the hip spherical joints, 6 DOFs for pelvis, 3 DOFs for the rotation angles between pelvis and thorax controlled by a spine rhythm that distribute the angles between each vertebra, 2x1 DOF at the elbow revolute joints, and 2x3 DOFs at the glenohumeral spherical joints. Since no markers were placed on the head, the neck joint was fixed in a neutral position.

The kinematic analysis for all trials was solved based on the approach explained in Andersen et al. (2009) but prior to this, a linear scaling of the segments was applied on one gait trial for each subject with the method from Andersen et al. (2010). The scaling is based on the time varying model marker positions which are found with an optimization-based kinematic analysis with a weighted least-square objective function, tracking both the trajectory of the fixed markers on bony landmarks (Labeled Fix. in Table 1) and simultaneously the trajectory of the free-moving markers (labeled Opt. in Table 1). The calculated segment lengths and model marker trajectories were saved and used for the kinematic analysis for all other trials.

Regarding the inverse dynamic analysis, the lower extremity was actuated with a total of 110 muscles divided into 318 individual muscle paths. These were modelled as constant strength muscles whereas the muscles in the upper body were modelled as ideal joint torque generators. Muscle strength was scaled according to the mass-fat scaling explained in Rasmussen et al. (2005), and the muscle recruitment problem, computing the muscle and joint reaction forces, was solved by minimizing the sum of the squared muscle activities (Damsgaard 2006). This approach was validated with a tibial implant equipped with a six DOFs force measuring sensor in Marra et al. (2015) and showed promising results.

The internal knee loads, presented in this study, are found in a tibia coordinate system based on Grood and Suntay (1983) with origin half way between the two tibial condyles. The Y-axis (inferior-superior) is aligned with an axis from ankle joint to origin, Z-axis (medial-lateral) is perpendicular to this axis and goes through the right tibial condyle (when looking from posterior to anterior, so Z points laterally in the right leg and medially in the left leg). The X-axis (anterior-posterior) is the cross product of Y and Z and the rotation axis is based on Klein Horsman et al. (2007).

References

Andersen, M. S., Damsgaard, M., Rasmussen, J., Andersen, M. S., Damsgaard, M., Rasmussen, J. 2009. Kinematic analysis of over-determinate biomechanical systems. Comput. Methods Biomech. Biomed. Engin. 12(4):371-384.

Andersen, M. S., Damsgaard, M., MacWilliams, B., Rasmussen, J. 2010. A computationally efficient optimisation-based method for parameter identification of kinematically determinate and over-determinate biomechanical systems. Comput. Methods Biomech. Biomed. Engin. 13(2):171-183.

Damsgaard, M., Rasmussen, J., Christensen, S. T., Surma, E., de Zee, M. 2006. Analysis of musculoskeletal systems in the AnyBody Modeling System. Comput. Methods Biomech. Biomed. Engin. 14(8):1100-1111.

de Zee, M., Hansen, L., Wong, C., Rasmussen, J., Simonsen, E. B. 2007. A generic detailed rigid-body lumbar spine model. J. Biomech. 40(6):1219-1227.

Grood, E. S., Suntay, W. J. 1983. A Joint Coordinate System for the Clinical Description of Three-Dimensional Motions Application to the Knee. J. Biomech. Eng. 105:136-143.

Klein Horsman, M. D., Koopman, H. F. J. M., van der Helm, F. C. T., Prosé, L. P., Veeger, H. E. J. 2007. Morphological muscle and joint parameters for musculoskeletal modelling of the lower extremity. Clin. Biomech. 22(2):239-247.

Marra, M. A., Vanheule, V., Fluit, R., Koopman, B. H. F. J. M., Rasmussen, J., Verdonschot, N., Andersen, M. S. 2015. A Subject-Specific Musculoskeletal Modeling Framework to Predict In Vivo Mechanics of Total Knee Arthroplasty. J. Biomech. Eng. 137(2):020904-1-020904-12.

Rasmussen, J., de Zee, M., Damsgaard, M., Christensen, S. T., Marek, C., Siebertz, K. 2005. A General Method for Scaling Musculo-Skeletal Models. International Symposium on Computer Simulation in Biomechanics, Cleveland, Ohio, United States

Skals, S., Jung, M., Damsgaard, M., Andersen, M. S. 2017. Prediction of ground reaction forces and moments during sports-related movements. Multibody Syst. Dyn. 39(3):175–195.

5. Paper II

Development and Functional Testing of An Unloading Concept for Knee Osteoarthritis Patients: A Pilot Study

Stoltze J. S., Palari J., Eskandari B., Oliveira A. S. C., Pirscoveanu C. I., Rasmussen J., Andersen M. S.

The paper has been published in
Journal of Biomechanical Engineering Vol. 143(8), pp. 63–74, 2021

https://doi.org/10.1115/1.4051847

© 2021 ASME Journals

Jonas S. Stoltze[1]
Department of Material and Production,
Aalborg University,
Fibigerstraede 16,
Aalborg East DK-9220, Denmark
e-mail: jss@mp.aau.dk

Jari Pallari
School of Engineering,
Newcastle University,
Newcastle upon Tyne NE1 7RU, UK
e-mail: jari.pallari@ncl.ac.uk

Behrokh Eskandari
Podfo Ltd.,
Quorum Business Park,
Benton Lane,
Newcastle upon Tyne NE12 8BU, UK
e-mail: becky.eskandari@podfo.com

Anderson S. C. Oliveira
Department of Material and Production,
Aalborg University,
Fibigerstraede 16,
Aalborg East DK-9220, Denmark
e-mail: oliveira@mp.aau.dk

Cristina I. Pirscoveanu
Department of Health Science and Technology,
Aalborg University,
Niels Jernes Vej 12,
Aalborg East DK-9220, Denmark
e-mail: civ@hst.aau.dk

John Rasmussen
Department of Material and Production,
Aalborg University,
Fibigerstraede 16,
Aalborg East DK-9220, Denmark
e-mail: jr@mp.aau.dk

Michael S. Andersen
Department of Material and Production,
Aalborg University,
Fibigerstraede 16,
Aalborg East DK-9220, Denmark
e-mail: msa@mp.aau.dk

Development and Functional Testing of an Unloading Concept for Knee Osteoarthritis Patients: A Pilot Study

This paper presents a knee brace design that applies an extension moment to unload the muscles in stance phase during gait, and thereby the knee, as alternative to conventional valgus braces for knee osteoarthritis patients. The concept was tested on one healthy subject during normal gait with a prototype, which was designed to activate and deactivate in order to apply the extension moment in the stance phase only and hereby avoid any interference during the swing phase. Electromyography measurements and musculoskeletal models were used to evaluate the brace effects on muscle activation and knee compressive forces, respectively. Simulations predicted an ideal reduction of up to 36%, whereas experimental tests revealed a reduction of up to 24% with the current prototype. The prototype brace also reduced the knee joint force impulse up to 9% and electromyography (EMG) peak signal of the vasti muscles with up to 19%. Due to these reductions on a healthy subject, this bracing approach seems promising for reducing knee loads during normal gait. However, further clinical experiments on knee osteoarthritis patients are required to evaluate the effect on both pain and disease progression.
[DOI: 10.1115/1.4051847]

Introduction

Osteoarthritis (OA) is a multifactorial, chronic joint disease, leading to an alteration of the articular cartilage due to soft tissue deterioration in the affected joint [1]. This causes inflammation, pain, and stiffness, which limits mobility during activities of daily living and reduces quality-of-life [2]. In the absence of a cure [3], and with a continuously increasing number of OA patients [4], there is a high demand for early disease management.

Multiple risk factors are known to contribute to knee OA (KOA) development [2,5,6]. Once a joint is affected, mechanical overloading is considered to be one of the causes for disease progression [7–9], since meniscus and cartilage deterioration rate depend on internal joint loads and stress distribution [10]. Thus, a common noninvasive treatment of KOA is knee bracing with the aim of reducing pain and disease progression, and thereby postponing the need for joint replacement by unloading the internal knee compressive forces (KCF) in the affected area by applying external loads [11]. However, the literature contains varying conclusions with this approach [12,13], which may be due to the predominant focus on reducing the external knee adduction moment (KAM) [11,12,14,15]. KAM is often considered as a surrogate measure of the medial KCF [16–18] even though a reduction of KAM has been shown in vivo not to guarantee a reduction of the internal loads on the medial compartment [19]. This interdependency between KAM and medial KCF is due to other factors influencing the internal knee joint load distribution, such as the knee flexion extension moment (KFM). Both peak KAM and peak KFM have been shown to be valid predictors of the medial KCF [19], which is supported by both in vivo [20] and *in silico* studies using musculoskeletal (MS) models [7,21–24]. Simulations by Miller et al. [23] showed that the joint contact forces were reduced

[1]Corresponding author.

Manuscript received April 3, 2021; final manuscript received July 10, 2021; published online September 1, 2021. Assoc. Editor: Francesco Travascio.

almost twice as much from gait modifications minimizing both KAM and knee flexor muscle activity compared to only minimizing KAM. Similarly, Richards et al. [24] used gait modifications to reduce first peak KAM but MS models revealed no reduction of the medial KCF due to a significant contribution from the knee flexor muscles. This may explain why the reduction of the external KAM is 2–3 times higher than the observed reduction in medial KCF [25]. The same trend was observed by Stoltze et al. [21], where the knee flexion extension moment had a high impact on the first peak KCF, whereas the second peak was governed by the ankle plantar flexion moment due to a large contribution from the bi-articular gastrocnemius muscle during late stance phase. These findings support a previous study [26] indicating that the main contributor to the KCF is the surrounding muscles for which reason a more efficient reduction may be achieved by reducing muscle activation.

The optimal combination of KAM and KFM, when dealing with bracing, is not clear. However, a combination of the two interventions would most likely improve the effect since a combined peak KAM and peak KFM significantly improves the prediction of medial KFM [19,20].

This paper presents a brace concept that aims to reduce the first peak total KCF during gait through muscle compensation by applying an external knee extension moment. The concept of applying a knee flexion/extension moment to assist human muscles is common within exoskeletons, which either apply the moment actively [27–30] or quasi-passively [31–34]. The latter refers to an active control, but the moment is applied passively from, e.g., springs and, hence, there is no mechanical energy added to the system. Active types use sensors and real-time feedback controllers to capture the wearer's intended motion to assist for both knee flexion and extension. The quasi-passive types are usually controlled in a simpler way using sensors to distinguish between stance and swing phases. An active clutch mechanism engages and disengages to either apply assistive moment passively or to let the knee move freely. Complete passive devices for the lower extremity, applying moments in the sagittal plane during walking, have only been possible to find for hip and ankle joints [35,36]. This is most likely due to the more complicated function of the knee joint during the stance phase, which includes more direction changes of the sagittal joint angle [37] and changes from flexion to extension moment [38] compared with the hip and ankle. Thus, applying moment at the knee with a completely passive device requires a passive countermechanism to determine when to apply assistance. An alternative approach is a quasi-passive solution using, e.g., sensors in the foot insole to detect heel strike and toe-off as in Shamaei et al. [39], although these devices and the installed clutch usually make the design more bulky.

The main goal of exoskeletons is to provide assistance and compensate for the joint moments to reduce muscle activation, but the purpose can vary. When dealing with the lower extremity, metabolic cost is most often the main evaluation factor [31,35,36,40], which improves endurance for various activities and load-carrying tasks. However, as previously mentioned, the muscle compensation in the sagittal plane may also lead to a reduced KCF and thereby potentially slow down KOA progression. Exoskeletons have previously been proposed as mobility assistance [28] and weight support [41] for KOA patients. Both designs span the full lower extremity though, which is not convenient for assisting patients during activities of daily living. A much more slim product, using the approach of applying a knee extension moment, is the Levitation brace (Spring Loaded Technology, Helifax, Canada) [42]. It uses liquid compression springs to apply a passive extension moment as function of knee flexion angle to assist the extensor muscles. The brace has been tested *in silico* during sit-to-stand [42] and deep knee bend [43] with KCF reduction of up to 27% and 40% body weight, respectively. However, the applied moment is limited during gait due to the peak flexion angle in the swing phase, which has been reported to be approximately 60 deg for a group of KOA patients [44]. At this angle, the Levitation brace would apply approximately 11 N·m [42], which could have a negative effect on the toe clearance and muscle cocontractions.

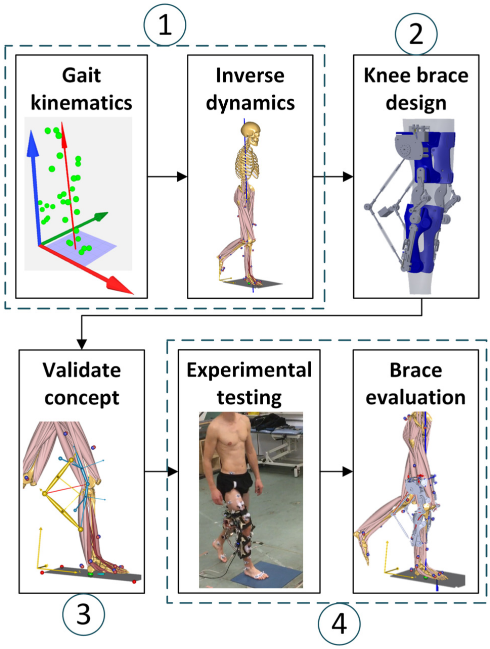


Fig. 1 Workflow diagram for prototype design and evaluation, which overall consists of four steps: (1) three-dimensional (3D) gait analysis using motion capture and musculoskeletal modeling, (2) knee brace design and adjustment, (3) validation of concept under ideal circumstances, and (4) experimental validation of the prototype brace

This paper describes the design process and experimental tests of a proof-of-concept prototype brace for unloading the knee joint by reducing the knee extensor muscle activation during the stance phase of gait. The aim was to develop a quasi-passive prototype, which targets the first peak KCF during gait without any interference during the swing phase. This ability of applying the intervention during stance phase only has not been possible to find in existing products. Furthermore, the brace should be limited to span the knee joint like a conventional knee brace and provide customization abilities to match the individual's knee extension moment. This is considered to be a novel feature, which potentially can improve the management of KOA. The concept was tested on one healthy subject, both *in silico* and in vivo, and evaluated based on estimates of the internal KCF and surface electromyography (EMG) measurements.

Method

One healthy subject (male, age: 33 years, height: 182.2 cm, weight: 68.9 kg) was recruited for this study to evaluate the developed knee brace prototype. The study procedure is shown with a flowchart diagram in Fig. 1 with four main tasks. The design in step 2 is based on a leg surface scan and the brace is adjusted according to the data obtained in step 1. The experimental testing of the prototype brace in step 4 is to quantify reductions in muscle activations, measured with EMG, and estimates of the knee contact forces with MS models. The subject provided informed

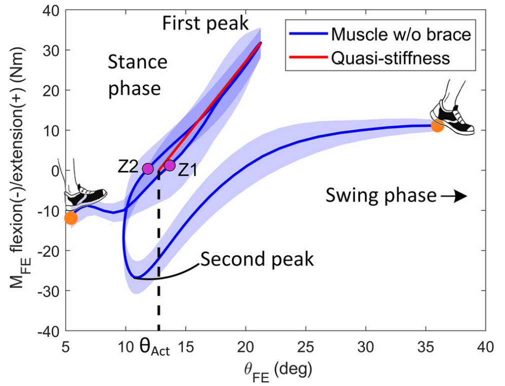


Fig. 2 Mean internal knee flexion–extension muscle moment as function of knee flexion angle over the stance phase to estimate the knee quasi-stiffness used for detecting the activation angle, θ_{Act}, among other individual factors. The points Z1 and Z2 are start and end points respectively of the brace activation period whereas the two foot symbols indicate start and end of simulation period containing stance phase and beginning of swing phase. The two muscle moment peaks correspond to the characteristic two knee compressive force peaks. The shaded area is ± one standard deviation.

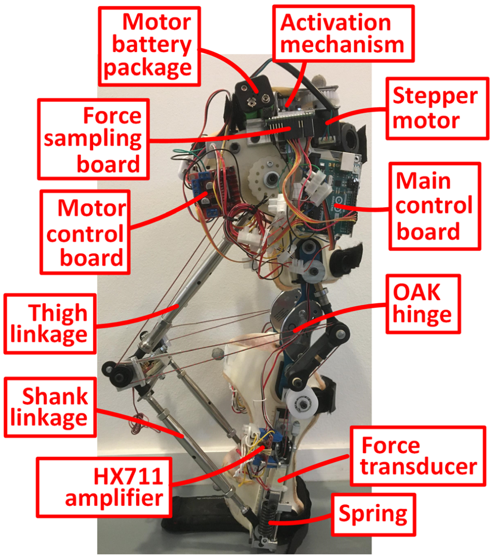


Fig. 3 The main components on the knee brace prototype

consent and the study followed the ethical guidelines of The North Denmark Region Committee on Health Research Ethics.

In the following sections, the methodologic four steps are further explained including how the collected data were used to design and control the prototype knee brace and also to perform a preliminary simulation study to evaluate the potential of the chosen unloading concept. Lastly, experimental tests for evaluating the prototype brace effects are described.

Initial Biomechanical Analyses. Initial 3D kinematics was obtained for five gait trials at a self-selected speed. The trajectories of 32 surface-mounted reflective markers on the lower extremity were recorded with eight infrared cameras (Oqus 300 series, Qualisys AB, Gothenburg, Sweden) sampling at 100 Hz, and the ground reaction force (GRF) was sampled at 1000 Hz using a force plate (Advanced Mechanical Technology, Inc., Watertown, MA, US) embedded in the floor. These recordings were used as inputs to MS models in the anybody modeling system 7.2 (AMS) (AnyBody Technology A/S, Aalborg, Denmark) to estimate the muscle forces and joint compressive forces by means of inverse dynamics analysis including muscle recruitment optimization [45]. All models in this study were based on the AnyMoCap template model from the AnyBody Managed Model Repository (AMMR) v. 2.1.1 [46].

Knee Brace Design. The knee brace concept applies the external moment passively with the use of elastic energy storage as a function of the knee flexion angle. The individual knee moment behavior was estimated from the knee joint quasi-stiffness as explained in Ref. [47]. This is found by plotting the internal knee flexion/extension muscle moment, M_{FE}, as a function of knee flexion angle, θ_{FE}, and gives an indication of the necessary external knee moment to balance M_{FE}. The mean graph across the five gait trials in step 1 is shown for 60% gait cycle in Fig. 2, which indicates an almost linear stiffness behavior through the first peak moment during gait as likewise observed in Ref. [47]. This peak corresponds to the first of the two characteristic KCF peaks during gait [48,49]. As mentioned previously, the second peak KCF is mainly governed by the ankle plantar flexion muscles, for which reason an additional device around the ankle is required to reduce both KCF peaks.

Note, M_{FE} in Fig. 2 crosses zero Nm twice at almost the same knee flexion angle, θ_{Act}, during stance phase. This angle is estimated as the average between the two values, where the moment curve of the first peak part crosses zero moment (Z_1 and Z_2 in Fig. 2). These two values are almost identical when walking with preferred gait speed and deviate from each other when walking faster or slower [47]. Identical Z_1 and Z_2 values causes the flexion and extension part of the first moment peak to be almost on top of each other, which makes an average stiffness (quasi-stiffness in Fig. 2) more accurate.

The stiffness line in Fig. 2 stretches from the instance that θ_{Act} occurs to the first muscle moment peak to illustrate the target brace moment, which, under ideal circumstances, with no loss of energy between brace and leg, should be applied when the knee flexion angle reaches θ_{Act} shortly after heel strike in order to compensate the first peak muscle moment.

Knee Brace Prototype. A prototype, using the brace concept explained above, has been developed for this study to evaluate the concept experimentally and is depicted in Fig. 3. It applies the extension moment through a four-bar mechanism consisting of a thigh and shank cuff and thigh and shank linkages on both lateral and medial sides. The two brace cuffs were 3D printed in PA12 nylon based on a surface scan of the subject's leg during full extension using a Structure Sensor (Occipital, Boulder, CO) and an iPad Pro 10.5 in. (Apple Inc., San Francisco, CA) to fit the brace to the specific anatomy of the subject. Postprocessing was done with the surface add-in in SOLIDWORKS 2016 (Dassault Systèmes, Vélizy-Villacoublay, France) and the cuffs were created with a 2 mm offset from the leg surface to make room for 10 mm of cushioning. The cuffs were connected on both the medial and lateral sides with osteo-arthritis knee (OAK) hinges (Fillauer LLC, Chattanooga, TN), which are designed to adapt to the complicated kinematics of the knee joint in the sagittal plane to avoid residual forces [41].

A string system on both the medial and lateral sides was embedded in the four-bar mechanism by means of pulley wheels, which was used to apply the extension moment as illustrated in

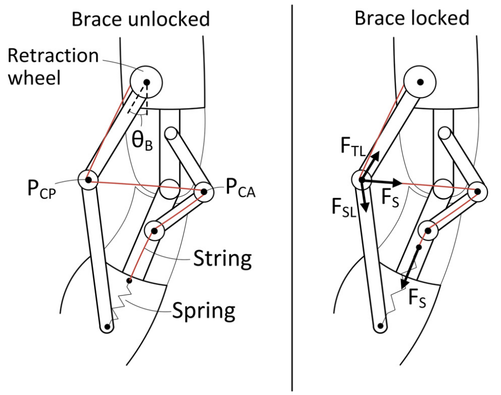


Fig. 4 Illustration of how the extension moment is generated with the prototype brace where the string line is a simplification of the string system. The two points P_{CP} and P_{CA} moves away from each other when flexing the knee, which pulls the string. When the brace is unlocked (left), the string can move freely during knee flexion but when the brace is locked (right), the string pulls the spring and generates a force F_S distributed through the two linkages (F_{TL} and F_{SL}). This generates an extension moment on thigh and shank as function of knee extension angle and spring stiffness. The brace angle, θ_B, is measured with a potentiometer and used to estimate the knee flexion angle.

Fig. 4. Inside the activation mechanism, the string was wound around a retraction wheel connected to a recoil spring. Since the string wraps around the posterior and anterior linkage connection points (P_{CP} and P_{CA}, respectively, in Fig. 4), the wheel feeds more string when flexing the knee and retracts when extending the knee. If the retraction wheel is locked, the string pulls the spring when flexing the knee, which induces a force, F_S, transferred from the string through the linkages (the forces F_{SL} and F_{TL} in Fig. 4). These forces apply extension moments on thigh and shank (M_{BT} and M_{BS} respectively) as function of knee flexion angle.

An aluminum piece with two 90 deg strain gage rosettes was connected in series with each spring to measure the spring force at 80 Hz using a SparkFun HX711 amplifier board (SparkFun Electronics, Boulder, USA). These two force transducers were calibrated with known weights within 24 h before experiments.

See Supplemental Material on the ASME Digital Collection for more details on the prototype design.

Activation Mechanism. As mentioned previously, the brace should only apply moment during the first muscle moment peak so the retraction wheel needs to be locked only during the stance phase and unlocked during the swing phase. This is handled by an activation mechanism at the retraction wheel, which is adjusted individually according to θ_{Act}.

The activation mechanism measures the knee flexion angle and the direction (flexion or extension) with a potentiometer (Alps Alpine, Tokyo, Japan) driven by the thigh linkage, so θ_{Act} must be converted to the corresponding value of θ_B (see Fig. 4). This is done with an analytical expression for θ_B as function of θ_{FE}, which is further explained in the Supplemental Material on the ASME Digital Collection. With this approach, the brace activation angle, $\theta_B(\theta_{Act})$, only requires setting once and is then used as the target value for sending a signal to the motor at the right time.

The potentiometer readings are converted to a θ_B-value based on a known reference measurement of the knee flexion angle, which was chosen to be standing in a neutral posture with the knee straight. This posture was recorded in step 1 and the knee flexion angle was estimated in AMS and used to calibrate the conversion function. Therefore, before conducting the experimental gait trials, the subject was asked to stand in that same posture to store the corresponding potentiometer reading. Additionally, the thigh linkage and the potentiometer were connected with gears and the gear ratio was used to find out how many degrees the thigh linkage had moved from the reference posture based on the potentiometer input. Ideally, when the current θ_B-value equals $\theta_B(\theta_{Act})$ during knee flexion right after heel strike, the brace should be locked instantly. However, a small time delay for the stepper motor to move the lock pawl must be taken into account. In addition, due to slack in the brace construction (induced in the string system and locking mechanism), soft tissue artifacts and cushioning between brace and leg, the applied moment is not transferred to the leg immediately when the string is locked. Therefore, the activation signal was sent to the motor at θ_{Act} during knee extension right before heel strike to be sure the brace could provide a substantial extension moment during the first peak muscle moment. The signal can be sent earlier or later to match the activation with the individual gait speed.

The prototype brace uses a 3.8 V hybrid permanent magnet stepper motor (RS Pro, RS Component, Corby, UK) with a 1.8 deg step angle and a dynamic torque of 60 mN·m. It is controlled with an L298N dual H-bridge motor controller through an Arduino Uno. When the brace activates, the motor pushes a lock pawl linearly into a gear connected to the retraction wheel. It keeps pushing the pawl until one of the force transducers measures 5 N to make sure the string is tightened. The motor retracts the lock when the knee extends after reaching the first muscle moment peak and one of the force transducers drops below 1 N.

Ideal Brace Compensation. The biomechanical potential of the prototype design was initially investigated with MS models in AMS under ideal circumstances using the aforementioned AMMR model and driven by the aforementioned normal gait data collected in step 1.

The prototype brace was modeled in AMS with rigid bodies connected with frictionless joints and the brace rotation point aligned with the knee rotation axis. The spring stiffness was adjusted individually to match the applied brace moment with the estimated muscle moment from Fig. 2. The contact between brace and leg was rigid and no slack in the strings was included. The peak KCF for different values of spring stiffness, K_S, was found with a parameter study of inverse dynamics analyses in AMS. The best suited spring stiffness across five trials was chosen based on the largest reduction of the first peak KCF but restricted such that the brace moment did not exceed the original muscle moment in order to minimize the potential gait alterations that the brace may cause.

Further details about the MS model for the ideal brace can be found in the Supplemental Material on the ASME Digital Collection.

Experimental Brace Tests. The developed prototype knee brace was tested experimentally to evaluate the unloading concept of applying a knee extension moment in practice during normal walking under seven different conditions: normal walking without brace (NoBrace), bracing without activation (K0), and active bracing with five spring stiffnesses; 8.91 N/mm (K9), 19.9 N/mm (K20), 50.8 N/mm (K50), 70 N/mm (K70) and 101.8 N/mm (K100). K9 was the optimal spring stiffness in the ideal setup described in step 3 but due to energy loss, we wanted to investigate higher stiffness values as well. The K0 condition was a completely passive intervention without any applied moments. Five successful trials were conducted for each condition. Over time, the brace unintentionally slides down while walking, and, therefore, the subject was asked to stand in a neutral posture prior to each condition to store the corresponding potentiometer reading for updating the potentiometer calibration.

EMG Measurements. The effect of the brace was evaluated with surface EMG measurements obtained from noraxon mini direct transmission system sensors and the TELEmyo direct transmission system belt receiver (Noraxon, Scottsdale, AZ) at 1500 Hz. EMG signals were collected for eight muscles; vastus lateralis (VL), vastus medialis (VM), rectus femoris (RF), biceps femoris (BF), semitendinosus (ST), gastrocnemius lateralis (GL), gastrocnemius medialis (GM) and tibialis anterior (TA). Electrodes were placed according to SENIAM guidelines [50]. The post-processing was done with a custom MATLAB code (version 2018b), which filtered the signal with a 4th-order Butterworth zero-phase, bandpass digital filter allowing frequencies between 10 and 500 Hz. Subsequently, a second order, zero-phase, low-pass Butterworth filter with a cutoff frequency of 6 Hz was applied to the rectified signal of the bandpass filtered data. Finally, the data were resampled to 0–100% stance phase timed by the ground reaction force signal.

Following the gait trials, eight maximal voluntary isometric contraction (MVIC) exercises were conducted to record maximal activation from each muscle. Exercises from two separate protocols were used: one for all muscles except TA [51] and the TA muscle [52]. All exercises were conducted twice, during which the subject performed maximum contraction as rapidly as possible and held it for at least three seconds against the resistance of a tester who encouraged verbally. The maximum amplitude for each muscle, regardless of the exercise, was used to normalize the signals from the walking trials [51]. The average normalized activation across VM and VL (VML) was used to estimate the overall effect from the brace on the vastus muscle group. Similarly, GM and GL were averaged (GML) to estimate the overall effect in the gastrocnemius muscle.

Musculoskeletal Models. Marker trajectory and GRF were recorded at 150 Hz and 1500 Hz, respectively, with the same equipment as previously described. These recordings and the measured spring forces were used as inputs for MS models by means of interpolation. The models were based on the same AMMR model as used for the initial gait analyses in step 1, and the same marker protocol was used, although the cluster markers on thigh and shank were positioned differently according to how the brace cuffs covered the skin. Additionally, six markers were placed on the knee brace: three on the upper part and three on the lower part to track the brace independently of the leg in AMS.

The four pelvis markers were used to calculate the average gait speed by means of a finite difference approach. The CAD model of the brace was exported from SOLIDWORKS into AMS with the ANYEXP4SOLIDWORKS 1.2 add-in from AnyBody Technology A/S (Aalborg, Denmark).

The MS models were used to estimate the internal KCF for the seven conditions and compare the braced conditions with the unbraced. The contact between brace and leg was modeled by 56 contact elements distributed in two rings of 14, on the thigh and shank, respectively. Each contact element was paired with an element on the upper or lower brace cuff giving a total of 112 contact elements. Each of these consisted of five unilateral contact actuators, which were included in the muscle recruitment solver in the same way as when predicting ground reaction forces in AMS [53–55]. Four of the actuators, in pairs of two, estimated shear static friction forces between the brace cuffs and the leg, based on a friction coefficient of 0.8, and the last actuator estimated the normal force. The strength of the linear actuators was constantly 10,000 N, which is higher than any muscle in the body and hereby ensures that the muscle recruitment algorithm will activate the contact elements when this is beneficial in terms of reducing the loads of the anatomical muscles. However, due to this high strength and given any minute moment arm, the contact forces will attempt to balance the external knee flexion extension moments, instead of only the applied spring forces from the brace. To avoid this, the OAK hinges were kinetically detached from the brace cuffs and all forces between the two cuffs were transferred through two weightless segments perfectly aligned with the knee rotation axis. This ensured that no moment arm was available for the contact forces and thus only generated forces for balancing the applied brace moment.

The knee rotation axis was aligned by the knee and ankle markers instead of a generic cadaver model as in step 1. This allowed matching of the individual's knee varus/valgus alignment and achieving the right fit of the exported brace, which in the experimental trials was positioned according to the knee axis based on the knee markers. A more detailed description can be seen in the Supplemental Material on the ASME Digital Collection.

Results

According to the ideal brace simulation, the first peak KCF was reduced by 35.9% compared to normal gait without brace, whereas the second peak was unaffected. This led to a 38.2% reduction of the impulse of the knee contact force across the stance phase. Furthermore, the peak medial and lateral compartment forces were reduced with 24.4% and 6.2%, respectively.

The mean experimental EMG signals across the stance phase of five trials for the muscles VM, VL, VML, and RF are shown in Fig. 5, and percentage reductions with respect to NoBrace condition for all muscles and brace conditions can be found in Table 1. The VM peak EMG decreased 10–37% for the active bracing conditions, whereas the peak VL EMG increased 4–44% during bracing. Table 1 also includes the average gait speed (V_{Avg}), first peak knee flexion angle ($\theta_{\mathrm{FE,P1}}$), first peak KCF ($\mathrm{KCF}_{\mathrm{P1}}$), impulse of the compressive force during stance phase (KCFi) and the peak spring force (PSF) for each condition. The speed was more or less constant for all conditions, whereas the first peak flexion angle was generally lower for all active bracing conditions (17.7 deg–19.5 deg) compared to the NoBrace condition (20.6 deg). The first peak KCF was unaffected in the K0 condition but all active bracing conditions reduced the first peak (9.5–24%) compared to NoBrace (1474 N) with a max reduction of 24% for K70 condition (1120 N). The total KCF through the stance phase for the experimental trials is shown for unbraced and braced conditions in Fig. 6. The impulse was reduced 2.7–9.1% for the active bracing conditions compared to NoBrace (1218 Ns) (see Table 1). The joint kinematics of the lower extremity is shown in Fig. 7 for the stance phase of all measured conditions. According to these graphs, the kinematics of the bracing conditions generally deviates from the NoBrace condition and especially the K0 condition. The larger peak in the knee flexion angle for K0 corresponds well with a higher muscle activation but, according to Fig. 6, the KCF is unaffected. Lastly, the knee moment-angle plot for the K70 condition is shown in Fig. 8 including the knee muscle moment, with and without brace, and the applied brace moment. The peak muscle moment is reduced from approximately 32 Nm for NoBrace condition to 22 N·m for the K70 condition and the applied brace moment peaks at 10 N·m.

Discussion

The use of knee braces is a common conservative intervention with the aim of reducing knee joint loads, in particular in the medial compartment. The clinical effects of conventional valgus braces are still debated [12,13] and in vivo studies have demonstrated that a reduction in KAM does not guarantee a reduction of the medial compartment load [19]. An alternative approach for unloading the knee is to reduce the muscle activation by applying a moment in the sagittal plane, since muscle contraction is the main contributor to the KCF [26]. This paper has demonstrated a reduction in KCF in using the prototyped knee brace that applied knee extension moment in the weight acceptance phase during normal gait. Despite being a pilot study, the obtained results are considered as a successful proof of concept for this unloading method.

The 35.9% reduction of the first peak KCF obtained with MS simulations indicates a significant potential for this type of bracing approach. This is supported from a similar simulation study [56], which demonstrated up to 64% reduction in knee joint loads

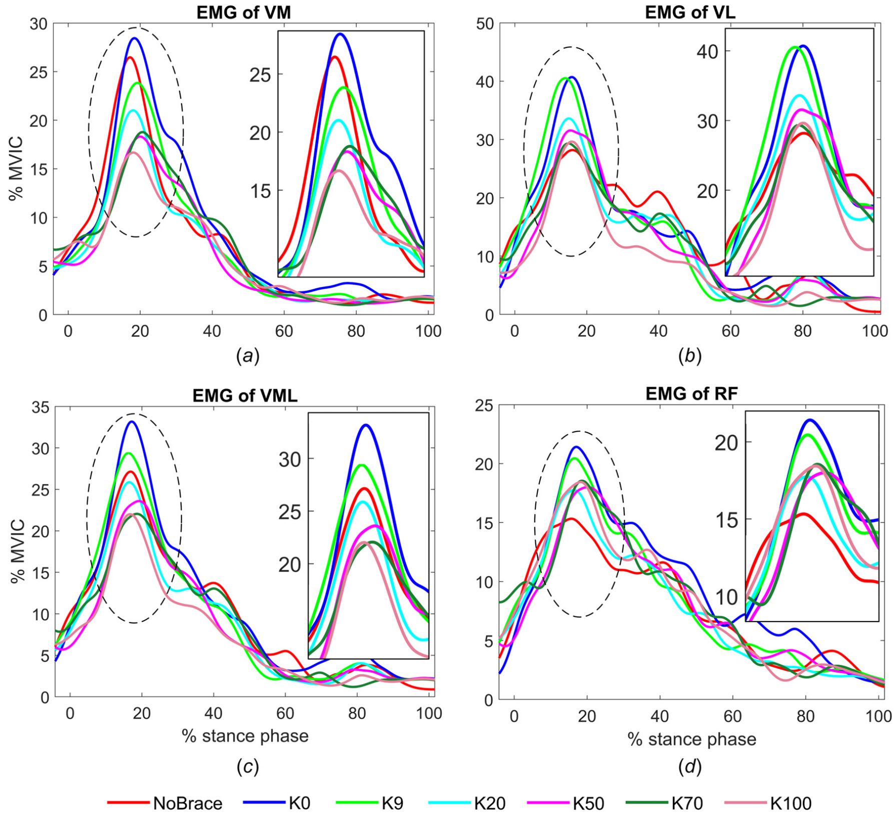


Fig. 5 Mean EMG signal of vastus medialis (VM), vastus lateralis (VL), average between VM and VL (VML), and rectus femoris (RF) through stance phase for each condition. The first peak signal, corresponding to the first peak muscle moment in Fig. 2, is highlighted in each graph.

during a deep squat motion. However, the kinematic changes, muscle cocontractions, soft tissue artifacts and slack in the brace mechanism are typically not taken into account in this type of simulation studies, and therefore the brace effect requires experimental verification.

Electromyography Measurement. The experimental effect was primarily observed through EMG measurements since the internal KCF is known to be primarily coming from the muscle forces [26]. Within bracing conditions, a peak reduction was obtained in the EMG signal for all three knee extensor muscles measured in this study (RF, VM and VL) when increasing the spring stiffness. However, only VM peak activation (Fig. 5(*a*)) was reduced for bracing conditions compared to NoBrace, whereas VL peak activation (Fig. 5(*b*)) was only reduced to approximately the NoBrace peak value for conditions K70 and K100 (see Table 1). Despite this, the reduced VL peak activation for high spring stiffness in Fig. 5(*b*) indicates that further improvements of the brace design and performance will most likely lead to a lower VL peak activation for the braced versus the NoBrace condition. The low VL peak signal for the NoBrace condition compared to bracing conditions can be due to a mispositioned VL electrode. This was adjusted to avoid contact with the upper brace cuff, which might have reduced the signal. However, the pressure from the brace strap might have increased the signal when wearing the brace and these issues must be taken into consideration when designing the brace cuffs for this kind of validation study. A detailed picture of the subject wearing the brace and EMG electrodes can be found in the Supplemental Material on the ASME Digital Collection.

Despite only the VM peak signal being reduced to a lower value than the NoBrace level, the peak of the averaged vastus signal, VML, (Fig. 5(*c*)) was reduced for all brace conditions except for K9. This indicates that the overall vasti muscle activation was reduced with the prototype brace during normal gait. However, vastus intermedius must be included to make this conclusion as in previous work [57], but this muscle was considered to be too deep to record with surface EMG during normal gait [58].

All of the bracing conditions had a higher peak RF signal compared to the NoBrace peak level (Fig. 5(*d*)), which could be caused by changes in the muscle recruitment. According to Fig. 5, RF has the lowest normalized peak activation of 15% during stance phase among the measured knee extensor muscles for the NoBrace condition. Therefore, when the applied brace moment reduces the activation of the two strong vasti muscles, the RF muscle may be recruited instead. However, the hip moment normally changes from extension to flexion at around 45% stance phase during gait [38,59,60], and the RF peak occurs already at 20% stance phase in this study.

Knee Compressive Forces. The first peak total KCF (see Fig. 6 and Table 1) was the main target for the prototype brace

Table 1 Top: percentage reduction of each muscle for each bracing condition compared to NoBrace, which is shown for peak value and area below the EMG signal curve. Bottom: absolute values and percentage reduction for each bracing condition compared to NoBrace for chosen gait parameters. Average gait velocity, VAVG, first peak knee flexion angle, θFE,P1, first peak knee compressive force, KCFP1, impulse of knee compressive force, KCFi, and peak spring force, PSF.

Variables		Conditions						
		NoBrace	K0	K9	K20	K50	K70	K100
RF	Peak	—	39.7	33.4	15.8	17.5	21.0	20.3
	Area	—	24.2	2.6	−2.5	2.5	7.7	5.2
VM	Peak	—	7.4	−9.9	−20.6	−30.8	−29.1	−37.0
	Area	—	17.5	−8.6	−15.1	−19.8	−6.6	−17.5
VL	Peak	—	44.4	43.8	19.2	11.9	4.1	5.2
	Area	—	−8.4	−19.7	−24.7	−28.7	−27.0	−30.9
VML	Peak	—	22.2	8.3	−4.7	−13.1	−18.8	−18.9
	Area	—	1.5	−15.5	−20.9	−25.3	−19.2	−25.8
BF	Peak	—	1.8	19.0	−3.4	−7.6	1.0	−2.7
	Area	—	−9.1	−12.4	11.6	−4.6	−0.2	10.4
ST	Peak	—	1.9	1.2	11.9	−8.9	−6.8	4.4
	Area	—	8.0	11.9	28.5	11.8	25.1	45.8
GM	Peak	—	18.6	34.9	45.3	30.4	52.8	39.4
	Area	—	21.3	39.9	43.2	28.6	58.3	69.1
GL	Peak	—	−37.7	−7.7	−38.7	1.2	−2.6	−11.8
	Area	—	3.7	21.0	0.3	13.4	28.0	31.5
GML	Peak	—	−5.9	13.6	8.7	15.6	30.1	18.4
	Area	—	13.5	31.6	24.2	21.9	44.9	52.5
TA	Peak	—	11.7	7.2	14.4	12.7	4.0	17.1
	Area	—	11.8	−11.9	−7.8	−11.6	−6.8	−9.1
V_{Avg} (km/h)		2.4 ± 0.06	2.3 ± 0.08	2.4 ± 0.03	2.3 ± 0.06	2.3 ± 0.06	2.3 ± 0.04	2.4 ± 0.06
$\theta_{FE,P1}$ (deg)		20.6 ± 0.6	22.0 ± 2.5	17.7 ± 0.7	18.5 ± 0.8	17.9 ± 1.0	18.1 ± 1.3	19.5 ± 1.1
KCF_{P1} (N)		1474.2 ± 35.1	1470.7 ± 114.8	1334.1 ± 25.6	1275.3 ± 60.6	1176.7 ± 36.0	1119.8 ± 43.4	1196.7 ± 72.7
KCF_{P1} (%)		—	−0.2	−9.5	−13.5	−20.2	−24.0	−18.8
KCF_i (Ns)		1218.2 ± 64.0	1326.1 ± 116.5	1158.9 ± 64.0	1185.8 ± 56.6	1107.5 ± 56.1	1132.8 ± 60.1	1151.7 ± 60.2
KCF_i (%)		—	8.9	−4.9	−2.7	−9.1	−7.0	−5.5
PSF (N)		—	—	20.5 ± 2.0	25.6 ± 4.4	28.1 ± 4.5	28.7 ± 4.1	29.0 ± 3.0

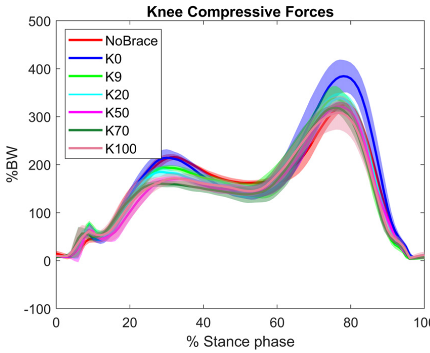


Fig. 6 Mean knee compressive forces in percentage body weight during stance phase for each condition. The shaded area is ± one standard deviation.

regarding force reduction. This peak followed the same trend as the vasti muscles activation with a decreasing peak value for increasing spring stiffness; however, a generally larger reduction was observed for the KCF peaks. Example, VML muscle activation for K0 condition was significantly higher than NoBrace but the first peak total KCF was approximately the same for the two conditions. The same trend was observed for K9, which indicates that the brace causes gait alteration changing the affect from the ground reaction force.

The expected achievable reduction of the medial KCF, using a commercial valgus brace, has been reported to be 25% before the applied valgus moment becomes painful and uncomfortable [25]. A similar reduction of the total KCF has been achieved in this study with 24% reduction for K70 condition, which leads to reduction of both the medial and lateral compartment loads as well. The 35.9% reduction of the KCF in the ideal in silico brace simulation, obtained with a K9 spring stiffness, demonstrates the loss of energy between brace and the leg, which depends on the brace design (e.g., slack in the brace), attachment of the brace and soft tissue artifacts. The former two can be reduced by mechanical design improvement, but the latter factor is subject-specific and difficult to capture in the models applied for brace design. Therefore, in order to predict the best suitable applied moment with the use of MS models, a realistic interaction between brace and leg is needed instead of the current rigid contact formulation. The literature includes varying results for devices applying knee extension moment during different tasks. Often, simulations predict substantial benefits regarding reduced knee joint kinetics [29,61,62] but the experimental tests on EMG signal or metabolic cost rarely confirm the simulated scenarios [28,30,33,39,63]. This may be caused by the lack of realistic contact formulations taking the energy loss between the device and leg into account. An example of a torque-driven planar model predicting the interaction between an exoskeleton and the leg has been presented by Serrancolí et al. [64]. They calibrated the model with experimental data of sit-to-stand trials to predict the motion and contact forces in the sagittal plane. However, the model in Ref. [64] was only validated for normal contact forces, and the individual soft tissue artifact is not included as a contact parameter in the optimized spring-damper systems. The contact simulation in this study could be improved by including force-dependent kinematics [65], which solves the motion of the brace by assuming quasi-static equilibrium between the brace gravity loads, contact forces, and a defined stiffness between brace and leg.

Figures 5(*c*) and 6 indicate that there is a limit on the first peak reduction of total KCF and vasti muscles activation with the current prototype, since K50, K70, and K100 are almost identical for these two measurements. This also applies to the measured peak

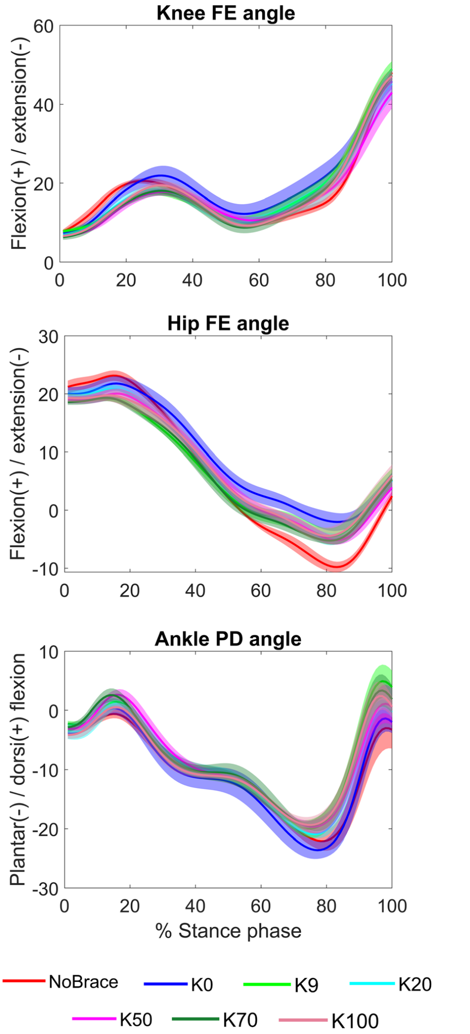


Fig. 7 Mean internal knee flexion–extension muscle moment for NoBrace condition and K70 bracing condition as function of knee flexion angle. Additionally, the applied brace moment is included, which is zero except during first peak moment. The shaded area is ± one standard deviation.

spring force (PSF in Table 1). The brace cuffs for this study were made of 3D printed PA12 nylon, and even though a cushioning layer was placed between the leg and the cuffs, the brace was too stiff to adapt to the changes of the soft tissue, e.g., when muscles contract. Therefore, the brace tended to slide down when the applied moment became too large, which sets an upper limit for the current prototype. This may be avoided if the inner layer is an elastic sleeve, which shapes according to the leg, although the applied moment must still be transferred to the leg through a rather stiff material. The vertical migration of the brace also reduces the advantage of manufacturing individual brace cuffs based on a 3D scan, since the migrated brace no longer fits the leg surface. Furthermore, the advanced flexion motion of the OAK hinges is irrelevant if the brace is misaligned with the knee axis. An air bladder on each upright, as already seen for conventional valgus braces [66], can help prevent the migration of the brace. Alternatively, a strap around the waist or over the shoulders will solve this issue but that would violate the aim of limiting the covered area to the knee only.

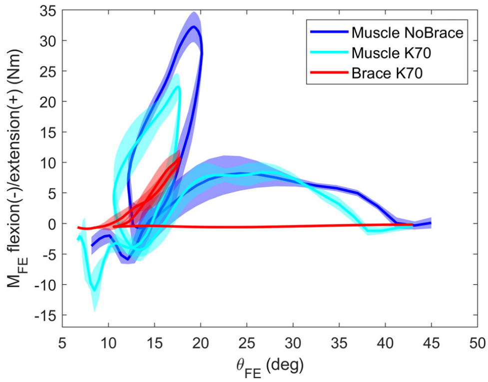


Fig. 8 Lower extremity joint kinematics from AMS for each condition during the stance phase. The shaded area is ± one standard deviation.

Anybody modeling system estimated the second peak KCF to be significantly higher for the K0 condition compared to NoBrace. However, that condition was the only bracing condition with a lower averaged EMG signal of the two gastrocnemius muscles (GML) (see Table 1), so the significantly higher recruited muscle activation for GM (125% higher peak compared to NoBrace) indicates poor model setup. It may be caused by errors in the kinematics or error in positioning of the foot markers leading to poor scaling of the calcaneus bone, which both have a big influence on the gastrocnemius recruitment. Another disagreement between the measured EMG signals and the estimated KCF is that K50 and K100 had the largest reduction in vasti muscle activation (25.3% and 25.8%, respectively), whereas K70 had the largest reduction in first peak KCF (24%). This demonstrates the biomechanical complexity of the knee joint and the importance in having experimental data to support the simulated results.

The KCF impulse (KCFi in Table 1) was reduced for the three highest spring conditions, and the impulse may be a more critical factor than the peak KCF regarding knee OA progression. A study by Bennell et al. [67] suggests KAM impulse as a significant risk factor for loss of medial tibial cartilage volume, whereas no association was found for peak KAM. Additionally, KAM impulse has been shown to be significantly different between knee OA severity groups [68,69], which could indicate that high impulse is responsible for OA progression and peak loads initiate OA.

Figure 8 shows the mean knee stiffness curve for muscle moment for the NoBrace and K70 conditions, where the latter was chosen because it had the largest reduction of KCF. The two conditions peak at around 23 and 33 N·m, respectively, and this reduction fits well with the applied brace moment of around 10 N·m.

Knee Brace Prototype. Exoskeletons are often heavy and bulky, whereas knee braces are known to be more slim and light. In order to achieve the largest applied moment possible, the presented prototype was designed in a bulky fashion to properly evaluate the concept. This design is clearly not suited for activities of daily living and a slimmer and more compact brace design is needed. However, this may lead to smaller moment arms and a narrower angle of action relative to the leg, so the string force must increase in order to provide the same applied moment. The previously mentioned Levitation brace has a slim design [42] and if using similar technology, the bulkiness of the brace prototype could be reduced. However, the prototype in this study applies 10 N·m at 18 deg knee flexion angle during stance phase with the K70 springs (see Fig. 6), whereas the Levitation brace would apply approximately 5 N·m at this angle [42]. Thus, a larger spring stiffness is needed, which may require more space. The lower value of the Levitation brace reduces the effect during gait but is expected to be a consequence of the constantly applied moment. If a compact control board is used instead of Arduino and a solenoid is responsible for locking the spring instead of a stepper motor, the additional activation mechanism would require limited space.

Previous work has demonstrated that hip and ankle joint kinematics are invariant when wearing quasi-passive exoskeletons targeting the knee joint [70]. However, despite instructions to walk as naturally as possible when wearing the brace, the joint kinematics for bracing conditions deviates from the NoBrace condition for all three joints in the lower extremity, especially the hip flexion–extension angle (see Fig. 7). This is most likely due to the bulky design in this study, and the gait alterations can have contributed to the observed reductions in EMG signals and KCF. Exoskeleton mass has previously been shown to be the main contributor to the increase of the joint moment [70], so reducing the overall weight of 2.97 kg for the current prototype would most likely improve the results.

Certain limitations and uncertainties should be mentioned. It is well known that marker-based motion capture introduces kinematics errors due to soft-tissue-artifacts [71], which causes less accurate estimation of the joint and muscle forces [72]. The prediction of these forces is sensitive to the choice of the muscle recruitment formulation [72] and muscle modeling [71] among others introducing errors in the model outputs. Other sources of error are the muscle moment arms and tendon slack length [73], which could be reduced by using subject-specific models. Also, the knee is modeled as an ideal hinge joint with only one DOF in all models, despite the known complexity of this joint [74]. Another uncertainty is how the brace moment is fitted to the individual muscle moment in Fig. 2 based on a linear curve. The moment-angle plot of the subject in this study shows a relatively linear relationship but it is unknown whether KOA patients exhibit the same trend during gait. Furthermore, the linear fit alone is not realistic due to slack and soft tissue, which will add nonlinearity to the brace moment curve as seen in Fig. 8. Thus, the amount of soft tissue on the subject's leg and individual contact models based on experimental tests must be included to find the optimal fitting. This will also provide information on the correct activation, which in this study was done earlier than θ_{Act} in Fig. 2, when testing the prototype. Therefore, brace design improvements and more experimental tests are required to find the optimal activation. Additionally, the human–machine interface in the MS models is formulated by means of a contact formulation, which has not yet been validated for this specific purpose. However, the same formulation has been validated for predicting GRF by Skals et al. [75], who demonstrated the best correlations when measuring high peak values. The contact forces in this study are small in magnitude compared to GRF, which increases the influence of noise. These forces could be validated using pressure sensors between the brace and the leg similar to how Ghadikolaee et al. did for a valgus brace [76]. Furthermore, this study has only investigated a momentary load reduction of a healthy knee joint, and it is unclear whether the prototype brace influences pain or provides any long-term effect on disease progression. Lastly, the limited number of one subject makes this study a case report from which general conclusions cannot be drawn.

Conclusion

In this study, we have designed and demonstrated a novel brace concept to unload the knee forces during gait and based on a 24% reduction of the first peak KCF, the authors see a potential in this bracing concept. However, future studies on knee OA patients are required to evaluate the potential of the brace in this patient group, its potential to relieve pain and the brace effect on long-term disease progression using longitudinal studies.

Acknowledgment

The authors thank Peacocks Medical Group for assisting in the initial design phase of the knee brace prototype.

Funding Data

- Innovation Fund Denmark under the Individualized Osteoarthritis Intervention Project (Styrelsen for Forskning og Innovation) (Grant No. 40-2014-3; Funder ID: 10.13039/501100001825).

Nomenclature

KCF_i = impulse of total knee compressive force (Ns)
KCF_{P1} = first peak total knee compressive force (N)
M_{FE} = knee flexion extension muscle moment (N·m)
PSF = peak spring force (N)
V_{AVG} = average gait velocity (m/s)
θ_{Act} = knee flexion angle for ideal activation of the knee brace (deg)
θ_B = angle between thigh linkage and vertical (deg)
θ_{FE} = knee flexion extension angle (deg)
$\theta_{FE,P1}$ = first peak knee flexion angle (deg)

References

[1] Amin, S., LaValley, M. P., Guermazi, A., Grigoryan, M., Hunter, D. J., Clancy, M., Niu, J., Gale, D. R., and Felson, D. T., 2005, "The Relationship Between Cartilage Loss on Magnetic Resonance Imaging and Radiographic Progression in Men and Women With Knee Osteoarthritis," Arthritis Rheum., **52**(10), pp. 3152–3159.

[2] Silverwood, V., Blagojevic-Bucknall, M., Jinks, C., Jordan, J. L., Protheroe, J., and Jordan, K. P., 2015, "Current Evidence on Risk Factors for Knee Osteoarthritis in Older Adults: A Systematic Review and Meta-Analysis," Osteoarthritis Cartilage, **23**(4), pp. 507–515.

[3] Fransen, M., Mcconnell, S., Harmer, A. R., Van Der Esch, M., Simic, M., and Bennell, K. L., 2015, "Exercise for Osteoarthritis of the Knee (Review)," Cochrane Libr., **49**(24), pp. 1–144.

[4] Neogi, T., 2013, "The Epidemiology and Impact of Pain in Osteoarthritis," Osteoarthritis Cartilage, **21**(9), pp. 1145–1153.

[5] Gardiner, B. S., Woodhouse, F. G., Besier, T. F., Grodzinsky, A. J., Lloyd, D. G., Zhang, L., and Smith, D. W., 2016, "Predicting Knee Osteoarthritis," Ann. Biomed. Eng., **44**(1), pp. 222–233.

[6] Dell'Isola, A., Allan, R., Smith, S. L., Marreiros, S. S. P., and Steultjens, M., 2016, "Identification of Clinical Phenotypes in Knee Osteoarthritis: A Systematic Review of the Literature," BMC Musculoskelet. Disord., **17**(1), p. 425.

[7] Meireles, S., De Groote, F., Reeves, N. D., Verschueren, S., Maganaris, C., Luyten, F., and Jonkers, I., 2016, "Knee Contact Forces Are Not Altered in Early Knee Osteoarthritis," Gait Posture, **45**, pp. 115–120.

[8] Miyazaki, T., Wada, M., Kawahara, H., Sato, M., Baba, H., and Shimada, S., 2002, "Dynamic Load at Baseline Can Predict Radiographic Disease Progression in Medial Compartment Knee Osteoarthritis," Ann. Rheum. Dis., **61**(7), pp. 617–622.

[9] Andriacchi, T. P., and Mündermann, A., 2006, "The Role of Ambulatory Mechanics in the Initiation and Progression of Knee Osteoarthritis," Curr. Opin. Rheumatol., **18**(5), pp. 514–518.

[10] Radin, E. L., Burr, D. B., Caterson, B., Fyhrie, D., Brown, T. D., and Boyd, R. D., 1991, "Mechanical Determinants of Osteoarthrosis," Semin. Arthritis Rheum., **21**(3), pp. 12–21.

[11] Brooks, K. S., 2014, "Osteoarthritic Knee Braces on the Market: A Literature Review," J. Prosthet. Orthot., **26**(1), pp. 2–30.

[12] Richard Steadman, J., Briggs, K. K., Pomeroy, S. M., and Wijdicks, C. A., 2016, "Current State of Unloading Braces for Knee Osteoarthritis," Knee Surg., Sport. Traumatol. Arthrosc., **24**(1), pp. 42–50.

[13] Gohal, C., Shanmugaraj, A., Tate, P., Horner, N. S., Bedi, A., Adili, A., and Khan, M., 2018, "Effectiveness of Valgus Offloading Knee Braces in the Treatment of Medial Compartment Knee Osteoarthritis: A Systematic Review," Sports Health, **10**(6), pp. 500–514.

[14] Petersen, W., Ellermann, A., Zantop, T., Rembitzki, I. V., Semsch, H., Liebau, C., and Best, R., 2016, "Biomechanical Effect of Unloader Braces for Medial Osteoarthritis of the Knee: A Systematic Review (CRD 42015026136)," Arch. Orthop. Trauma Surg., **136**(5), pp. 649–656.

[15] Dessery, Y., Belzile, É. L., Turmel, S., and Corbeil, P., 2014, "Comparison of Three Knee Braces in the Treatment of Medial Knee Osteoarthritis," Knee, **21**(6), pp. 1107–1114.
[16] Baliunas, A., Hurwitz, D., Ryals, A., Karrar, A., Case, J., Block, J., and Andriacchi, T., 2002, "Increased Knee Joint Loads During Walking Are Present in Subjects With Knee Osteoarthritis," Osteoarthr. Cartil., **10**(7), pp. 573–579.
[17] Della Croce, U., Crapanzano, F., Li, L., Kasi, P. K., Patritti, B. L., Mancinelli, C., Hunter, D. J., Stamenovic, D., Harvey, W. F., and Bonato, P., 2013, "A Preliminary Assessment of a Novel Pneumatic Unloading Knee Brace on the Gait Mechanics of Patients With Knee Osteoarthritis," PM R, **5**(10), pp. 816–824.
[18] Ro, D. H., Lee, D. Y., Moon, G., Lee, S., Seo, S. G., Kim, S. H., Park, I. W., and Lee, M. C., 2017, "Sex Differences in Knee Joint Loading: Cross-Sectional Study in Geriatric Population," J. Orthop. Res., **35**(6), pp. 1283–1289.
[19] Walter, J. P., D'Lima, D. D., Colwell, C. W., and Fregly, B. J., 2010, "Decreased Knee Adduction Moment Does Not Guarantee Decreased Medial Contact Force During Gait," J. Orthop. Res., **28**(10), pp. 1348–1354.
[20] Meyer, A. J., D'Lima, D. D., Besier, T. F., Lloyd, D. G., Colwell, C. W., and Fregly, B. J., 2013, "Are External Knee Load and EMG Measures Accurate Indicators of Internal Knee Contact Forces During Gait?," J. Orthop. Res., **31**(6), pp. 921–929.
[21] Stoltze, J. S., Rasmussen, J., and Andersen, M. S., 2018, "On the Biomechanical Relationship Between Applied Hip, Knee and Ankle Joint Moments and the Internal Knee Compressive Forces," Int. Biomech., **5**(1), pp. 63–74.
[22] Kumar, D., Manal, K. T., and Rudolph, K. S., 2013, "Knee Joint Loading During Gait in Healthy Controls and Individuals With Knee Osteoarthritis," Osteoarthr. Cartil., **21**(2), pp. 298–305.
[23] Miller, R. H., Esterson, A. Y., and Shim, J. K., 2015, "Joint Contact Forces When Minimizing the External Knee Adduction Moment by Gait Modification: A Computer Simulation Study," Knee, **22**(6), pp. 481–489.
[24] Richards, R. E., Andersen, M. S., Harlaar, J., and van den Noort, J. C., 2018, "Relationship Between Knee Joint Contact Forces and External Knee Joint Moments in Patients With Medial Knee Osteoarthritis: Effects of Gait Modifications," Osteoarthr. Cartil., **26**(9), pp. 1203–1214.
[25] Kutzner, I., Küther, S., Heinlein, B., Dymke, J., Bender, A., Halder, A. M., and Bergmann, G., 2011, "The Effect of Valgus Braces on Medial Compartment Load of the Knee Joint—In Vivo Load Measurements in Three Subjects," J. Biomech., **44**(7), pp. 1354–1360.
[26] Herzog, W., Longino, D., and Clark, A., 2003, "The Role of Muscles in Joint Adaptation and Degeneration," Langenbeck's Arch. Surg., **388**(5), pp. 305–315.
[27] Pratt, J. E., Krupp, B. T., Morse, C. J., and Collins, S. H., 2004, "The RoboKnee: An Exoskeleton for Enhancing Strength and Endurance During Walking," IEEE International Conference on Robotics and Automation Proceedings (ICRA '04), New Orleans, LA, Apr. 26–May 1, pp. 2430–2435.
[28] McGibbon, C. A., Brandon, S. C. E., Brookshaw, M., and Sexton, A., 2017, "Effects of an Over-Ground Exoskeleton on External Knee Moments During Stance Phase of Gait in Healthy Adults," Knee, **24**(5), pp. 977–993.
[29] Shepherd, M. K., and Rouse, E. J., 2017, "Design and Validation of a Torque-Controllable Knee Exoskeleton for Sit-to-Stand Assistance," IEEE/ASME Trans. Mechatronics, **22**(4), pp. 1695–1704.
[30] Knaepen, K., Beyl, P., Duerinck, S., Hagman, F., Lefeber, D., and Meeusen, R., 2014, "Human-Robot Interaction: Kinematics and Muscle Activity Inside a Powered Compliant Knee Exoskeleton," IEEE Trans. Neural Syst. Rehabil. Eng., **22**(6), pp. 1128–1137.
[31] Shamaei, K., Adams, A. A., Cenciarini, M., Gregorczyk, K. N., and Dollar, A. M., 2014, "Preliminary Investigation of Effects of a Quasi-Passive Knee Exoskeleton on Gait Energetics," 36th Annual International Conference IEEE Engineering in Medicine and Biology Society (EMBC 2014), Chicago, IL, Aug. 26–30, pp. 3061–3064.
[32] Collo, A., Bonnet, V., and Venture, G., 2016, "A Quasi-Passive Lower Limb Exoskeleton for Partial Body Weight Support," Proceedings of IEEE RAS EMBS International Conference for Biomedical Robotics and Biomechatronics, Singapore, June 26–29, pp. 643–648.
[33] Rogers, E., Polygerinos, P., Allen, S., Panizzolo, F. A., Walsh, C. J., and Holland, D. P., 2017, "A Quasi-Passive Knee Exoskeleton to Assist During Descent," Biosyst. Biorobot., **16**, pp. 63–67.
[34] Elliott, G., Sawicki, G. S., Marecki, A., and Herr, H., 2013, "The Biomechanics and Energetics of Human Running Using an Elastic Knee Exoskeleton," IEEE Int. Conf. Rehabil. Robot., (4).
[35] Van Dijk, W., and Van Der Kooij, H., 2014, "XPED2: A Passive Exoskeleton With Artificial Tendons," IEEE Robot. Autom. Mag., **21**(4), pp. 56–61.
[36] Collins, S. H., Wiggin, M. B., and Sawicki, G. S., 2015, "Reducing the Energy Cost of Human Walking Using an Unpowered Exoskeleton," Nature, **522**(7555), pp. 212–215.
[37] Trinler, U., Schwameder, H., Baker, R., and Alexander, N., 2019, "Muscle Force Estimation in Clinical Gait Analysis Using AnyBody and OpenSim," J. Biomech., **86**, pp. 55–63.
[38] Samaan, M. A., Schwaiger, B. J., Gallo, M. C., Sada, K., Link, T. M., Zhang, A. L., Majumdar, S., and Souza, R. B., 2017, "Joint Loading in the Sagittal Plane During Gait is Associated With Hip Joint Abnormalities in Patients With Femoroacetabular Impingement," Am. J. Sports Med., **45**(4), pp. 810–818.
[39] Shamaei, K., Cenciarini, M., Adams, A. A., Gregorczyk, K. N., Schiffman, J. M., and Dollar, A. M., 2015, "Biomechanical Effects of Stiffness in Parallel With the Knee Joint During Walking," IEEE Trans. Biomed. Eng., **62**(10), pp. 2389–2401.
[40] Dollar, A. M., and Herr, H., 2008, "Lower Extremity Exoskeletons and Active Orthoses: Challenges and State-of-the-Art," IEEE Trans. Robot., **24**(1), pp. 144–158.
[41] Lee, K., and Wang, D., 2015, "Design Analysis of a Passive Weight—Support Lower—Extremity—Exoskeleton With Compliant Knee—Joint," IEEE International Conference on Robotics and Automation (ICRA), IEEE, Seattle, WA, May 26–30, pp. 5572–5577.
[42] Budarick, A. R., MacKeil, B. E., Fitzgerald, S., and Cowper-Smith, C. D., 2020, "Design Evaluation of a Novel Multicompartment Unloader Knee Brace," ASME J. Biomech. Eng., **142**(1), pp. 1–8.
[43] McGibbon, C. A., Brandon, S., Bishop, E. L., Cowper-Smith, C., and Biden, E. N., 2021, "Biomechanical Study of a Tricompartmental Unloader Brace for Patellofemoral or Multicompartment Knee Osteoarthritis," Front. Bioeng. Biotechnol., **8**, p. 1528.
[44] Richards, J. D., Sanchez-Ballester, J., Jones, R. K., Darke, N., and Livingstone, B. N., 2005, "A Comparison of Knee Braces During Walking for the Treatment of Osteoarthritis of the Medial Compartment of the Knee," J. Bone Jt. Surg. Br., **87-B**(7), pp. 937–939.
[45] Damsgaard, M., Rasmussen, J., Christensen, S. T., Surma, E., and de Zee, M., 2006, "Analysis of Musculoskeletal Systems in the AnyBody Modeling System," Simul. Model. Pract. Theory, **14**(8), pp. 1100–1111.
[46] Lund, M. E., Tørholm, S., and Jung, M., 2018, "The AnyBody Managed Model Repository (AMMR) v. 2.1.1," Zenodo, Geneva, Switzerland.
[47] Shamaei, K., Sawicki, G. S., and Dollar, A. M., 2013, "Estimation of Quasi-Stiffness of the Human Knee in the Stance Phase of Walking," PLoS One, **8**(3), p. e59993.
[48] Navacchia, A., Myers, C. A., Rullkoetter, P. J., and Shelburne, K. B., 2016, "Prediction of In Vivo Knee Joint Loads Using a Global Probabilistic Analysis," ASME J. Biomech. Eng., **138**(3), p. 031002.
[49] Lin, Y. C., Walter, J. P., Banks, S. A., Pandy, M. G., and Fregly, B. J., 2010, "Simultaneous Prediction of Muscle and Contact Forces in the Knee During Gait," J. Biomech., **43**(5), pp. 945–952.
[50] Hermens, H. J., Freriks, B., Disselhorst-Klug, C., and Rau, G., 2000, "Development of Recommendations for SEMG Sensors and Sensor Placement Procedures," J. Electromyogr. Kinesiol., **10**(5), pp. 361–374.
[51] Hubley-Kozey, C. L., Deluzio, K. J., Landry, S. C., Mcnutt, J. S., and Stanish, W. D., 2006, "Neuromuscular Alterations During Walking in Persons With Moderate Knee Osteoarthritis," J. Electromyogr. Kinesiol., **16**(4), pp. 365–378.
[52] Hsu, W. L., Krishnamoorthy, V., and Scholz, J. P., 2006, "An Alternative Test of Electromyographic Normalization in Patients," Muscle Nerve, **33**(2), pp. 232–241.
[53] Jung, Y., Jung, M., Lee, K., and Koo, S., 2014, "Ground Reaction Force Estimation Using an Insole-Type Pressure Mat and Joint Kinematics During Walking," J. Biomech., **47**(11), pp. 2693–2699.
[54] Fluit, R., Andersen, M. S., Kolk, S., Verdonschot, N., and Koopman, H. F. J. M., 2014, "Prediction of Ground Reaction Forces and Moments During Various Activities of Daily Living," J. Biomech., **47**(10), pp. 2321–2329.
[55] Jung, Y., Jung, M., Ryu, J., Yoon, S., Park, S., and Koo, S., 2016, "Dynamically Adjustable Foot-Ground Contact Model to Estimate Ground Reaction Force During Walking and Running," Gait Posture, **45**, pp. 62–68.
[56] McGibbon, C. A., and Mohamed, A., 2018, "Knee Load Reduction From an Energy Storing Mechanical Brace: A Simulation Study," The 20th Biennial Meeting of the Canadian Society for Biomechanics, Halifax, Nova Scotia, Aug. 14–17, p. P067.
[57] Salzman, A., Torburn, L., and Perry, J., 1993, "Contribution of Rectus Femoris and Vasti to Knee Extension: An Electromyographic Study," Clin. Orthop. Relat. Res., (290), pp. 236–243.
[58] Watanabe, K., and Akima, H., 2011, "Validity of Surface Electromyography for Vastus Intermedius Muscle Assessed by Needle Electromyography," J. Neurosci. Methods, **198**(2), pp. 332–335.
[59] Eitzen, I., Fernandes, L., Kalleru, H., Nordsletten, L., Knarr, B., and Risberg, M. A., 2015, "Gait Characteristics, Symptoms, and Function in Persons With Hip Osteoarthritis: A Longitudinal Study With 6 to 7 Years of Follow-Up," J. Orthop. Sports Phys. Ther., **45**(7), pp. 539–549.
[60] Fukui, T., Ueda, Y., and Kamijo, F., 2016, "Ankle, Knee, and Hip Joint Contribution to Body Support During Gait," J. Phys. Ther. Sci., **28**(10), pp. 2834–2837.
[61] Karavas, N., Ajoudani, A., Tsagarakis, N., Saglia, J., Bicchi, A., and Caldwell, D., 2015, "Tele-Impedance Based Assistive Control for a Compliant Knee Exoskeleton," Rob. Auton. Syst., **73**, pp. 78–90.
[62] Hassani, W., Mohammed, S., Rifai, H., and Amirat, Y., 2013, "EMG Based Approach for Wearer-Centered Control of a Knee Joint Actuated Orthosis," IEEE International Conference on Intelligent Robots and Systems, Tokyo, Japan, Nov. 3–7, pp. 990–995.
[63] Walsh, C. J., Endo, K., and Herr, H., 2007, "A Quasi-Passive Leg Exoskeleton for Load-Carrying Augmentation," Int. J. Humanoid Robot., **04**(03), pp. 487–506.
[64] Serrancoli, G., Falisse, A., Dembia, C., Vantilt, J., Tanghe, K., Lefeber, D., Jonkers, I., De Schutter, J., and De Groote, F., 2019, "Subject-Exoskeleton Contact Model Calibration Leads to Accurate Interaction Force Predictions," IEEE Trans. Neural Syst. Rehabil. Eng., **27**(8), p. 1597.
[65] Marra, M. A., Vanheule, V., Rasmussen, J., Verdonschot, N. J. J., Andersen, M. S., Fluit, R., Koopman, B. H. F. J., M. Rasmussen, J., Verdonschot, N. J. J., and Andersen, M. S., 2015, "A Subject-Specific Musculoskeletal Modeling Framework to Predict In Vivo Mechanics of Total Knee Arthroplasty," ASME J. Biomech. Eng., **137**(2), p. 020904.
[66] Cherian, J. J., Bhave, A., Kapadia, B. H., Starr, R., Mcelroy, M. J., and Mont, M. A., 2015, "Strength and Functional Improvement Using Pneumatic Brace With Extension Assist for End-Stage Knee Osteoarthritis : A Prospective, Randomized Trial," J. Arthroplasty, **30**(5), pp. 747–753.

[67] Bennell, K. L., Bowles, K. A., Wang, Y., Cicuttini, F., Davies-Tuck, M., and Hinman, R. S., 2011, "Higher Dynamic Medial Knee Load Predicts Greater Cartilage Loss Over 12 Months in Medial Knee Osteoarthritis," Ann. Rheum. Dis., **70**(10), pp. 1770–1774.
[68] Kean, C. O., Hinman, R. S., Bowles, K. A., Cicuttini, F., Davies-Tuck, M., and Bennell, K. L., 2012, "Comparison of Peak Knee Adduction Moment and Knee Adduction Moment Impulse in Distinguishing Between Severities of Knee Osteoarthritis," Clin. Biomech., **27**(5), pp. 520–523.
[69] Thorp, L. E., Sumner, D. R., Block, J. A., Moisio, K. C., Shott, S., and Wimmer, M. A., 2006, "Knee Joint Loading Differs in Individuals With Mild Compared With Moderate Medial Knee Osteoarthritis," Arthritis Rheum., **54**(12), pp. 3842–3849.
[70] Shamaei, K., Cenciarini, M., Adams, A. A., Gregorczyk, K. N., Schiffman, J. M., and Dollar, A. M., 2015, "Effects of Exoskeletal Stiffness in Parallel With the Knee on the Motion of the Human Body Center of Mass During Walking," IEEE International Conference on Robotics and Automation (ICRA), IEEE, Seattle, WA, May 26–30, pp. 5557–5564.
[71] Hicks, J. L., Uchida, T. K., Seth, A., Rajagopal, A., and Delp, S. L., 2015, "Is My Model Good Enough? Best Practices for Verification and Validation of Musculoskeletal Models and Simulations of Movement," ASME J. Biomech. Eng., **137**(2), pp. 1–24.
[72] Rasmussen, J., Damsgaard, M., and Voigt, M., 2001, "Muscle Recruitment by the Min/Max Criterion—A Comparative Numerical Study," J. Biomech., **34**(3), pp. 409–415.
[73] Ackland, D. C., Lin, Y. C., and Pandy, M. G., 2012, "Sensitivity of Model Predictions of Muscle Function to Changes in Moment Arms and Muscle-Tendon Properties: A Monte Carlo Analysis," J. Biomech., **45**(8), pp. 1463–1471.
[74] Hirschmann, M. T., and Müller, W., 2015, "Complex Function of the Knee Joint: The Current Understanding of the Knee," Knee Surg., Sport. Traumatol. Arthrosc., **23**(10), pp. 2780–2788.
[75] Skals, S., Jung, M. K., Damsgaard, M., and Andersen, M. S., 2017, "Prediction of Ground Reaction Forces and Moments During Sports-Related Movements," Multibody Syst. Dyn., **39**(3), pp. 175–195.
[76] Ghadikolaee, M. S., Sharifmoradi, K., Karimi, M. T., and Tafti, N., 2020, "Evaluation of a Functional Brace in Acl-Deficient Subjects Measuring Ground Reaction Forces and Contact Pressure: A Pilot Study," J. Prosthet. Orthot., **32**(2), pp. 142–148.

Development and Functional Testing of An Unloading Concept for Knee Osteoarthritis Patients: A Pilot Study – Supplemental Material

METHOD

All experiments for this study were conducted at the Department of Health Science and Technology, Aalborg University, Denmark. One healthy subject (male, age: 31 years, height: 182.2 cm, weight: 68.9 kg) was included. During all measurements, the subject wore shorts and walked barefoot.

Initially, five trials of normal walk were performed at a self-selected speed to gain knowledge about the subject's gait pattern. A start position was found through trial-and-error approach until the subject was able to consistently hit a force plate with the right foot. 3D kinematics were measured from 32 skin surface markers taped to the skin at bony landmarks and in between the landmarks as clusters. The marker locations are listed in Table 1 and illustrated in Figure 1.

Table 1: The marker label, position and whether the marker positions were fixed (Fix.) or optimized (Opt.) in the anterior-posterior (A-P), medial-lateral (M-L) and proximal-distal (P-D) directions. Markers placed on well-defined bony landmarks were generally fixed while the rest were optimized.

Label	**Position**	**A-P**	**M-L**	**P-D**
RPSI	Right posterior superior iliac spine	Fix.	Fix.	Fix.
LPSI	Left posterior superior iliac spine	Fix.	Fix.	Fix.
RASI	Right anterior superior iliac spine	Fix.	Fix.	Fix.
LASI	Left anterior superior iliac spine	Fix.	Fix.	Fix.
RTHI	Right thigh laterally	Opt.	Opt.	Opt.
RTHI1	Right thigh anteriorly	Opt.	Opt.	Opt.
RTHI2	Right thigh anteriorly	Opt.	Opt.	Opt.
LTHI	Left thigh laterally	Opt.	Opt.	Opt.
LTHI1	Left thigh anteriorly	Opt.	Opt.	Opt.
LTHI2	Left thigh anteriorly	Opt.	Opt.	Opt.
RKNE	Right lateral femoral epicondyle	Fix.	Fix.	Fix.
RKNE	Right medial femoral epicondyle	Fix.	Fix.	Fix.
LKNE	Left lateral femoral epicondyle	Fix.	Fix.	Fix.
LMKNE	Left medial femoral epicondyle	Fix.	Fix.	Fix.
RTIB	Right tibia laterally	Opt.	Opt.	Opt.
RTIB1	Right tibia anteriorly	Opt.	Opt.	Opt.
RTIB2	Right tibia anteriorly	Opt.	Opt.	Opt.
LTIB	Left tibia laterally	Opt.	Opt.	Opt.
LTIB1	Left tibia anteriorly	Opt.	Opt.	Opt.
LTIB2	Left tibia anteriorly	Opt.	Opt.	Opt.
RANK	Right lateral malleolus	Fix.	Fix.	Fix.
RMANK	Right medial malleolus	Fix.	Fix.	Fix.
LANK	Left lateral malleolus	Fix.	Fix.	Fix.
LMANK	Left medial malleolus	Fix.	Fix.	Fix.
RHEE	Right calcaneus	Fix.	Fix.	Fix.
LHEE	Left calcaneus	Fix.	Fix.	Fix.
RTOE	Right metatarsus	Fix.	Fix.	Fix.
LTOE	Left metatarsus	Fix.	Fix.	Fix.
RMT5	Right fifth metatarsal	Fix.	Fix.	Fix.
LMT5	Left fifth metatarsal	Fix.	Fix.	Fix.

Figure 1. The marker placements used to obtain initial kinematics for brace development.

The marker trajectories were recorded with eight infrared cameras (Oqus 300 series, Qualisys AB, Gothenburg, Sweden) sampling at 100 Hz and analyzed in Qualisys Track Manager v. 2019.3. A force plate (width/length = 464/508 mm) (Advanced Mechanical Technology, Inc., Watertown, MA, US) embedded in the floor measured the ground reaction force at 1000 Hz. A low-pass filter with second order zero-phase Butterworth filters was used to compensate for the noise in the recording of the force plate and marker data using a cut-off frequency of 15 and 5 Hz respectively.

All musculoskeletal (MS) models in this study were developed in the AnyBody Modeling System v. 7.2 (AMS) (AnyBody Technology A/S, Aalborg, Denmark) based on the AnyMoCap template model from the AnyBody Managed Model Repository (AMMR) v. 2.1.1. The lower extremity model is based on the cadaver dataset of Klein Horsman et al. (2007) and had a total of 18 degrees-of-freedom (DOF); 2x1 DOFs for the ankle revolute joints, 2x1 DOF for the subtalar revolute joints, 2x1 DOF for the knee revolute joints, 2x3 DOF for the hip spherical joint and 6 DOF for pelvis. Since no markers were placed above pelvis, the thorax and neck joints were fixed in a neutral position and arms were excluded.

Initially, a linear scaling of pelvis and the segments in the lower extremity was applied in a standing reference trial with the method from Andersen et al. [1]. The calculated segment lengths were saved and imported for the kinematic analysis for all gait trials and solved based on the approach explained in [2]. Both the scaling and the gait trials use experimental time varying model marker positions which are found with an optimization-based kinematic analysis with a weighted least-square objective function, tracking both the trajectory of the fixed markers on bony landmarks (labelled Fix. in Table 1) and simultaneously the trajectory of the free-moving markers (labelled Opt. in Table 1).

The joint angles were exported from a kinematic study and used as input for the inverse dynamic analysis where the lower extremity was modelled as described in [3]. All muscles were modelled as constant strength muscles where the strength was scaled according to the mass-fat scaling explained in Rasmussen et al. [4]. The muscle and joint reaction forces were estimated with a muscle recruitment problem solved by minimizing the sum of the muscle activities to the power of 3 [5]. This approach was validated with a tibial implant equipped with a six DOF force measuring sensor in Marra et al. [6].

The knee is modelled as a hinge joint with the rotation axis based on Carbone et al. [3]. The internal knee compressive loads, presented throughout the study, were found in a tibia coordinate system based on Grood and Suntay [7] with origin half way between the two tibial condyles. The Y-axis (inferior-superior) is aligned with an axis from ankle joint to origin, Z-axis (medial-lateral) is perpendicular to Y and goes through the right tibial condyle (when looking from posterior to anterior, so Z points laterally in the right leg and medially in the left leg). The X-axis (anterior-posterior) is the cross product of Y and Z.

Knee Brace Prototype

The knee brace concept aims to be a personalized treatment adjusted to fit the individual patient, and the developed prototype is shown in Figure 2a and Figure ***2***b.

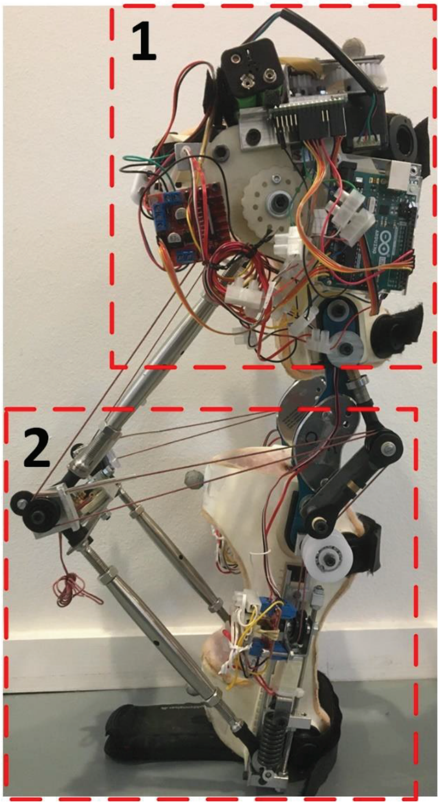


Figure 2a. The developed knee brace prototype. The numbers 1 and 2 refers to the detailed description in Figure 2b.

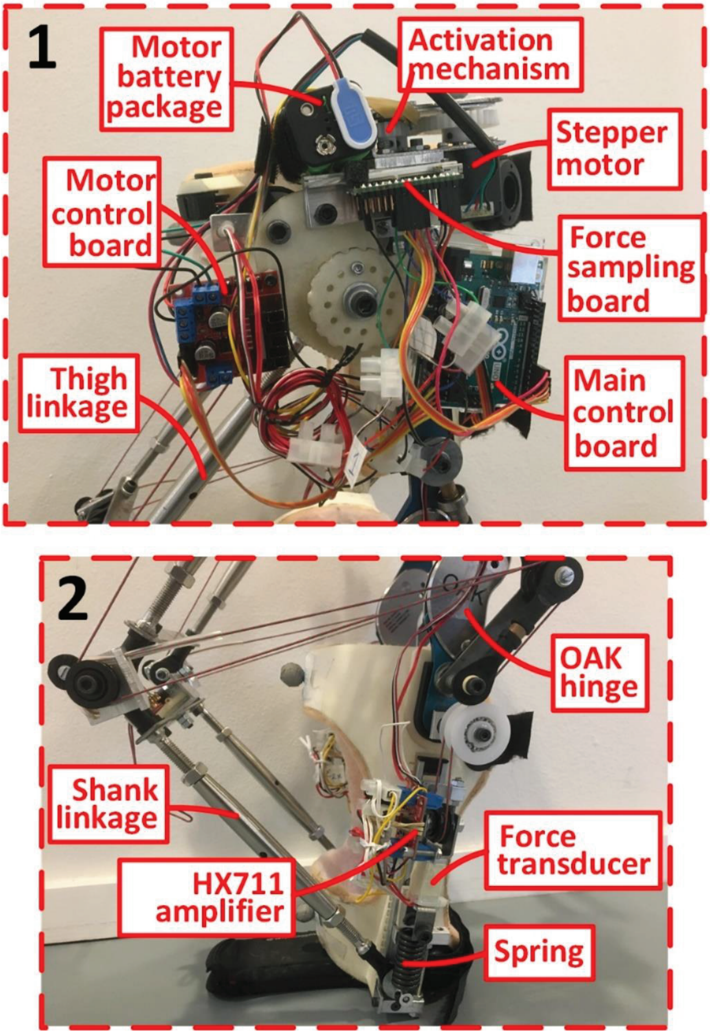


Figure 2b: A detailed description of the components of the knee brace prototype based on close-up images from Figure 2a.

The brace cuffs for the prototype are designed based on a leg surface scan with a 2 mm offset to make room for cushioning between the cuffs and the leg. The cuffs are connected with OAK hinges and when these are fully extended, there is an angle, θ_{OAK}, of 12 degrees between the shank and thigh upright brackets, which is shown in Figure 3.

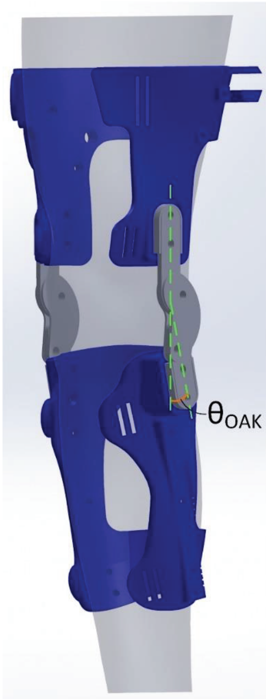


Figure 3. Thigh and shank cuffs (blue) extruded from the leg surface scan (shaded grey) with the knee fully extended. The cuffs are connected with an OAK hinge on each side, and when fully extended, the thigh and shank hinge uprights are angled $\theta_{OAK} = 12^{o}$.

Another adjustment in the brace concept is the activation timing depending on the subject's gait pattern and this is based on the activation angle, θ_{Act}, which is found from an individual stiffness plot like the one in Figure 4A.

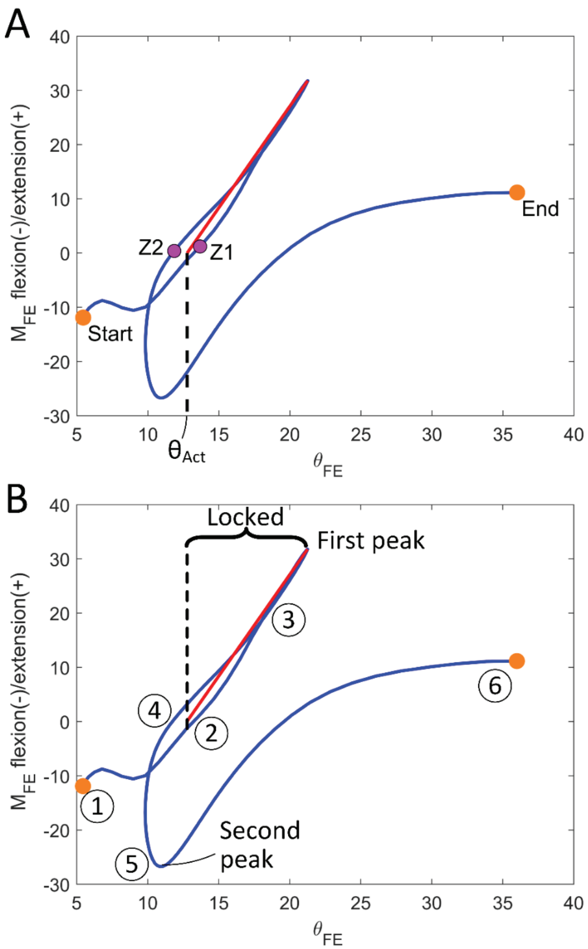


Figure 4. Mean stiffness plots across five trials with muscle moment, M_{FE}, as a function of the knee flexion angle, θ_{FE} (standard deviation has been omitted for visibility reasons). Both plots are from heel strike to 60% gait cycle. Plot A contains the information to determine the individual activation angle, θ_{Act}, and plot B shows the time points of interest in the process of brace activation and de-activation.

As illustrated in Figure 4A, θ_{Act} is found as the value of θ_{FE} in between the two points closest to zero moment on the initial and last part of first peak, Z1 and Z2 respectively. θ_{Act} is used to estimate when the brace should activate and de-activate and the process for this through a gait cycle is illustrated in Figure 5, which is based on the time points in Figure 4B.

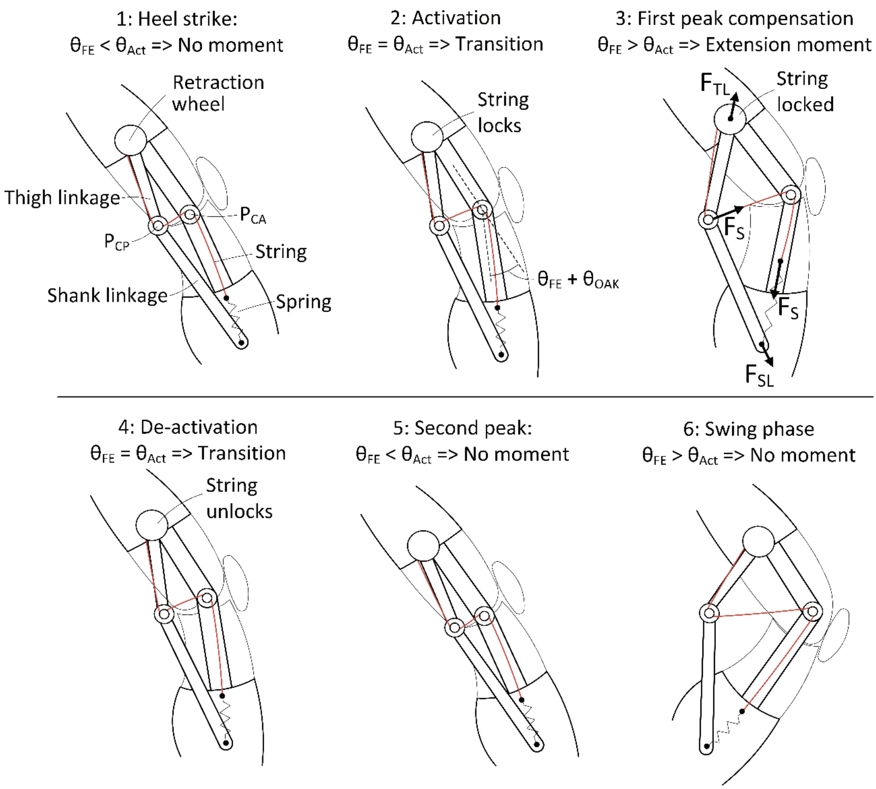


Figure 5. Activation and de-activation process during a gait cycle divided into the six steps illustrated in Figure 4B. The string (red line) is locked when applying brace moment in step 3 and loose the rest of the cycle.

Ideally, when θ_{FE} passes θ_{Act} right after heel strike during knee extension, the activation mechanism should lock the string (step 2 in Figure 5). However, this would require no loss of energy between brace and leg and an instant activation of the brace when the knee flexion angle passes θ_{Act}. The brace prototype was programed to activate right before step 1 in Figure 5 to have time to generate a sufficient moment in step 3. Since the string passes through the linkage connection points, P_{CP} and P_{CA}, and is connected to a spring in the end, knee flexion causes an extension moment from the brace around the knee. The force induced through thigh linkage, F_{TL}, applies an extension moment on thigh and the force through shank linkage, F_{SL}, applies an extension moment on shank.

A 12x12x25mm aluminum specimen, with two 90 degrees strain gauge rosettes attached on opposite sides, were manufactured to act as force transducers connected in series with each spring in order to measure how much the string pulls the spring when compensating the first peak. These measurements were applied in MS models to evaluate the magnitude of the moment transferred from the brace to the leg. One of the force transducers is shown in Figure 6.

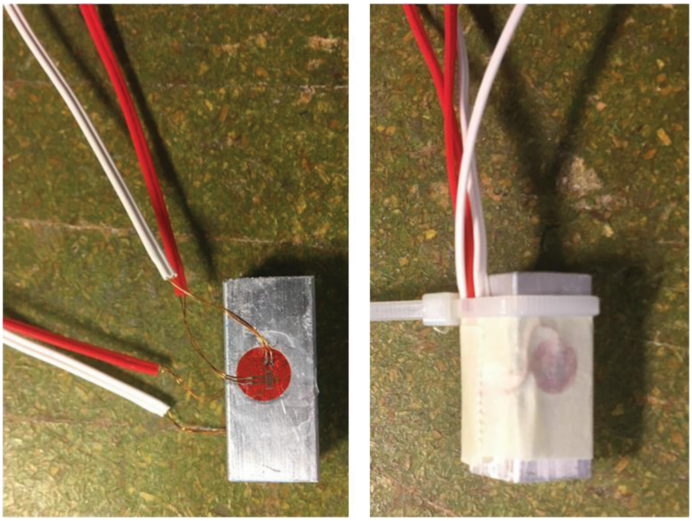


Figure 6. Homemade force transducer made from an aluminum specimen and two 90° strain gauge rosettes to measure uniaxial tension.

Threaded holes were made in each end to attach a pulley wheel for the string and a fork joint to connect the spring. The voltage change was detected with a full Wheatstone bridge and sent to a SparkFun HX711 amplifier board (SparkFun Electronics, Boulder, USA) sampling at 80 Hz. This is the max rate, due to the onboard analogue to digital converter integrated in the load cell amplifier, which is considered sufficient since no sudden spikes in the signal are expected during normal gait. The amplified signal was sent to an Arduino Nano and converted to Newton with a calibration factor. The individual calibration factor was adjusted based on trial and error approach by lifting known weights vertically with the force transducers until the output matched with the mass of the weight times acceleration of gravity. A calibration sequence consisted of three load repetitions for each weight is shown in Figure 7.

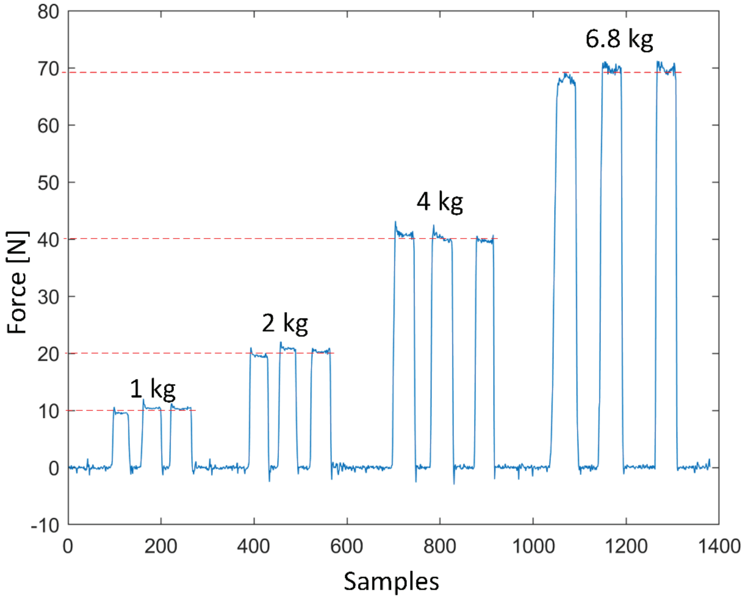


Figure 7. A calibration sequence for one of the force transducers to find the calibration factor used to convert the amplified digital signal to Newton. The masses are known weights, which are multiplied with 9.82 m/s^2 to find the force, and the red lines are manually added for visually evaluate the estimated force on the y-axis.

As seen in Figure 7, the signal varies within a couple of Newton across the three load repetitions for the same applied weight, which is considered acceptable for this purpose. During each trial, the spring forces were stored on an SD card for later use as input in the MS models.

Activation Mechanism

A CAD model of the activation mechanism is shown in Figure 8 and highlights the main components.

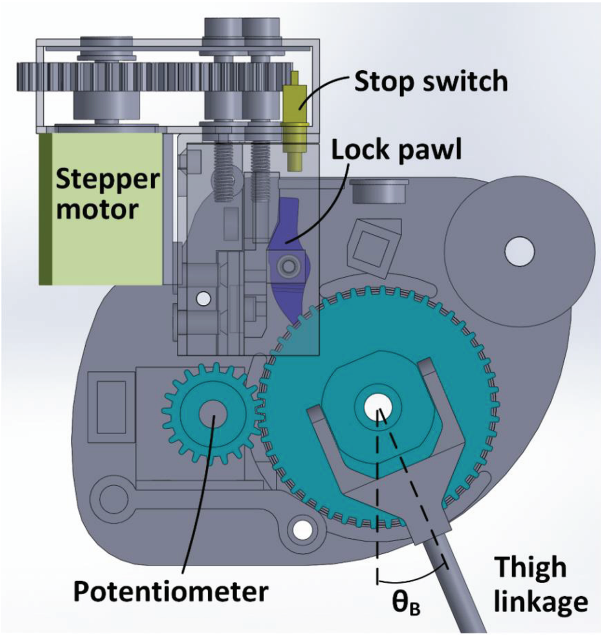


Figure 8. The activation mechanism including the thigh linkage to illustrate the brace angle θ_B. The green components are gears to relate θ_B to the potentiometer.

A potentiometer is used to determine when to lock the string, so the found θ_{Act} is converted to the corresponding θ_B. This is done with an analytical expression for θ_B as function of θ_{FE} and the two linkage lengths (L_3 and L_4 in Figure 9) derived from the system of equations in Equation (1), which is based on a 2D formulation of the brace design as illustrated in Figure 10. Linkage lengths L_1 and L_2 are constant.

$$\begin{bmatrix} \boldsymbol{r}_2 + \boldsymbol{A}_2 \cdot \boldsymbol{s'}_2^B - (\boldsymbol{r}_3 + \boldsymbol{A}_3 \cdot \boldsymbol{s'}_3^B) \\ \boldsymbol{r}_3 + \boldsymbol{A}_3 \cdot \boldsymbol{s'}_3^C - (\boldsymbol{r}_4 + \boldsymbol{A}_4 \cdot \boldsymbol{s'}_4^C) \\ \boldsymbol{r}_D - (\boldsymbol{r}_4 + \boldsymbol{A}_4 \cdot \boldsymbol{s'}_4^D) \end{bmatrix} \tag{1}$$

where $\boldsymbol{A}_i = \begin{bmatrix} \cos(\theta_i) & -\sin(\theta_i) \\ \sin(\theta_i) & \cos(\theta_i) \end{bmatrix}$, $\theta_2 = 90^\circ - \theta_{FE} - \theta_{OAK}$, $\theta_4 = 90^\circ - \theta_B$

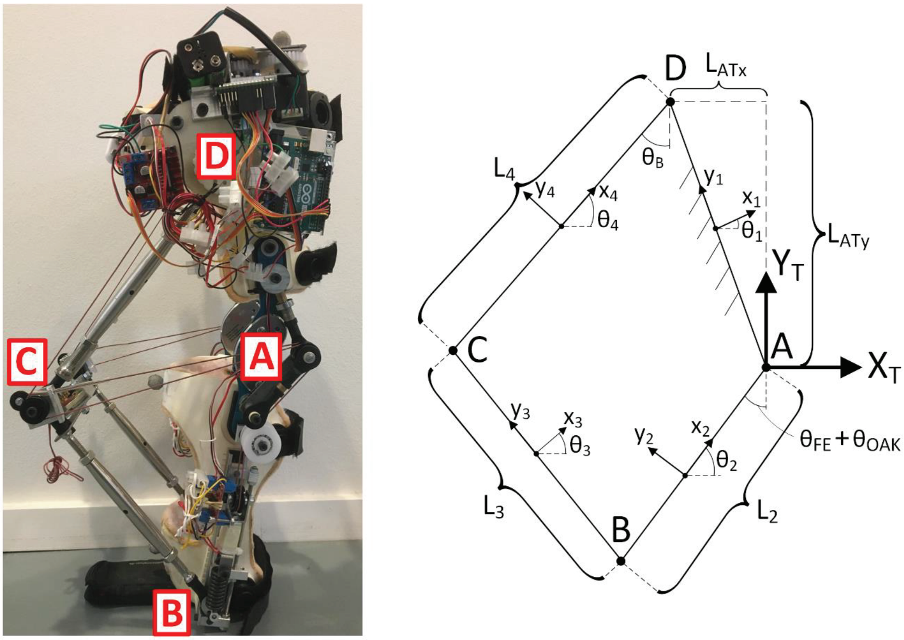


Figure 10. Right: 2D sketch for deriving an analytical expression for θ_B as function of θ_{FE}. Left: The main points on the prototype knee brace to clarify the sketch.

Since the kinematics are formulated in 2D, Equation (1) consist of six equations and these are used to compute $\mathbf{r}_3$, θ_3, $\mathbf{r}_4$ and θ_4. The two direction vectors are found in the thigh upright frame (X_T, Y_T) from point A to the local frames 3 and 4 respectively. Point A is simplified to a hinge rotation joint in the 2D sketch, even though the OAK hinges have a more advanced motion to mimic the kinematics of femur during flexion.

However, a hinge joint is considered accurate enough for estimating the brace activation, and the expression for $\theta_B(\theta_{FE})$ is found from $\theta_B = 90^o - \theta_4$ (see Figure 10).

The activation mechanism is driven by a stepper motor, and as mentioned when $\theta_B(P_C) = \theta_B(\theta_{Act})$ during knee extension between step 6 and 1 in Figure 5, a signal is sent to the motor. The motor pushes a lock pawl, using a threaded rod, into a gear attached to the string wheel (behind the big green gear in Figure 8). Since the activation mechanism only locks and releases the string, the brace moment is solely generated from the spring force transferred through the string and linkages. The stop switch in Figure 8 is used to detect the starting point for the lock pawl right before it hits the gear on the string wheel.

Controlling Circuit

The circuit for controlling the prototype brace is depicted in Figure 11.

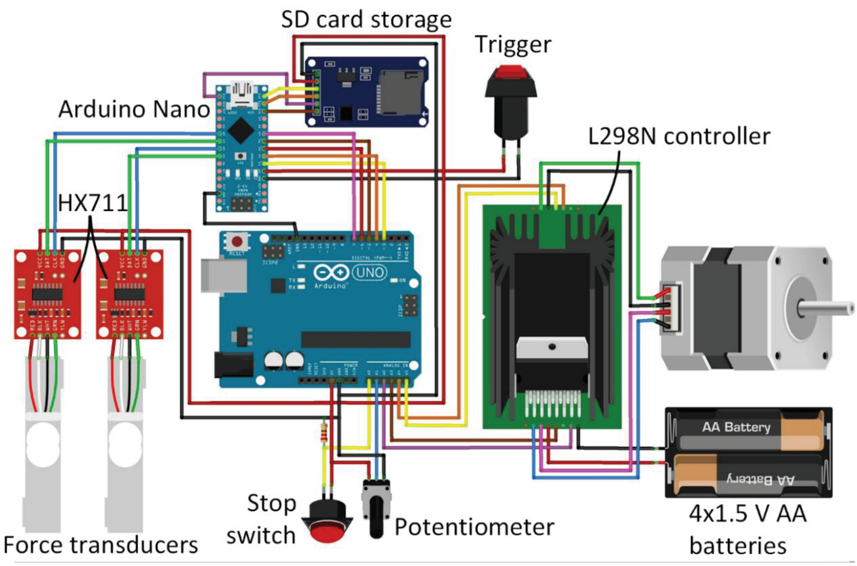


Figure 11. The circuit to control the prototype brace.

The trigger is used to synchronize the spring force sampling with the camera system recording the markers in order to apply the force at the right time samples in the MS models, which are driven by marker trajectory. The Arduino Nano board is used to measure and store the spring force. The Arduino Uno board controls the stepper motor based on the potentiometer input and the spring force, which is sent from the Nano board. The L298N controller has a 2 V drop across the integrated circuit, so it is powered with a 6 V power supply to match the 3.8 V stepper motor.

Experimental Brace Evaluation

The knee brace prototype strapped to the leg in the experimental setup with markers and surface EMG electrodes is depicted in Figure 12 below. This picture illustrates how the vastus medialis and lateralis EMG electrodes were in risk of being affected by the pressure from the thigh brace cuff.

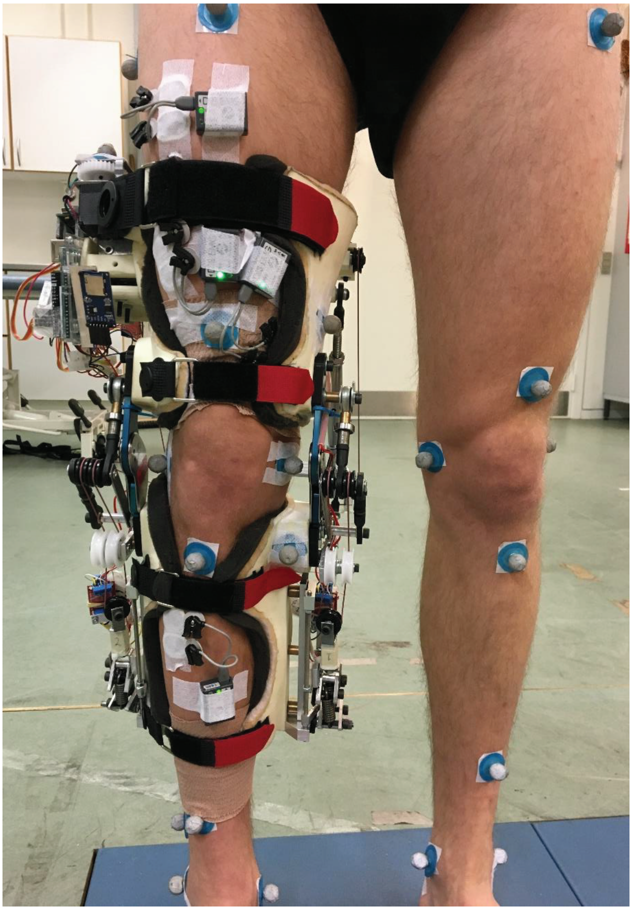


Figure 12. The prototype knee brace on the subject's leg for experimental validation of the brace concept. Additionally, reflective markers and surface EMG electrodes were used for evaluating the internal knee compressive forces and muscle activity respectively.

Musculoskeletal modeling

The position and orientation of the exported brace was tracked independently of the leg in a kinematic analysis in AMS and used as input for an inverse dynamic analysis. Since the high-strength contact force elements between brace and leg are included in the muscle recruitment, which minimizes the muscle activity, the brace should only be able to apply a moment aligned with the knee joint axis. This is to avoid the contact elements from applying forces with the purpose of compensating knee flexion/extension moment instead of the generated moment from the spring forces. To achieve this moment alignment, the OAK hinges were kinetically detached from the brace cuffs but still attached kinematically. This means that the hinges were still attached to the cuffs to obtain the right motion, but all reaction forces were switched off. Instead, all forces between the two cuffs were transferred through two weightless segments perfectly aligned with the knee rotation axis and connected as a revolute joint. This is explained in Figure 13 below.

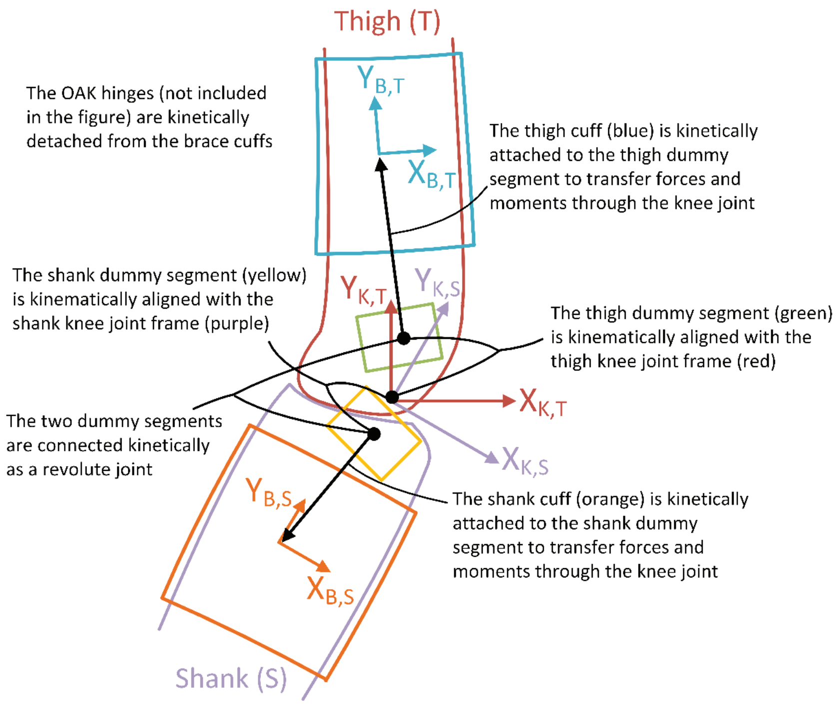


Figure 13. Connections through the knee brace by using dummy segments instead of the OAK hinges (not included in the figure for simplification). The dummy segments are aligned with the two knee joint frames ($X_{K,T}$ - $Y_{K,T}$ and $X_{K,S}$ - $Y_{K,S}$) but separated in the figure for visual purpose.

The default knee rotation axis is defined based on cadaver femoral epicondyles, so the knee rotation axis was made subject-specific based on marker positions to position the knee brace properly on the leg. The subject-specific alignment is obtained based on the illustrations in Figure 14.

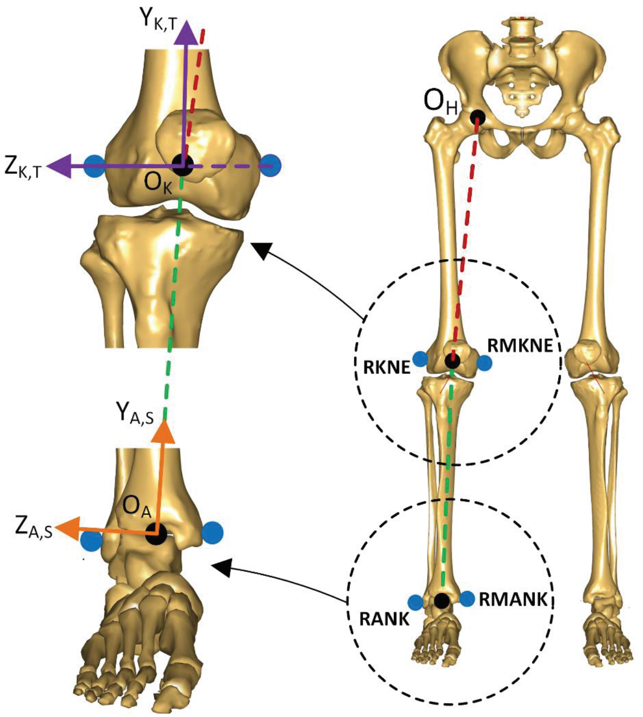


Figure 14. Frontal view of the lower extremity including markers (blue), local joint coordinate systems (purple and orange) and alignment lines (green and red).

Joint coordinate systems (frames) were created on femur (purple) and on shank (orange) with origin (O_K and O_A respectively) placed halfway between the two medial/lateral joint markers (RKNE/RMKNE and RANK/RMANK respectively). The $Z_{K,T}$ (medial-lateral in thigh frame) represents the knee joint rotation axis aligned with RKNE and $Y_{K,T}$ (inferior-superior in thigh frame) is perpendicular to $Z_{K,T}$ and aligned with the spanned plane between O_K, RKNE and O_H. The $Y_{A,S}$ (inferior-superior in ankle frame) was aligned with an axis from O_A to O_K. The $Z_{A,S}$ (medial-lateral in ankle frame) was made perpendicular to $Y_{A,S}$ and aligned with the plane spanned between O_A, RANK and O_K. The

X-axis (anterior-posterior) for both frames was created as the cross product of each individual Y and Z-axes.

3D Tait–Bryan angles (Cardan angles), between these two frames were stored in a rotation matrix, R_{KA}, during the standing reference trial and used to create a knee frame on shank with origin at O_K. It was locally oriented as the ankle frame described above with respect to shank's local frame. The knee frame on shank was additionally rotated the measured Cardan angles to obtain a rotation matrix identical to R_{KA} when the two knee joint origins are constrained and align $Z_{K,T}$ with $Z_{K,S}$.

A visual illustration of the default (left) and the modified alignment (right) is shown in Figure 15.

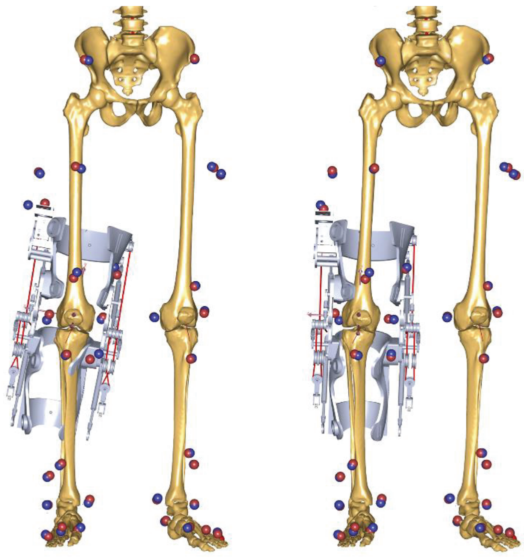


Figure 15. Visual comparison of the default knee alignment based on cadaver femora epicondyle bony landmarks and the modified subject-specific knee alignment based on the marker positions.

NOMENCLATURE

θ_{OAK}	Initial angle between thigh and shank upright of the OAK hinges when fully extended [deg]
θ_{Act}	Knee flexion angle for activating the knee brace [deg]
θ_{FE}	Knee flexion-extension angle [deg]
M_{FE}	Knee muscle flexion-extension moment [Nm]
F_S	Spring force transferred through the string [N]
F_{SL}	Force transferred through the shank linkage [N]
F_{TL}	Force transferred through the thigh linkage [N]
P_{CP}	Posterior connection point in the linkage system
P_{CA}	Anterior connection point in the linkage system
$\boldsymbol{r}_i$	Global vector from global origin to local frame *i* [m]
$\boldsymbol{A}_i$	Rotation matrix of local frame of body *i* [rad]
θ_i	Rotation angle of the local frame of body *i* [rad]
$\boldsymbol{s'}_i^X$	Local vector from origin of frame *i* to the point X [m]
$\boldsymbol{r}_X$	Global vector from global origin to the point X [m]
θ_B	Angle between thigh linkage and vertical [deg]
P_C	Current potentiometer reading [V]
O_H	Origin of local hip joint frame

O_K	Origin of local knee joint frame
O_A	Origin of local ankle joint frame
R_{KA}	Rotation matrix between the local knee joint frame and ankle joint frame

REFERENCES

[1] Andersen, M. S., Damsgaard, M., MacWilliams, B., and Rasmussen, J., 2010, “A Computationally Efficient Optimisation-Based Method for Parameter Identification of Kinematically Determinate and over-Determinate Biomechanical Systems.,” Comput. Methods Biomech. Biomed. Engin., **13**(2), pp. 171–183. DOI: 10.1080/10255840903067080

[2] Andersen, M. S., Damsgaard, M., and Rasmussen, J., 2009, “Kinematic Analysis of Over-Determinate Biomechanical Systems.,” Comput. Methods Biomech. Biomed. Engin., **12**(4), pp. 371–384. DOI: 10.1080/10255840802459412

[3] Carbone, V., Fluit, R., Pellikaan, P., Krogt, M. M. Van Der, Janssen, D., Damsgaard, M., Vigneron, L., Feilkas, T., Koopman, H. F. J. M., and Verdonschot, N., 2015, “TLEM 2 . 0 – A Comprehensive Musculoskeletal Geometry Dataset for Subject-Speci Fi c Modeling of Lower Extremity,”

[4] Rasmussen, J., De Zee, M., Damsgaard, M., Tørholm Christensen, S., Marek, C., and Siebertz, K., 2005, “A General Method for Scaling Musculo-Skeletal Models,” *2005 International Symposium on Computer Simulation in Biomechanics*, p. 1

[5] Damsgaard, M., Rasmussen, J., Christensen, S. T., Surma, E., and de Zee, M., 2006, “Analysis of Musculoskeletal Systems in the AnyBody Modeling System,” Simul. Model. Pract. Theory, **14**(8), pp. 1100–1111. DOI: 10.1016/j.simpat.2006.09.001

[6] Marra, M. A., Vanheule, V., Rasmussen, J., Verdonschot, N. J. J., Andersen, M. S., Fluit, R., Koopman, B. H. F. J. M., Rasmussen, J., Verdonschot, N. J. J., and Andersen, M. S., 2015, “A Subject-Specific Musculoskeletal Modeling Framework to Predict in Vivo Mechanics of Total Knee Arthroplasty,” J. Biomech. Eng., **137**(2), pp. 020904-1-020904–12. DOI: 10.1115/1.4029258

[7] Grood, E. S., and Suntay, W. J., 1983, “A Joint Coordinate System for the Clinical Description of Three-Dimensional Motions Application to the Knee,” J. Biomech. Eng., **105**, pp. 136–143. DOI: 10.1115/1.3138397

6. Paper III

Evaluation of an Unloading Concept for Knee Osteoarthritis: A Pilot Study in a Small Patient Group

Stoltze J. S., Oliveira A. S. C., Rasmussen J., Andersen M. S.

The paper has been submitted to
Osteoarthritis and Cartilage

Part II

Discussion

7. Discussion

This final chapter sums up and discusses the main findings, the contribution of the results to the research society and the limitations of the conducted studies. Additionally, subjects for future work within this research are suggested and lastly concluding remarks are presented.

7.1 Summary of Key findings

The key results from the three publications within the thesis are presented in this section. Paper I investigated how applied moments around the joints in the lower extremity influence the internal knee compressive forces (KCF) and was used to determine the most efficient brace concept regarding KCF reduction. Paper II introduced a prototype knee brace using an unloading concept based on the results from Paper I and the current research. Furthermore, Paper II presented a workflow for individual adjustment of the prototype, and the effects on internal KCF were demonstrated with both simulations and experimental tests on a single healthy subject. Paper III investigated gait behaviour of six knee osteoarthritis (KOA) patients to determine whether the developed concept is valid to apply on this patient group. The developed concept from Paper II was applied *in silico* on all patients and the prototype was experimentally tested on a single patient.

Paper I - On the biomechanical relationship between applied hip, knee and ankle joint moments and the internal knee compressive forces

This paper used *in silico* results to determine the optimal intervention concept, which was used as basis for designing a prototype brace for the next studies. Musculoskeletal (MS) gait models of ten healthy subjects were used to simulate the effect of externally applied moments on the internal KCF. The moments were applied whenever needed around the two local axes perpendicular to the coronal and sagittal plane of the hip, knee and ankle joints. The magnitude was defined as a certain percentage of the net moment around the respective axis needed during normal gait without any intervention. Initially, each of the six moments were applied individually with 20, 40, 60, 80 and 100% of the net moment and for each load case, the total, medial and lateral KCF were computed and compared with a baseline case with no external moments applied. All results presented in this chapter are for the 40% load case.

Among the investigated moments, hip flexion-extension (HFM), knee flexion-extension (KFM) and ankle plantarflexion-dorsiflexion (APM) provided the largest reduction of the total KCF at various times during the stance phase. These three moments reduced muscle activation leading to a reduction of the knee joint loads, and the effect of HFM and APM moments on KCF is due to biarticular muscles. HFM and KFM mainly affected the first peak of the total KCF, revealing reductions of 8.8% and 13.5%, respectively, by compensating for rectus femoris and quadriceps muscle activation, respectively. Additionally, KFM reduced the impulse of the total KCF by 15.7%. APM solely reduced the second peak with 11.4% through a reduced gastrocnemius activation, and these results demonstrated the potential for reducing joint loads using a brace concept, which compensates for muscle loads.

The applied knee adduction moment (KAM) showed the largest effect on the medial KCF, reducing the first and second peaks by 13.5% and 11.5%, respectively. However, as expected, this moment shifted the joint loads causing an increase of the lateral compartment load by 30.1% and 23.8% for the first and second peaks, respectively, leaving the total KCF unaffected.

These findings suggested moments in the sagittal plane to be most efficient regarding reduction of the total KCF, and KFM to obtain the largest reduction of the impulse. However, if combining the applied moments in the sagittal plane, larger reductions of the KCF and impulse were achieved. The combinations HFM+KFM, HFM+APM and KFM+APM reduced the first peak by 24.1%, 9.4% and 13.7%, respectively, and second peak by 16.7%, 17.8% and 22.6%, respectively. Additionally, applying all three moments simultaneously, yielded even larger reductions, although this combination would be very challenging to include in a brace-like intervention. Even a combination of two moments would be difficult to comprise into a slim design, for which reason the concept of applying moments in the sagittal plane, was limited to a single joint in this thesis. The results did not reveal a clear suggestion of the best suited intervention, which will most likely vary between patients, so similar *in silico* analyses can be made before a treatment is prescribed.

Paper II - Development and Functional Testing of An Unloading Concept for Knee Osteoarthritis Patients: A Pilot Study

The second paper applied the findings in Paper I to develop a prototype knee brace and is therefore considered as a proof-of-concept case study. A workflow to adjust the brace individually was established and tested on a single healthy subject to investigate the effect on muscle activity and internal joint loads during normal gait. The prototype brace applies a knee extension moment from stored potential energy in springs and the stiffness of these can be chosen individually. To avoid interference during swing phase, a switch mechanism ensures that the brace moment is only applied in the early stance phase to target the first peak KCF.

Initially, the prototype brace concept was tested *in silico* using MS models revealing a 35.9% reduction of the first peak total KCF and a 38.2% reduction of the impulse. Additionally, the medial and lateral compartment loads were reduced 24.4% and 6.2% respectively, illustrating the potential of the unloading concept.

Subsequently, experimental tests were conducted to support the simulated results using EMG measurements and motion capture recordings. Various spring stiffnesses were used and it was hypothesised that a larger stiffness would cause a larger muscle activity reduction compared to normal gait without brace. The target muscles were mainly vastus medialis (VM), vastus lateralis (VL) and rectus femoris (RF) and the peak activation of VM was reduced with up to 37%. VL and RF on the other hand increased with up to 43.8% and 7.7% respectively, for which reason the KCF could have been expected to be unchanged or even increased. However, according to the MS models, the prototype brace reduced the first peak KCF and the impulse with up to 24% and 9.1% respectively. The estimated knee flexion-extension muscle moment in the MS models was reduced with up to 10 Nm when wearing the brace going from 32 Nm to 22 Nm. The joint kinematics of the lower extremity differed when wearing the brace, so it is uncertain how much of the effect is due to these kinematic changes and how much the applied moment is responsible for.

The paper concluded that the concept of applying a knee extension moment has the potential to efficiently reduce the total KCF by compensating muscle activation. However, this study only included a single healthy subject and since the brace is intended for delaying KOA progression and reducing pain, the concept needed to be tested on KOA patients.

Paper III - Evaluation of an Unloading Concept for Knee Osteoarthritis: A Pilot Study in a Small Patient Group

Paper III included a small group of KOA patients and the *in silico* brace was analysed with MS models for all patients in the same way as in Paper II. The reduction of the first peak total KCF varied from 3.5% to 33.8%, and this large variation was expected since the first peak knee flexion-extension muscle moment ranged from 4.2 Nm to 59.6 Nm. Likewise, the medial and lateral first peak KCF reduction ranged from 0.1% to 24.4% and 18.4% to 56%, respectively. This illustrated the importance of including biomechanical analyses to determine which patients are suited for a specific intervention.

The knee brace prototype was tested on one of the patients with the same workflow as in Paper II, resulting in a VM muscle activity reduction of up to 28.7% whereas the VL and RF muscle activation increased with 2% and 18.3%, respectively. The MS models estimated the first peak total KCF to be reduced with up to 26.3% but the impulse increased with up to 13.7% due to a larger second peak KCF. The applied brace moment peaked at 8.5 Nm causing the first peak knee flexion-extension muscle moment to be reduced with 37.5%. Similar to the subject in Paper II, the joint kinematics of the lower extremity deviated when wearing the brace prototype compared to normal gait without brace, which most likely influenced the results. Additionally, the gait speed was generally higher for the trials without brace, with a mean of 3.0 km/h, compared to the braced condition, ranging from 2.1 to 2.9 km/h. The gait speed influences muscle activation (Den Otter et al. [2004]), for which reason the reduced gait speed could have caused lower KCF. However, the gait speed was also reduced in the placebo condition, where no moment was applied but without the patient's knowledge. For this condition, the first peak of the KCF was larger when compared to the active braced conditions, demonstrating the effect of the applied brace moment. Furthermore, these findings highlight the importance of having a placebo condition to detect what factors influence the outcome. After each condition, a VAS pain score was evaluated but no effect was observed for this measure.

The findings of this paper concluded that not all KOA patients are suited for this brace concept so initial gait analyses are needed before prescribing this intervention. The experimental results illustrated the potential of reducing KCF despite an increased VL and RF muscle activity, but more patient tests are needed to draw any conclusions. Although no immediate pain relief was detected, a future long-term study of the brace method may imply a pain reduction.

7.2 Contributions and Impact

The initial *in silico* results from Paper I demonstrated the complexity of the knee joint and the challenge of detecting the contributors to the internal knee joint loads, since the muscles crossing the hip and ankle also influence the KCF. Similar biomechanical analyses of patients can be used to detect the best suited intervention and increase the chance for a positive outcome from bracing to improve quality of life. The outcome of the analyses indicate at which periods the different interventions unload the knee joint during the gait cycle, and similar results could be obtained for other activities. Thus, if a patient complaints about knee pain at a specific time during a certain activity, the analyses can indicate which intervention would be most efficient regarding reduction of joint loads, which can lead to pain relief. The results indicate whether the patient needs a valgus brace, a knee extension brace or another brace type either strapped around the hip, knee or ankle joint. These information combined with the recent knowledge of phenotyping in KOA patients (Dell'Isola et al. [2016], Deveza et al. [2017]) can potentially reduce the amount of consultations with the health care system, since the correct intervention can be chosen initially leading to a costly advantage for the society (Neogi [2013]).

The functionality of the developed prototype is similar to the commercially available Levitation brace from Spring Loaded Technology (McGibbon et al. [2021]). A questionnaire has been used to collect individual evaluation of this brace (Budarick et al. [2021]) to assess pain, function and physical activity in KOA patients, but no experimental studies have been conducted to scientifically support this type of intervention. This thesis has experimentally tested and demonstrated the potential of the method in papers II and III. The effect from the prototype brace was supported by collecting the forces in the springs to estimate the transferred extension moment to the leg by means of MS models. When this is combined with estimated muscle and joint loads, the actual effect is more clear minimising the influence from placebo and other psychological factors. The main difference between the tested prototype and the Levitation brace is the activation switch that enables the possibility of applying a larger moment, and thus larger KCF reduction, compared to a constantly applied moment. Since the used unloading method of applying a knee extension moment is acting in the "moving" degree of freedom of the knee, unlike a valgus brace, it most likely feels uncomfortable to wear a brace applying an extension moment during the swing phase. Thus, the activation switch can have a positive impact on the compliance, since discomfort represents a large part of the complaints among patients using a valgus brace (Brandon et al. [2019]). Improved compliance ensures a long-term use of bracing, which is one of the main challenges: to maintain the use of knee braces beyond the first year (Squyer et al. [2013]). This will help postponing the need for surgery and thereby reduce the chance for revision operations (Kurtz et al. [2009]). Furthermore, if the patient experiences an improved effect from the new brace, the compliance will most likely increase since lack of effect is another reported complaint among patients (Brouwer et al. [2006]).

The developed workflow, including gait analysis to determine the magnitude of the applied brace moment, helps ensuring the correct brace settings to obtain the most efficient unloading and improved functionality of the patient. The possibility of choosing among an additional unloading concept, besides the conventional valgus braces, will provide more options for the physiotherapists and therefore increases the chance for prescribing the correct treatment. This is ensured with the biomechanical analyses, which will most likely improve the scientific evidence of bracing since an individual intervention can be provided.

Lastly, unlike a valgus brace, the approach of decreasing KCF through reduced muscle contraction has the potential to reduce the load in the entire knee joint instead of only unicompartment reduction. Thus, the new brace method can be used to treat both tibio-femoral and patella-femoral OA, and thereby improve functionality in more patients.

7.3 Limitations and Suggestions for Future Work

The main limitation of the studies within this thesis is the cohort size including a healthy subject and a patient for brace testing. Additionally, six patients were investigated with *in silico* brace testing, so no general conclusions can be made based on the results. A large variation of the knee muscle moment was observed across the six patients in Paper III, so more KOA patients are required to investigate the prevalence of potential subjects for the developed brace method. Additionally, the prototype must be tested on more patients to determine the effect from the brace on KCF and pain.

The prototype brace has only been examined temporally including short-term effect but the response may be different for longer gait trials. Fantini Pagani et al. [2010a] observed a positive effect from a valgus brace in short gait trials but no effect during longer gait trials of 6 minutes duration. This indicates that the prototype brace should have been tested for longer gait trials on e.g. a treadmill. Similarly, only immediate pain relief can be observed and the short duration of each trial may be the reason for the patient to only report minor changes in the VAS pain score. A significant pain reduction may require longer gait trials to detect. The lack of pain relief could also be due to the patient walking barefoot, which has been shown to increase medial loading during the latter period of stance (Jones et al. [2015]). Thus, if the patient walked with shoes, a reduced pain may have been observed. Furthermore, some patients with advanced KOA can experience an increased responsiveness in the pain receptors causing an increased pressure pain sensitivity as well (Skou et al. [2016]). This can be relevant, if the brace provides pressure around the knee causing the pain to increase no matter how much the knee is unloaded.

A meta-analysis by Fan et al. [2020] concluded that no clinical evidence supports long-term effects from valgus braces on pain improvement and functional activity. Thus, if long-term studies can demonstrate positive effects from the developed brace concept, including reduced knee pain, joint functionality and quality-of-life, the scientific evidence can have a positive impact on the compliance, since the results are based on feedback from KOA patients. The studies within this thesis have presented the brace effect based on both peak loads and impulse, of which the latter is a measure of loading over the entire stance period. However, in a study by Bennell et al. [2011], only the impulse of KAM at baseline was associated with cartilage volume loss at a 12 month follow-up suggesting cumulative loading to be stronger associated with KOA progression than peak loading. Thus, the joint load impulse should be used as target measure when adjusting the knee brace in long-term studies. The effect from a reduced muscle flexion-extension moment is limited to the first peak KCF in early-stance whereas the second peak in late-stance is governed by gastrocnemius muscle contraction (Stoltze et al. [2018], Brandon et al. [2019]). Thus, an additional ankle brace can be added to obtain an even larger impulse reduction, and if using stored potential energy to apply an ankle moment, inspiration can be found in Collins et al. [2015] who used a spring to compensate for the gastrocnemius muscle leading to reduced energy consumption during gait.

Long-term studies would require a more slim brace design. A lighter version of the prototype brace could be inspired by the Levitation brace which uses a liquid compression spring and a tension member crossing the hinge joint to generate the extension moment. This brace only applies a moment in the lateral upright but the developed prototype applies the moment equally in both hinges. It is expected, that most patients need a relatively large moment to gain an effect and if this is applied in only a single upright, the brace may rotate internally/externally. Additionally, the activation switch must be installed with a compact printed circuit and e.g. a solenoid instead of a stepper motor to obtain a less bulky design. Currently, the Arduino boards are powered through a USB cable, so a battery package will be needed to allow mobility with the brace.

When computing the *in silico* effects from the prototype brace in the MS models, the contact formulation between the brace and leg is rigid without any damping, which should be included to provide more accurate results. If additional subject-specific data are collected, the individual amount of soft tissue can be taken into account, predicting the brace effect more precisely, since the results from the MS models are the basis for the brace settings. Thus, an improved contact formulation will most likely provide an initially optimal treatment causing less post adjustment when the brace has been provided to the patient. However, the brace must still be designed with the ability to be adjusted regularly to adapt any future changes in the patient's gait style after prescription. Similarly, the brace cuffs must adapt to any changes of the leg surface caused by e.g. changed muscle volume. Despite the cushioning, the 3D printed brace cuffs are too stiff to ensure a tight fit if the leg circumference decreases over time. This will cause the brace to slide down more easily, so a more elastic material for the cuffs may be advantageous.

Another limitation of the *in silico* results in this thesis is the lack of kinematical changes when simulating the applied moments in Paper I and the effect from the simulated brace in papers II and III using inverse dynamics analyses. Kinematic alterations affect the muscle force prediction and thus also the internal joint loads (Guess et al. [2014]). Additionally, antagonist muscle co-contractions have not been considered in this thesis. The phenomenon increases with KOA severity (Richards and Higginson [2010]) and has been observed during bracing (Ramsey et al. [2007]). Thus, co-contractions must be included in the MS models to estimate realistic KCF in KOA patients when evaluating an intervention. Recent studies demonstrated that valgus braces reduce quadriceps/hamstring and quadriceps/gastrocnemius co-contraction ratios (Moyer et al. [2015a]) and the recorded EMG data can be used in future work to investigate whether the prototype brace has the same effect.

Generally, limitations in the MS models should be addressed to improve the models and estimated results in future studies. Typical improvements, without using time-consuming subject-specific data, are the joint degrees-of-freedom, muscle model, and objective function for the optimisation problem (Moissenet et al. [2017]). Several of these model parameters are chosen to obtain faster analyses, so a time-effective workflow will compromise the accuracy of the estimated outcome. These loads also depend on the measured kinematics, so any deviations in these measurements will cause errors in the kinetics. The individual kinematic data provide information on knee alignment, joint angles and gait speed, which is useful information when choosing the right treatment. Furthermore, the estimated joint and muscle loads from the MS models provide additional knowledge for obtaining a successful unloading of the internal joint structures. Thus, experienced personnel should be responsible for collecting motion data to provide correct information of the patient's gait patterns and best possible basis for choosing an optimal patient-specific treatment.

The experimentally investigated intervention in papers II and III is limited to the prototype knee brace, so the effects on KCF are only measured based on the approach of unloading muscles from an applied knee extension moment. Future studies testing this approach may consider comparing the results with a conventional valgus brace to assess the two unloading concepts. Additionally, the concept with an activation switch can be compared with a Levitaion brace, which applies a constant extension moment. This moment can be estimated based on the flexion angle of the brace, found with e.g. optical markers, and a calibrated stiffness of the brace, which can be estimated using a test setup as in Budarick et al. [2020]. The same approach has been used for valgus braces to estimate the applied abduction moment (Brandon et al. [2019]). The comparison between the developed brace method and conventional valgus braces would provide an indication of the future potential for being the dominant brace approach since valgus braces are the most common unloading concept on the market (Brooks [2014]). However, due to the unclear scientific evidence, unloading braces are much less frequently used compared to other non-invasive treatments such as NSAIDs and intra-articular joint injections (Gohal et al. [2018]). Thus, a novel subject-specific unloading concept may be necessary to obtain an efficient brace treatment and thereby acknowledgement from the patients. However, it is important to note that too much unloading is not beneficial since reduced knee joint loading has been associated with early KOA due to underloading of the articular cartilage (Wellsandt et al. [2016], Moelgaard [2015]). Furthermore, the overall aim with the prototype brace is to compensate the quadriceps muscle group, but knee extensor muscle weakness is a risk factor for development of knee osteoarthritis (Øiestad et al. [2015]). However, reduced KCF is expected to enable a more active lifestyle for the KOA patients, due to reduced inflammation and pain, which maintains muscles strength and keeps the knee articular structures healthy and improves the general health (Skou and Roos [2017]).

A major challenge with the concept of applying a knee extension moment at specific periods during an activity is to identify which activity the patient is performing. The prototype in this project is programmed to activate and deactivate only during gait, so if the patient e.g. starts to walk on stairs or sits down, the applied moment will interfere with the intended motion. The Levitation brace avoids this issue by using a constantly applied moment but this also sets a limit to the magnitude of the moment in the interest of the swing phase and hence reduces the effect. It requires live recordings from e.g. inertial measurement unit combined with artificial intelligence to detect the current activity and the correct activation timing. Additionally, force myography of the extensor muscles can contribute with information on when to activate the brace. This approach identifies when the muscles contract based on surface pressure on the skin and is common within exoskeletons to detect human intention (Islam et al. [2020]). The pressure combined with the knee flexion angle can be used as input for the activation switch to achieve a comfortable and safe knee brace concept.

7.4 Concluding Remarks

The aim with the work behind this dissertation was to advance the field of knee bracing for KOA patients. The benefits from the currently available products are debated by researchers for which reason a prototype brace was developed using a novel unloading principle. The principle was determined based on *in silico* results from Paper I and the prototype was tested on a healthy subject in Paper II and a KOA patient in Paper III. The intervention settings were based on MS modelling taking individual biomechanical factors into account to increase efficiency. Although no effect on pain was reported during the tests, the prototype revealed positive effect regarding reduced muscle activation and internal KCF.

According to Paper III, not all KOA patients are suited for the developed brace approach suggesting that biomechanical analyses are necessary to prescribe the correct intervention and obtain a more efficient treatment. These analyses are part of a workflow, which should be included in the consultation and therefore needs to be easy to conduct for the health personnel.

If a more slim design can be achieved in the future with the same applied moment and an improved activation switch, the developed brace method is expected to have the potential to improve intervention quality for KOA patients. However, this must be demonstrated with large scale experimental tests and further development of the knee brace design.

References

Andriacchi, T. P. and Mündermann, A. (2006a). The role of ambulatory mechanics in the initiation and progression of knee osteoarthritis. *Current Opinion in Rheumatology*, 18(5):514–518.

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

Arazpour, M., Hutchins, S. W., Bani, M. A., Curran, S., and Aksenov, A. (2014). The influence of a bespoke unloader knee brace on gait in medial compartment osteoarthritis: A pilot study. *Prosthetics and Orthotics International*, 38(5):379–386.

Arthritis Research UK (2013). Osteoarthritis in general practice - Data and Perspectives - Arthritis Research UK. Technical report, Arthritis Research UK.

Baert, I. A., Jonkers, I., Staes, F., Luyten, F. P., Truijen, S., and Verschueren, S. M. (2013). Gait characteristics and lower limb muscle strength in women with early and established knee osteoarthritis. *Clinical Biomechanics*, 28(1):40–47.

Baghaei Roodsari, R., Esteki, A., Aminian, G., Ebrahimi, I., Mousavi, M. E., Majdoleslami, B., and Bahramian, F. (2017). The effect of orthotic devices on knee adduction moment, pain and function in medial compartment knee osteoarthritis: a literature review. *Disability and Rehabilitation: Assistive Technology*, 12(5):441–449.

Balsamo, B., Geil, M. D., Ellis, R., and Wu, J. (2018). Confirmation bias affects user perception of knee braces. *Journal of Biomechanics*, 75:164–170.

Barenius, B., Ponzer, S., Shalabi, A., Bujak, R., Norlén, L., and Eriksson, K. (2014). Increased risk of osteoarthritis after anterior cruciate ligament reconstruction: A 14-year follow-up study of a randomized controlled trial. *American Journal of Sports Medicine*, 42(5):1049–1057.

Bayliss, L. E., Culliford, D., Monk, A. P., Glyn-Jones, S., Prieto-Alhambra, D., Judge, A., Cooper, C., Carr, A. J., Arden, N. K., Beard, D. J., and Price, A. J. (2017). The effect of patient age at intervention on risk of implant revision after total replacement of the hip or knee: a population-based cohort study. *The Lancet*, 389(10077):1424–1430.

Beaudreuil, J., Bendaya, S., Faucher, M., Coudeyre, E., Ribinik, P., Revel, M., and Rannou, F. (2009). Clinical practice guidelines for rest orthosis, knee sleeves, and unloading knee braces in knee osteoarthritis. *Joint Bone Spine*, 76(6):629–636.

Bedson, J. and Croft, P. R. (2008). The discordance between clinical and radiographic knee osteoarthritis: A systematic search and summary of the literature. *BMC Musculoskeletal Disorders*, 9:1–11.

Bellamy, N. (2005). The WOMAC knee and hip osteoarthritis indices: Development, validation, globafization and influence on the development of the AUSCAN hand osteoarthritis indices. *Clinical and Experimental Rheumatology*, 23(5, 39):S148–S153.

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

Bellamy, N., Campbell, J., and Syrotuik, J. (1999). Comparative study of self-rating pain scales in osteoarthritis patients. *Current Medical Research and Opinion*, 15(2):121–127.

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

Bennell, K. L., Dobson, F., and Hinman, R. S. (2014). Exercise in osteoarthritis: Moving from prescription to adherence. *Best Practice and Research: Clinical Rheumatology*, 28(1):93–117.

Bhatia, D., Bejarano, T., and Novo, M. (2013). Current interventions in the management of knee osteoarthritis. *Journal of Pharmacy and Bioallied Sciences*, 5(1):30.

Bierma-Zeinstra, S. M. and Van Middelkoop, M. (2017). Osteoarthritis: In search of phenotypes. *Nature Reviews Rheumatology*, 13(12):705–706.

Birmingham, T. B., Bryant, D. M., Giffin, J. R., Litchfield, R. B., Kramer, J. F., Donner, A., and Fowler, P. J. (2008). A Randomized Controlled Trial Comparing the Effectiveness of Functional Knee Brace and Neoprene Sleeve Use After Anterior Cruciate Ligament Reconstruction. *The American Journal of Sports Medicine*, 36(4):648–655.

Bosomworth, N. J. (2009). Exercise and knee osteoarthritis: Benefit or hazard? *Canadian Family Physician*, 55(9):871–878.

Bourne, R. B., Chesworth, B. M., Davis, A. M., Mahomed, N. N., and Charron, K. D. (2010). Patient satisfaction after total knee arthroplasty: Who is satisfied and who is not? *Clinical Orthopaedics and Related Research*, 468(1):57–63.

Boyan, B. D., Tosi, L. L., Coutts, R. D., Enoka, R. M., Hart, D. A., Nicolella, D. P., Berkley, K. J., Sluka, K. A., Kwoh, C. K., O'Connor, M. I., Kohrt, W. M., and Resnick, E. (2013). Addressing the gaps: Sex differences in osteoarthritis of the knee. *Biology of Sex Differences*, 4(1):1–5.

Brand, A., Klöpfer-Krämer, I., Morgenstern, M., Kröger, I., Michel, B., Thannheimer, A., Müßig, J. A., and Augat, P. (2017). Effects of knee orthosis adjustment on biomechanical performance and clinical outcome in patients with medial knee osteoarthritis. *Prosthetics and Orthotics International*, 41(6):587–594.

Brandon, S. C., Brown, M. J., Clouthier, A. L., Campbell, A., Richards, J. D., and Deluzio, K. J. (2019). Contributions of muscles and external forces to medial knee load reduction due to osteoarthritis braces. *Knee*, 26(3):564–577.

Brisson, N., Wiebenga, E., Stratford, P., Beattie, K., Totterman, S., Tamez-Peña, J., Callaghan, J., Adachi, J., and Maly, M. (2016). Knee mechanics interact with body mass index to predict cartilage loss over 2.5 years in people with clinical knee osteoarthritis. In *Osteoarthritis and Cartilage*, volume 24, page S47.

Brooks, K. S. (2014). Osteoarthritic Knee Braces on the Market: A Literature Review. *Journal of Prosthetics & Orthotics*, 26(1):2–30.

Brouwer, R. W., van Raaij, T. M., Verhaar, J. A. N., Coene, L. N. J. E. M., and Bierma-Zeinstra, S. M. A. (2006). Brace treatment for osteoarthritis of the knee: a prospective randomized multi-centre trial. *Osteoarthritis and Cartilage*, 14(8):777–783.

Bruyère, O., Cooper, C., Pelletier, J. P., Branco, J., Luisa Brandi, M., Guillemin, F., Hochberg, M. C., Kanis, J. A., Kvien, T. K., Martel-Pelletier, J., Rizzoli, R., Silverman, S., and Reginster, J. Y. (2014). An algorithm recommendation for the management of knee osteoarthritis in Europe and internationally: A report from a task force of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). *Seminars in Arthritis and Rheumatism*, 44(3):253–263.

Buckwalter, J. A., Saltzman, C., and Brown, T. (2004). The Impact of Osteoarthritis: Implications for Research. *Clinical Orthopedics and Related Research*, 427 Suppl(1):S6–S15.

Budarick, A. R., Bishop, E. L., Clark, M. L., and Cowper-smith, C. D. (2021). Preliminary evaluation of a new orthotic for patellofemoral and multi-compartment knee osteoarthritis. *Rehabilitation Research and Practice*, 2021:1–10.

Budarick, A. R., MacKeil, B. E., Fitzgerald, S., and Cowper-Smith, C. D. (2020). Design Evaluation of a Novel Multicompartment Unloader Knee Brace. *Journal of Biomechanical Engineering*, 142(1):1–8.

Callaghan, M. J., Parkes, M. J., Hutchinson, C. E., Gait, A. D., Forsythe, L. M., Marjanovic, E. J., Lunt, M., Felson, D. T., and Kvien, T. K. (2015). A randomised trial of a brace for patellofemoral osteoarthritis targeting knee pain and bone marrow lesions. *Annals of the Rheumatic Diseases*, 74(6):1164–1170.

Carlson, V. R., Ong, A. C., Orozco, F. R., Hernandez, V. H., Lutz, R. W., and Post, Z. D. (2018). Compliance with the AAOS Guidelines for Treatment of Osteoarthritis of the Knee: A Survey of the American Association of Hip and Knee Surgeons.

Chawla, H., van der List, J. P., Christ, A. B., Sobrero, M. R., Zuiderbaan, H. A., and Pearle, A. D. (2017). Annual revision rates of partial versus total knee arthroplasty: A comparative meta-analysis. *Knee*, 24(2):179–190.

Chen, F. H. and Tuan, R. S. (2008). Mesenchymal stem cells in arthritic diseases. *Arthritis Research and Therapy*, 10(5):1–12.

Chen, R. K., an Jin, Y., Wensman, J., and Shih, A. (2016). Additive manufacturing of custom orthoses and prostheses-A review. *Additive Manufacturing*, 12:77–89.

Cherian, J. J., Bhave, A., Kapadia, B. H., Starr, R., Mcelroy, M. J., and Mont, M. A. (2015). Strength and Functional Improvement Using Pneumatic Brace with Extension Assist for End-Stage Knee Osteoarthritis : A Prospective , Randomized trial. *Journal of Arthroplasty*, 30(5):747–753.

Cicuttini, F., Forbes, A., Morris, K., Darling, S., Bailey, M., and Stuckey, S. (1999). Gender differences in knee cartilage volume as measured by magnetic resonance imaging. *Osteoarthritis and Cartilage*, 7(3):265–271.

Collins, S. H., Wiggin, M. B., and Sawicki, G. S. (2015). Reducing the energy cost of human walking using an unpowered exoskeleton. *Nature*, 522(7555):212–215.

Conaghan, P. G., Dickson, J., and Grant, R. L. (2008). Guidelines: Care and management of osteoarthritis in adults: Summary of NICE guidance. *Bmj*, 336(1):502–503.

Creaby, M. W. (2015). It's not all about the knee adduction moment: The role of the knee flexion moment in medial knee joint loading. *Osteoarthritis and Cartilage*, 23(7):1038–1040.

Croff, L. J. (2013). Use of NSAIDs in treating patients with arthritis. *Arthritis Research & Therapy*, 15(Suppl 3):1–10.

Dakin, H., Gray, A., Fitzpatrick, R., MacLennan, G., and Murray, D. (2012). Rationing of total knee replacement: A cost-effectiveness analysis on a large trial data set. *BMJ Open*, 2(1):1–9.

Dell'Isola, A., Allan, R., Smith, S. L., Marreiros, S. S. P., and Steultjens, M. (2016). Identification of clinical phenotypes in knee osteoarthritis: a systematic review of the literature. *BMC Musculoskeletal Disorders*, 17(1):425.

Den Otter, A. R., Geurts, A. C., Mulder, T., and Duysens, J. (2004). Speed related changes in muscle activity from normal to very slow walking speeds. *Gait and Posture*, 19(3):270–278.

Dessery, Y., Belzile, É. L., Turmel, S., and Corbeil, P. (2014). Comparison of three knee braces in the treatment of medial knee osteoarthritis. *Knee*, 21(6):1107–1114.

Dessery, Y. and Pallari, J. (2018). Measurements agreement between low-cost and high-level handheld 3D scanners to scan the knee for designing a 3D printed knee brace. *PLoS ONE*, 13(1).

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

Ding, C., Jones, G., Wluka, A. E., and Cicuttini, F. (2010). What can we learn about osteoarthritis by studying a healthy person against a person with early onset of disease? *Current Opinion in Rheumatology*, 22(5):520–527.

Doherty, M. and Dieppe, P. (2009). The "placebo" response in osteoarthritis and its implications for clinical practice. *Osteoarthritis and Cartilage*, 17(10):1255–1262.

Downie, W. W., Leatham, P. A., Rhind, V. M., Wright, V., Branco, J. A., and Anderson, J. A. (1978). Studies with pain rating scales. *Annals of the Rheumatic Diseases*, 37(4):378–381.

Draganich, L. (2006). The Effectiveness of Self-Adjustable Custom and Off-the-Shelf Bracing in the Treatment of Varus Gonarthrosis. *The Journal of Bone and Joint Surgery (American)*, 88(12):2645.

Duffell, L. D., Southgate, D. F., Gulati, V., and McGregor, A. H. (2014). Balance and gait adaptations in patients with early knee osteoarthritis. *Gait and Posture*, 39(4):1057–1061.

Duivenvoorden, T., Brouwer, R., Rw, B., Tm, V. R., Ap, V., Jan, V., and Sma, B.-z. (2015a). Duivenvoorden_et_al-2015-The_Cochrane_library.sup-2. *The Cochrane*, 1(3):54 pág.

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

Ebert, J. R., Hambly, K., Joss, B., Ackland, T. R., and Donnelly, C. J. (2014). Does an Unloader Brace Reduce Knee Loading in Normally Aligned Knees? *Clinical Orthopaedics and Related Research®*, 472(3):915–922.

Fan, Y., Li, Z., Zhang, H., Hong, G., Wu, Z., Li, W., Chen, L., Wu, Y., Wei, Q., He, W., and Chen, Z. (2020). Valgus knee bracing may have no long-term effect on pain improvement and functional activity in patients with knee osteoarthritis: A meta-analysis of randomized trials.

Fantini Pagani, C. H., Bhle, C., Potthast, W., and Brggemann, G. P. (2010a). Short-term effects of a dedicated knee orthosis on knee adduction moment, pain, and function in patients with osteoarthritis. *Archives of Physical Medicine and Rehabilitation*, 91(12):1936–1941.

Fantini Pagani, C. H., Potthast, W., and Brüggemann, G.-P. (2010b). The effect of valgus bracing on the knee adduction moment during gait and running in male subjects with varus alignment. *Clinical Biomechanics*, 25(1):70–76.

Fantini Pagani, C. H., Willwacher, S., Kleis, B., and Brüggemann, G. P. (2013). Influence of a valgus knee brace on muscle activation and co-contraction in patients with medial knee osteoarthritis. *Journal of Electromyography and Kinesiology*, 23(2):490–500.

Favre, J., Erhart-Hledik, J. C., Chehab, E. F., and Andriacchi, T. P. (2016). General scheme to reduce the knee adduction moment by modifying a combination of gait variables. *Journal of Orthopaedic Research*, 34(9):1547–1556.

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

Fernandez-Fernandez, R. and Rodriguez-Merchan, E. C. (2015). Better survival of total knee replacement in patients older than 70 years: A prospective study with 8 to 12 years follow-up. *Archives of Bone and Joint Surgery*, 3(1):22–28.

Fitzgerald, G. K., Fritz, J. M., Childs, J. D., Brennan, G. P., Talisa, V., Gil, A. B., Neilson, B. D., and Abbott, J. H. (2016). Exercise, manual therapy, and use of booster sessions in physical therapy for knee osteoarthritis: a multi-center, factorial randomized clinical trial. *Osteoarthritis and Cartilage*, 24(8):1340–1349.

France, E. P. and Paulos, L. E. (1994). Knee Bracing. *Journal of the AAOS - American Academy of Orthopaedic Surgeons*, 2(5):281–287.

Fransen, M., McConnell, S., Harmer, A. R., Van Der Esch, M., Simic, M., and Bennell, K. L. (2015). Exercise for osteoarthritis of the knee: A Cochrane systematic review. *British Journal of Sports Medicine*, 49(24):1554–1557.

Fregly, B. J., Besier, T. F., Lloyd, D. G., Delp, S. L., Banks, S. a., Pandy, M. G., and D'Lima, D. D. (2012). Grand challenge competition to predict in vivo knee loads. *Journal of Orthopaedic Research*, 30(4):503–513.

Fregly, B. J., Reinbolt, J. A., Rooney, K. L., Mitchell, K. H., and Chmielewski, T. L. (2007). Erratum: Design of patient-specific gait modifications for knee osteoarthritis rehabilitation (IEEE Transactions on Biomedical Engineering (2007)). *IEEE Transactions on Biomedical Engineering*, 54(10):1905.

Gabay, O., Hall, D. J., Berenbaum, F., Henrotin, Y., and Sanchez, C. (2008). Osteoarthritis and obesity: Experimental models. *Joint Bone Spine*, 75(6):675–679.

Gallelli, L., Galasso, O., Falcone, D., Southworth, S., Greco, M., Ventura, V., Romualdi, P., Corigliano, A., Terracciano, R., Savino, R., Gulletta, E., Gasparini, G., and De Sarro, G. (2013). The effects of nonsteroidal anti-inflammatory drugs on clinical outcomes, synovial fluid cytokine concentration and signal transduction pathways in knee osteoarthritis. A randomized open label trial. *Osteoarthritis and Cartilage*, 21(9):1400–1408.

Gardiner, B. S., Woodhouse, F. G., Besier, T. F., Grodzinsky, A. J., Lloyd, D. G., Zhang, L., and Smith, D. W. (2016). Predicting Knee Osteoarthritis. *Annals of Biomedical Engineering*, 44(1):222–233.

Gohal, C., Shanmugaraj, A., Tate, P., Horner, N. S., Bedi, A., Adili, A., and Khan, M. (2018). Effectiveness of Valgus Offloading Knee Braces in the Treatment of

Medial Compartment Knee Osteoarthritis: A Systematic Review. *Sports Health*, 10(6):500–514.

Gore, M., Tai, K. S., Sadosky, A., Leslie, D., and Stacey, B. R. (2012). Use and Costs of Prescription Medications and Alternative Treatments in Patients with Osteoarthritis and Chronic Low Back Pain in Community-Based Settings. *Pain Practice*, 12(7):550–560.

Gross, K. D. and Hillstrom, H. J. (2008). Noninvasive Devices Targeting the Mechanics of Osteoarthritis. *Rheumatic diseases clinics of North America*, 34(3):755–776.

Guess, T. M., Stylianou, A. P., and Kia, M. (2014). Concurrent Prediction of Muscle and Tibiofemoral Contact Forces During Treadmill Gait. *Journal of Biomechanical Engineering*, 136(2):021032.

Guo, M., Axe, M. J., and Manal, K. (2007). The influence of foot progression angle on the knee adduction moment during walking and stair climbing in pain free individuals with knee osteoarthritis. *Gait and Posture*, 26(3):436–441.

Haladik, J. A., Vasileff, W. K., Peltz, C. D., Lock, T. R., and Bey, M. J. (2014). Bracing improves clinical outcomes but does not affect the medial knee joint space in osteoarthritic patients during gait. *Knee Surgery, Sports Traumatology, Arthroscopy*, 22(11):2715–2720.

Hall, M., Diamond, L. E., Lenton, G. K., Pizzolato, C., and Saxby, D. J. (2019). Immediate effects of valgus knee bracing on tibiofemoral contact forces and knee muscle forces. *Gait and Posture*, 68(November 2018):55–62.

Hangalur, G., Bakker, R., Tomescu, S., and Chandrashekar, N. (2018). New adjustable unloader knee brace and its effectiveness. *Journal of Medical Devices, Transactions of the ASME*, 12(1).

Hanna, F., Teichtahl, A. J., Bell, R., Davis, S. R., Wluka, A. E., O'Sullivan, R., and Cicuttini, F. M. (2007). The cross-sectional relationship between fortnightly exercise and knee cartilage properties in healthy adult women in midlife. *Menopause*, 14(5):830–834.

Haroon, N., Kim, T. H., and Inman, R. D. (2012). NSAIDs and radiographic progression in ankylosing spondylitis: Bagging big game with small arms? *Annals of the Rheumatic Diseases*, 71(10):1593–1595.

Hart, H. F., Crossley, K. M., Ackland, D. C., Cowan, S. M., and Collins, N. J. (2016). Effects of an unloader knee brace on knee-related symptoms and function in people with post-traumatic knee osteoarthritis after anterior cruciate ligament reconstruction. *Knee*, 23(1):85–90.

Healy, W. L., Della Valle, C. J., Iorio, R., Berend, K. R., Cushner, F. D., Dalury, D. F., and Lonner, J. H. (2013). Complications of total knee arthroplasty: Standardized list and definitions of the knee society knee. *Clinical Orthopaedics and Related Research*, 471(1):215–220.

Heidari, B. (2011). Knee osteoarthritis prevalence, risk factors, pathogenesis and features: Part I. *Caspian Journal of Internal Medicine*, 2(2):205–212.

Heidari, B., Hajian-Tilaki, K., and Babaei, M. (2016). Determinants of pain in patients with symptomatic knee osteoarthritis. *Caspian Journal of Internal Medicine*, 7(3):153–161.

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

Herzog, W., Longino, D., and Clark, A. (2003). The role of muscles in joint adaptation and degeneration. *Langenbeck's Archives of Surgery*, 388(5):305–315.

Hicks, J. L., Uchida, T. K., Seth, A., Rajagopal, A., and Delp, S. L. (2015). Is My Model Good Enough? Best Practices for Verification and Validation of Musculoskeletal Models and Simulations of Movement. *Journal of Biomechanical Engineering*, 137(2):1–24.

Hubley-Kozey, C. L., Robbins, S. M., Rutherford, D. J., and Stanish, W. D. (2013). Reliability of surface electromyographic recordings during walking in individuals with knee osteoarthritis. *Journal of Electromyography and Kinesiology*, 23(2):334–341.

Hunter, D. J., Harvey, W., Gross, K. D., Felson, D., McCree, P., Li, L., Hirko, K., Zhang, B., and Bennell, K. (2011). A randomized trial of patellofemoral bracing for treatment of patellofemoral osteoarthritis. *Osteoarthritis and Cartilage*, 19(7):792–800.

Islam, M. R. U., Waris, A., Kamavuako, E. N., and Bai, S. (2020). A comparative study of motion detection with FMG and sEMG methods for assistive applications. *Journal of Rehabilitation and Assistive Technologies Engineering*, 7:1–11.

Isola, A. D., Smith, S. L., Andersen, M. S., and Steultjens, M. (2017). Knee internal contact force in a varus malaligned phenotype in knee osteoarthritis (KOA). *Osteoarthritis and Cartilage*, 25(12):2007–2013.

Jafarnezhadgero, A. A., Oliveira, A. S., Mousavi, S. H., and Madadi-Shad, M. (2018). Combining valgus knee brace and lateral foot wedges reduces external forces and moments in osteoarthritis patients. *Gait and Posture*, 59(April 2017):104–110.

Jamtvedt, G., Dahm, K. T., Christie, A., Moe, R. H., Haavardsholm, E., Holm, I., and Hagen, K. B. (2008). Physical Therapy Interventions for Patients With Osteoarthritis of the Knee: An Overview of Systematic Reviews. *Physical Therapy*, 88(1):123–136.

Jenkyn, T. R., Hunt, M. A., Jones, I. C., Giffin, J. R., and Birmingham, T. B. (2008). Toe-out gait in patients with knee osteoarthritis partially transforms external knee adduction moment into flexion moment during early stance phase of gait: A tri-planar kinetic mechanism. *Journal of Biomechanics*, 41(2):276–283.

Jones, R. K., Chapman, G. J., Parkes, M. J., Forsythe, L., and Felson, D. T. (2015). The effect of different types of insoles or shoe modifications on medial loading of the knee in persons with medial knee osteoarthritis: A randomised trial. *Journal of Orthopaedic Research*, 33(11):1646–1654.

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

Karavas, N., Ajoudani, A., Tsagarakis, N., Saglia, J., Bicchi, A., and Caldwell, D. (2015). Tele-impedance based assistive control for a compliant knee exoskeleton. *Robotics and Autonomous Systems*, 73:78–90.

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

Kellgren, J. H. and Lawrence, J. S. (1957). Radiological Assessment of Osteo-Arthrosis. *Annals of the rheumatic diseases*, 16(4):494–502.

Khalaj, N., Osman, N. A., Mokhtar, A. H., Mehdikhani, M., and Wan Abas, W. A. (2014). Effect of exercise and gait retraining on knee adduction moment in people with knee osteoarthritis. *Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine*, 228(2):190–199.

Kiadaliri, A. A., Lohmander, L. S., Moradi-Lakeh, M., Petersson, I. F., and Englund, M. (2018). High and rising burden of hip and knee osteoarthritis in the Nordic region, 19902015: Findings from the Global Burden of Disease Study 2015. *Acta Orthopaedica*, 89(2):177–183.

Kingsbury, S. R. and Conaghan, P. G. (2012). Current osteoarthritis treatment, prescribing influences and barriers to implementation in primary care. *Primary Health Care Research & Development*, 13(04):373–381.

Kirkley, A., Webster-Bogaert, S., Litchfield, R., Amendola, A., MacDonald, S., McCalden, R., and Fowler, P. (1999). The effect of bracing on varus gonarthrosis. *The Journal of bone and joint surgery. American volume*, 81(4):539–48.

Kumar, D., Manal, K. T., and Rudolph, K. S. (2013). Knee joint loading during gait in healthy controls and individuals with knee osteoarthritis. *Osteoarthritis and Cartilage*, 21(2):298–305.

Kurtz, S. M., Lau, E., Ong, K., Zhao, K., Kelly, M., and Bozic, K. J. (2009). Future young patient demand for primary and revision joint replacement: National projections from 2010 to 2030. *Clinical Orthopaedics and Related Research*, 467(10):2606–2612.

Kutzner, I., Küther, S., Heinlein, B., Dymke, J., Bender, A., Halder, A. M., and Bergmann, G. (2011). The effect of valgus braces on medial compartment load of the knee joint in vivo load measurements in three subjects. *Journal of Biomechanics*, 44(7):1354–1360.

Kutzner, I., Trepczynski, A., Heller, M. O., and Bergmann, G. (2013). Knee adduction moment and medial contact force-facts about their correlation during gait. *PLoS ONE*, 8(12):8–15.

Labek, G., Thaler, M., Janda, W., Agreiter, M., and Stöckl, B. (2011). Revision rates after total joint replacement: Cumulative results from worldwide joint register datasets. *Journal of Bone and Joint Surgery - Series B*, 93 B(3):293–297.

Laroche, D., Morisset, C., Fortunet, C., Gremeaux, V., Maillefert, J. F., and Ornetti, P. (2014). Biomechanical effectiveness of a distraction-rotation knee brace in medial knee osteoarthritis: Preliminary results. *Knee*, 21(3):710–716.

Le, D. H., Goodman, S. B., Maloney, W. J., and Huddleston, J. I. (2014). Current modes of failure in TKA: Infection, instability, and stiffness predominate. *Clinical Orthopaedics and Related Research*, 472(7):2197–2200.

Lee, P. Y. F., Winfield, T. G., Harris, S. R. S., Storey, E., and Chandratreya, A. (2017). Unloading knee brace is a cost-effective method to bridge and delay surgery in unicompartmental knee arthritis. *BMJ Open Sport & Exercise Medicin*, 2(1):1–8.

Lonner, J. H., Jasko, J. G., and Thomas, B. S. (2008). Anthropomorphic differences between the distal femora of men and women. *Clinical Orthopaedics and Related Research*, 466(11):2724–2729.

Lowitz, T., Museyko, O., Bousson, V., Laouisset, L., Kalender, W. A., Laredo, J. D., and Engelke, K. (2013). Bone marrow lesions identified by MRI in knee osteoarthritis are associated with locally increased bone mineral density measured by QCT. *Osteoarthritis and Cartilage*, 21(7):957–964.

Lund, M. E., Andersen, M. S., de Zee, M., and Rasmussen, J. (2015). Scaling of musculoskeletal models from static and dynamic trials. *International Biomechanics*, 2(1):1–11.

Lund, M. E., de Zee, M., Andersen, M. S., and Rasmussen, J. (2012). On validation of multibody musculoskeletal models. *Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine*, 226(2):82–94.

Maleki, M., Arazpour, M., Joghtaei, M., Hutchins, S. W., Aboutorabi, A., and Pouyan, A. (2016). The effect of knee orthoses on gait parameters in medial knee compartment osteoarthritis: A literature review. *Prosthetics and Orthotics International*, 40(2):193–201.

Manal, K., Gardinier, E., Buchanan, T. S., and Snyder-Mackler, L. (2015a). A more informed evaluation of medial compartment loading: The combined use of the knee adduction and flexor moments. *Osteoarthritis and Cartilage*, 23(7):1107–1111.

Manal, K., Gardinier, E., Buchanan, T. S., and Snyder-Mackler, L. (2015b). A more informed evaluation of medial compartment loading: The combined use of the knee adduction and flexor moments. *Osteoarthritis and Cartilage*, 23(7):1107–1111.

Maniar, K. H., Jones, I. A., Gopalakrishna, R., and Vangsness, C. T. (2018). Lowering side effects of NSAID usage in osteoarthritis: recent attempts at minimizing dosage. *Expert Opinion on Pharmacotherapy*, 19(2):93–102.

Marra, M. A., Vanheule, V., Rasmussen, J., Verdonschot, N. J. J., Andersen, M. S., Fluit, R., Koopman, B. H. F. J. M., Rasmussen, J., Verdonschot, N. J. J., and Andersen, M. S. (2015). A Subject-Specific Musculoskeletal Modeling Framework to Predict in Vivo Mechanics of Total Knee Arthroplasty. *Journal of biomechanical engineering*, 137(2):020904–1–020904–12.

Martel-Pelletier, J., Barr, A. J., Cicuttini, F. M., Conaghan, P. G., Cooper, C., Goldring, M. B., Goldring, S. R., Jones, G., Teichtahl, A. J., and Pelletier, J. P. (2016). Osteoarthritis. *Nature Reviews Disease Primers*, 2.

Mazzuca, S. A., Page, M. C., Meldrum, R. D., Brandt, K. D., and Petty-Saphon, S. (2004). Pilot study of the effects of a heat-retaining knee sleeve on joint pain, stiffness, and function in patients with knee osteoarthritis. *Arthritis Care and Research*, 51(5):716–721.

McAlindon, T. E., Bannuru, R. R., Sullivan, M. C., Arden, N. K., Berenbaum, F., Bierma-Zeinstra, S. M., Hawker, G. A., Henrotin, Y., Hunter, D. J., Kawaguchi, H., Kwoh, K., Lohmander, S., Rannou, F., Roos, E. M., and Underwood, M. (2014). OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis and Cartilage*, 22(3):363–388.

McConnell, S., Kolopack, P., and Davis, a. M. (2001). The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): a review of its utility and measurement properties. *Arthritis and rheumatism*, 45(5):453–461.

McCormack, H. M., Horne, D. J. L., and Sheather, S. (1988). Clinical applications of visual analogue scales: A critical review. *Psychological Medicine*, 18(4):1007–1019.

McGibbon, C. A., Brandon, S., Bishop, E. L., Cowper-Smith, C., and Biden, E. N. (2021). Biomechanical Study of a Tricompartmental Unloader Brace for Patellofemoral or Multicompartment Knee Osteoarthritis. *Frontiers in Bioengineering and Biotechnology*, 8:1528.

McKean, K. A., Landry, S. C., Hubley-Kozey, C. L., Dunbar, M. J., Stanish, W. D., and Deluzio, K. J. (2007). Gender differences exist in osteoarthritic gait. *Clinical Biomechanics*, 22(4):400–409.

Meireles, S., De Groote, F., Reeves, N. D., Verschueren, S., Maganaris, C., Luyten, F., and Jonkers, I. (2016). Knee contact forces are not altered in early knee osteoarthritis. *Gait and Posture*, 45:115–120.

Messier, S. P., Gutekunst, D. J., Davis, C., and DeVita, P. (2005). Weight loss reduces knee-joint loads in overweight and obese older adults with knee osteoarthritis. *Arthritis and Rheumatism*, 52(7):2026–2032.

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

Miller, L. E., Fredericson, M., and Altman, R. D. (2020). Hyaluronic Acid Injections or Oral Nonsteroidal Anti-inflammatory Drugs for Knee Osteoarthritis: Systematic Review and Meta-analysis of Randomized Trials. *Orthopaedic Journal of Sports Medicine*, 8(1):1–11.

Miller, R. H., Esterson, A. Y., and Shim, J. K. (2015). Joint contact forces when minimizing the external knee adduction moment by gait modification: A computer simulation study.

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

Moelgaard, C. M. (2015). *Mechanical and Physiological Factors in Knee Joint Contact Mechanics - Early Changes Following Meniscectomy and Conservative Intervention Strategies*. PhD thesis, Aalborg University.

Moissenet, F., Modenese, L., and Dumas, R. (2017). Alterations of musculoskeletal models for a more accurate estimation of lower limb joint contact forces during normal gait: A systematic review. *Journal of Biomechanics*, 63:8–20.

Moyer, R., Birmingham, T., Dombroski, C., Walsh, R., and Giffin, J. R. (2017). Combined versus individual effects of a valgus knee brace and lateral wedge foot orthotic during stair use in patients with knee osteoarthritis. *Gait and Posture*, 54:160–166.

Moyer, R. F., Birmingham, T. B., Bryant, D. M., Giffin, J. R., Marriott, K. a., and Leitch, K. M. (2015a). Biomechanical effects of valgus knee bracing: a systematic review and meta-analysis. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society*, 23(2):178–88.

Moyer, R. F., Birmingham, T. B., Bryant, D. M., Giffin, J. R., Marriott, K. A., and Leitch, K. M. (2015b). Valgus bracing for knee osteoarthritis: A meta-analysis of randomized trials. *Arthritis Care and Research*, 67(4):493–501.

Moyer, R. F., Birmingham, T. B., Bryant, D. M., Giffin, J. R., Marriott, K. A., and Leitch, K. M. (2015c). Valgus bracing for knee osteoarthritis: A meta-analysis of randomized trials. *Arthritis Care and Research*, 67(4):493–501.

Moyer, R. F., Birmingham, T. B., Dombroski, C. E., Walsh, R. F., Leitch, K. M., Jenkyn, T. R., and Giffin, J. R. (2013). Combined effects of a valgus knee brace and lateral wedge foot orthotic on the external knee adduction moment in patients with varus gonarthrosis. *Archives of Physical Medicine and Rehabilitation*, 94(1):103–112.

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

Nadaud, M. C., Komistek, R. D., Mahfouz, M. R., Dennis, D. A., Anderle, M. R., and Anonymous (2005). In Vivo Three-Dimensional Determination of the Effectiveness of the Osteoarthritic Knee Brace: A Multiple Brace Analysis. *Journal of Bone and Joint Surgery, American Volume*, 87(S2):114–119.

Neogi, T. (2013). The epidemiology and impact of pain in osteoarthritis. *Osteoarthritis and Cartilage*, 21(9):1145–1153.

Nicolella, D. P., O'Connor, M. I., Enoka, R. M., Boyan, B. D., Hart, D. A., Resnick, E., Berkley, K. J., Sluka, K. A., Kwoh, C. K., Tosi, L. L., Coutts, R. D., Havill, L. M., and Kohrt, W. M. (2012). Mechanical contributors to sex differences in idiopathic knee osteoarthritis. *Biology of Sex Differences*, 3(1):1–11.

Nur, H., Sertkaya, B. S., and Tuncer, T. (2018). Determinants of physical functioning in women with knee osteoarthritis. *Aging Clinical and Experimental Research*, 30(4):299–306.

Øiestad, B. E., Juhl, C. B., Eitzen, I., and Thorlund, J. B. (2015). Knee extensor muscle weakness is a risk factor for development of knee osteoarthritis. A systematic review and meta-analysis. *Osteoarthritis and Cartilage*, 23(2):171–177.

Orishimo, K. F., Kremenic, I. J., Lee, S. J., McHugh, M. P., and Nicholas, S. J. (2013). Is valgus unloader bracing effective in normally aligned individuals: Implications for post-surgical protocols following cartilage restoration procedures. *Knee Surgery, Sports Traumatology, Arthroscopy*, 21(12):2661–2666.

Ostrander, R. V., Leddon, C. E., Hackel, J. G., O'Grady, C. P., and Roth, C. A. (2016). Efficacy of Unloader Bracing in Reducing Symptoms of Knee Osteoarthritis. *American journal of orthopedics (Belle Mead, N.J.)*, 45(5):306–311.

Park, Y. L., Santos, J., Galloway, K. G., Goldfield, E. C., and Wood, R. J. (2014). A soft wearable robotic device for active knee motions using flat pneumatic artificial muscles. *Proceedings - IEEE International Conference on Robotics and Automation*, pages 4805–4810.

Parkes, M. J., Maricar, N., Lunt, M., LaValley, M. P., Jones, R. K., Segal, N. A., Takahashi-Narita, K., and Felson, D. T. (2013). Lateral wedge insoles as a conservative treatment for pain in patients with medial knee osteoarthritis a meta-analysis. *JAMA - Journal of the American Medical Association*, 310(7):722–730.

Parween, R., Shriram, D., Mohan, R. E., Lee, Y. H. D., and Subburaj, K. (2019). Methods for evaluating effects of unloader knee braces on joint health: a review. *Biomedical Engineering Letters*, 9(2):153–168.

Paskins, Z., Sanders, T., and Hassell, A. B. (2014). Comparison of patient experiences of the osteoarthritis consultation with GP attitudes and beliefs to OA: a narrative review. *BMC family practice*, 15(1):46.

Pedersen, A. B., Mehnert, F., Odgaard, A., and Schrøder, H. M. (2012). Existing data sources for clinical epidemiology: The Danish knee Arthroplasty register. *Clinical Epidemiology*, 4(1):125–135.

Peters, T. J., Sanders, C., Dieppe, P., and Donovan, J. (2005). Factors associated with change in pain and disability over time: a community-based prospective observational study of hip and knee osteoarthritis. *British Journal ofGeneral Practice*, 55:205–211.

Petersen, W., Ellermann, A., Zantop, T., Rembitzki, I. V., Semsch, H., Liebau, C., and Best, R. (2016). Biomechanical effect of unloader braces for medial osteoarthritis of the knee: a systematic review (CRD 42015026136). *Archives of Orthopaedic and Trauma Surgery*, 136(5):649–656.

Pierrat, B., Molimard, J., Navarro, L., Avril, S., and Calmels, P. (2014a). Evaluation of the mechanical efficiency of knee orthoses: A combined experimentalnumerical approach. *Computer methods in biomechanics and biomedical engineering*, 228(6):533–546.

Pierrat, B., Oullion, R., Molimard, J., Navarro, L., Combreas, M., Avril, S., Philippot, R., and Calmels, P. (2014b). Characterisation of in-vivo mechanical action of knee braces regarding their anti-drawer effect. *The Knee*, 22(2):80–87.

Pollo, F. E., Otis, J. C., Backus, S. I., Warren, R. F., and Wickiewicz, T. L. (2002). Reduction of medial compartment loads with valgus bracing of the osteoarthritic knee. *The American journal of sports medicine*, 30(3):414–421.

Radin, E. L., Burr, D. B., Caterson, B., Fyhrie, D., Brown, T. D., and Boyd, R. D. (1991). Mechanical Determinants of Osteoarthrosis. *Seminars in Arthritis and Rheumatism*, 21(3):12–21.

Ramsey, D. K., Briem, K., Axe, M. J., and Snyder-Mackler, L. (2007). A mechanical hypothesis for the effectiveness of knee bracing for medial compartment knee osteoarthritis. *J Bone Joint Surg Am.*, 89(11):2398–2407.

Ravi, B., Croxford, R., Reichmann, W. M., Losina, E., Katz, J. N., and Hawker, G. A. (2012). The changing demographics of total joint arthroplasty recipients in the United States and Ontario from 2001 to 2007. *Best Practice and Research: Clinical Rheumatology*, 26(5):637–647.

Reinsdorf, D. S., Richburg, C. A., Czerniecki, J. M., and Aubin, P. M. (2019). Development of a robotic unloader brace for investigation of conservative treatment of medial knee osteoarthritis. In *IEEE International Conference on Rehabilitation Robotics*, volume 16, pages 931–937. IEEE.

Richard Steadman, J., Briggs, K. K., Pomeroy, S. M., and Wijdicks, C. A. (2016). Current state of unloading braces for knee osteoarthritis. *Knee Surgery, Sports Traumatology, Arthroscopy*, 24(1):42–50.

Richards, C. and Higginson, J. S. (2010). Knee contact force in subjects with symmetrical OA grades: Differences between OA severities. *Journal of Biomechanics*, 43(13):2595–2600.

Richards, J. D., Sanchez-Ballester, J., Jones, R. K., Darke, N., and Livingstone, B. N. (2005). A comparison of knee braces during walking for the treatment of osteoarthritis of the medial compartment of the knee. *The Journal of bone and joint surgery. British volume*, 87(7):937–939.

Richards, R. E., Andersen, M. S., Harlaar, J., and van den Noort, J. C. (2018). Relationship between knee joint contact forces and external knee joint moments in patients with medial knee osteoarthritis: effects of gait modifications. *Osteoarthritis and Cartilage*, 26(9):1203–1214.

Richette, P., Poitou, C., Garnero, P., Vicaut, E., Bouillot, J. L., Lacorte, J. M., Basdevant, A., Clément, K., Bardin, T., and Chevalier, X. (2011). Benefits of massive weight loss on symptoms, systemic inflammation and cartilage turnover in obese patients with knee osteoarthritis. *Annals of the Rheumatic Diseases*, 70(1):139–144.

Ro, D. H., Lee, D. Y., Moon, G., Lee, S., Seo, S. G., Kim, S. H., Park, I. W., and Lee, M. C. (2017). Sex differences in knee joint loading: Cross-sectional study in geriatric population. *Journal of Orthopaedic Research*, 35(6):1283–1289.

Roberts, B. C., Solomon, L. B., Mercer, G., Reynolds, K. J., Thewlis, D., and Perilli, E. (2017). Joint loading and proximal tibia subchondral trabecular bone microarchitecture differ with walking gait patterns in end-stage knee osteoarthritis. *Osteoarthritis and Cartilage*, 25(10):1623–1632.

Segal, N. a. (2012). Bracing and Orthoses: A Review of Efficacy and Mechanical Effects for Tibiofemoral Osteoarthritis. *PM and R*, 4(5 SUPPL.):S89–S96.

Segal, N. A., Torner, J. C., Felson, D. T., Niu, J., Sharma, L., Lewis, C. E., and Nevitt, M. (2009). Knee Extensor Strength Does Not Protect Against Incident Knee Symptoms at 30 Months in the Multicenter Knee Osteoarthritis (MOST) Cohort. *PM and R*, 1(5):459–465.

Shaw, K. E., Charlton, J. M., Perry, C. K., De Vries, C. M., Redekopp, M. J., White, J. A., and Hunt, M. A. (2018). The effects of shoe-worn insoles on gait biomechanics in people with knee osteoarthritis: A systematic review and meta-analysis. *British Journal of Sports Medicine*, 52(4):238–253.

Shepherd, M. K. and Rouse, E. J. (2017). Design and Validation of a Torque-Controllable Knee Exoskeleton for Sit-to-Stand Assistance. *IEEE/ASME Transactions on Mechatronics*, 22(4):1695–1704.

Skou, S. T., Hojgaard, L., and Simonsen, O. H. (2013). Customized Foot Insoles Have a Positive Effect on Pain, Function, and Quality of Life in Patients with Medial Knee Osteoarthritis. *Journal of the American Podiatric Medical Association*, 103(1):50–55.

Skou, S. T. and Roos, E. M. (2017). Good Life with osteoArthritis in Denmark (GLA:D): evidence-based education and supervised neuromuscular exercise delivered by certified physiotherapists nationwide. *BMC Musculoskeletal Disorders*, 18(1):1–13.

Skou, S. T., Roos, E. M., Simonsen, O., Laursen, M. B., Rathleff, M. S., Arendt-Nielsen, L., and Rasmussen, S. (2016). The efficacy of non-surgical treatment on pain and sensitization in patients with knee osteoarthritis: A pre-defined ancillary analysis from a randomized controlled trial. *Osteoarthritis and Cartilage*, 24(1):108–116.

Sofat, N., Beith, I., G. Anilkumar, P., and Mitchell, P. (2011). Recent Clinical Evidence for the Treatment of Osteoarthritis: What we have Learned. *Reviews on Recent Clinical Trials*, 6(2):114–126.

Squyer, E., Stamper, D. L., Hamilton, D. T., Sabin, J. A., and Leopold, S. S. (2013). Unloader knee braces for osteoarthritis: Do patients actually wear them? *Clinical Orthopaedics and Related Research*, 471(6):1982–1991.

Stoltze, J. S., Rasmussen, J., and Andersen, M. S. (2018). On the biomechanical relationship between applied hip, knee and ankle joint moments and the internal knee compressive forces. *International Biomechanics*, 5(1):63–74.

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

Trepczynski, A., Kutzner, I., Schwachmeyer, V., Heller, M. O., Pfitzner, T., and Duda, G. N. (2018). Impact of antagonistic muscle co-contraction on in vivo knee contact forces. *Journal of NeuroEngineering and Rehabilitation*, 15(1):1–10.

Turner, A. B. and Craig, E. (1980). Knee Anatomy: A Brief Review. *Physical Therapy*, 60(12):1556–1560.

Van Der Esch, M., Steultjens, M., Wieringa, H., Dinant, H., and Dekker, J. (2005). Structural joint changes, malalignment, and laxity in osteoarthritis of the knee. *Scandinavian Journal of Rheumatology*, 34(4):298–301.

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

Vannini, F., Spalding, T., Andriolo, L., Berruto, M., Denti, M., Espregueira-Mendes, J., Menetrey, J., Peretti, G. M., Seil, R., and Filardo, G. (2016). Sport and early osteoarthritis: the role of sport in aetiology, progression and treatment of knee osteoarthritis. *Knee Surgery, Sports Traumatology, Arthroscopy*, 24(6):1786–1796.

Wallace, I. J., Worthington, S., Felson, D. T., Jurmain, R. D., Wren, K. T., Maijanen, H., Woods, R. J., and Lieberman, D. E. (2017). Knee osteoarthritis has doubled in prevalence since the mid-20th century. *Proceedings of the National Academy of Sciences of the United States of America*, 114(35):9332–9336.

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

Wellsandt, E., Gardinier, E. S., Manal, K., Axe, M. J., Buchanan, T. S., and Snyder-Mackler, L. (2016). Decreased knee joint loading associated with early knee osteoarthritis after anterior cruciate ligament injury. *Am J Sports Med*, 44(1):143–151.

wen Li, J., shuo Ma, Y., and kun Xiao, L. (2019). Postoperative Pain Management in Total Knee Arthroplasty. *Orthopaedic Surgery*, 11(5):755–761.

Wilson, D. R., Mc Walter, E. J., and Johnston, J. D. (2009). The Measurement of Joint Mechanics and Their Role in Osteoarthritis Genesis and Progression. *Medical Clinics of North America*, 93(1):67–82.

Xing, F., Lu, B., Kuang, M. J., Wang, Y., Zhao, Y. L., Zhao, J., Sun, L., Wang, Y., Ma, J. X., and Ma, X. L. (2017). A systematic review and meta-analysis into the effect of lateral wedge arch support insoles for reducing knee joint load in patients with medial knee osteoarthritis. *Medicine (United States)*, 96(24):1–10.

Yan, T., Cempini, M., Oddo, C. M., and Vitiello, N. (2015). Review of assistive strategies in powered lower-limb orthoses and exoskeletons. *Robotics and Autonomous Systems*, 64:120–136.

YU, S. P., Williams, M., Eyles, Jillian, P., Chen, J. S., Makovey, J., and Hunter, D. J. (2015). Effectiveness of Knee Bracing in Osteoarthritis; pragmatic trial in a multidisciplinary clinic. *International Journal of Rheumatic Diseases*, 19(3):279–286.

Yusuf, E. (2016). Pharmacologic and Non-Pharmacologic Treatment of Osteoarthritis. *Current Treatment Options in Rheumatology*, 2(2):111–125.

Zhang, W., Doherty, M., Peat, G., Bierma-Zeinstra, S. M., Arden, N. K., Bresnihan, B., Herrero-Beaumont, G., Kirschner, S., Leeb, B. F., Lohmander, L. S., Mazières, B., Pavelka, K., Punzi, L., So, A. K., Tuncer, T., Watt, I., and Bijlsma, J. W. (2010). EULAR evidence-based recommendations for the diagnosis of knee osteoarthritis. *Annals of the Rheumatic Diseases*, 69(3):483–489.

Zhang, W., Robertson, J., Jones, A. C., Dieppe, P. A., and Doherty, M. (2008). The placebo effect and its determinants in osteoarthritis: Meta-analysis of randomised controlled trials. *Annals of the Rheumatic Diseases*, 67(12):1716–1723.

Zimmerman, W. F., Miller, M. A., Cleary, R. J., Izant, T. H., and Mann, K. A. (2016). Damage in total knee replacements from mechanical overload. *Journal of Biomechanics*, 49(10):2068–2075.

SUMMARY

Mechanical devices are common non-invasive treatments for knee osteoarthritis, and various brace methods have been proposed with the aim of unloading the knee joint to relieve pain. However, the effect from these devices is debated in the literature and with a globally increasing number of osteoarthritis patients, combined with the absence of a cure, the demand for an efficient treatment with scientific evidence is high.

Often knee osteoarthritis patients experience multiple consultations with the health care system before reaching a satisfactory result, which might be due to the many risk factors for developing the disease. Therefore, subject-specific treatments might be necessary to target the different subgroups based on individual risk factors.

The aim with this PhD work was 1) to analyse various approaches for efficiently unloading the knee joint and 2) to develop and experimentally test a subject-specific knee brace prototype using a concept based on the findings from the first step. It is believed that the findings in this thesis have the potential to advance the state-of-the-art within knee braces, which will improve the quality-of-life for the patients.

ISSN (online): 2446-1636
ISBN (online): 978-87-7573-939-4

AALBORG UNIVERSITY PRESS